

PRODRUG MOIETIES AND COMPOUNDS COMPRISING THE SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to and the benefit of U.S. Provisional Application No. 63/600,382, filed on November 17, 2023, which is incorporated herein by reference in its entirety.

FIELD

Provided herein are compounds that can be used to prepare prodrugs, methods of producing prodrugs using the compounds, and prodrugs produced by such methods. The prodrugs produced using the compounds disclosed herein are highly soluble, allowing for good oral bioavailability.

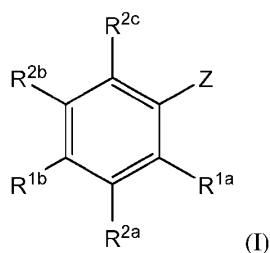
BACKGROUND

A significant number of currently marketed small molecule pharmaceutical compounds are nearly insoluble. However, improvements in solubility tend to increase hydrophilicity, which can reduce target engagement. Prodrug moieties, such as succinic acid esters and formyl phosphates, can be used to increase solubility of the compounds without ultimately affecting target engagement, as the solubilizing prodrug moiety is eventually cleaved to release the active compound. However, such methodology is largely limited to drugs with alcohols or NH-containing heterocycles. Certain prodrug moieties can also cleave too quickly; in the case of orally-administered drugs, early cleavage can result in precipitation of the pharmaceutical compound in the stomach or intestine.

SUMMARY

Disclosed herein are compounds that can be used as building blocks to prepare prodrugs with significantly increased solubility. Also disclosed herein are prodrug compounds prepared from the building block compounds, and methods of preparing prodrug compounds. The resulting prodrugs can be cleaved *in vivo*, e.g., by phosphatases. In some embodiments, the prodrugs can undergo controlled cleavage, so as to maximize oral bioavailability.

In one aspect, disclosed herein is a compound of formula (I):



or a salt thereof, wherein:

Z is $-\text{CR}^{3a}\text{R}^{3b}-\text{O}-\text{CR}^{4a}\text{R}^{4b}-\text{LG}$, $-(\text{CR}^{5a}\text{R}^{5b})_p-\text{CO}-\text{E}$, $-(\text{CR}^{6a}\text{R}^{6b})-\text{LG}$, or $-\text{CR}^{7a}\text{R}^{7b}-\text{O}-\text{CR}^{8a}\text{R}^{8b}-\text{O}-\text{CR}^{9a}\text{R}^{9b}-\text{LG}$;

5 one of R^{1a} and R^{1b} is $-\text{OPO}(\text{OR}^a)_2$, and the other is selected from hydrogen, alkyl, halo, haloalkyl, and $-(\text{CR}^b\text{R}^c)_m-\text{X}$;

R^{2a} , R^{2b} , and R^{2c} are each independently selected from hydrogen, alkyl, halo, haloalkyl, and $-(\text{CR}^d\text{R}^e)_n-\text{Y}$;

10 wherein, when R^{1a} is $-\text{OPO}(\text{OR}^a)_2$, R^{1b} and R^{2a} , together with the carbon atoms to which they are attached, are optionally taken together to form an optionally substituted ring;

X and Y are each independently selected from cyano, nitro, $-\text{OR}^f$, $-\text{NR}^g\text{R}^h$, $-\text{COOR}^i$, $-\text{CONR}^j\text{R}^k$, $-\text{S}(\text{O})_2\text{NR}^l\text{R}^m$, $-\text{PO}(\text{OR}^n)_2$, and $-\text{PO}(\text{OR}^o)\text{CH}_2\text{PO}(\text{OR}^p)_2$;

m, n, and p are each independently 0, 1, or 2;

15 R^{3a} , R^{3b} , R^{6a} , R^{6b} , R^{7a} , and R^{7b} are each independently selected from hydrogen and alkyl;

R^{4a} and R^{4b} are each hydrogen, or are taken together to form an oxo group;

R^{5a} and R^{5b} are each independently selected from hydrogen, alkyl, halo, and alkoxy;

R^{8a} and R^{8b} are each hydrogen, or are taken together to form an oxo group;

20 R^{9a} and R^{9b} are each selected from hydrogen and alkyl, or are taken together to form an oxo group;

R^a , R^f , R^g , R^h , R^i , R^j , R^k , R^l , R^m , R^n , R^o , and R^p are each independently selected from hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, and arylalkyl; wherein R^g and R^h , R^j and R^k , and R^l and R^m , together with the nitrogen atoms to which they are attached, are optionally taken together to form an optionally substituted ring;

25 R^b , R^c , R^d , and R^e are each independently selected from hydrogen and alkyl;

E is halo or $-\text{OH}$; and

LG is selected from $-\text{O}-\text{Q}$, halo, and hydroxy, wherein Q is optionally substituted aryl, optionally substituted heterocyclyl, or $-\text{SO}_2\text{R}^s$, wherein R^s is selected from alkyl and optionally substituted aryl.

In some embodiments, when R^{1a} is $-OPO(OR^a)_2$, then either: R^{1b} is $-(CR^bR^c)_m-X$, wherein X is $-COOR^i$ or $-PO(OR^n)_2$; or at least one of R^{2a} , R^{2b} , and R^{2c} is $-(CR^dR^e)_n-Y$, wherein Y is $-COOR^i$ or $-PO(OR^n)_2$. In some embodiments, when R^{1b} is $-OPO(OR^a)_2$, then either: R^{1a} is $-(CR^bR^c)_m-X$, wherein X is $-COOR^i$ or $-PO(OR^n)_2$; or at least one of R^{2a} , R^{2b} , and R^{2c} is $-(CR^dR^e)_n-Y$, wherein Y is $-COOR^i$ or $-PO(OR^n)_2$.

In some embodiments, Z is $-CR^{3a}R^{3b}-O-CR^{4a}R^{4b}-LG$, $-(CR^{5a}R^{5b})_p-CO-E$, or $-(CR^{6a}R^{6b})-LG$.

In some embodiments, Z is $-CR^{3a}R^{3b}-O-CR^{4a}R^{4b}-LG$.

In some embodiments, R^{3a} and R^{3b} are each independently selected from hydrogen and methyl.

In some embodiments, R^{4a} and R^{4b} are taken together to form an oxo group. In some embodiments, R^{4a} and R^{4b} are each hydrogen.

In some embodiments, Z is $-(CR^{5a}R^{5b})_p-CO-E$. In some embodiments, p is 2, each R^{5a} and R^{5b} is independently selected from hydrogen and methyl, and E is selected from chloro and hydroxy.

In some embodiments, Z is $-(CR^{6a}R^{6b})-LG$. In some embodiments, R^{6a} and R^{6b} are each independently selected from hydrogen and methyl, and LG is halo or hydroxy. In some embodiments, LG is bromo or hydroxy.

In some embodiments, Z is $-CR^{7a}R^{7b}-O-CR^{8a}R^{8b}-O-CR^{9a}R^{9b}-LG$. In some embodiments, R^{7a} and R^{7b} are each hydrogen. In some embodiments, R^{8a} and R^{8b} are each hydrogen, and R^{9a} and R^{9b} are taken together to form an oxo group. In some embodiments, R^{8a} and R^{8b} taken together to form an oxo group, and R^{9a} and R^{9b} are each hydrogen.

In some embodiments, R^a , R^f , R^g , R^h , R^i , R^j , R^k , R^l , R^m , R^n , R^o , and R^p are each independently selected from hydrogen, C_1 - C_4 alkyl, phenyl, and phenyl- C_1 - C_2 -alkyl.

In some embodiments, R^b , R^c , R^d , and R^e are each independently selected from hydrogen and methyl.

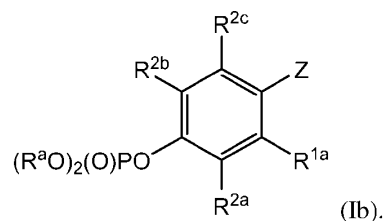
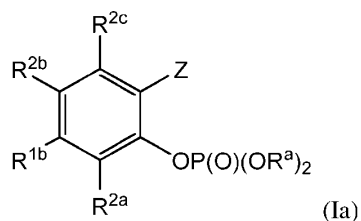
In some embodiments, R^{2a} , R^{2b} , and R^{2c} are each independently selected from hydrogen, C_1 - C_4 alkyl, halo, and $-(CR^dR^e)_n-Y$, wherein n is 0 or 1, R^d and R^e are each hydrogen, and Y is selected from cyano, $-OR^f$, $-COOR^i$, and $-PO(OR^n)_2$, wherein each R^f , R^i , and R^n is independently selected from hydrogen and C_1 - C_4 alkyl.

In some embodiments, LG is $-O-Q$, wherein Q is optionally substituted phenyl or an optionally substituted 5- or 6-membered heterocyclyl having 1 or 2 heteroatoms independently selected from N, O, and S. In some embodiments, LG is $-O-Q$, wherein Q is phenyl substituted with 1, 2, 3, 4, or 5 substituents independently selected from nitro and

halo. In some embodiments, LG is -O-(4-nitrophenyl) or -O-pentafluorophenyl. In some embodiments, LG is -O-Q, wherein Q is an optionally substituted pyrrolidine-2,5-dione. In some embodiments, LG is -O-Q, wherein Q is -SO₂R^s, wherein R^s is methyl.

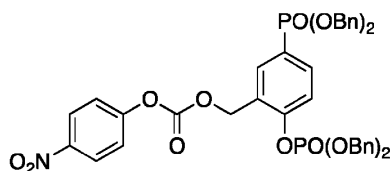
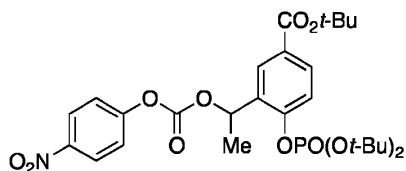
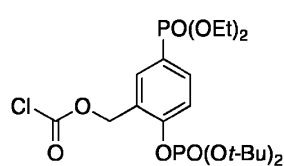
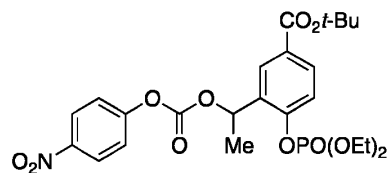
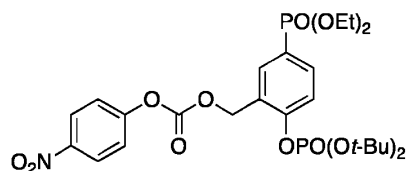
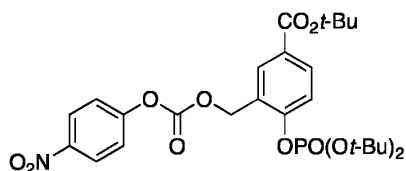
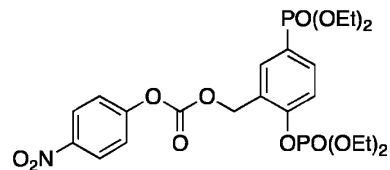
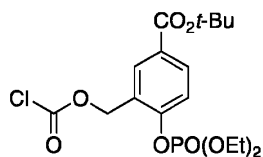
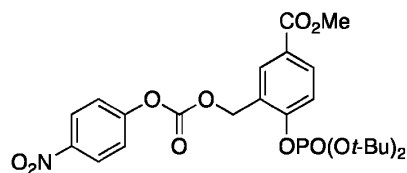
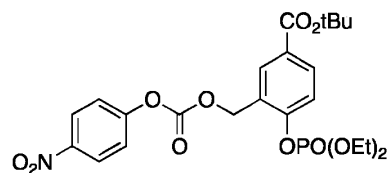
In some embodiments, LG is halo or hydroxy.

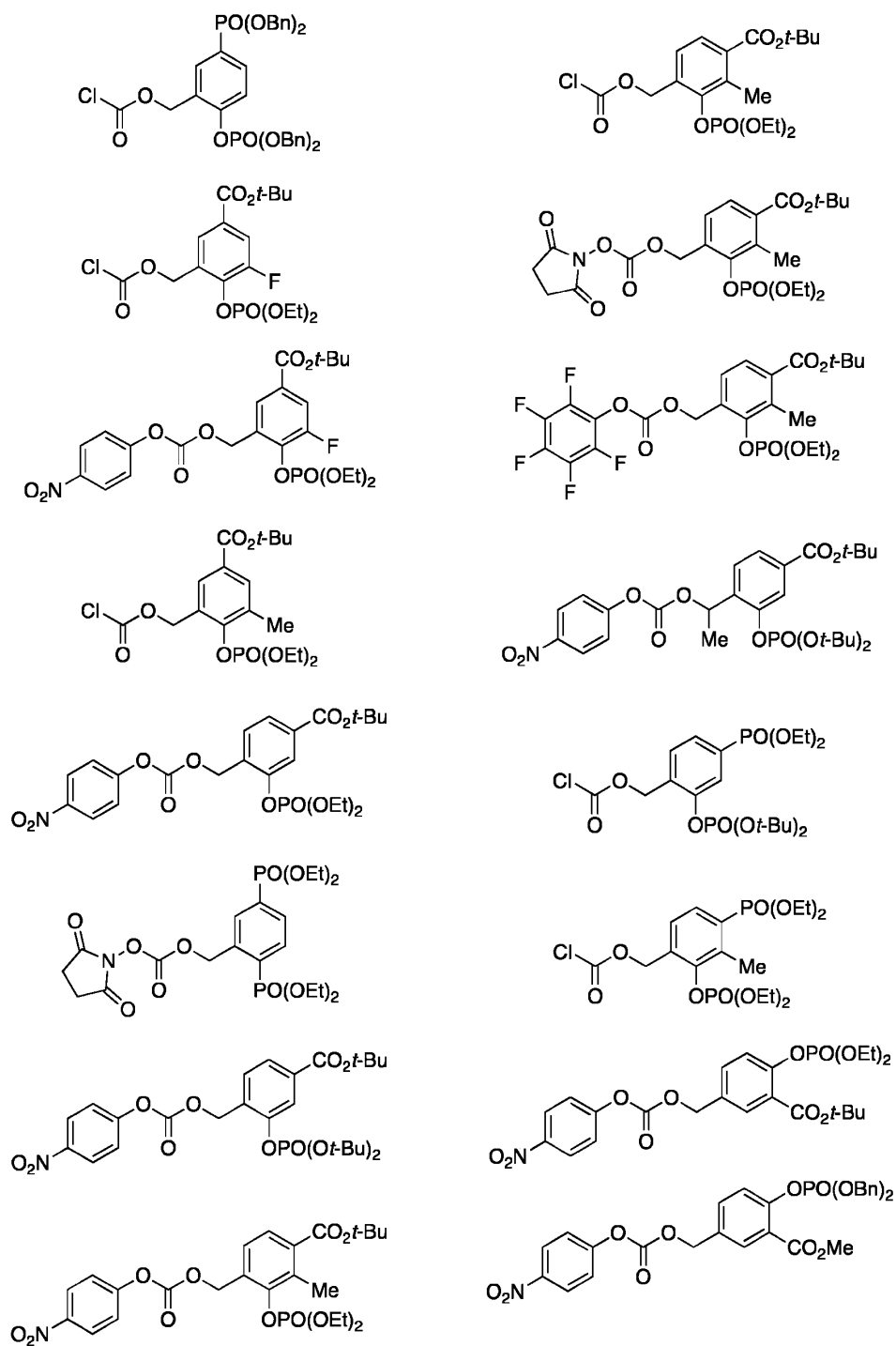
5 In some embodiments, the compound has formula (Ia) or (Ib):

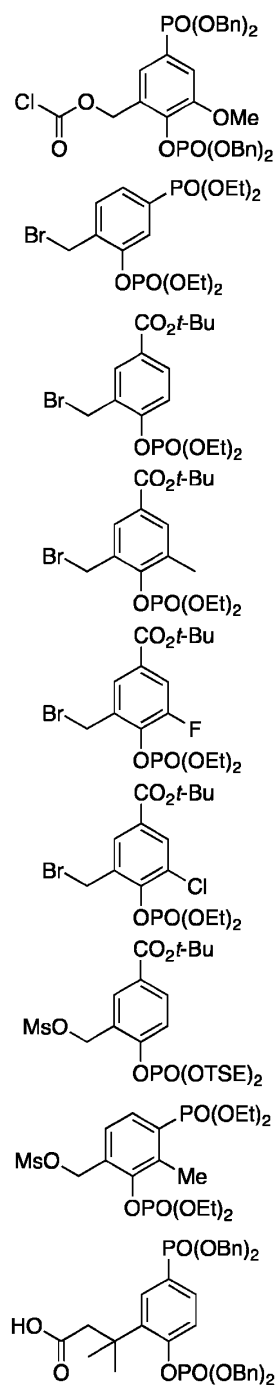
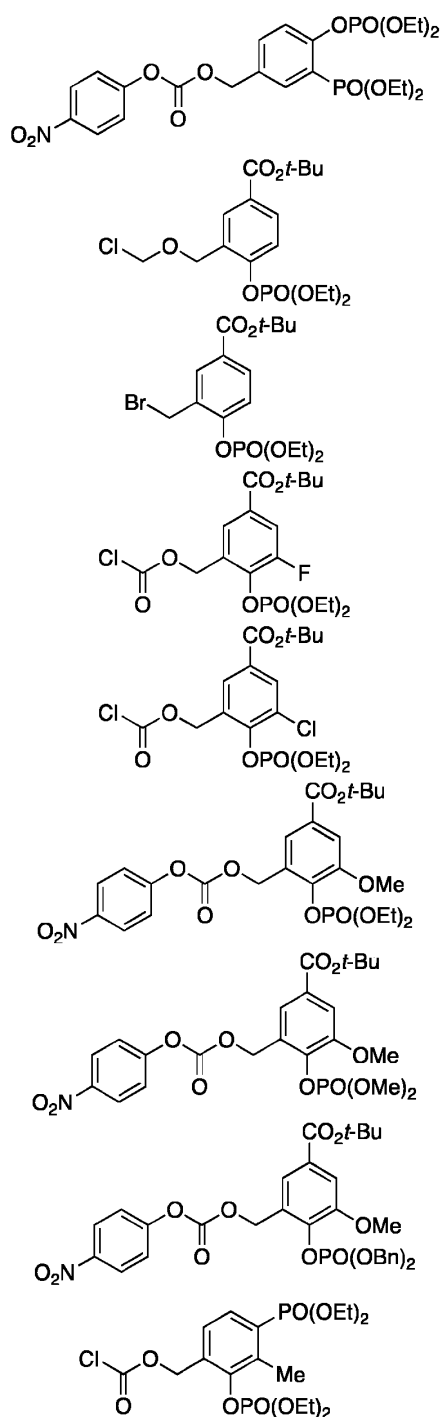


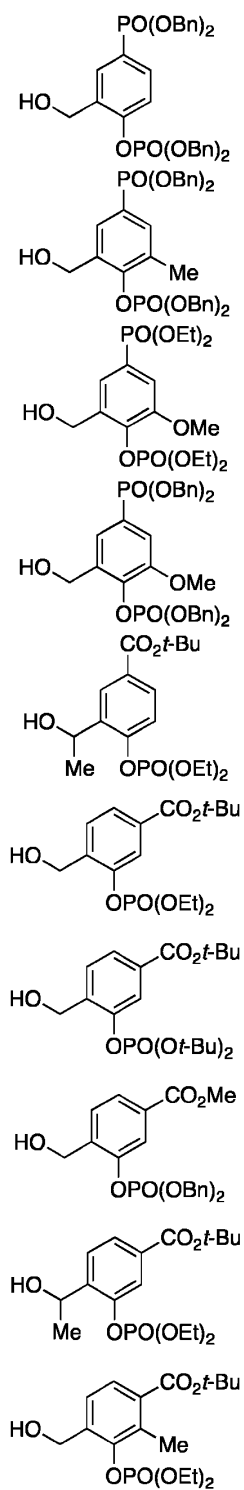
In some embodiments, the compound has formula (Ia).

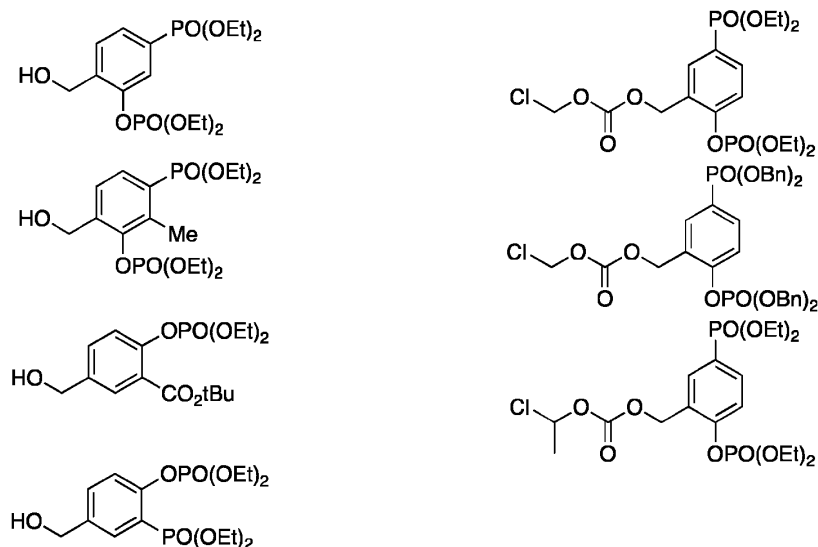
In some embodiments, the compound is selected from the group consisting of:





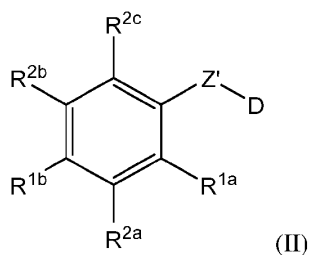






and salts thereof.

In some embodiments, disclosed herein is a compound of formula (II):



5 or a pharmaceutically acceptable salt thereof, wherein:

Z' is $-\text{CR}^{3a}\text{R}^{3b}-\text{O}-\text{CR}^{4a}\text{R}^{4b}-$, $-(\text{CR}^{5a}\text{R}^{5b})_p-\text{CO}-$, $-(\text{CR}^{6a}\text{R}^{6b})-$, or $-\text{CR}^{7a}\text{R}^{7b}-\text{O}-\text{CR}^{8a}\text{R}^{8b}-\text{O}-\text{CR}^{9a}\text{R}^{9b}-$;

one of R^{1a} and R^{1b} is $-\text{OPO}(\text{OR}^a)_2$, and the other is selected from hydrogen, alkyl, halo, haloalkyl, and $-(\text{CR}^b\text{R}^c)_m-\text{X}$;

10 R^{2a} , R^{2b} , and R^{2c} are each independently selected from hydrogen, alkyl, halo, haloalkyl, and $-(\text{CR}^d\text{R}^e)_n-\text{Y}$;

wherein, when R^{1a} is $-\text{OPO}(\text{OR}^a)_2$, R^{1b} and R^{2a} , together with the carbon atoms to which they are attached, are optionally taken together to form an optionally substituted ring;

X and Y are each independently selected from cyano, nitro, $-\text{OR}^f$, $-\text{NR}^g\text{R}^h$, $-\text{COOR}^i$, $-\text{CONR}^j\text{R}^k$, $-\text{S}(\text{O})_2\text{NR}^l\text{R}^m$, $-\text{PO}(\text{OR}^n)_2$, and $-\text{PO}(\text{OR}^o)\text{CH}_2\text{PO}(\text{OR}^p)_2$;

m, n, and p are each independently 0, 1, or 2;

R^{3a} , R^{3b} , R^{6a} , R^{6b} , R^{7a} , and R^{7b} are each independently selected from hydrogen and alkyl;

R^{4a} and R^{4b} are each hydrogen, or are taken together to form an oxo group;

R^{5a} and R^{5b} are each independently selected from hydrogen, alkyl, halo, and alkoxy;

5 R^{8a} and R^{8b} are each hydrogen, or are taken together to form an oxo group;

R^{9a} and R^{9b} are each selected from hydrogen and alkyl, or are taken together to form an oxo group;

R^a , R^f , R^g , R^h , R^i , R^j , R^k , R^l , R^m , R^n , R^o , and R^p are each independently selected from hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, and arylalkyl; wherein R^g and R^h , R^i and R^k , and
10 R^l and R^m , together with the nitrogen atoms to which they are attached, are optionally taken together to form an optionally substituted ring;

R^b , R^c , R^d , and R^e are each independently selected from hydrogen and alkyl; and

D is a pharmaceutically active compound.

In some embodiments, when R^{1a} is $-OPO(OR^a)_2$, then either: R^{1b} is $-(CR^bR^c)_m-X$,
15 wherein X is $-COOR^i$ or $-PO(OR^n)_2$; or at least one of R^{2a} , R^{2b} , and R^{2c} is $-(CR^dR^e)_n-Y$, wherein Y is $-COOR^i$ or $-PO(OR^n)_2$. In some embodiments, when R^{1b} is $-OPO(OR^a)_2$, then either: R^{1a} is $-(CR^bR^c)_m-X$, wherein X is $-COOR^i$ or $-PO(OR^n)_2$; or at least one of R^{2a} , R^{2b} , and R^{2c} is $-(CR^dR^e)_n-Y$, wherein Y is $-COOR^i$ or $-PO(OR^n)_2$.

In some embodiments, Z' is $-CR^{3a}R^{3b}-O-CR^{4a}R^{4b}-$, $-(CR^{5a}R^{5b})_p-CO-$, or $-(CR^{6a}R^{6b})-$.

20 In some embodiments, Z' is $-CR^{3a}R^{3b}-O-CR^{4a}R^{4b}-$.

In some embodiments, R^{3a} and R^{3b} are each independently selected from hydrogen and methyl.

In some embodiments, R^{4a} and R^{4b} are each hydrogen. In some embodiments, R^{4a} and R^{4b} are taken together to form an oxo group.

25 In some embodiments, Z' is $-CH_2-$.

In some embodiments, Z' is $-(CR^{5a}R^{5b})_p-CO-$. In some embodiments, p is 2, and R^{5a} and R^{5b} are each independently selected from hydrogen and methyl.

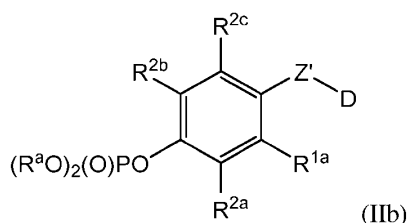
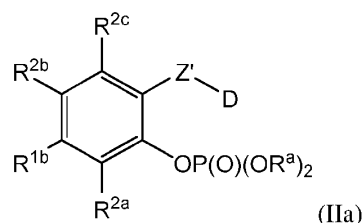
In some embodiments, Z' is $-(CR^{6a}R^{6b})-$. In some embodiments, R^{6a} and R^{6b} are each independently selected from hydrogen and methyl.

30 In some embodiments, Z' is $-CR^{7a}R^{7b}-O-CR^{8a}R^{8b}-O-CR^{9a}R^{9b}-LG$. In some embodiments, R^{7a} and R^{7b} are each hydrogen. In some embodiments, R^{8a} and R^{8b} are each hydrogen, and R^{9a} and R^{9b} are taken together to form an oxo group. In some embodiments, R^{8a} and R^{8b} taken together to form an oxo group, and R^{9a} and R^{9b} are each hydrogen.

In some embodiments, R^a , R^f , R^g , R^h , R^i , R^j , R^k , R^l , R^m , R^n , R^o , and R^p are each independently selected from hydrogen, C_1 - C_4 alkyl, phenyl, and phenyl- C_1 - C_2 -alkyl. In some embodiments, R^b , R^c , R^d , and R^e are each independently selected from hydrogen and methyl.

In some embodiments, R^{2a} , R^{2b} , and R^{2c} are each independently selected from hydrogen, C_1 - C_4 alkyl, halo, and $-(CR^dR^e)_n-Y$, wherein n is 0 or 1, R^d and R^e are each hydrogen, and Y is selected from cyano, $-OR^f$, $-COOR^i$, and $-PO(OR^n)_2$, wherein each R^f , R^i , and R^n is independently selected from hydrogen and C_1 - C_4 alkyl.

In some embodiments, the compound has formula (IIa) or (IIb):



In some embodiments, group D is attached to the compound via a nitrogen atom or an oxygen atom. In some embodiments, the pharmaceutically active compound is selected from the group consisting of: analgesics; anesthetics; antibacterials; anticonvulsants; antidementia agents; antidepressants; antiemetics; antifungals; antigout agents; anti-inflammatories; antimigraine agents; antimuscarinic agents; antimycobacterials; antineoplastics; antiparasitics; antiparkinson agents; antipsychotics; antispasmodic agents; antivirals; anxiolytics; bipolar agents; blood glucose regulators; blood products / modifiers / volume expanders; cardiovascular agents; central nervous system agents; dental and oral agents; dermatological agents; enzyme replacements/modifiers; gastrointestinal agents; genitourinary agents; hormonal agents; immunological agents; inflammatory bowel disease agents; metabolic bone disease agents; ophthalmic agents; otic agents; respiratory tract agents; sedatives/hypnotics; and skeletal muscle relaxants. In some embodiments, the pharmaceutically active compound is an antineoplastic agent.

In some embodiments, the pharmaceutically active compound is selected from the group consisting of abrocitinib, acalabrutinib, amisulpride, apalutamide, apixaban, aprepitant, ARV-766, asciminib, atorvastatin, avacopan, avapritinib, bavdegalutamide, bicalutamide, cabazitaxel, carvedilol, cefdinir, cefprozil, celecoxib, clarithromycin, dabrafenib, desloratadine, docetaxel, doravirine, doxorubicin, DT2216, efavirenz, enzalutamide, eragidomide, etravirine, ezetimibe, FHD-609, glimepiride, glipizide, glyburide, golcadomide, hydrochlorothiazide, hydroxyzine pamoate, ibrutinib, idelalisib, imatinib, ivacaftor,

lamotrigine, lenalidomide, linezolid, lopinavir, meloxicam, metaxalone, methylphenidate, mezigdomide, modafinil, N-desalkylquetiapine, niclosamide, nilotinib, NX-2127, olanzapine, olaparib, oliceridine, osimertinib, oteseconazole, oxcarbazepine, paclitaxel, pacritinib, palbociclib, pioglitazone, pomalidomide, pralsetinib, quetiapine, raloxifene, rilpivirine, rilzabrutinib, rimegepant, ripretinib, ritonavir, rivaroxaban, selpercatinib, selumetinib, simvastatin, SN-38, sorafenib, sotorasib, tacrolimus, tazemetostat, tucatinib, valdecocix, vemurafenib, vepdegestrant, vociprotafib, and zanubrutinib. In some embodiments, the pharmaceutically active compound is selected from the group consisting of apixaban, carvedilol, dabrafenib, desloratadine, enzalutamide, lenalidomide, paclitaxel, and vemurafenib. In some embodiments, the pharmaceutically active compound is paclitaxel.

In some embodiments, the compound of formula (II) is a compound shown in FIGS. 1-51 and Table 2.

Also disclosed herein is a method of preparing a prodrug of a pharmaceutically active compound, comprising: reacting a compound of formula (I) with a pharmaceutically active compound in the presence of a base to form a protected prodrug compound; and removing protecting groups from the protected prodrug compound, to thereby provide the prodrug of the pharmaceutically active compound.

In some embodiments, the reacting step comprises: (a) combining the compound of formula (I) and the pharmaceutically active compound to form a mixture; and (b) adding the base to the mixture. In some embodiments, the reacting step comprises: (a) reacting the pharmaceutically active compound with a base to form a mixture; and (b) adding the compound of formula (I) to the mixture.

In another aspect, disclosed herein is a method of treating a disorder in a subject in need of treatment, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), or a pharmaceutically acceptable salt thereof.

In another aspect, disclosed herein is a system or kit comprising a compound of formula (I), or a salt thereof, and a pharmaceutically active compound.

In another aspect, disclosed herein is a compound of formula (I), or a salt thereof, for use in preparing a prodrug compound.

In another aspect, disclosed herein is a compound of formula (II), or a pharmaceutically acceptable salt thereof, for use as a medicament.

Other aspects and embodiments of the disclosure will become apparent in light of the following description and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is apalutamide.

FIG. 2 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is apixaban.

FIG. 3 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is aprepitant.

FIGS. 4A-4C show structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is atorvastatin.

FIG. 5 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is bicalutamide.

FIGS. 6A-6B show structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is carvedilol.

FIG. 7 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is cefdinir.

FIG. 8 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is cefprozil.

FIG. 9 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is celecoxib.

FIGS. 10A-10B show structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is clarithromycin.

FIG. 11 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is dabrafenib.

FIG. 12 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is doravirine.

FIG. 13 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is efavirenz.

FIG. 14 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is enzalutamide.

FIG. 15 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is etravirine.

FIG. 16 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is ezetimibe.

FIG. 17 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is glimepiride.

FIG. 18 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is glipizide.

5 FIG. 19 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is glyburide.

FIG. 20 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is hydrochlorothiazide.

10 FIG. 21 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is hydroxyzine pamoate.

FIG. 22 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is ibrutinib.

FIG. 23 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is imatinib.

15 FIG. 24 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is ivacaftor.

FIG. 25 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is lamotrigine.

20 FIG. 26 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is lenalidomide.

FIG. 27 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is lopinavir.

FIG. 28 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is desloratadine.

25 FIG. 29 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is meloxicam.

FIG. 30 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is metaxalone.

30 FIG. 31 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is methylphenidate.

FIG. 32 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is modafinil.

FIGS. 33A-33B show structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is niclosamide.

FIGS. 34A-34B show structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is nilotinib.

FIG. 35 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is olanzapine.

5 FIG. 36 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is oxcarbazepine.

FIG. 37 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is osimertinib.

10 FIGS. 38A-38B show structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is paclitaxel.

FIG. 39 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is palbociclib.

FIG. 40 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is pomalidomide.

15 FIG. 41 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is pioglitazone.

FIGS. 42A-42B show structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is quetiapine or its active metabolite, *N*-desalkylquetiapine.

20 FIG. 43 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is raloxifene.

FIG. 44 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is rilpivirine.

25 FIG. 45 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is ritonavir.

FIG. 46 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is rivaroxaban.

FIG. 47 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is simvastatin.

30 FIGS. 48A-48B show structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is SN-38.

FIGS. 49A-49B show structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is tacrolimus.

FIG. 50 shows structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is valdecoxib.

FIGS. 51A-51B show structures of exemplary prodrug compounds, wherein the pharmaceutically active compound is vemurafenib.

5 FIG. 52 shows a comparison of caco-2 experiments to measure i) Permeability of Sol-moiety-drug conjugate; ii) Permeability of the released drug from Sol-moiety; and iii) the permeability of the parent drug (Papp A to B) measured in a separate experiment. The permeability of the Sol-moiety by products X and Y were also measured as well as the hydrolysis rate using human placental alkaline phosphatase.

10 FIG. 53 shows comparison of mouse PK AUC's of the Sol-moiety drug conjugates 7, 49, 62, 41, 148, 78, 155, 131 and Sol-moiety by-products X and Y, with a bar chart to highlight the AUC values for the Sol-moiety drug conjugates 7, 49, 62, 41, 148, 78, 155, and 131.

FIGS. 54A-B show a comparison of mouse pharmacokinetic data of enzalutamide.

15 FIG. 54A: Plasma concentrations of enzalutamide were measured over a 72-hour time course. Enzalutamide was dosed intravenously using a standard DMSO-based formulation and orally using a carboxymethylcellulose/Tween 80 suspension, and PO dosing of Sol-enzalutamide 7 and 10 was performed using deionized water as a vehicle. FIG. 54B: Bar chart to show the difference in oral bioavailability observed for enzalutamide comparing a standard formulation and delivery due to Sol-enzalutamide 7 and 10.

20 FIG. 55 shows a comparison of alkaline phosphatase, Caco-2 and mouse pharmacokinetic data using the Sol-moiety-drug conjugates 7, 10, 11 and 13. Compounds were dosed at an equivalent of 5 mg/kg of enzalutamide in saline solution and plasma concentrations measured over 24 hours.

25 FIGS. 56A-B show a comparison of pharmacokinetic profiles of vemurafenib and Sol-vemurafenib 49 and 51. FIG. 56A: Plasma concentrations of vemurafenib were measured over 24 h following IV and PO dose of vemurafenib (Vem) in a lipid-based vehicle. Sol-vemurafenib analogs 49 and 51 were dosed via oral gavage in saline solution. FIG. 56B: Bar chart displaying oral bioavailability of vemurafenib using a 20% PEG 400 based formulation compared to delivery with Sol-vemurafenib 49 and 51 dosed via oral gavage in saline solution.

30 FIGS. 57A-B show a comparison of mouse pharmacokinetic data for paclitaxel. FIG. 57A: Plasma concentrations of paclitaxel were measured over 24 hours. Paclitaxel was administered intravenously in a DMSO-based formulation whereas the Sol-paclitaxel analog

133 and the paclitaxel formyl phosphate prodrug Compound Z were all dosed via oral gavage in saline solution. FIG. 57B Comparison of oral bioavailability between Sol-paclitaxel 133 and paclitaxel possessing a formyl phosphate prodrug Compound Z.

FIGS. 58A-C show results of an efficacy study using pancreatic BxPC-3 xenograft mouse model. FIG. 58A: Comparison of paclitaxel administered intravenously once a week (QWK) as a dose of 12.5 mg/kg formulated in Cremophor® EL, ethanol and saline solution and Sol-paclitaxel 133 dosed orally once every other day (QOD) at 25 mg/kg and 75 mg/kg (18 mg/kg and 55 mg/kg equivalent of paclitaxel dose respectively) formulated in saline solution. Drug was administered over 21-day period and then monitored for an additional 25 days with tumor volume measured twice a week. FIG. 58B: Mouse weight plotted for the duration of the efficacy study (46 days). FIG. 58A: Plasma and tumor concentrations of paclitaxel 6 and 24 h post dose for each dose group. ND = not detectable.

DETAILED DESCRIPTION

Provided herein are building block compounds that can be used to prepare soluble prodrug compounds. The building block compounds are capable of installing a prodrug moiety that can be cleaved *in vivo* (e.g., by phosphatases) to release the active form of the pharmaceutical compound. Also disclosed herein are prodrug compounds comprising the prodrug moieties provided by the building blocks, and methods of synthesizing prodrug compounds from the building blocks. These highly soluble prodrug moieties provide a platform technology for preparing soluble prodrugs of pharmaceutical compounds, which may be particularly useful for insoluble pharmaceutical compounds, such as BCS Class II and BCS Class IV drugs. Increasing the solubility of such compounds could allow more widespread use of highly effective drugs that are currently challenging to formulate, and could allow for more straightforward routes of administration.

25 Definitions

Unless otherwise defined herein, scientific and technical terms used in connection with the present disclosure shall have the meanings that are commonly understood by those of ordinary skill in the art. For example, any nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics, and protein and nucleic acid chemistry and hybridization described herein are those that are well known and commonly used in the art. The meaning and scope of the terms should be clear; in the event, however of any latent ambiguity, definitions provided herein

take precedent over any dictionary or extrinsic definition. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

As used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise.

5 For the recitation of numeric ranges herein, each intervening number there between with the same degree of precision is explicitly contemplated. For example, for the range of 6-9, the numbers 7 and 8 are contemplated in addition to 6 and 9, and for the range 6.0-7.0, the numbers 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, and 7.0 are explicitly contemplated.

Definitions of specific functional groups and chemical terms are described in more
10 detail below. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Sorrell, Organic Chemistry, 2nd edition,
15 University Science Books, Sausalito, 2006; Smith, March's Advanced Organic Chemistry: Reactions, Mechanism, and Structure, 7th Edition, John Wiley & Sons, Inc., New York, 2013; Larock, Comprehensive Organic Transformations, 3rd Edition, John Wiley & Sons, Inc., New York, 2018; and Carruthers, Some Modern Methods of Organic Synthesis, 3rd Edition, Cambridge University Press, Cambridge, 1987; the entire contents of each of which are
20 incorporated herein by reference.

As used herein, the term “alkyl” refers to a radical of a straight or branched saturated hydrocarbon chain. The alkyl chain can include, e.g., from 1 to 24 carbon atoms (C₁-C₂₄ alkyl), 1 to 16 carbon atoms (C₁-C₁₆ alkyl), 1 to 14 carbon atoms (C₁-C₁₄ alkyl), 1 to 12 carbon atoms (C₁-C₁₂ alkyl), 1 to 10 carbon atoms (C₁-C₁₀ alkyl), 1 to 8 carbon atoms (C₁-C₈
25 alkyl), 1 to 6 carbon atoms (C₁-C₆ alkyl), 1 to 4 carbon atoms (C₁-C₄ alkyl), 1 to 3 carbon atoms (C₁-C₃ alkyl), or 1 to 2 carbon atoms (C₁-C₂ alkyl). Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, and n-dodecyl.

30 As used herein, the term “aryl” refers to a radical of a monocyclic, bicyclic, or tricyclic 4n+2 aromatic ring system (e.g., having 6, 10, or 14 π electrons shared in a cyclic array) having 6-14 ring carbon atoms and zero heteroatoms (“C₆-C₁₄ aryl”). In some embodiments, an aryl group has six ring carbon atoms (“C₆ aryl,” i.e., phenyl). In some embodiments, an aryl group has ten ring carbon atoms (“C₁₀ aryl,” e.g., naphthyl such as 1-

naphthyl and 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms (“C₁₄ aryl,” e.g., anthracenyl and phenanthrenyl).

As used herein, the term “arylalkyl” refers to an alkyl group, as defined herein, in which at least one hydrogen atom is replaced with an aryl group, as defined herein.

- 5 Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, and 3-phenylpropyl.

As used herein, the term “cycloalkyl” refers to a radical of a saturated carbocyclic ring system containing three to ten carbon atoms and zero heteroatoms. The cycloalkyl may be monocyclic, bicyclic, bridged, fused, or spirocyclic. Representative examples of
10 cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, adamantyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl, and bicyclo[5.2.0]nonanyl.

As used herein, the term “cyano” refers to a -CN group.

As used herein, the term “halogen” or “halo” refers to F, Cl, Br, or I.

- 15 As used herein, the term “haloalkyl” refers to an alkyl group, as defined herein, in which at least one hydrogen atom (e.g., one, two, three, four, five, six, seven or eight hydrogen atoms) is replaced with a halogen. In some embodiments, each hydrogen atom of the alkyl group is replaced with a halogen (“perhaloalkyl”). Representative examples of haloalkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-
20 fluoroethyl, 2,2,2-trifluoroethyl, and 3,3,3-trifluoropropyl.

As used herein, “heteroaryl” refers to a radical of a 5-10 membered monocyclic or bicyclic 4n+2 aromatic ring system (e.g., having 6 or 10 π electrons shared in a cyclic array) having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur (“5-10 membered heteroaryl”). In
25 heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. “Heteroaryl” also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of
30 ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (e.g., indolyl, quinolinyl, and the like) the point of attachment can be on either ring, i.e., either the ring bearing a heteroatom (e.g., 2-indolyl) or the ring that does not contain a heteroatom (e.g., 5-indolyl). Exemplary 5-membered heteroaryl groups containing one heteroatom include,

without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5-membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indoliziny, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

As used herein, the term “heterocyclyl” refers to a radical of a 3- to 10-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon (“3-10 membered heterocyclyl”). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic (“monocyclic heterocyclyl”) or a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic heterocyclyl”), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. “Heterocyclyl” also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more cycloalkyl groups wherein the point of attachment is either on the cycloalkyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. A heterocyclyl group may be described as, e.g., a 3-7-membered heterocyclyl, wherein the term “membered” refers to the non-hydrogen ring atoms, i.e., carbon, nitrogen, oxygen, sulfur, boron, phosphorus, and silicon, within the moiety.

Exemplary 3-membered heterocyclyl groups containing one heteroatom include, without limitation, aziridinyl, oxiranyl, and thioirenyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, without limitation, azetidiny, oxetanyl, and thietanyl. Exemplary 5-membered heterocyclyl groups containing one heteroatom include, without
5 limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazoliny, oxadiazoliny, and thiadiazoliny.

10 Exemplary 6-membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl (e.g., 2,2,6,6-tetramethylpiperidinyl), tetrahydropyranyl, dihydropyridiny, pyridinonyl (e.g., 1-methylpyridin-2-onyl), and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, pyridazinonyl (2-methylpyridazin-3-onyl), pyrimidinonyl (e.g., 1-
15 methylpyrimidin-2-onyl, 3-methylpyrimidin-4-onyl), dithianyl, dioxanyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and
20 thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C₆ aryl ring (also referred to herein as a 5,6-bicyclic heterocyclyl ring) include, without limitation, indoliny, isoindoliny, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 5-membered heterocyclyl groups fused to a heterocyclyl ring (also referred to herein as a 5,5-bicyclic heterocyclyl ring) include, without limitation,
25 octahydropyrrolopyrrolyl (e.g., octahydropyrrolo[3,4-c]pyrrolyl), and the like. Exemplary 6-membered heterocyclyl groups fused to a heterocyclyl ring (also referred to as a 4,6-membered heterocyclyl ring) include, without limitation, diazaspirononanyl (e.g., 2,7-diazaspiro[3.5]nonanyl). Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclyl ring) include, without limitation,
30 tetrahydroquinoliny, tetrahydroisoquinoliny, and the like. Exemplary 6-membered heterocyclyl groups fused to a cycloalkyl ring (also referred to herein as a 6,7-bicyclic heterocyclyl ring) include, without limitation, azabicyclooctanyl (e.g., (1,5)-8-azabicyclo[3.2.1]octanyl). Exemplary 6-membered heterocyclyl groups fused to a cycloalkyl

ring (also referred to herein as a 6,8-bicyclic heterocyclyl ring) include, without limitation, azabicyclononanyl (e.g., 9-azabicyclo[3.3.1]nonanyl).

As used herein, the term “nitro” refers to an -NO₂ group.

When a group or moiety can be substituted, the term “substituted” indicates that one or more (e.g., 1, 2, 3, 4, 5, or 6; in some embodiments 1, 2, or 3; and in other embodiments 1 or 2) hydrogens on the group indicated in the expression using “substituted” can be replaced with a selection of recited indicated groups or with a suitable substituent group known to those of skill in the art (e.g., one or more of the groups recited below), provided that the designated atom’s normal valence is not exceeded. Substituent groups include, but are not limited to, alkyl, alkenyl, alkynyl, alkoxy, acyl, amino, amido, amidino, aryl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, cycloalkyl, cycloalkenyl, guanidino, halo, haloalkyl, haloalkoxy, heteroaryl, heterocyclyl, hydroxy, hydrazino, imino, oxo, nitro, phosphate, phosphonate, sulfonic acid, thiol, thione, or combinations thereof.

As used herein, in chemical structures the indication:



represents a point of attachment of one moiety to another moiety (e.g., a substituent group to the rest of the compound).

For compounds described herein, groups and substituents thereof may be selected in accordance with permitted valence of the atoms and the substituents, such that the selections and substitutions result in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

When substituent groups are specified by their conventional chemical formulae, written from left to right, such indication also encompass substituent groups resulting from writing the structure from right to left. For example, if a bivalent group is shown as -CH₂O-, such indication also encompasses -OCH₂-; similarly, -OC(O)NH- also encompasses -NHC(O)O-.

The terms “administer,” “administering,” or “administration,” as used herein refer to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing a compound or a pharmaceutical composition.

As used herein, the terms “condition,” “disease,” and “disorder” are used interchangeably.

An “effective amount” of a compound or composition refers to an amount sufficient to elicit a desired biological response (e.g., treating a condition). As will be appreciated by

those skilled in the art, the effective amount of a compound may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount encompasses therapeutic and prophylactic treatment. For example, in
5 treating cancer, an effective amount of a compound or composition may reduce tumor burden or stop the growth or spread of a tumor.

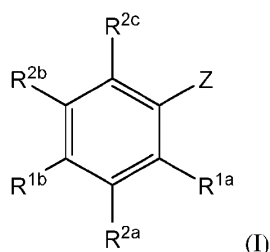
A “therapeutically effective amount” of a compound or composition is an amount sufficient to provide a therapeutic benefit in the treatment of a condition, or to delay or minimize one or more symptoms associated with the condition. In some embodiments, a
10 therapeutically effective amount is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, that provides a therapeutic benefit in the treatment of the condition. The term “therapeutically effective amount” can encompass an
15 amount that improves overall therapy, reduces or avoids symptoms or causes of the condition, or enhances the therapeutic efficacy of another therapeutic agent.

A “subject” to which administration is contemplated includes, but is not limited to, a human (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
20 other non-human animals, for example, mammals (e.g., primates (e.g., cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs) and birds (e.g., commercially relevant birds such as chickens, ducks, geese, and/or turkeys).

As used herein, the terms “treatment,” “treat,” and “treating” refer to reversing,
25 alleviating, delaying the onset of, or inhibiting the progress of a disease or condition, or one or more signs or symptoms thereof. In some embodiments, “treatment,” “treat,” and “treating” require that signs or symptoms of the disease disorder or condition have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease or condition. For example, treatment may be
30 administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

Compounds

Disclosed herein are compounds of formula (I):



or a salt thereof, wherein:

- 5 Z is $-\text{CR}^{3a}\text{R}^{3b}-\text{O}-\text{CR}^{4a}\text{R}^{4b}-\text{LG}$, $-(\text{CR}^{5a}\text{R}^{5b})_p-\text{CO}-\text{E}$, $-(\text{CR}^{6a}\text{R}^{6b})-\text{LG}$, or $-\text{CR}^{7a}\text{R}^{7b}-\text{O}-\text{CR}^{8a}\text{R}^{8b}-\text{O}-\text{CR}^{9a}\text{R}^{9b}-\text{LG}$;

one of R^{1a} and R^{1b} is $-\text{OPO}(\text{OR}^a)_2$, and the other is selected from hydrogen, alkyl, halo, haloalkyl, and $-(\text{CR}^b\text{R}^c)_m-\text{X}$;

- 10 R^{2a} , R^{2b} , and R^{2c} are each independently selected from hydrogen, alkyl, halo, haloalkyl, and $-(\text{CR}^d\text{R}^e)_n-\text{Y}$;

wherein, when R^{1a} is $-\text{OPO}(\text{OR}^a)_2$, R^{1b} and R^{2a} , together with the carbon atoms to which they are attached, are optionally taken together to form an optionally substituted ring;

X and Y are each independently selected from cyano, nitro, $-\text{OR}^f$, $-\text{NR}^g\text{R}^h$, $-\text{COOR}^i$, $-\text{CONR}^j\text{R}^k$, $-\text{S}(\text{O})_2\text{NR}^l\text{R}^m$, $-\text{PO}(\text{OR}^n)_2$, and $-\text{PO}(\text{OR}^o)\text{CH}_2\text{PO}(\text{OR}^p)_2$;

- 15 m , n , and p are each independently 0, 1, or 2;

R^{3a} , R^{3b} , R^{6a} , R^{6b} , R^{7a} , and R^{7b} are each independently selected from hydrogen and alkyl;

R^{4a} and R^{4b} are each hydrogen, or are taken together to form an oxo group;

R^{5a} and R^{5b} are each independently selected from hydrogen, alkyl, halo, and alkoxy;

- 20 R^{8a} and R^{8b} are each hydrogen, or are taken together to form an oxo group;

R^{9a} and R^{9b} are each selected from hydrogen and alkyl, or are taken together to form an oxo group;

R^a , R^f , R^g , R^h , R^i , R^j , R^k , R^l , R^m , R^n , R^o , and R^p are each independently selected from hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, and arylalkyl; wherein R^g and R^h , R^j and R^k , and

- 25 R^l and R^m , together with the nitrogen atoms to which they are attached, are optionally taken together to form an optionally substituted ring;

R^b , R^c , R^d , and R^e are each independently selected from hydrogen and alkyl;

E is halo or $-\text{OH}$; and

LG is selected from -O-Q, halo, and hydroxy, wherein Q is optionally substituted aryl, optionally substituted heterocyclyl, or -SO₂R⁸, wherein R⁸ is selected from alkyl and optionally substituted aryl.

In some embodiments, one of R^{1a} and R^{1b} is -OPO(OR^a)₂, wherein each R^a is independently selected from hydrogen, C₁-C₆ alkyl (e.g., C₁-C₄ alkyl, such as ethyl or *tert*-butyl), and benzyl; and the other one of R^{1a} and R^{1b} is selected from hydrogen and -
 5 (CR^bR^c)_m-X, wherein m is 0 or 1, R^c and R^d are each hydrogen, and X is selected from -OR^f, -COORⁱ, and -PO(ORⁿ)₂, wherein each R^f, Rⁱ, and Rⁿ is independently selected from hydrogen and C₁-C₄ alkyl.

10 In some embodiments, R^{1a} is -OPO(OR^a)₂, and R^{1b} and R^{2a}, together with the carbon atoms to which they are attached, form an optionally substituted ring. In some embodiments, the optionally substituted ring is a phenyl ring that is optionally substituted with at least one substituent selected from alkyl, -OR^f, -COORⁱ, and -PO(ORⁿ)₂, wherein each R^f, Rⁱ, and Rⁿ is independently selected from hydrogen and C₁-C₄ alkyl.

15 In some embodiments, Z' is -CR^{3a}R^{3b}-O-CR^{4a}R^{4b}-, -(CR^{5a}R^{5b})_p-CO-, or -(CR^{6a}R^{6b})_p-.

In some embodiments, Z is -CR^{3a}R^{3b}-O-CR^{4a}R^{4b}-LG.

In some embodiments, R^{3a} and R^{3b} are each independently selected from hydrogen and C₁-C₄ alkyl. In some embodiments, R^{3a} and R^{3b} are each independently selected from hydrogen and methyl. In some embodiments, R^{3a} and R^{3b} are each hydrogen. In some
 20 embodiments, R^{3a} is hydrogen and R^{3b} is methyl. In some embodiments, R^{3a} and R^{3b} are each methyl.

In some embodiments, R^{4a} and R^{4b} are taken together to form an oxo group. In some embodiments, R^{4a} and R^{4b} are each hydrogen.

In some embodiments, Z is -(CR^{5a}R^{5b})_p-CO-E, wherein E is halo or -OH. In some
 25 embodiments, p is 2, each R^{5a} and R^{5b} is independently selected from hydrogen and methyl, and E is chloro or -OH. In some embodiments, Z is -C(CH₃)₂CH₂COOH or -C(CH₃)₂CH₂COCl.

In some embodiments, Z is -(CR^{6a}R^{6b})_p-LG. In some embodiments, R^{6a} and R^{6b} are each independently selected from hydrogen and hydrogen and C₁-C₄ alkyl. In some
 30 embodiments, R^{6a} and R^{6b} are each independently selected from hydrogen and methyl. In some embodiments, R^{6a} and R^{6b} are each hydrogen. In some embodiments, R^{6a} is hydrogen and R^{6b} is methyl. In some embodiments, R^{6a} and R^{6b} are each methyl.

In some embodiments, Z' is -CR^{7a}R^{7b}-O-CR^{8a}R^{8b}-O-CR^{9a}R^{9b}-LG. In some
 embodiments, R^{7a} and R^{7b} are each hydrogen. In some embodiments, R^{8a} and R^{8b} are each

hydrogen, and R^{9a} and R^{9b} are taken together to form an oxo group. In some embodiments, R^{8a} and R^{8b} taken together to form an oxo group, and R^{9a} and R^{9b} are each hydrogen.

In some embodiments, R^a , R^f , R^g , R^h , R^i , R^j , R^k , R^l , R^m , R^n , R^o , and R^p are each independently selected from hydrogen, C_1 - C_4 alkyl, phenyl, and phenyl- C_1 - C_2 -alkyl. In some
5 embodiments, R^a , R^f , R^g , R^h , R^i , R^j , R^k , R^l , R^m , R^n , R^o , and R^p are each independently selected from hydrogen, methyl, ethyl, iso-propyl, tert-butyl, phenyl, and benzyl.

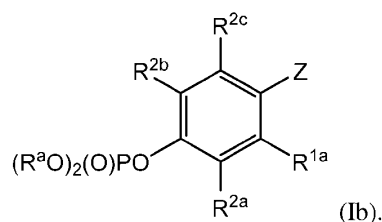
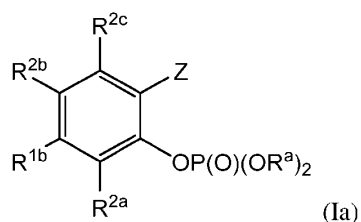
In some embodiments, R^b , R^c , R^d , and R^e are each independently selected from hydrogen and methyl.

In some embodiments, R^{2a} , R^{2b} , and R^{2c} are each independently selected from
10 hydrogen, C_1 - C_4 alkyl, halo, and $-(CR^dR^e)_n-Y$, wherein n is 0 or 1, R^d and R^e are each hydrogen, and Y is selected from cyano, $-OR^f$, $-COOR^i$, and $-PO(OR^n)_2$, wherein each R^f , R^i , and R^n is independently selected from hydrogen and C_1 - C_4 alkyl. In some embodiments, R^{2a} , R^{2b} , and R^{2c} are each independently selected from hydrogen, methyl, fluoro, chloro, cyano, methoxy, $-COOH$, $-COO(tBu)$, $-CH_2COOH$, $-CH_2COOCH_3$, $-P(O)(OH)_2$, and $-P(O)(OEt)_2$.

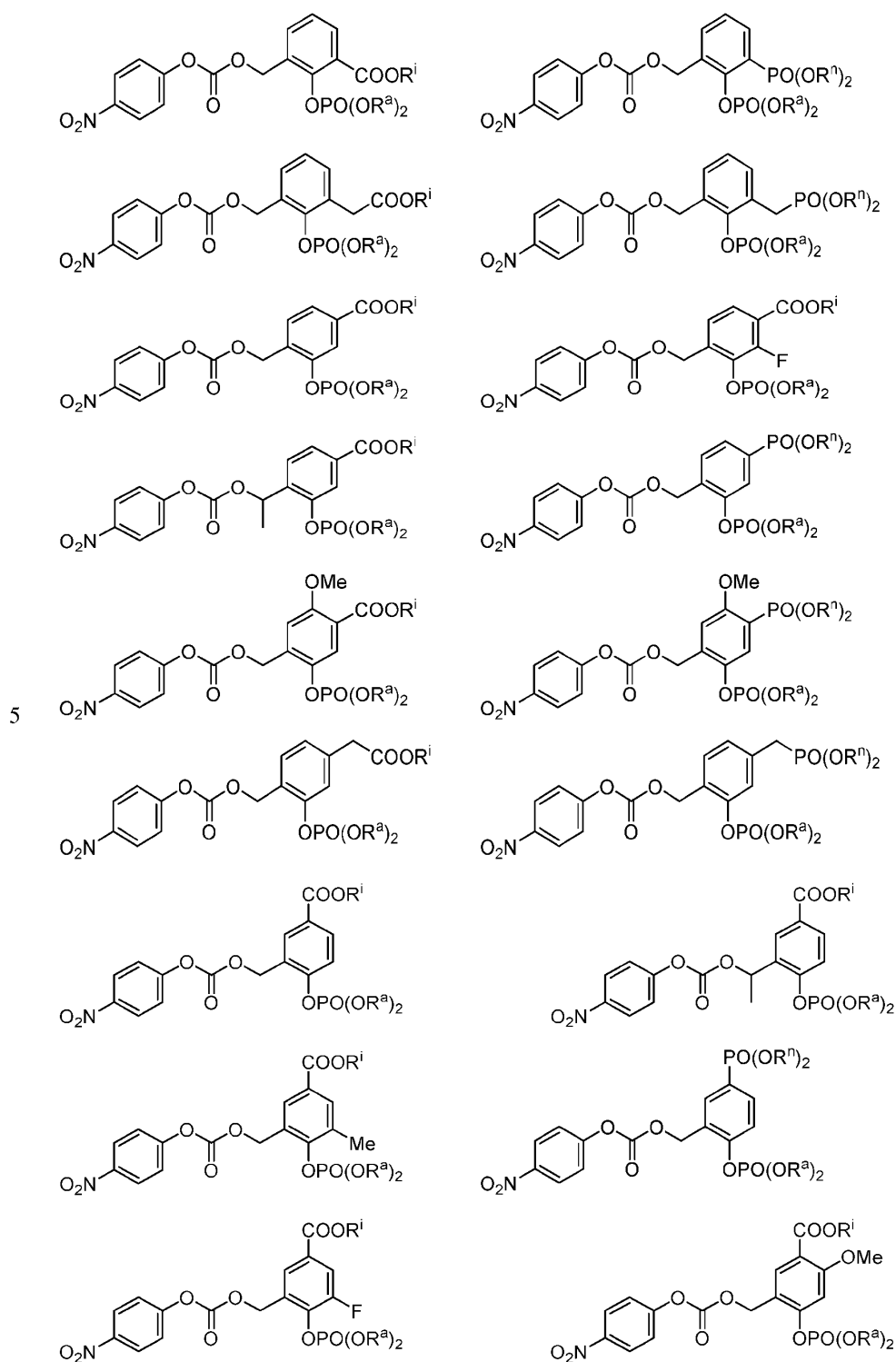
In some embodiments, LG is $-O-Q$. In some embodiments, LG is $-O-Q$, wherein Q is
15 optionally substituted phenyl or an optionally substituted 5- or 6-membered heterocyclyl having 1 or 2 heteroatoms independently selected from N, O, and S. In some embodiments, LG is $-O-Q$, wherein Q is phenyl substituted with 1, 2, 3, 4, or 5 substituents independently selected from nitro and halo. In some embodiments, LG is $-O$ -(4-nitrophenyl), $-O$ -(2,4-
20 dinitrophenyl), or $-O$ -(pentafluorophenyl). In some embodiments, LG is $-O$ -(4-nitrophenyl) or $-O$ -(pentafluorophenyl). In some embodiments, LG is $-O$ -(4-nitrophenyl). In some embodiments, LG is O -(pentafluorophenyl). In some embodiments, LG is $-O-Q$, wherein Q is an optionally substituted pyrrolidine-2,5-dione. In some embodiments, LG is $-O-Q$, wherein Q is pyrrolidine-2,5-dione.

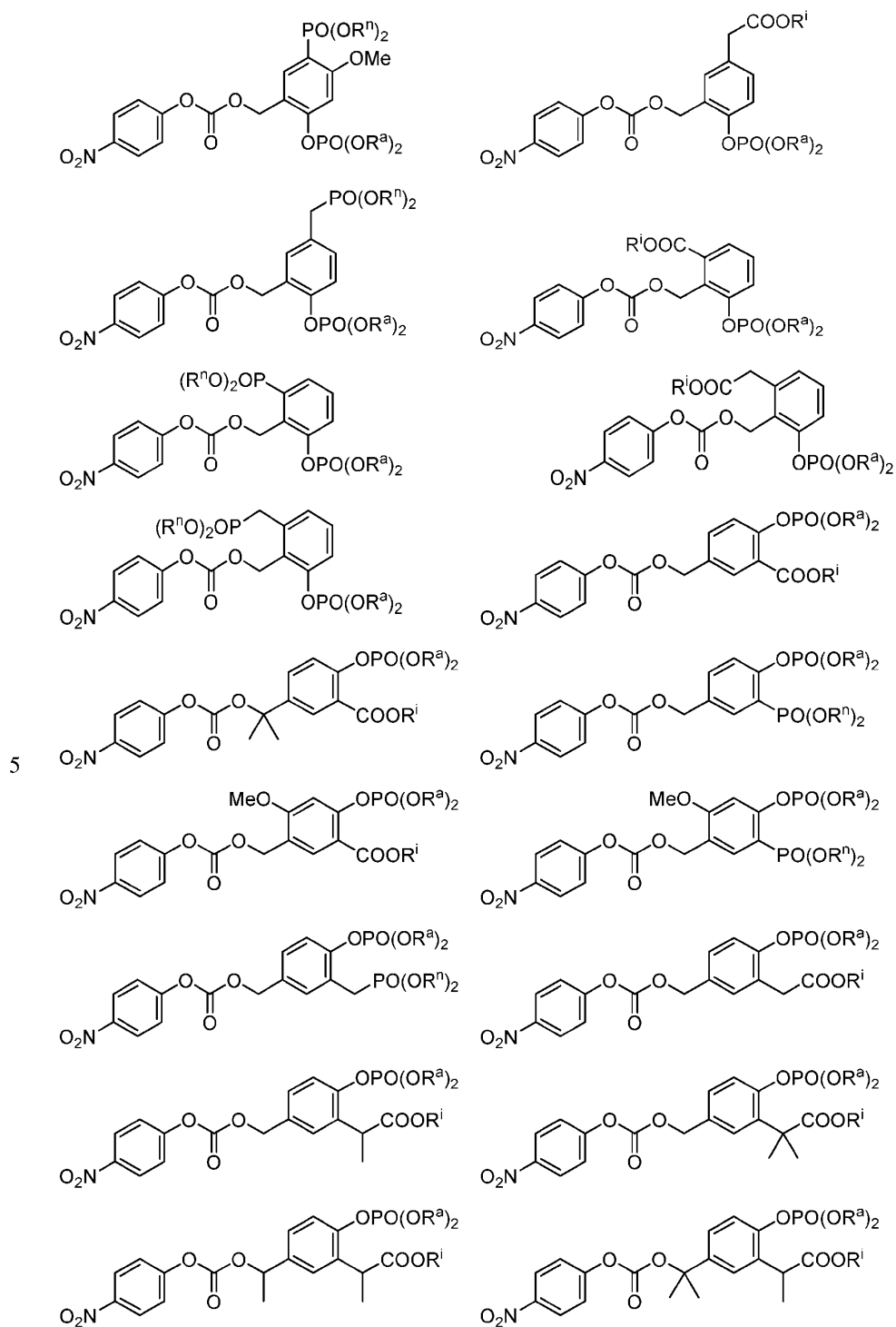
25 In some embodiments, LG is halo. In some embodiments, LG is bromo.

In some embodiments, the compound has formula (Ia) or (Ib):

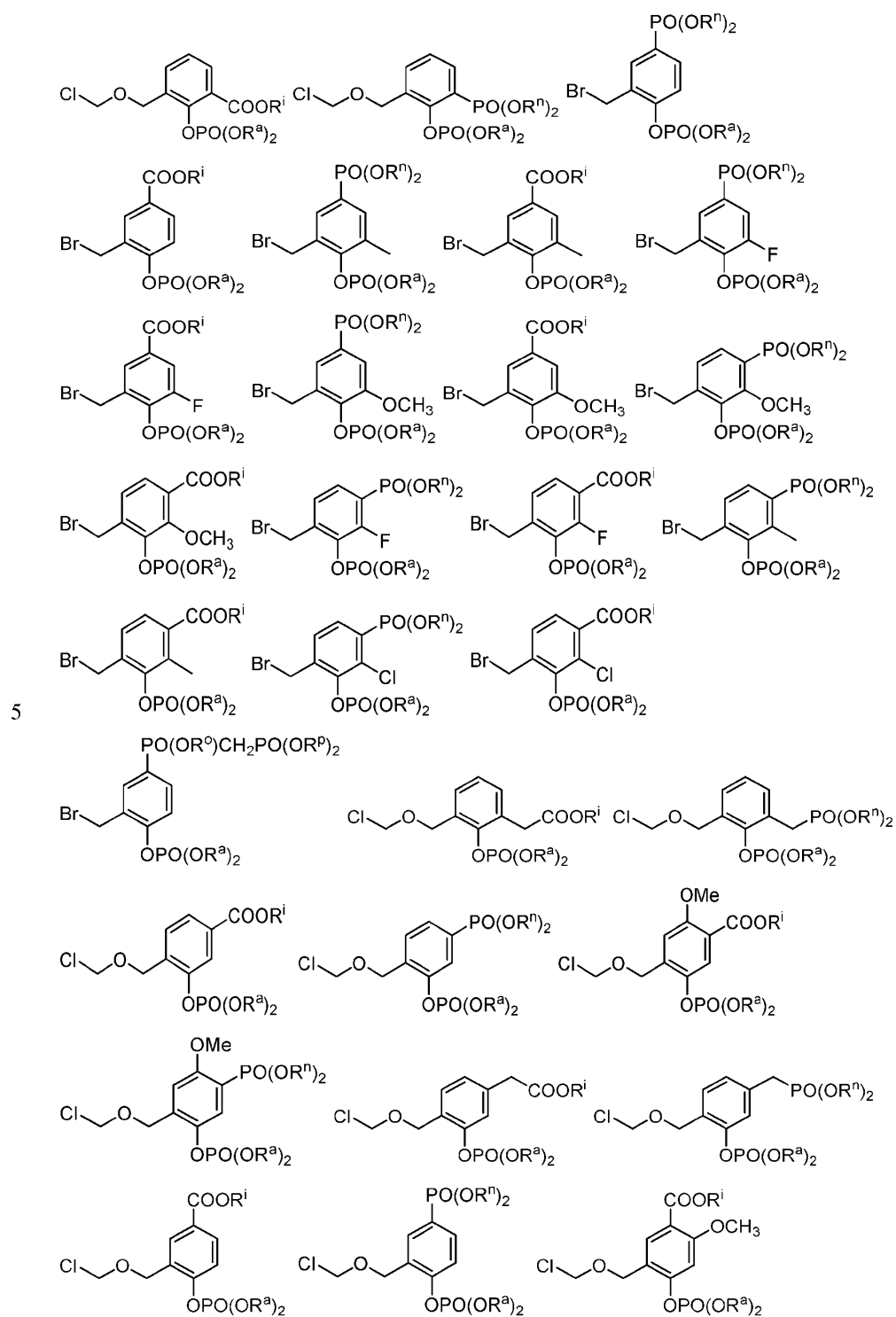


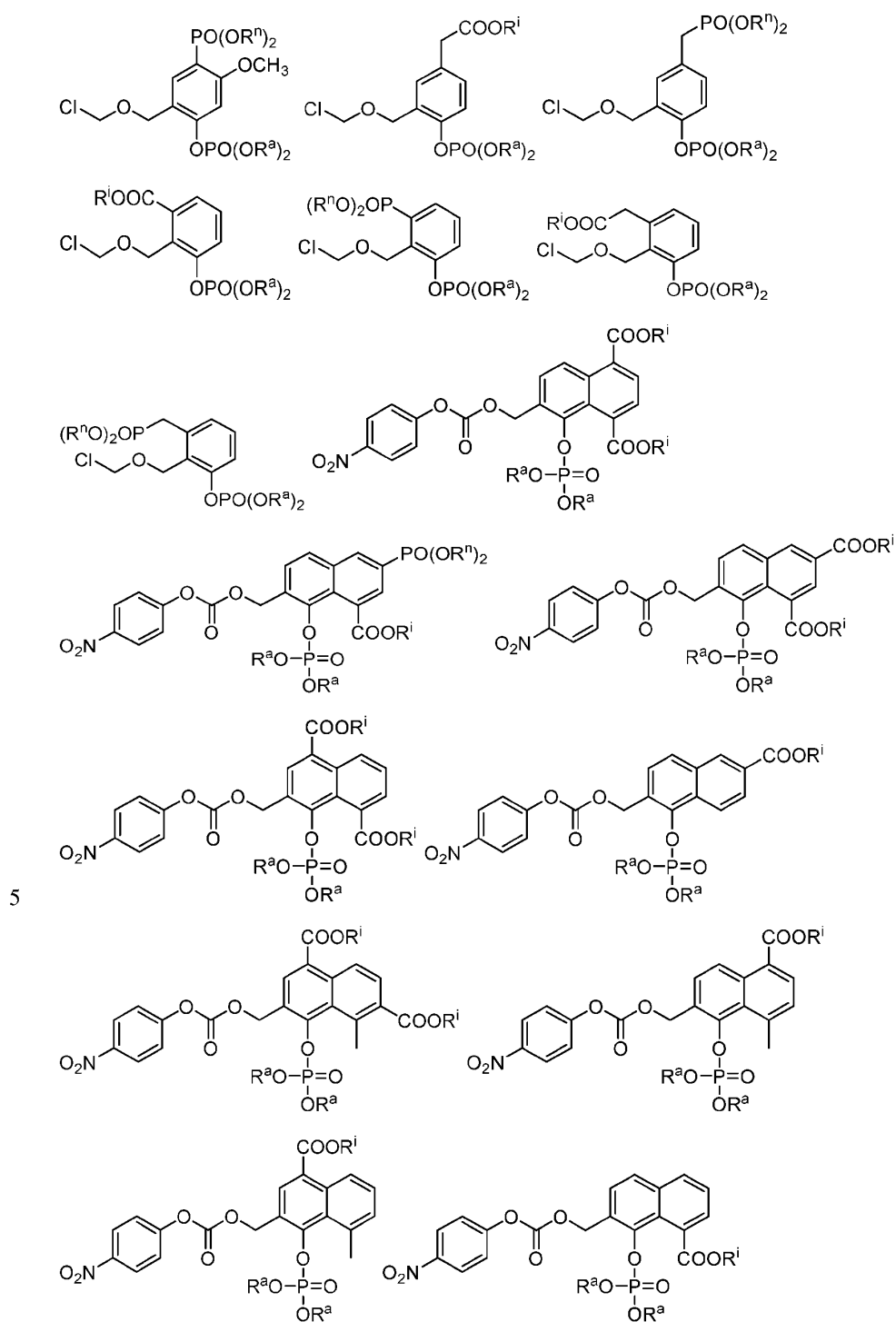
In some embodiments, the compound has a structure selected from:



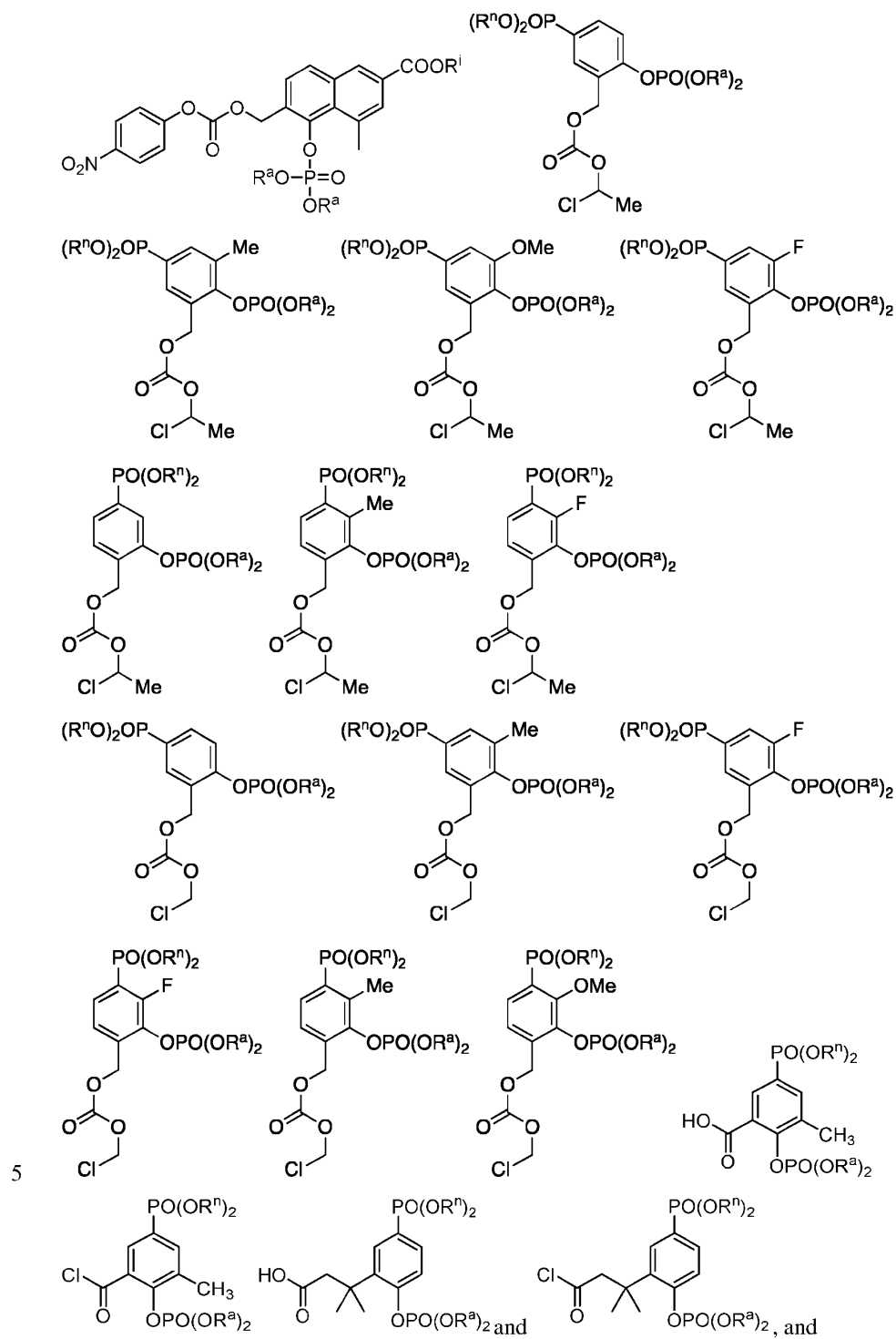






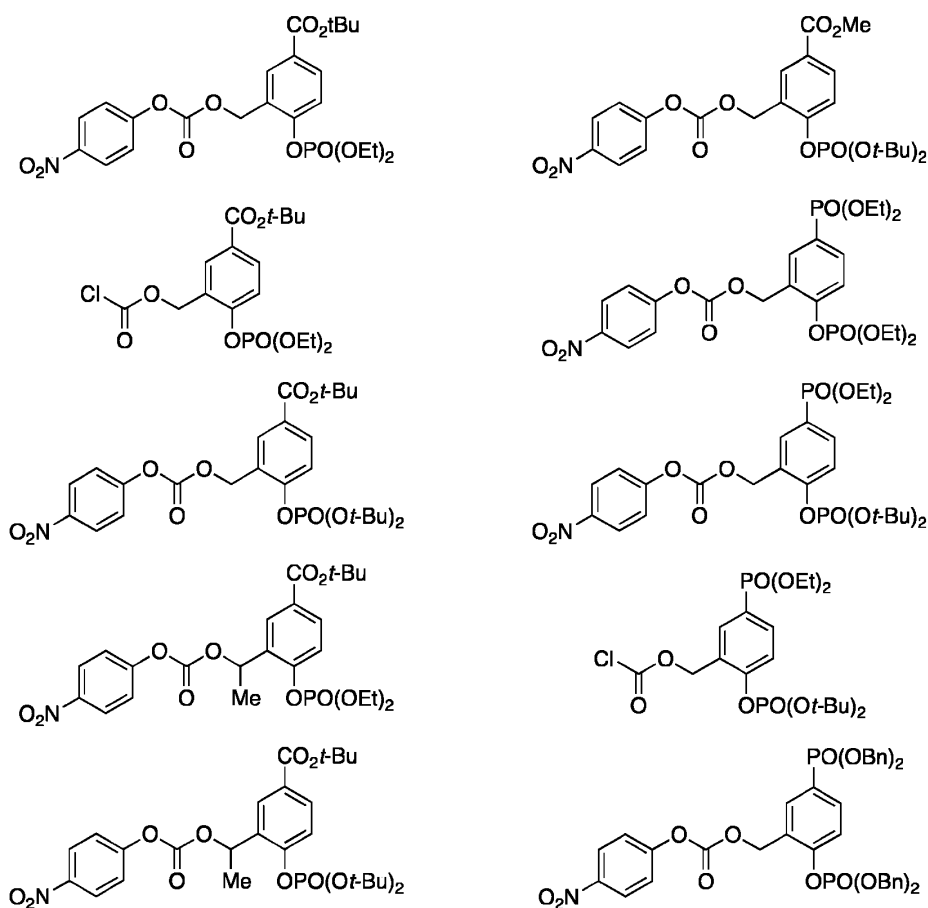


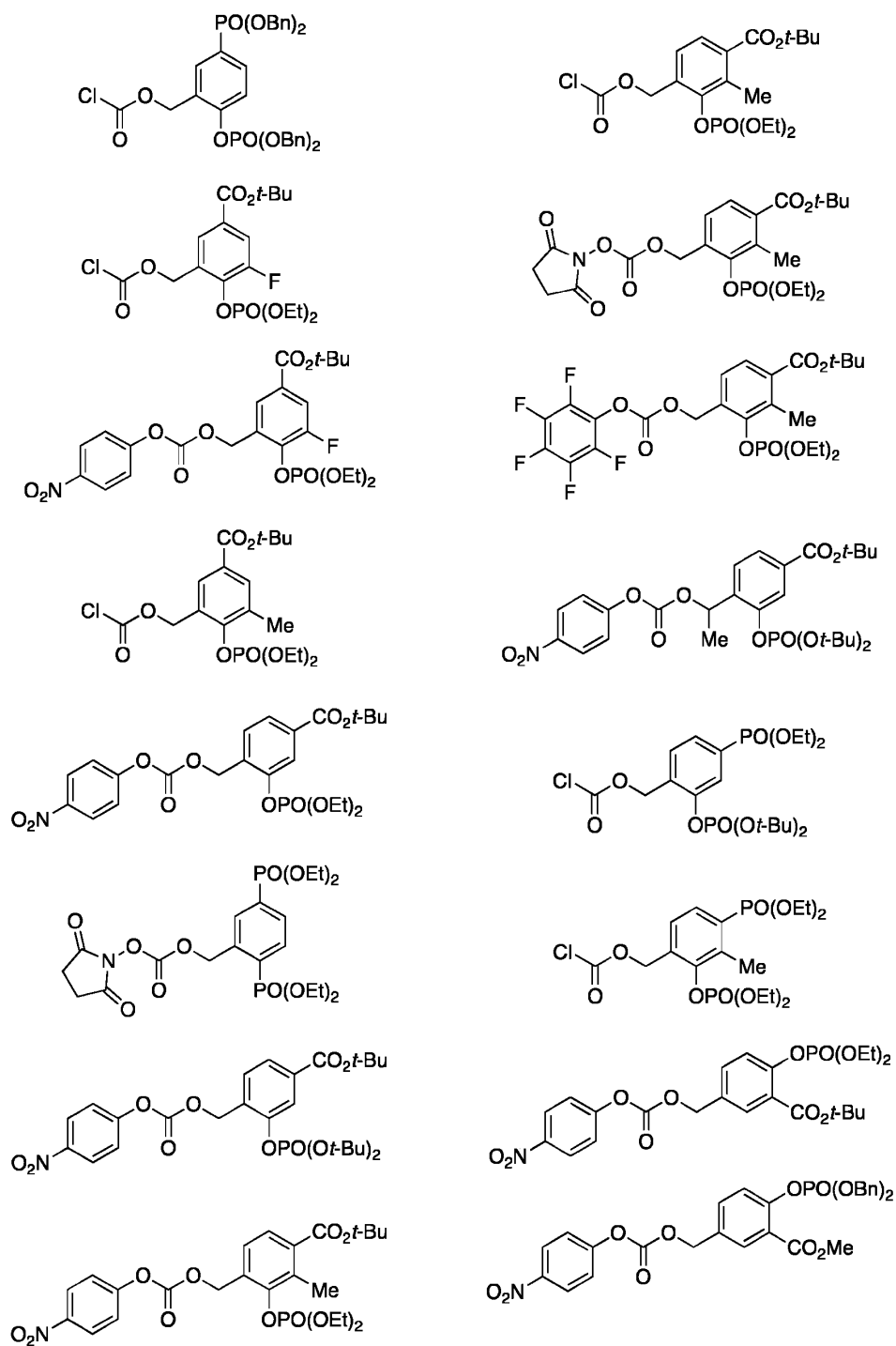
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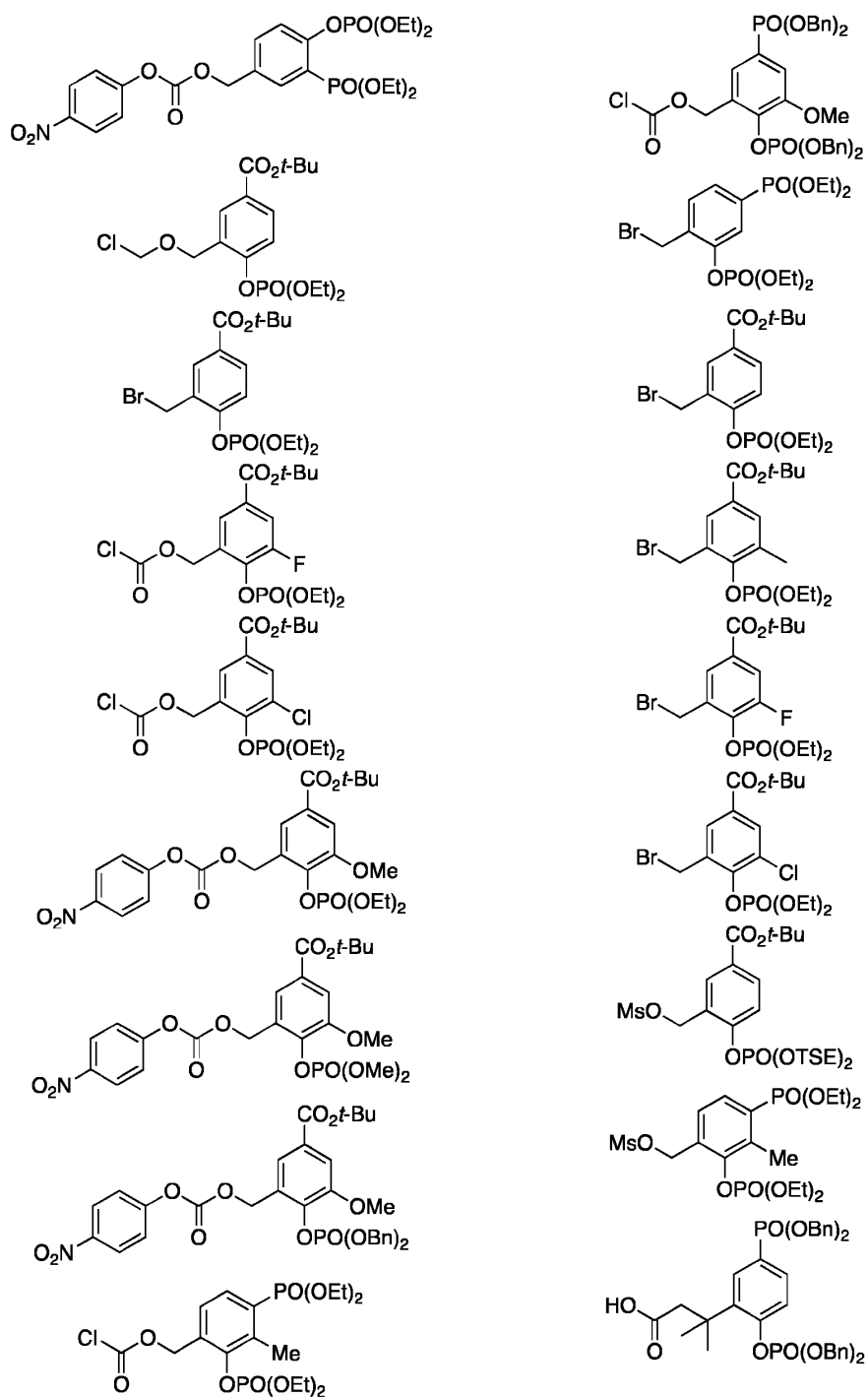


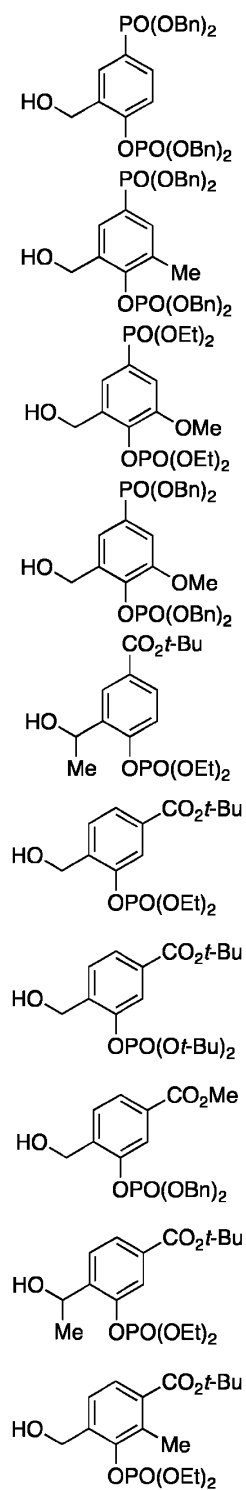
pharmaceutically acceptable salts thereof, wherein each R^a , R^i , and R^n is independently selected from hydrogen, alkyl (e.g., C_1 - C_4 alkyl), and benzyl. One skilled in the art will recognize that in the above compounds, in some embodiments, R^a , R^i , and R^n are independently alkyl or benzyl, such that these building block compounds are in protected form. Such forms are particularly suitable for reaction with a pharmaceutically active compound, to form a protected prodrug compound. In other embodiments, the disclosure also provides the building blocks in their unprotected forms (i.e., wherein R^a , R^i , and R^n are hydrogen). In some embodiments, such compounds could be reacted directly with a pharmaceutically active compound to form a prodrug compound, or the compounds could be protected before such reactions.

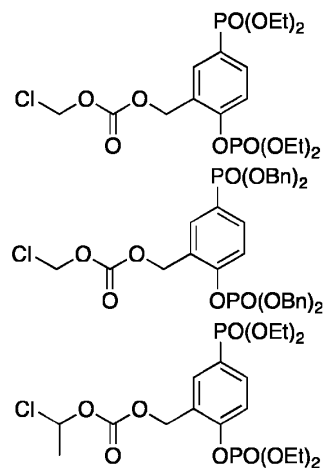
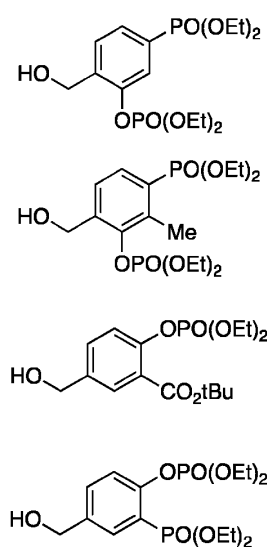
In some embodiments, the compound is selected from the group consisting of:





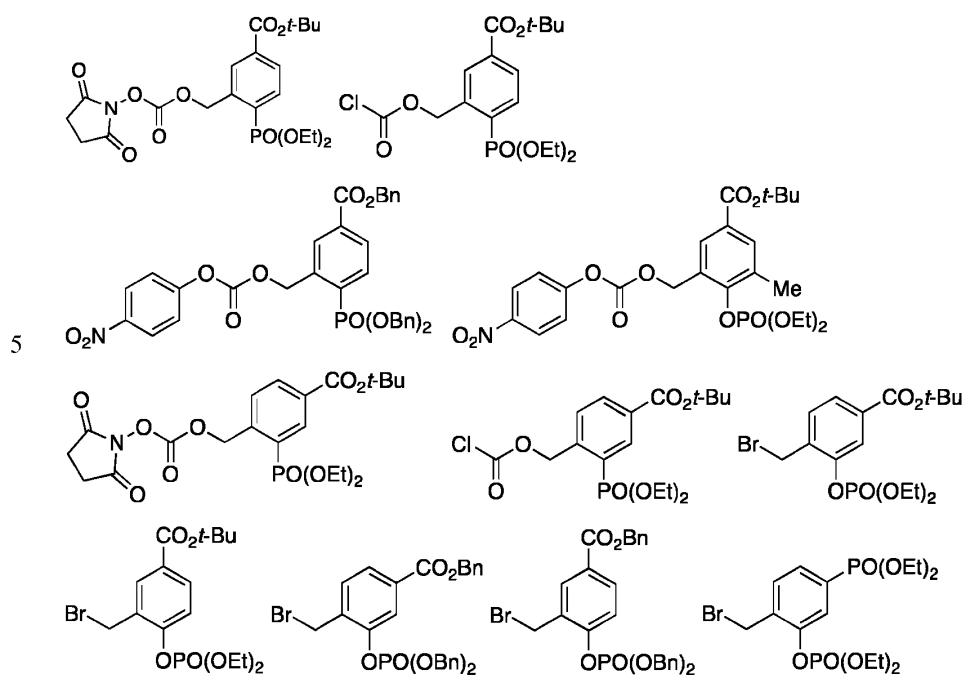


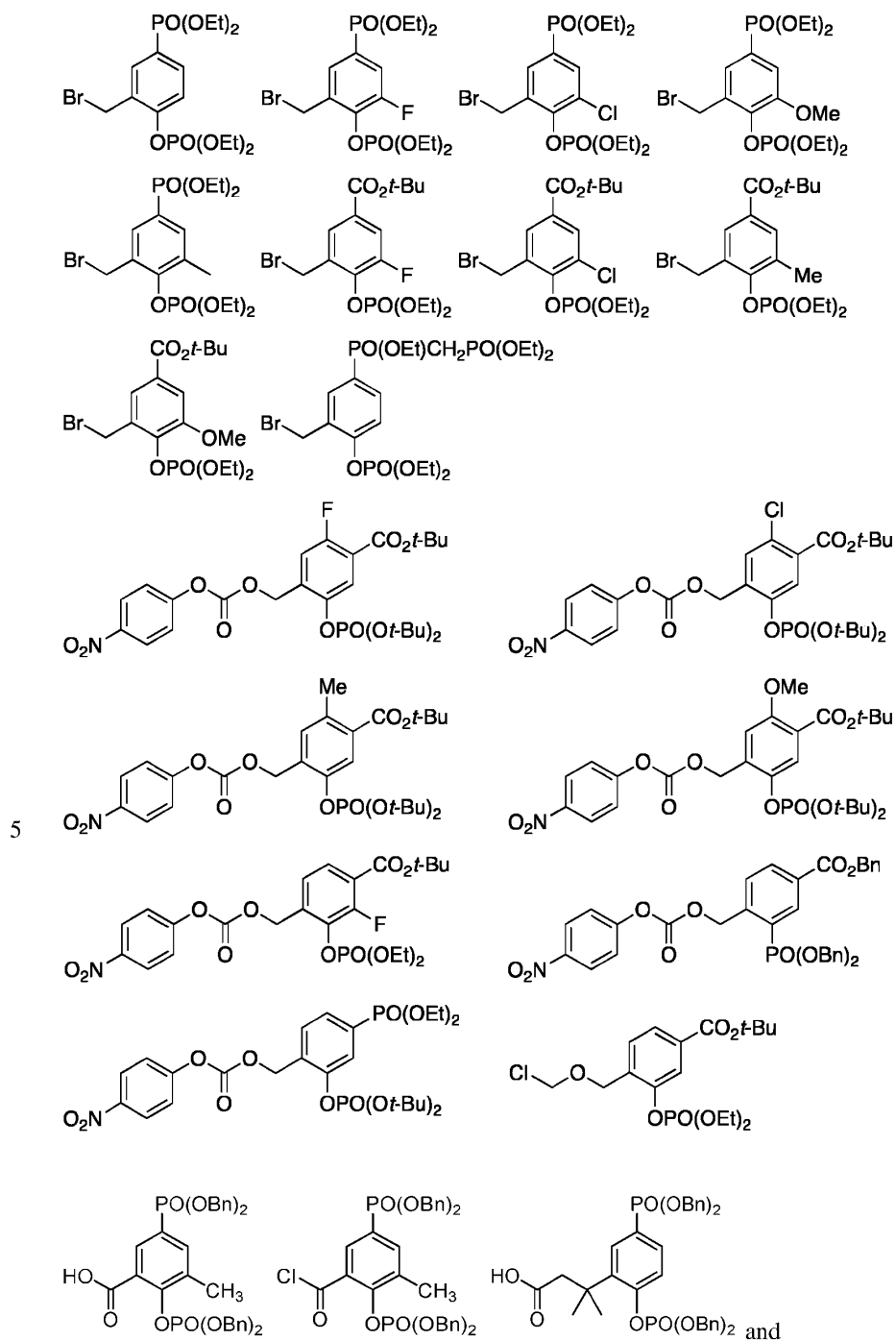


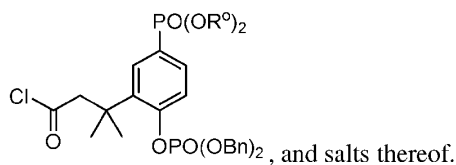


and salts thereof.

Additional compounds of formula (I) include:

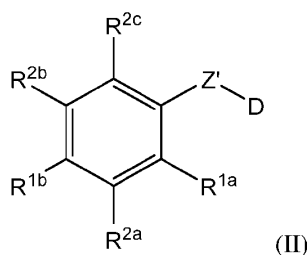






Compounds of formula (I) (including compounds of formula (Ia) and (Ib)) are building blocks that can be used to prepare prodrug compounds. The compounds of formula (I) provide a moiety that aids in solubilization of a pharmaceutically active compound, and allows for cleavage of the prodrug moiety *in vivo* (e.g., by a phosphatase) to release the pharmaceutically active compound. The compounds of formula (I) can react with suitable groups on pharmaceutically active compounds, such as amines, to provide prodrug compounds.

Accordingly, also disclosed herein are compounds of formula (II):



or a pharmaceutically acceptable salt thereof, wherein:

Z' is -CR^{3a}R^{3b}-O-CR^{4a}R^{4b}-, -(CR^{5a}R^{5b})_p-CO-, -(CR^{6a}R^{6b})-, or -CR^{7a}R^{7b}-O-CR^{8a}R^{8b}-O-CR^{9a}R^{9b}-;

one of R^{1a} and R^{1b} is -OPO(OR^a)₂, and the other is selected from hydrogen, alkyl, halo, haloalkyl, and -(CR^bR^c)_m-X;

R^{2a}, R^{2b}, and R^{2c} are each independently selected from hydrogen, alkyl, halo, haloalkyl, and -(CR^dR^e)_n-Y;

wherein, when R^{1a} is -OPO(OR^a)₂, R^{1b} and R^{2a}, together with the carbon atoms to which they are attached, are optionally taken together to form an optionally substituted ring

X and Y are each independently selected from cyano, nitro, -OR^f, -NR^gR^h, -COORⁱ, -CONR^jR^k, -S(O)₂NR^lR^m, -PO(ORⁿ)₂, and -PO(OR^o)CH₂PO(OR^p)₂;

m, n, and p are each independently 0, 1, or 2;

R^{3a}, R^{3b}, R^{6a}, R^{6b}, R^{7a}, and R^{7b} are each independently selected from hydrogen and alkyl;

R^{4a} and R^{4b} are each hydrogen, or are taken together to form an oxo group;

R^{5a} and R^{5b} are each independently selected from hydrogen, alkyl, halo, and alkoxy;

R^{8a} and R^{8b} are each hydrogen, or are taken together to form an oxo group;

R^{9a} and R^{9b} are each selected from hydrogen and alkyl, or are taken together to form an oxo group;

R^a , R^f , R^g , R^h , R^i , R^j , R^k , R^l , R^m , R^n , R^o , and R^p are each independently selected from hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, and arylalkyl; wherein R^g and R^h , R^i and R^k , and R^l and R^m , together with the nitrogen atoms to which they are attached, are optionally taken together to form an optionally substituted ring;

R^b , R^c , R^d , and R^e are each independently selected from hydrogen and alkyl; and

D is a pharmaceutically active compound.

In some embodiments, one of R^{1a} and R^{1b} is $-OPO(OR^a)_2$, wherein each R^a is independently selected from hydrogen, C_1 - C_6 alkyl (e.g., C_1 - C_4 alkyl, such as ethyl or *tert*-butyl), and benzyl; and the other one of R^{1a} and R^{1b} is selected from hydrogen and $-(CR^bR^c)_m-X$, wherein m is 0 or 1, R^c and R^d are each hydrogen, and X is selected from $-OR^f$, $-COOR^i$, and $-PO(OR^n)_2$, wherein each R^f , R^i , and R^n is independently selected from hydrogen and C_1 - C_4 alkyl.

In some embodiments, Z' is $-CR^{3a}R^{3b}-O-CR^{4a}R^{4b}-$, $-(CR^{5a}R^{5b})_p-CO-$, or $-(CR^{6a}R^{6b})-$.

In some embodiments, Z' is $-CR^{3a}R^{3b}-O-CR^{4a}R^{4b}-$.

In some embodiments, R^{3a} and R^{3b} are each independently selected from hydrogen and C_1 - C_4 alkyl. In some embodiments, R^{3a} and R^{3b} are each independently selected from hydrogen and methyl. In some embodiments, R^{3a} and R^{3b} are each hydrogen. In some embodiments, R^{3a} is hydrogen and R^{3b} is methyl. In some embodiments, R^{3a} and R^{3b} are each methyl.

In some embodiments, R^{4a} and R^{4b} are taken together to form an oxo group. In some embodiments, R^{4a} and R^{4b} are each hydrogen.

In some embodiments, Z' is $-CH_2-$.

In some embodiments, Z' is $-(CR^{5a}R^{5b})_p-CO-$. In some embodiments, p is 2, and R^{5a} and R^{5b} are each independently selected from hydrogen and methyl. In some embodiments, Z' is $-C(CH_3)_2CH_2CO-$.

In some embodiments, Z' is $-(CR^{6a}R^{6b})-$. In some embodiments, R^{6a} and R^{6b} are each independently selected from hydrogen and hydrogen and C_1 - C_4 alkyl. In some embodiments, R^{6a} and R^{6b} are each independently selected from hydrogen and methyl. In some embodiments, R^{6a} and R^{6b} are each hydrogen. In some embodiments, R^{6a} is hydrogen and R^{6b} is methyl. In some embodiments, R^{6a} and R^{6b} are each methyl.

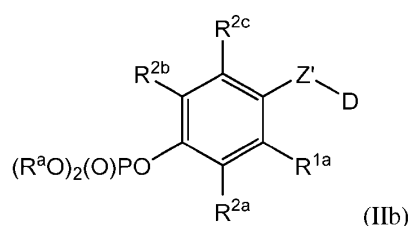
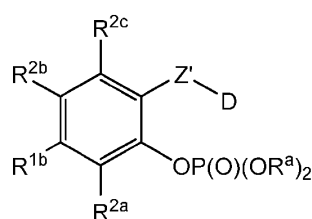
In some embodiments, Z' is $-\text{CR}^{7a}\text{R}^{7b}-\text{O}-\text{CR}^{8a}\text{R}^{8b}-\text{O}-\text{CR}^{9a}\text{R}^{9b}-\text{LG}$. In some embodiments, R^{7a} and R^{7b} are each hydrogen. In some embodiments, R^{8a} and R^{8b} are each hydrogen, and R^{9a} and R^{9b} are taken together to form an oxo group. In some embodiments, R^{8a} and R^{8b} taken together to form an oxo group, and R^{9a} and R^{9b} are each hydrogen.

5 In some embodiments, R^a , R^f , R^g , R^h , R^i , R^j , R^k , R^l , R^m , R^n , R^o , and R^p are each independently selected from hydrogen, C_1 - C_4 alkyl, phenyl, and phenyl- C_1 - C_2 -alkyl. In some embodiments, R^a , R^f , R^g , R^h , R^i , R^j , R^k , R^l , R^m , R^n , R^o , and R^p are each independently selected from hydrogen, methyl, ethyl, iso-propyl, tert-butyl, phenyl, and benzyl.

10 In some embodiments, R^b , R^c , R^d , and R^e are each independently selected from hydrogen and methyl.

In some embodiments, R^{2a} , R^{2b} , and R^{2c} are each independently selected from hydrogen, C_1 - C_4 alkyl, halo, and $-(\text{CR}^d\text{R}^e)_n-\text{Y}$, wherein n is 0 or 1, R^d and R^e are each hydrogen, and Y is selected from cyano, $-\text{OR}^f$, $-\text{COOR}^i$, and $-\text{PO}(\text{OR}^n)_2$, wherein each R^f , R^i , and R^n is independently selected from hydrogen and C_1 - C_4 alkyl. In some embodiments, R^{2a} ,
15 R^{2b} , and R^{2c} are each independently selected from hydrogen, methyl, fluoro, chloro, cyano, methoxy, $-\text{COOH}$, $-\text{COO}(\text{tBu})$, $-\text{CH}_2\text{COOH}$, $-\text{CH}_2\text{COOCH}_3$, $-\text{P}(\text{O})(\text{OH})_2$, and $-\text{P}(\text{O})(\text{OEt})_2$.

In some embodiments, the compound has formula (IIa) or (IIb):



20 D is a pharmaceutically active compound. In some embodiments, the pharmaceutically active compound is attached to the remainder of the compound via a nitrogen atom, e.g., from an amine, an amide, an aniline, a sulfonamide, a heterocyclic moiety, or a heteroaryl moiety. In some embodiments, the pharmaceutically active compound is attached to the remainder of the compound via an oxygen atom, e.g., from an alcohol.

25 The group D can be any pharmaceutically active compound. In particular embodiments, the group D is a small molecule therapeutic. In some embodiments, the pharmaceutically active compound is selected from the group consisting of: analgesics (e.g., opioid analgesics and non-opioid analgesic); anesthetics (e.g., local anesthetics); antibacterials (e.g., aminoglycosides, beta-lactams such as cephalosporins and penicillins, macrolides, quinolones, sulfonamides, tetracyclines, antifolates, glycopeptides, lincomycins,

- nitrofurans, oxazolidinones, and the like); anticonvulsants (e.g., calcium channel modifying agents, gamma-aminobutyric acid augmenting agents, glutamate reducing agents, sodium channel inhibitors, and the like); antidementia agents (e.g., cholinesterase inhibitors, glutamate pathway modifiers); antidepressants (e.g., monoamine oxidase inhibitors,
- 5 serotonin/norepinephrine reuptake inhibitors, tricyclics, and the like); antiemetics; antifungals; antigout agents; anti-inflammatories (e.g., nonsteroidal anti-inflammatories, glucocorticoids, and the like); antimigraine agents; antimuscarinic agents; antimycobacterials (e.g., antituberculars); antineoplastics (e.g., alkylating agents, antiangiogenic agents, antiestrogens/modifiers, antimetabolites, aromatase inhibitors, molecular target inhibitors,
- 10 retinoids, topoisomerase I inhibitors, and the like); antiparasitics (e.g., anthelmintics, antiprotozoals, pediculicides/scabicides); antiparkinson agents; antipsychotics (e.g., atypical antipsychotics, conventional antipsychotics); antispasticity agents; antivirals (e.g., anti-cytomegalovirus agents, antihepatitis agents, antiherpetic agents, anti-human immunodeficiency virus agents (e.g., fusion inhibitors, non-nucleoside reverse transcriptase
- 15 inhibitors, nucleoside and nucleotide reverse transcriptase inhibitors, protease inhibitors), anti-influenza agents, and the like); anxiolytics (e.g., antidepressants); bipolar agents; blood glucose regulators (e.g., antidiabetic agents, glycemic agents); blood products / modifiers / volume expanders (e.g., anticoagulants, blood formation products, coagulants, platelet aggregation inhibitors); cardiovascular agents (e.g., alpha-adrenergic agonists, alpha-
- 20 adrenergic blocking agents, antiarrhythmics, beta-adrenergic blocking agents, calcium channel blocking agents, diuretics, dyslipidemics, renin-angiotensin-aldosterone system inhibitors, vasodilators, and the like); central nervous system agents (e.g., amphetamines, non-amphetamines); dental and oral agents; dermatological agents; enzyme replacements/modifiers; gastrointestinal agents (e.g., antispasmodics, H2 blocking agents,
- 25 irritable bowel syndrome agents, protectants, proton pump inhibitors, and the like); genitourinary agents (e.g., antispasmodics, benign prostatic hypertrophy agents, phosphate binders); hormonal agents (e.g., glucocorticoids/mineralcorticoids, androgens, estrogens, progestins, selective estrogen receptor modifying agents, antiandrogens, antithyroid agents); immunological agents (e.g., immune stimulants, immune suppressants, immunomodulators);
- 30 inflammatory bowel disease agents (e.g., glucocorticoids, salicylates, sulfonamides); metabolic bone disease agents; ophthalmic agents (e.g., ophthalmic anti-allergy agents, antiglaucoma agents, ophthalmic anti-inflammatories, ophthalmic prostaglandin and prostamide compounds); otic agents; respiratory tract agents (e.g., antihistamines, anti-inflammatories, antileukotrienes, bronchodilators, mast cell stabilizers, pulmonary

hypertensives); sedatives/hypnotics; and skeletal muscle relaxants. The above groups include therapeutic categories and pharmacologic classes listed in the United States Pharmacopeia (USP), which model-guidelines.

The prodrug moieties disclosed herein may be particularly useful for Class II and
5 Class IV compounds according to the Biopharmaceutical Classification System (BCS), which classifies pharmaceutical compounds based on their solubility and permeability (see, e.g., Tsume *et al. Eur. J. Pharm. Sci.* 2014, 57: 152-163). Class II compounds have high permeability but low solubility, and BCS Class IV compounds have low permeability and low solubility. The prodrug moieties disclosed herein may aid in solubilization of these low
10 solubility compounds, allowing for more straightforward modes of formulation and administration. Accordingly, in some embodiments, the pharmaceutically active compound is a BCS Class II compound or a BCS Class IV compound.

In some embodiments, the pharmaceutically active compound is an anticoagulant (e.g., a factor Xa inhibitor such as apixaban or rivaroxaban). In some embodiments, the
15 pharmaceutically active compound is an antineoplastic agent, such as an anti-angiogenic agent (e.g., pomalidomide, lenalidomide), a kinase inhibitor (e.g., abrocitinib, acalabrutinib, asciminib, avapritinib, dabrafenib, osimertinib, ibrutinib, idelalisib, imatinib, nilotinib, palbociclib, pacritinib, pralsetinib, rilzabrutinib ripretinib, selpercatinib, selumetinib, sorafenib, tucatinib, vemurafenib, zanubrutinib), an antimicrotubule agent (e.g., cabazitaxel,
20 docetaxel, paclitaxel), a topoisomerase I inhibitor (e.g., SN-38), a protein degrader (e.g., bavdegalutamide, eragidomide, golcadomide, mezigdomide, vepdegestrant, NX-2127, DT2216, ARV-766, FHD-609), an intercalating agent (e.g., doxorubicin), a PARP inhibitor (e.g., olaparib), a KRAS inhibitor (e.g., sotorasib), an EZH2 inhibitor (e.g., tazemetostat). In some embodiments, the pharmaceutically active compound is an antiandrogen (e.g.,
25 enzalutamide, apalutamide, bicalutamide). In some embodiments, the pharmaceutically active compound is an antiemetic (e.g., aprepitant, amisulpride). In some embodiments, the pharmaceutically active compound is an antiparasitic, such as an anthelmintic (e.g., niclosamide). In some embodiments, the pharmaceutically active compound is a cardiovascular agent, such as a beta-adrenergic blocking agent (e.g., carvedilol), a
30 dyslipidemic agent such as a statin (e.g., atorvastatin, simvastatin), a cholesterol absorption inhibitor (e.g., ezetimibe), an antiplatelet agent (e.g., clopidogrel), or a diuretic (e.g., hydrochlorothiazide). In some embodiments, the pharmaceutically active compound is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, such as ivacaftor. In some embodiments, the pharmaceutically active compound is an antibacterial agent, such

as a cephalosporin (e.g., cefdinir, cefprozil), a macrolide (e.g., clarithromycin), or an oxazolidinone (e.g., linezolid). In some embodiments, the pharmaceutically active compound is an anti-inflammatory, such as a nonsteroidal anti-inflammatory (e.g., celecoxib, meloxicam, valdecoxib). In some embodiments, the pharmaceutically active compound is an

5 antiviral agent, such as a non-nucleoside reverse transcriptase inhibitor (e.g., doravirine, efavirenz, etravirine, rilpivirine), or a protease inhibitor (e.g., lopinavir, nelfinavir, ritonavir). In some embodiments, the pharmaceutically active compound is a blood glucose regulator, such as an antidiabetic agent (e.g., ezetimibe, glimepiride, glipizide, glyburide, pioglitazone). In some embodiments, the pharmaceutically active compound is an anticonvulsant, such as

10 lamotrigine or oxcarbazepine. In some embodiments, the pharmaceutically active compound is an antihistamine, such as desloratadine or hydroxyzine pamoate. In some embodiments, the pharmaceutically active compound is a skeletal muscle relaxant, such as metaxalone. In some embodiments, the pharmaceutically active compound is a central nervous system agent, such as a CNS stimulant (e.g., methylphenidate, modafinil). In some embodiments, the

15 pharmaceutically active compound is an antipsychotic, such as an atypical antipsychotic (e.g., olanzapine, quetiapine, *N*-desalkylquetiapine, amisulpride). In some embodiments, the pharmaceutically active compound is a hormonal agent, such as a selective estrogen receptor modifying agent (e.g., raloxifene). In some embodiments, the pharmaceutically active compound is an immunological agent, such as an immune suppressant (e.g., tacrolimus). In

20 some embodiments, the pharmaceutically active compound is a cytochrome P450 3A4 inhibitor (e.g., avacopan). In some embodiments, the pharmaceutically active compound is an opioid agonist (e.g., oliceridine). In some embodiments, the pharmaceutically active compound is an antifungal agent (e.g., oteseconazole). In some embodiments, the pharmaceutically active compound is a calcitonin gene-related peptide receptor antagonist

25 (e.g., rimegepant). In some embodiments, the pharmaceutically active compound is an active metabolite of a drug compound.

In some embodiments, the pharmaceutically active compound is selected from the group consisting of apixaban, carvedilol, dabrafenib, desloratadine, enzalutamide, lenalidomide, paclitaxel, and vemurafenib. In some embodiments, the pharmaceutically

30 active compound is paclitaxel.

As with compounds of formula (I), compounds of formula (II) (including compounds of formula (IIa) and (IIb)) include groups such as R^a , R^i , and R^n (among others) which in some embodiments are independently selected from hydrogen, alkyl (e.g., C₁-C₄ alkyl), and benzyl. One skilled in the art will recognize that, in some embodiments, R^a , R^i , and R^n are

independently alkyl or benzyl, such that the prodrug compounds are in protected form. Such forms may be produced, for example, from a reaction of a compound of formula (I) with a pharmaceutically active compound to form the compounds of formula (II), and produce protected prodrug compound. These groups may be subsequently deprotected to provide
5 compounds in which R^a , R^i , and R^n are hydrogen. All protected and deprotected forms of compounds of formula (II) are contemplated herein.

In some embodiments, the compound of formula (II) is a compound shown in the Drawings (e.g., a compound shown in any one of FIGS. 1-51), or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of formula (II) is a compound
10 shown in Table 2 herein, or a pharmaceutically acceptable salt thereof.

The compounds of the present disclosure may have at least one asymmetric center. Compounds with asymmetric centers give rise to enantiomers (optical isomers), diastereomers (configurational isomers) or both, and it is intended that all of the possible enantiomers and diastereomers in mixtures and as pure or partially purified compounds are
15 included within the scope of this disclosure.

The independent syntheses of the enantiomerically or diastereomerically enriched compounds, or their chromatographic separations, may be achieved as known in the art by appropriate modification of the methodology disclosed herein. The absolute stereochemistry of a compound may be determined by using X-ray crystallography to determine the crystal
20 structure of crystalline products or crystalline intermediates that are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

If desired, racemic mixtures of compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well-known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure
25 compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to pure enantiomers by cleavage of the added chiral residue. Racemic mixtures of compounds can also be separated directly by
30 chromatographic methods using chiral stationary phases, which methods are well known in the art. Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

The compound (e.g., a compound of formula (I) or formula (II)) may possess tautomeric forms, and tautomers also constitute embodiments of the disclosure.

The present disclosure also includes isotopically-labeled compounds (e.g., an isotopically-labeled compound of formula (I) or formula (II)), which are identical to those recited in formula (I) or formula (II), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the disclosure are hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine, such as, but not limited to ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{31}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Substitution with heavier isotopes such as deuterium, i.e. ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. The compound may incorporate positron-emitting isotopes for medical imaging and positron-emitting tomography (PET) studies for determining the distribution of receptors. Suitable positron-emitting isotopes that can be incorporated in compounds of formula (I) or (II) are ^{11}C , ^{13}N , ^{15}O , and ^{18}F . Isotopically-labeled compounds of formula (I) or (II) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein using an appropriate isotopically-labeled reagent in place of a non-isotopically-labeled reagent.

Compounds of formula (I) or (II) can be synthesized by a variety of methods, including those illustrated in the Examples. Compounds and intermediates may be isolated and purified by methods well-known to those skilled in the art of organic synthesis. Examples of conventional methods for isolating and purifying compounds can include, but are not limited to, chromatography on solid supports such as silica gel, alumina, or silica derivatized with alkylsilane groups, by recrystallization at high or low temperature with an optional pretreatment with activated carbon, thin-layer chromatography, distillation at various pressures, sublimation under vacuum, and trituration, as described for instance in "Vogel's Textbook of Practical Organic Chemistry," 5th edition (1989), by Furniss, Hannaford, Smith, and Tatchell, pub. Longman Scientific & Technical, Essex CM20 2JE, England.

Reaction conditions and reaction times for each individual step can vary depending on the particular reactants employed and substituents present in the reactants used. Reactions can be worked up in a conventional manner, e.g., by eliminating the solvent from the residue and further purified according to methodologies generally known in the art such as, but not limited to, crystallization, distillation, extraction, trituration and chromatography. Unless

otherwise described, the starting materials and reagents are either commercially available or can be prepared by one skilled in the art from commercially available materials using methods described in the chemical literature.

Standard experimentation, including appropriate manipulation of the reaction
5 conditions, reagents and sequence of the synthetic route, protection of any chemical
functionality that cannot be compatible with the reaction conditions, and deprotection at a
suitable point in the reaction sequence of the method are included in the scope of the
disclosure. Suitable protecting groups and the methods for protecting and deprotecting
different substituents using such suitable protecting groups are well known to those skilled in
10 the art; examples of which can be found in PGM Wuts and TW Greene, in Greene's book
titled Protective Groups in Organic Synthesis (4th ed.), John Wiley & Sons, NY (2006).

When an optically active form of a disclosed compound is required, it can be obtained
by carrying out one of the procedures described herein using an optically active starting
material (prepared, for example, by asymmetric induction of a suitable reaction step), or by
15 resolution of a mixture of the stereoisomers of the compound or intermediates using a
standard procedure (such as chromatographic separation, recrystallization or enzymatic
resolution).

Similarly, when a pure geometric isomer of a compound is required, it can be
obtained by carrying out one of the procedures described herein using a pure geometric
20 isomer as a starting material, or by resolution of a mixture of the geometric isomers of the
compound or intermediates using a standard procedure such as chromatographic separation.

The synthetic schemes and specific examples as described are illustrative and are not
to be read as limiting the scope of the disclosure or the claims. Alternatives, modifications,
and equivalents of the synthetic methods and specific examples are contemplated.

25 The disclosed compounds may exist as salts, including pharmaceutically acceptable
salts. The term "pharmaceutically acceptable salt" refers to salts or zwitterions of the
compounds which are water or oil-soluble or dispersible, suitable for treatment of disorders
without undue toxicity, irritation, or allergic response, commensurate with a reasonable
benefit/risk ratio and effective for their intended use.

30 Salts may be prepared during the final isolation and purification of the compounds, or
separately. For example, salts may be prepared by reacting an amino group of the compounds
with a suitable acid. For example, a compound may be dissolved in a suitable solvent, such as
but not limited to methanol and water, and treated with at least one equivalent of an acid, like
hydrochloric acid. The resulting salt may precipitate out and be isolated by filtration and

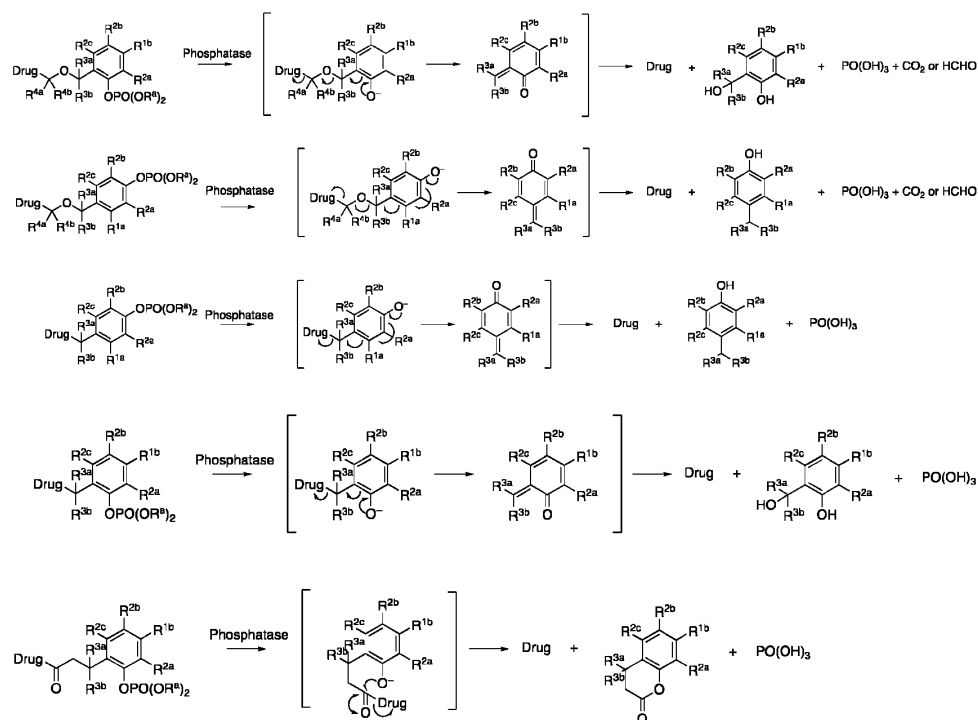
dried under reduced pressure. Alternatively, the solvent and excess acid may be removed under reduced pressure to provide a salt. Representative salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, 5 formate, isethionate, fumarate, lactate, maleate, methanesulfonate, naphthylenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, oxalate, maleate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, glutamate, para-toluenesulfonate, undecanoate, hydrochloric, hydrobromic, sulfuric, phosphoric and the like. The amino groups of the compounds may also be quaternized with alkyl chlorides, 10 bromides and iodides such as methyl, ethyl, propyl, isopropyl, butyl, lauryl, myristyl, stearyl, and the like. In one embodiment, the compound is in the form of a trifluoroacetate salt.

Basic addition salts may be prepared during the final isolation and purification of the disclosed compounds by reaction of a phosphate, phosphonate or carboxyl group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation such as 15 lithium, sodium, potassium, calcium, magnesium, or aluminum, or an organic primary, secondary, or tertiary amine. Quaternary amine salts can be prepared, such as those derived from methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, 1-phenamine 20 and N,N'-dibenzylethylenediamine, ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine, and the like.

Compounds disclosed herein can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present disclosure. Certain compounds of the 25 disclosure may also exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present disclosure and are intended to be within the scope of the present disclosure.

Compounds of formula (II) disclosed herein are prodrug compounds, which can be cleaved *in vivo* (e.g., by phosphatases) to provide the pharmaceutically active agents. 30 Exemplary mechanisms by which the compounds can be cleaved is shown in Scheme 1.

Scheme 1



Pharmaceutical Compositions

The disclosed prodrug compounds may be incorporated into pharmaceutical

5 compositions suitable for administration to a subject (such as a patient, which may be a human or non-human). The pharmaceutical compositions may include a “therapeutically effective amount” or a “prophylactically effective amount” of the agent. A “therapeutically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the
10 composition may be determined by a person skilled in the art and may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the composition to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of a compound of the disclosure are outweighed by the therapeutically beneficial effects. A “prophylactically effective amount”
15 refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease or condition, the prophylactically effective amount will be less than the therapeutically effective amount.

The pharmaceutical compositions may include pharmaceutically acceptable carriers. The term “pharmaceutically acceptable carrier,” as used herein, means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as, but not limited to, lactose, glucose and sucrose; starches such as, but not limited to, corn starch and potato starch; cellulose and its derivatives such as, but not limited to, sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as, but not limited to, cocoa butter and suppository waxes; oils such as, but not limited to, peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols; such as propylene glycol; esters such as, but not limited to, ethyl oleate and ethyl laurate; agar; buffering agents such as, but not limited to, magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer’s solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as, but not limited to, sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

Thus, the compounds and their pharmaceutically acceptable salts may be formulated for administration by, for example, solid dosing, eye drop, in a topical oil-based formulation, injection, inhalation (either through the mouth or the nose), implants, or oral, buccal, parenteral, or rectal administration. Techniques and formulations may generally be found in “Remington’s Pharmaceutical Sciences,” (Meade Publishing Co., Easton, Pa.). Therapeutic compositions must typically be sterile and stable under the conditions of manufacture and storage.

The route by which the disclosed compounds are administered and the form of the composition will dictate the type of carrier to be used. The composition may be in a variety of forms, suitable, for example, for systemic administration (e.g., oral, rectal, nasal, sublingual, buccal, implants, or parenteral) or topical administration (e.g., dermal, pulmonary, nasal, aural, ocular, liposome delivery systems, or iontophoresis). In some embodiments, the composition is in a form suitable for parenteral administration, e.g., intravenous, intramuscular, or subcutaneous administration. In some embodiments, the composition is in a form suitable for an implant, e.g., an ocular implant.

Carriers for systemic administration typically include at least one of diluents, lubricants, binders, disintegrants, colorants, flavors, sweeteners, antioxidants, preservatives,

glidants, solvents, suspending agents, wetting agents, surfactants, combinations thereof, and others. All carriers are optional in the compositions.

Suitable diluents include sugars such as glucose, lactose, dextrose, and sucrose; diols such as propylene glycol; calcium carbonate; sodium carbonate; sugar alcohols, such as glycerin; mannitol; and sorbitol. The amount of diluent(s) in a systemic or topical composition is typically about 50 to about 90% by weight of the composition.

Suitable lubricants include silica, talc, stearic acid and its magnesium salts and calcium salts, calcium sulfate; and liquid lubricants such as polyethylene glycol and vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma. The amount of lubricant(s) in a systemic or topical composition is typically about 5 to about 10% by weight of the composition.

Suitable binders include polyvinyl pyrrolidone; magnesium aluminum silicate; starches such as corn starch and potato starch; gelatin; tragacanth; and cellulose and its derivatives, such as sodium carboxymethylcellulose, ethyl cellulose, methylcellulose, microcrystalline cellulose, and sodium carboxymethylcellulose. The amount of binder(s) in a systemic composition is typically about 5 to about 50% by weight of the composition.

Suitable disintegrants include agar, alginic acid and the sodium salt thereof, effervescent mixtures, croscarmellose, crospovidone, sodium carboxymethyl starch, sodium starch glycolate, clays, and ion exchange resins. The amount of disintegrant(s) in a systemic or topical composition is typically about 0.1 to about 10% by weight of the composition.

Suitable colorants include a colorant such as an FD&C dye. When used, the amount of colorant in a systemic or topical composition is typically about 0.005 to about 0.1% by weight of the composition.

Suitable flavors include menthol, peppermint, and fruit flavors. The amount of flavor(s), when used, in a systemic or topical composition is typically about 0.1 to about 1.0%.

Suitable sweeteners include aspartame and saccharin. The amount of sweetener(s), when used, in a systemic or topical composition is typically about 0.001 to about 1% by weight of the composition.

Suitable antioxidants include butylated hydroxyanisole ("BHA"), butylated hydroxytoluene ("BHT"), and vitamin E. The amount of antioxidant(s) in a systemic or topical composition is typically about 0.1 to about 5% by weight of the composition.

Suitable preservatives include benzalkonium chloride, methyl paraben, and sodium benzoate. The amount of preservative(s) in a systemic or topical composition is typically about 0.01 to about 5% by weight of the composition.

5 Suitable glidants include silicon dioxide. The amount of glidant(s) in a systemic or topical composition is typically about 1 to about 5% by weight of the composition.

 Suitable solvents include water, saline (e.g., isotonic saline), ethyl oleate, glycerin, hydroxylated castor oils, alcohols such as ethanol, and aqueous buffer solutions, such as phosphate buffer solutions. In some embodiments, the solvent is water. In some
10 embodiments, the solvent is saline. In some embodiments, the solvent is an aqueous buffer solution, such as phosphate-buffered saline. The amount of solvent(s) in a systemic or topical composition is typically from about 0 to about 100% by weight of the composition.

 Suitable suspending agents include AVICEL RC-591 (from FMC Corporation of Philadelphia, PA) and sodium alginate. The amount of suspending agent(s) in a systemic or topical composition is typically about 1 to about 8% by weight of the composition.

15 Suitable surfactants include lecithin, Polysorbate 80, and sodium lauryl sulfate, and the TWEENS from Atlas Powder Company of Wilmington, Delaware. Suitable surfactants include those disclosed in the C.T.F.A. Cosmetic Ingredient Handbook, 1992, pp.587-592; Remington's Pharmaceutical Sciences, 15th Ed. 1975, pp. 335-337; and McCutcheon's
20 Volume 1, Emulsifiers & Detergents, 1994, North American Edition, pp. 236-239. The amount of surfactant(s) in the systemic or topical composition is typically about 0.1% to about 5% by weight of the composition.

 Although the amounts of components in the systemic compositions may vary depending on the type of systemic composition prepared, in general, systemic compositions include 0.01% to 50% by weight of an active compound and 50% to 99.99% by weight of
25 one or more carriers. Compositions for parenteral administration typically include 0.1% to 10% by weight of actives and 90% to 99.9% by weight of a carrier including a diluent and a solvent.

 Compositions for oral administration can have various dosage forms. For example, solid forms include tablets, capsules, granules, and bulk powders. These oral dosage forms
30 include a safe and effective amount, usually at least about 5% by weight, and more particularly from about 25% to about 50% by weight of actives. The oral dosage compositions include about 50% to about 95% by weight of carriers, and more particularly, from about 50% to about 75% by weight.

Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed. Tablets typically include an active component, and a carrier comprising ingredients selected from diluents, lubricants, binders, disintegrants, colorants, flavors, sweeteners, glidants, and combinations thereof. Specific diluents include calcium carbonate, sodium carbonate, mannitol, lactose and cellulose. Specific binders include starch, gelatin, and sucrose. Specific disintegrants include alginic acid and croscarmellose. Specific lubricants include magnesium stearate, stearic acid, and talc. Specific colorants are the FD&C dyes, which can be added for appearance. Chewable tablets preferably contain sweeteners such as aspartame and saccharin, or flavors such as menthol, peppermint, fruit flavors, or a combination thereof.

Capsules (including implants, time release and sustained release formulations) typically include an active compound (e.g., a prodrug compound disclosed herein), and a carrier including one or more diluents disclosed above in a capsule comprising gelatin. Granules typically comprise a disclosed compound, and preferably glidants such as silicon dioxide to improve flow characteristics. Implants can be of the biodegradable or the non-biodegradable type.

The selection of ingredients in the carrier for oral compositions depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of this disclosure.

Solid compositions may be coated by conventional methods, typically with pH or time-dependent coatings, such that a disclosed compound is released in the gastrointestinal tract in the vicinity of the desired application, or at various points and times to extend the desired action. The coatings typically include one or more components selected from the group consisting of cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, EUDRAGIT® coatings (available from Evonik Industries of Essen, Germany), waxes and shellac.

Compositions for oral administration can have liquid forms. For example, suitable liquid forms include aqueous solutions, emulsions, suspensions, solutions reconstituted from non-effervescent granules, suspensions reconstituted from non-effervescent granules, effervescent preparations reconstituted from effervescent granules, elixirs, tinctures, syrups, and the like. Liquid orally administered compositions typically include a disclosed compound and a carrier, namely, a carrier selected from diluents, colorants, flavors, sweeteners, preservatives, solvents, suspending agents, and surfactants. Peroral liquid compositions preferably include one or more ingredients selected from colorants, flavors, and sweeteners.

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically include one or more of soluble filler substances such as diluents including sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose, and hydroxypropyl methylcellulose. Such compositions may further include lubricants, colorants, flavors, sweeteners, antioxidants, and glidants.

The disclosed compounds can be topically administered. Topical compositions that can be applied locally to the skin may be in any form including solids, solutions, oils, creams, ointments, gels, lotions, shampoos, leave-on and rinse-out hair conditioners, milks, cleansers, moisturizers, sprays, skin patches, and the like. Topical compositions include: a disclosed compound (e.g., a prodrug compound disclosed herein), or a pharmaceutically acceptable salt thereof), and a carrier. The carrier of the topical composition preferably aids penetration of the compounds into the skin. The carrier may further include one or more optional components.

The amount of the carrier employed in conjunction with a disclosed compound is sufficient to provide a practical quantity of composition for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods of this disclosure are described in the following references: Modern Pharmaceutics, Chapters 9 and 10, Banker & Rhodes, eds. (1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms, 2nd Ed., (1976).

A carrier may include a single ingredient or a combination of two or more ingredients. In the topical compositions, the carrier includes a topical carrier. Suitable topical carriers include one or more ingredients selected from phosphate buffered saline, isotonic water, deionized water, monofunctional alcohols, symmetrical alcohols, aloe vera gel, allantoin, glycerin, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, dimethyl isosorbide, castor oil, combinations thereof, and the like. More particularly, carriers for skin applications include propylene glycol, dimethyl isosorbide, and water, and even more particularly, phosphate buffered saline, isotonic water, deionized water, monofunctional alcohols, and symmetrical alcohols.

The carrier of a topical composition may further include one or more ingredients selected from emollients, propellants, solvents, humectants, thickeners, powders, fragrances, pigments, and preservatives, all of which are optional.

Suitable emollients include stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, isopropyl

isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate, and combinations thereof. Specific emollients for skin include stearyl alcohol and polydimethylsiloxane. The amount of emollient(s) in a skin-based topical composition is typically about 5% to about 95% by weight of the composition.

Suitable propellants include propane, butane, isobutane, dimethyl ether, carbon dioxide, nitrous oxide, and combinations thereof. The amount of propellant(s) in a topical composition is typically about 0% to about 95% by weight of the composition.

Suitable solvents include water, ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethylsulfoxide, dimethyl formamide, tetrahydrofuran, and combinations thereof. Specific solvents include ethyl alcohol and homotopic alcohols. The amount of solvent(s) in a topical composition is typically about 0% to about 95% by weight of the composition.

Suitable humectants include glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, gelatin, and combinations thereof. Specific humectants include glycerin. The amount of humectant(s) in a topical composition is typically 0% to 95% by weight of the composition.

The amount of thickener(s) in a topical composition is typically about 0% to about 95% by weight of the composition.

Suitable powders include beta-cyclodextrins, hydroxypropyl cyclodextrins, chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically-modified magnesium aluminum silicate, organically-modified montmorillonite clay, hydrated aluminum silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate, and combinations thereof. The amount of powder(s) in a topical composition is typically 0% to 95% by weight of the composition.

The amount of fragrance in a topical composition is typically about 0% to about 0.5%, particularly, about 0.001% to about 0.1% by weight of the composition.

Suitable pH adjusting additives include HCl or NaOH in amounts sufficient to adjust the pH of a topical pharmaceutical composition.

Methods of Use

Compounds of formula (I) can be used as building blocks to synthesis prodrug compounds, such as compounds of formula (II). Accordingly, disclosed herein are methods of synthesizing compounds of formula (II) from compounds of formula (I). The prodrug compounds of formula (II) can be used as pharmaceutical compounds. Accordingly, disclosed herein are methods of treating a subject by administering a therapeutically effective amount of a compound of formula (II).

For example, in some embodiments, disclosed herein is a method of preparing a prodrug of a pharmaceutically active compound (e.g., a compound of formula (I)), comprising reacting a compound of formula (I) with the pharmaceutically active compound in the presence of a suitable base. In some embodiments, the method comprises first combining the compound of formula (I) and the pharmaceutically active compound to form a mixture, and subsequently adding the base to the mixture. In other embodiments, the method comprises first reacting the pharmaceutically active compound with a base to form a mixture, and subsequently adding the compound of formula (I) to the mixture.

Any suitable base can be used in the disclosed methods. For example, in some embodiments the base is selected from a hydride-containing base (e.g., sodium hydride), an organic base such as 4-dimethylaminopyridine, triethylamine, 2,6-lutidine, pyridine, or *N,N*-diisopropylethylamine, or a lithium-containing base such as lithium bis(trimethylsilyl)amide or lithium diisopropylamide, or an inorganic carbonate such as potassium carbonate or cesium carbonate.

The reactions can be carried out in any suitable solvent or solvent system. For example, in some embodiments, the reaction is carried out in an organic solvent selected from *N,N*-dimethylformamide, ethyl acetate, tetrahydrofuran, methyltetrahydrofuran, 1,4-dioxane, dichloromethane, 1,2-dichloroethane, acetonitrile, or the like.

In some embodiments, the reaction is carried out at a temperature above room temperature (i.e., in the presence of heat). In some embodiments, the reaction is carried out at a temperature below room temperature (i.e., with cooling). One skilled in the art will understand how to manipulate the reaction conditions based on the selection of the particular starting materials.

After the initial reaction steps, the prodrug compound (e.g., compound of formula (II)) can be isolated and purified from the reaction mixture via any suitable means, such as those discussed generally above.

The prodrug compounds of formula (II) can be used in methods of treating a disorder in a subject. The disorder to be treated will vary depending on the identity of the pharmaceutically active compound. For example, in some embodiments, disclosed herein is a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is an antineoplastic agent (e.g., an anti-angiogenic agent (e.g., pomalidomide, lenalidomide), a kinase inhibitor (e.g., abrocitinib, acalbrutinib, asciminib, avapritinib, dabrafenib, osimertinib, ibrutinib, idelalisib, imatinib, nilotinib, palbociclib, pacritinib, pralsetinib, rilzabrutinib, ripretinib, selpercatinib, selumetinib, sorafenib, tucatinib, vemurafenib, zanubrutinib), an antimicrotubule agent (e.g., cabazitaxel, docetaxel, paclitaxel), a topoisomerase I inhibitor (e.g., SN-38)), a protein degrader (e.g., bavdegalutamide, eragidomide, golcadomide, mezigdomide, vepdegestrant, NX-2127, DT2216, ARV-766, FHD-609), an intercalating agent (e.g., doxorubicin), a PARP inhibitor (e.g., olaparib), a KRAS inhibitor (e.g., sotorasib), an EZH2 inhibitor (e.g., tazemetostat), or an antiandrogen (e.g., enzalutamide, apalutamide, bicalutamide). In some embodiments, the cancer is selected from breast cancer, colorectal cancer, ovarian cancer, prostate cancer, lung cancer (e.g., non-small cell lung cancer), a blood cancer (e.g., multiple myeloma), a lymphoma (e.g., mantle cell lymphoma, follicular lymphoma, marginal zone lymphoma), a melanoma (e.g., unresectable or metastatic melanoma), or a leukemia (e.g., chronic lymphocytic leukemia).

In some embodiments, disclosed herein is a method of treating or reducing risk of stroke, embolism, or deep vein thrombosis in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is an anticoagulant (e.g., a factor Xa inhibitor such as apixaban or rivaroxaban).

In some embodiments, disclosed herein is a method of treating or preventing nausea and/or vomiting in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is an antiemetic (e.g., aprepitant, amisulpride). In some embodiments, the subject has cancer and the nausea and/or vomiting is chemotherapy induced.

In some embodiments, disclosed herein is a method of treating a tapeworm infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is an antiparasitic, such as an anthelmintic (e.g., niclosamide).

In some embodiments, disclosed herein is a method of treating or preventing a cardiovascular disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is a cardiovascular agent, such as a beta-adrenergic blocking agent (e.g., carvedilol), a dyslipidemic agent such as a statin (e.g., atorvastatin, simvastatin), a cholesterol absorption inhibitor (e.g., ezetimibe), an antiplatelet agent (e.g., clopidogrel), or a diuretic (e.g., hydrochlorothiazide). In some embodiments, the cardiovascular disorder is selected from high blood pressure, high cholesterol, stroke, or the like.

In some embodiments, disclosed herein is a method of treating cystic fibrosis in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, such as ivacaftor.

In some embodiments, disclosed herein is a method of treating a bacterial infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is an antibacterial agent, such as a cephalosporin (e.g., cefdinir, cefprozil), a macrolide (e.g., clarithromycin), or an oxazolidinone (e.g., linezolid).

In some embodiments, disclosed herein is a method of treating inflammation in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is an anti-inflammatory, such as a nonsteroidal anti-inflammatory (e.g., celecoxib, meloxicam, valdecoxib).

In some embodiments, disclosed herein is a method of treating a viral infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is an antiviral agent, such as a non-nucleoside

reverse transcriptase inhibitor (e.g., doravirine, efavirenz, etravirine, rilpivirine), or a protease inhibitor (e.g., lopinavir, nelfinavir, ritonavir). In some embodiments,

In some embodiments, disclosed herein is a method of treating diabetes in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is a blood glucose regulator, such as an antidiabetic agent (e.g., ezetimibe, glimepiride, glipizide, glyburide, pioglitazone).

In some embodiments, disclosed herein is a method of treating seizures in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is an anticonvulsant, such as lamotrigine or oxcarbazepine.

In some embodiments, disclosed herein is a method of treating allergies in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is an antihistamine, such as desloratadine or hydroxyzine pamoate.

In some embodiments, disclosed herein is a method of treating muscle spasms in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is a skeletal muscle relaxant, such as metaxalone.

In some embodiments, disclosed herein is a method of treating a sleep disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is a central nervous system agent, such a CNS stimulant (e.g., methylphenidate, modafinil).

In some embodiments, disclosed herein is a method of treating attention deficit hyperactivity disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is a central nervous system agent, such a CNS stimulant (e.g., methylphenidate).

In some embodiments, disclosed herein is a method of treating a mental disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is an antipsychotic, such as an atypical

antipsychotic (e.g., olanzapine, quetiapine, *N*-desalkylquetiapine, amisulpride). In some embodiments, the mental disorder is selected from bipolar disorder, schizophrenia, and major depressive disorder.

5 In some embodiments, disclosed herein is a method of treating osteoporosis in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is a hormonal agent, such as a selective estrogen receptor modifying agent (e.g., raloxifene).

10 In some embodiments, disclosed herein is a method of treating an immune disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is an immunological agent, such as an immune suppressant (e.g., tacrolimus). In some embodiments, the immune disorder comprises a transplant rejection. In some embodiments, disclosed herein is a method of treating an
15 immune disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is a cytochrome P450 3A4 inhibitor (e.g., avacopan). In some embodiments, the immune disorder is anti-neutrophil cytoplasmic autoantibody-associated vasculitis.

20 In some embodiments, disclosed herein is a method of treating pain in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is an opioid receptor agonist (e.g., oliceridine).

25 In some embodiments, disclosed herein is a method of treating a fungal infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is an antifungal agent (e.g., oteseconazole).

30 In some embodiments, disclosed herein is a method of treating migraine in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (II), wherein the pharmaceutically active compound (i.e., group D in the compound of formula (II)) is a calcitonin gene-related peptide receptor antagonist (e.g., rimegepant).

Systems and Kits

For use in methods described herein, systems, kits, and articles of manufacture are also provided, which include a compound or pharmaceutical composition described herein (e.g., a compound of formula (I) or a salt thereof, a compound of formula (II) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of formula (II) or a pharmaceutically acceptable salt thereof). In some
5 embodiments, such systems and kits comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The
10 containers are formed from a variety of materials such as glass or plastic.

The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products include those found in, e.g., U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags,
15 vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. For example, in some embodiments the container(s) includes a compound of formula (I) or a salt thereof, or a compound formula (II) or a pharmaceutically acceptable salt thereof, optionally in a composition or in combination with another agent as disclosed herein. In particular
20 embodiments (e.g., for prodrug compounds of formula (II)), the container(s) have a sterile access port (for example the container is an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprise a compound with an identifying description or label or instructions relating to its use in the methods described herein.

Also disclosed herein are systems and kits for preparing prodrug compounds, comprising a compound of formula (I) or a salt thereof, and optionally a pharmaceutically active compound. Such systems and kits can be used for the preparation of prodrug compounds of formula (II) described herein. For example, in some embodiments, disclosed herein is a kit comprising a compound of formula (I) or a salt thereof, and instructions for
30 using the compound of formula (I) to prepare a prodrug of a pharmaceutically active compound. In some embodiments, disclosed herein is a system comprising a compound of formula (I) or a salt thereof, and a pharmaceutically active compound. Such a system can be used in a method described herein, such as a method of preparing a prodrug compound of formula (II).

Examples

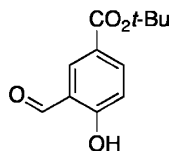
Abbreviations used in the Examples include the following: Bn is benzyl; *t*-Bu is *tert*-butyl; DCC is dicyclohexyl carbodiimide; DCM is dichloromethane; DIPEA is *N,N*-diisopropylethylamine; DMAP is 4-dimethylaminopyridine; DMF is *N,N*-dimethylformamide; DMSO is dimethylsulfoxide; EtOAc is ethyl acetate; EtOH is ethanol; h is hours; LCMS is liquid chromatography mass spectrometry; MeCN is acetonitrile; MeOH is methanol; and THF is tetrahydrofuran.

General Methods. Reactions were performed under ambient atmosphere unless otherwise noted. Qualitative TLC analysis was performed on 250 mm thick, 60 G, glass-backed, F254 silica (EMD Millipore). All solvents used were ACS grade Sure-Seal, and all other reagents were used as received unless otherwise noted. Chromatography was performed on a Biotage Selekt instrument using either Biotage Sfär silica HC columns or Biotage Sfär C-18 HP Sphere 25 μ m pre-packed cartridges. Compounds were stored in a freezer (-20°C) following synthesis. Structure determination was performed using ^1H , ^{13}C , ^{19}F , and ^{31}P spectra that were recorded on a Bruker Neo-500 spectrometer, and low-resolution mass spectra (ESI-MS) that were collected on an Agilent LCMS iQ instrument. Unless stated, all chemical building blocks were purchased from commercial sources or were synthesized according to the protocols included in the Supplementary Information. Final compounds were submitted at a purity of $>95\%$ by NMR and LCMS.

The following reagents were purchased from commercial sources: Dibenzyl phosphite (CAS: 17176-77-1); di-*tert*-butyl phosphite (CAS: 13086-84-5); 2-hydroxybenzyl alcohol (CAS: 99-90-01); 4-hydroxybenzyl alcohol (CAS: 623-05-2); 4-nitrophenyl chloroformate (CAS: 7693-46-1); 6-bromo-2,2-dimethyl-4H-benzodioxin (CAS: 52113-69-6).

Example 1: Synthesis of Precursor Compounds

Synthesis of *tert*-butyl 3-formyl-4-hydroxy-benzoate

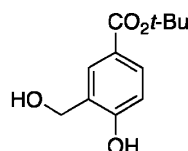


A mixture of 3-formyl-4-hydroxy-benzoic acid (3.0 g, 18.06 mmol), 1,1-di-*tert*-butoxy-*N,N*-dimethyl-methanamine (8.34 mL, 36.12 mmol) in THF (1.2 mL) was heated at 100 $^{\circ}\text{C}$ for 1 h. Additional di-*tert*-butoxy-*N,N*-DMF (3 mL) was added. Heated for 2 h at 100

°C. Cooled, evaporated to dryness under reduced pressure. White solid forms upon standing. Chromatography (2–20% EtOAc in hexanes) provided the desired product as a white solid (1.74 g; 43%). ¹H NMR (500 MHz, CDCl₃) δ 11.35 (s, 1H), 9.95 (s, 1H), 8.25 (d, *J* = 2 Hz, 1H), 8.14 (dd, *J* = 8.6 and 2 Hz, 1H), 7.01 (d, *J* = 8.6 Hz) and 1.60 (s, 9H).

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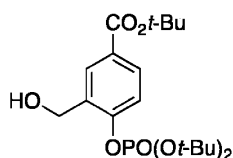
Synthesis of *tert*-butyl 4-hydroxy-3-(hydroxymethyl)benzoate



Sodium borohydride (430 mg) was added to a solution of *tert*-butyl 3-formyl-4-hydroxy-benzoate (1.25 g; 5.6 mmol) in 10 ml THF. The reaction was stirred at 70 °C 1h, cooled to room temperature and then evaporated to dryness under reduced pressure. The residue was dissolved in water, acidified to pH 1 with 2N HCl solution and extracted into EtOAc, washed with brine, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (5–60% EtOAc in hexanes) provided the title product (1.09 g; 87%) as a crystalline white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.89–7.83 (m, 2H), 7.69 (d, *J* = 2.1 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 4.93 (s, 2H), 1.57 (s, 9H).

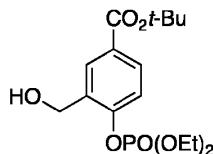
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Synthesis of *tert*-butyl 4-ditert-butoxyphosphoryloxy-3-(hydroxymethyl)benzoate

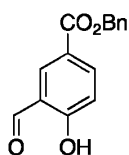


Di-*tert*-butoxyphosphine (943 mg; 4.86 mmol) was added to a cooled (5 °C) solution of *tert*-butyl 4-hydroxy-3-(hydroxymethyl)benzoate (1.09 g; 4.86 mmol), *N,N*-diisopropylethylamine (2.53 mL; 14.58 mmol) and carbon tetrabromide (8.05 g; 24.30 mmol) in CH₃CN (20 mL). Added additional DMAP (100 mg; 0.81 mmol) with every addition. After 3 h, the reaction mixture was quenched with water and extracted into EtOAc. The organic phase was washed with brine, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (10–80% EtOAc in hexanes) provide the desired product (0.79 g; 39%) as a colorless solid. ¹H NMR (500 MHz, CDCl₃) δ 8.32–8.25 (m, 2H), 8.09 (t, *J* = 1.8 Hz, 1H), 7.99 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.53 (dd, *J* = 8.7, 0.8 Hz, 1H), 7.44–7.37 (m, 2H), 5.42 (s, 2H), 1.59 (d, *J* = 1.6 Hz, 9H), 1.52 (d, *J* = 0.7 Hz, 18H).

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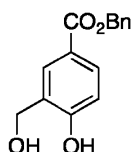
Synthesis of *tert*-butyl 4-diethoxyphosphoryloxy-3-(hydroxymethyl)benzoate

Diethyl chlorophosphate (0.497 mL; 2.74 mmol) was added to a cooled (5 °C)
 5 solution of *tert*-butyl 4-hydroxy-3-(hydroxymethyl)benzoate (0.71 g; 5.48 mmol), *N,N*-diethylisopropylamine (0.95 mL; 5.48 mmol) in CH₃CN (20 mL). After 3 h, the reaction mixture was quenched with water and extracted into EtOAc. The organic phase was washed with brine, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (10–80% EtOAc in hexanes) provide the desired product (0.79 g; 39%) as a
 10 colorless solid. ¹H NMR (500 MHz, CDCl₃) δ 8.14–8.08 (m, 1H), 7.95 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.28–7.23 (m, 2H), 4.69 (s, 2H), 4.32–4.14 (m, 4H), 1.59 (s, 9H), 1.37 (td, *J* = 7.1, 1.1 Hz, 6H).

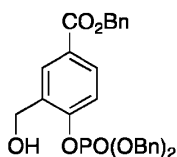
Synthesis of benzyl 3-formyl-4-hydroxybenzoate

15 Paraformaldehyde (0.79 g, 26.29 mmol), was added to a flask containing benzyl 4-hydroxybenzoate (2.0 g, 8.76 mmol), triethylamine (2.44 mL, 17.52 mmol) and MgCl₂ (1.66 g, 17.5 mmol) in acetonitrile (30 mL). The mixture was stirred at reflux for 12 h, cooled to room temperature and diluted with EtOAc (~150 mL). The resulting solution was washed
 20 with 1M HCl (3 × 100 mL) solution, water (2 × 100 mL), brine solution and dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (0–10% EtOAc in hexanes) provided the desired product as a white solid (1.24 g, 55%). ¹H NMR (500 MHz, CDCl₃) δ 11.43 (s, 1H), 9.97 (s, 1H), 8.37 (d, *J* = 2.1 Hz, 1H), 8.25 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.49–7.45 (m, 2H), 7.45–7.32 (m, 3H), 7.06 (d, *J* = 8.7 Hz, 1H), 5.40 (s, 2H).

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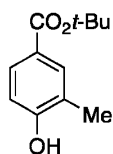
Synthesis of benzyl 4-hydroxy-3-(hydroxymethyl)benzoate

Sodium Borohydride (366 mg, 9.68 mmol) was added to a solution of benzyl 3-formyl-4-hydroxy-benzoate (1.24 g, 4.84 mmol) in tetrahydrofuran (20 mL) and then heated at 70 °C 1 hour and then cooled to room temperature and then acidified by the addition aqueous 1N HCl solution. The product was extracted with EtOAc, washed with brine solution, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (20–80% EtOAc in hexanes) provided the desired product (1.09 g, 87%) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.97 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.78 (d, *J* = 2.1 Hz, 1H), 7.49–7.32 (m, 5H), 6.93 (d, *J* = 8.5 Hz, 1H), 5.34 (s, 2H), 4.94 (s, 2H).

Synthesis of benzyl 4-dibenzyloxyphosphoryloxy-3-(hydroxymethyl)benzoate

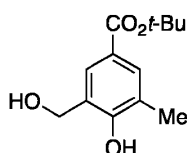
A solution of benzyl 4-hydroxy-3-(hydroxymethyl)benzoate (1.09 g, 4.22 mmol) in MeCN (14 mL) was slowly added to a cooled (5 °C) solution of diisopropylethylamine (2.21 mL, 12.66 mmol), dibenzyl phosphonate (0.94 mL, 4.22 mmol), 4-dimethylaminopyridine (103 mg, 0.84 mmol), carbon tetrachloride (1.63 mL, 16.88 mmol) in acetonitrile (10 mL). The reaction mixture was left to stir at room temperature for 16 h and then diluted with EtOAc, washed with aqueous 1M HCl solution, brine solution, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (20–80% EtOAc in hexanes) provided the desired product (0.78 g, 35%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 8.17 (dd, *J* = 2.4, 1.0 Hz, 1H), 7.94 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.49–7.25 (m, 16H), 7.25–7.06 (m, 2H), 5.38 (s, 2H), 5.15 (d, *J* = 9.0 Hz, 4H), 4.62 (s, 2H).

Synthesis of *tert*-butyl 4-hydroxy-3-methyl-benzoate



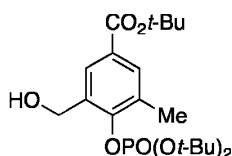
- A solution of DCC (712 mg, 3.45 mmol) in THF (35 mL) was slowly added to a mixture of 4-hydroxy-3-methyl-benzoic acid (500 mg, 3.29), 4-dimethylaminopyridine (150 mg, 1.23 mmol) in *tert*-butanol (45 mL). After stirring for 4 h, the reaction mixture was
- 5 filtered, and then evaporated to dryness under reduced pressure. Chromatography (0–40% EtOAc in hexanes) provided the desired product (324 mg, 47%) as a colorless waxy solid. ¹H NMR (500 MHz, CDCl₃) δ 7.98–7.78 (m, 1H), 7.73–7.64 (m, 2H), 6.70 (d, *J* = 8.3 Hz, 1H), 2.29–2.17 (m, 3H) and 1.51 (s, 9H).

10 Synthesis of *tert*-butyl 4-hydroxy-3-methyl-5-(hydroxymethyl)-benzoate



- To a vial containing *tert*-butyl 4-hydroxy-3-methyl-benzoate (2.677 g, 12.86 mmol) precooled at 0 °C was added dropwise 1M aq. NaOH solution (32.14 mL, 32.14 mmol). The mixture was then stirred at 0 °C for 5 min to assure full dissolution. Formalin solution (37% in water, 8.12 mL, 299.9 mmol) was added dropwise and the vial was warmed up to 55 °C
- 15 overnight. The reaction was then diluted with sat. aq. NH₄Cl and EtOAc, and the phases were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine solution, dried (Na₂SO₄) and evaporated to dryness under reduced pressure. Chromatography (0–50% EtOAc in hexanes) provided the desired product (1.50 g,
- 20 49% yield) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.74–7.72 (m, 1H), 7.53 (dt, *J* = 2.1, 0.7 Hz, 1H), 4.91 (d, *J* = 5.6 Hz, 2H), 2.27 (s, 3H), 1.57 (s, 9H).

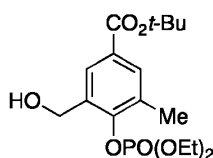
Synthesis of *tert*-butyl 4-((di-*tert*-butoxyphosphoryl)oxy)-3-(hydroxymethyl)-5-methylbenzoate



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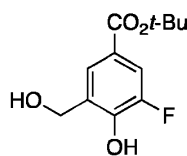
CCl₄ (0.47 mL, 3.36 mmol, 4.0 equiv) was added dropwise to a cooled (−10 °C) flask containing 2-*tert*-butoxyphosphonyloxy-2-methyl-propane (0.17 mL, 0.86 mmol), DIPEA (0.44 mL, 2.52 mmol), and DMAP (0.021 g, 0.17 mmol). The resulting mixture was stirred at this temperature for 30 min before the dropwise addition of a solution of *tert*-butyl 4-hydroxy-3-(hydroxymethyl)-5-methyl-benzoate (0.20 g, 0.84 mmol) in MeCN (2.5 mL). The mixture was allowed to warm to room temperature over 12 h and then quenched with sat. aq. NH₄Cl. The aqueous phase was extracted with CH₂Cl₂, washed with brine, dried (Na₂SO₄) and evaporated to dryness under reduced pressure to give the crude product as a yellow syrup. ¹H NMR (500 MHz, CDCl₃) δ 7.71 – 7.70 (m, 1H), 7.52 (d, *J* = 2.1 Hz, 1H), 4.9 (s, 2H), 2.5 (s, 3H), 1.58 (s, 9H), 1.57 (s, 18H).

Synthesis of *tert*-butyl 4-((diethoxyphosphoryl)oxy)-3-(hydroxymethyl)-5-methylbenzoate



1-[Chloro(ethoxy)phosphoryl]oxyethane (0.07 mL, 0.5 mmol) was added dropwise to a solution of *tert*-butyl 4-hydroxy-3-(hydroxymethyl)-5-methyl-benzoate (100 mg, 0.42 mmol) in DCM (2 mL). The mixture cooled to 0 °C and DIPEA (0.11 mL) was added slowly. The resulting mixture was allowed to stir at room temperature for 12 h and then diluted with EtOAc, washed with water, sat. aq. NH₄Cl solution, brine solution, dried (MgSO₄), and evaporated to dryness under reduced pressure. Chromatography (10–100% EtOAc in hexanes) provided the desired product (16 mg, 10% yield) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.93 (d, *J* = 2.3 Hz, 1H), 7.81 (d, *J* = 2.1 Hz, 1H), 4.63 (s, 2H), 4.33–4.15 (m, 4H), 2.37 (s, 3H), 1.58 (s, 9H), 1.34 (td, *J* = 7.1, 1.2 Hz, 6H).

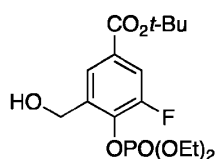
Synthesis of *tert*-butyl 3-fluoro-4-hydroxy-5-(hydroxymethyl)benzoate



Formaldehyde 30% (2.39 mL, 29.45 mmol) was added dropwise to a solution of *tert*-butyl 3-fluoro-4-hydroxy-benzoate (250 mg, 1.18 mmol) in sodium hydroxide (0.98 mL, 2.95

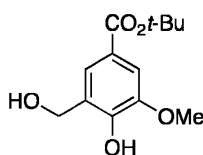
mmol). In water (1 mL). The resulting solution was heated at 60 °C for 12 h, cooled to room temperature and then acidified by the addition of aq. 1M HCl solution. Extraction with EtOAc, washed with brine solution, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (10–50% EtOAc in hexanes) provided the desired product (46 mg, 16%) as colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.76–7.63 (m, 1H), 7.61 (dd, *J* = 2.1, 1.1 Hz, 1H), 4.91 (s, 2H), 1.59 (s, 9H).

Synthesis of *tert*-butyl 4-((diethoxyphosphoryl)oxy)-3-fluoro-5-(hydroxymethyl)benzoate



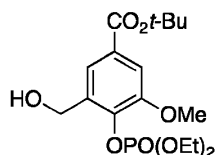
N,N-Diisopropylethylamine (2.9 mL, 16.8 mmol) was added to a solution of *tert*-butyl 3-fluoro-4-hydroxy-5-(hydroxymethyl)benzoate (1.36 g, 5.61 mmol), and diethyl chlorophosphate (1.22 mL, 8.42 mmol) in DCM (18 mL). After stirring at room temperature for 12 h, the solution was extracted into EtOAc, washed with aq. 1N HCl solution, brine, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (10–60% EtOAc in hexanes) provided the desired product (1.05 g, 49%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.90 (t, *J* = 1.9 Hz, 1H), 7.73 (dd, *J* = 10.3, 2.1 Hz, 1H), 4.67 (s, 2H), 4.36–4.16 (m, 4H), 1.58 (s, 9H), 1.38 (td, *J* = 7.0, 1.2 Hz, 6H).

Synthesis of *tert*-butyl 4-hydroxy-3-(hydroxymethyl)-5-methoxybenzoate



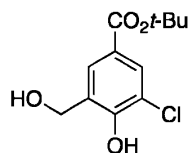
NaBH₄ (66.24 mg, 1.75 mmol) was added portion wise to a solution of *tert*-butyl 4-diethoxyphosphoryloxy-3-formyl-5-methoxybenzoate (680 mg, 1.75 mmol) in THF (8 mL) and cooled to 0 °C. The resulting solution was stirred for 2 h and then treated with a sat'd aq. soln. NH₄Cl solution and extracted with EtOAc. The organic phase was separated, washed with brine, dried (Na₂SO₄) and evaporated to dryness under reduced pressure to provide the desired product (445 mg, 100% yield) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.58 (d, *J* = 1.9 Hz, 1H), 7.48 (d, *J* = 1.9 Hz, 1H), 4.77 (s, 2H), 3.94 (s, 3H), 1.59 (s, 9H). MS (ESI) *m/z* = 253.1 [M–H]⁺.

Synthesis of *tert*-butyl 4-((diethoxyphosphoryl)oxy)-3-(hydroxymethyl)-5-methoxybenzoate



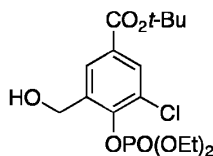
- 5 *Tert*-butyl 4-hydroxy-3-(hydroxymethyl)-5-methoxy-benzoate (500 mg, 1.97 mmol) and 4-DMAP (0.03 mL, 0.2 mmol) were dissolved in acetonitrile (14 mL). The flask was then cooled to 0 °C in an ice water bath before diethyl chlorophosphate (0.37 mL, 2.56 mmol) was added dropwise, followed by *N,N*-diisopropylethylamine (0.69 mL, 3.93 mmol). The flask was then removed from the ice water bath and heated to 50 °C. The reaction
- 10 mixture was then allowed to stir for 2 hours before diluting the mixture with EtOAc (50 mL) and washing with saturated aq. ammonium chloride solution followed by brine, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (20-60% EtOAc and hexanes) to give the desired product (594 mg, 69%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.69 (s, 1H), 7.55 (s, 1H), 4.64 (d, *J* = 5.3 Hz, 2H), 4.30–4.18 (m, 4H),
- 15 3.89 (s, 3H), 1.57 (s, 9H), 1.39–1.30 (m, 6H). MS (ESI) *m/z* = 391.1 [M+H]⁺.

Synthesis of *tert*-butyl 3-chloro-4-hydroxy-5-(hydroxymethyl)benzoate



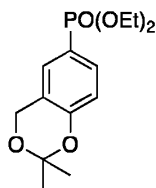
- NaBH₄ (2.06 g, 54.54 mmol) was added portion-wise to a stirred solution of *tert*-butyl
- 20 3-chloro-5-formyl-4-hydroxy-benzoate (14.0 g, 54.54 mmol) in THF (250 mL) cooled to 0°C. The reaction mixture was stirred at 0 °C for about 30 min and the excess borohydride quenched by the addition of sat'd aq. NH₄Cl solution. The organic phase was extracted with EtOAc, dried over sodium sulfate, and then evaporated to dryness under reduced pressure. Chromatography (SiO₂; 20–80 EtOAc in hexanes) provided the title product (8.71 g, 61%) as
- 25 an off-white solid. ¹H NMR 400MHz (DMSO-*d*₆): δ 10.13 (s, 1H), 7.84 (s, 1H), 7.72 (d, *J*=2.0 Hz, 1H), 5.41(s, 1H), 4.54 (s, 2H), 1.52 (s, 9H). MS (ESI) *m/z* = 258 [M+H]⁺.

Synthesis of *tert*-butyl 4-((diethoxyphosphoryl)oxy)-3-chloro-5-(hydroxymethyl)benzoate

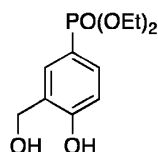


1-[Chloro(ethoxy)phosphoryl]oxyethane (3.96 g, 23.0 mmol) was then added dropwise to a flask containing a mixture of *tert*-butyl 3-chloro-4-hydroxy-5-(hydroxymethyl)benzoate (3.5 g, 13.52 mmol) and *N,N*-diisopropylethylamine (0.2 mL, 1.16 mmol) in DCM (67 mL). The reaction mixture was allowed to stir under an atmosphere of argon at room temperature overnight. Excess chlorophosphate was quenched by the addition of water. The organic phase was extracted with DCM, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (SiO₂; 40–80% EtOAc in hexanes) gave the desired product (as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 8.01 (s, 2H), 4.66 (s, 2H), 4.36–4.19 (m, 4H), 1.59 (s, 9H), 1.36 (td, *J* = 7.0, 1.2 Hz, 6H).

Synthesis of 6-diethoxyphosphoryl-2,2-dimethyl-4H-1,3-benzodioxine

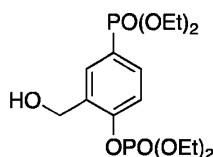


6-Bromo-2,2-dimethyl-4H-1,3-benzodioxine (100 mg, 0.41 mmol) was added to a heat gun-dried flask and purged with nitrogen, followed by THF (2 mL). The resulting solution was cooled to –78 °C and then, 2.5 M *n*-BuLi solution in hexanes (0.18 mL, 0.45 mmol) was added dropwise. Once complete, the reaction was permitted to stir at this temperature for 1 hour. Finally, a solution of diethyl chlorophosphate (0.09 mL, 0.62 mmol) in anhydrous THF (2 mL) was added dropwise. The reaction was warmed to room temperature, quenched by addition of sat'd aq. NH₄Cl solution and extracted with CH₂Cl₂, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (40% EtOAc in hexanes) gave the desired product (0.06 g; 46%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.57 (ddd, 12.8, 8.4, 1.8 Hz, 1H), 7.48 (dd, *J* = 12.8, 1.8, 1H), 6.88 (dd, *J* = 8.4, 3.6 Hz, 1H) 4.86 (s, 2H), 4.02–4.18 (m, 4H), 1.55 (s, 6H), 1.32 (t, *J* = 7.1 Hz, 6H)

Synthesis of 4-diethoxyphosphoryl-2-(hydroxymethyl)phenol

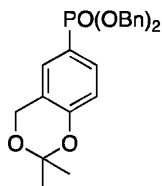
- 6-Diethoxyphosphoryl-2,2-dimethyl-4H-1,3-benzodioxine (1.g, 3.33 mmol) was dissolved in 16 mL of THF and 16 mL of 1 M HCl. The reaction was washed with sat'd aq. NaHCO₃ solution and extracted with EtOAc, dried (MgSO₄) and evaporated to dryness under reduced pressure to give the desired product (0.94 g; 95%) as a colorless oil which was used in the following step without further purification. ¹H NMR (500 MHz, CDCl₃) δ 7.71–7.65 (m, 2H), 7.09 (dd, *J* = 8.2, 3.7), 5.43 (s, 2H), 4.15–4.04 (m, 8H), 1.36–1.31 (m, 2H). LC-MS: *m/z* = 262.1 [M+H]⁺ and 260.9 [M–H]⁺.

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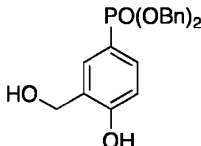
Synthesis of [4-diethoxyphosphoryl-2-(hydroxymethyl)phenyl] diethyl phosphate

- DIPEA (0.09 mL, 0.51 mmol) was added to a cooled (0 °C) solution of 4-diethoxyphosphoryl-2-(hydroxymethyl)phenol (121 mg, 0.46 mmol) in CH₂Cl₂ (2.3 mL). The reaction mixture was left to stir for 10 min. under a nitrogen atmosphere and then diethoxy chlorophosphate (0.07 mL, 0.51 mmol) was added. The reaction was warmed to room temperature over 3 h and then quenched by addition of saturated aq. NaHCO₃ solution, extracted with CH₂Cl₂, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (0–10% MeOH in CH₂Cl₂) provided the desired product (109 mg; 56%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.98 (td, *J* = 13.1, 1.2 Hz, 1H), 7.73 (ddd, *J* = 13.1, 8.3, 2.7 Hz, 1H), 7.35 (ddd, *J* = 8.4, 32.7, 1.8 Hz, 1H), 4.73 (s, 2H), 4.28–4.21 (m, 4H), 4.16–4.04 (m, 4H), 1.37 (td, *J* = 7.1, 1.14, 6H), 1.31 (t, *J* = 7.1 Hz, 6H).

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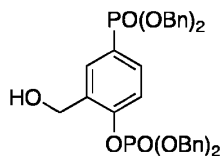
Synthesis of 6-dibenzyloxyphosphoryl-2,2-dimethyl-4H-1,3-benzodioxine

- A mixture of 6-bromo-2,2-dimethyl-4H-1,3-benzodioxine (100 mg, 0.41 mmol), tetrakis(triphenylphosphine)palladium (47 mg, 0.04 mmol) and
- 5 benzyloxyposphonoyloxymethylbenzene (0.1 mL, 0.41 mmol) and triethylamine (0.07 mL, 0.49 mmol) in anhydrous THF (2 mL) was heated in a microwave reactor for 10 min at 120 °C. The reaction was filtered, washing with DCM and evaporated to dryness under reduced pressure. Chromatography (10–50% EtOAc in hexanes) provided 6-dibenzyloxyphosphoryl-2,2-dimethyl-4H-1,3-benzodioxine (84 mg, 48 % yield) as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.60 (ddd, *J* = 12.9, 8.4, 1.9 Hz, 1H), 7.43 (dd, *J* = 13.6, 1.8 Hz, 1H), 7.34 (d, *J* = 3.6 Hz, 10H), 6.87 (dd, *J* = 8.4, 3.8 Hz, 1H), 5.14–5.02 (m, 4H), 4.82 (s, 2H), 1.56 (s, 6H). LRMS (ESI+) *m/z* calcd for C₂₄H₂₅O₅P [M + H]⁺ 424.23, found 425.1 [M + H]⁺.
- 10

Synthesis of dibenzyl (4-hydroxy-3-(hydroxymethyl)phenyl)phosphonate

- 15 6-Dibenzyloxyphosphoryl-2,2-dimethyl-4H-1,3-benzodioxine (408 mg, 0.96 mmol) was dissolved in acetone (1 mL) and 1M aq. HCl solution (1 mL). The mixture was left to stir at room temperature for 24 h and then diluted with EtOAc, dried (MgSO₄), and evaporated to dryness under reduced pressure to give the desired product (330 mg, 80%) as a white solid.
- 20 ¹H NMR 400MHz (DMSO-*d*₆): δ 10.28 (s, 1H), 7.77 (d, *J* = 13.2Hz, 1H), 7.49–7.45 (m, 1H), 7.35–7.32 (m, 10H), 6.90–6.88 (m, 1H), 5.16 (t, *J* = 5.2Hz, 1H), 5.01–4.94 (m, 4H) and 4.48 (d, *J* = 5.2Hz, 2H).

Synthesis of dibenzyl (4-(bis(benzyloxy)phosphoryl)-2-(hydroxymethyl)phenyl) phosphate

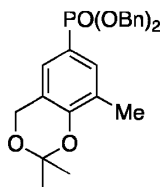


4-Dibenzoyloxyphosphoryl-2-(hydroxymethyl)phenol (0.33 g, 0.86 mmol) was dissolved in 1.7 mL of MeCN (2 mL) and carbon tetrachloride (0.33 mL, 3.43 mmol) before the addition of benzyloxyphosphonoyloxymethylbenzene (0.23 mL, 1.03 mmol), *N,N*-diisopropylethylamine (0.45 mL, 2.58 mmol), and DMAP (20 mg, 0.17 mmol) at 0 °C. After 2 hours, the reaction was diluted with DCM, washed with brine, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (0–10% MeOH in DCM) provided the desired product (0.310 g, 53%) as a colorless oil. ¹H NMR (500 MHz, MeOD) δ 7.90 (dt, *J* = 13.6, 1.6 Hz, 1H), 7.60 (ddd, *J* = 13.2, 8.3, 2.0 Hz, 1H), 7.35–7.30 (m, 21 H), 5.48 (s, 4H), 5.16 (d, *J* = 9.5 Hz, 2H), 5.09–5.03 (m, 4H).

Synthesis of 6-substituted [4-diethoxyphosphoryl-2-(hydroxymethyl)phenyl] diethyl phosphates

Prepared according to the synthetic procedure for the synthesis of [4-diethoxyphosphoryl-2-(hydroxymethyl)phenyl] diethyl phosphate.

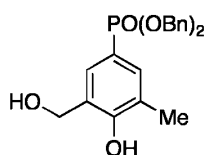
Synthesis of 6-dibenzoyloxyphosphoryl-2,2,8-trimethyl-4H-1,3-benzodioxine



6-Bromo-2,2,8-trimethyl-4H-1,3-benzodioxine (0.259 g, 1.01 mmol, 1.0 equiv.) was azeotroped with toluene until a viscous oil was obtained. The residue was dissolved in anhydrous THF (4 mL), and then cooled to –78 °C under an atmosphere of nitrogen. A solution of 2.8 M *n*-butyl lithium (0.41 mL, 1.1 mmol) was added dropwise over 1 min and then left to stir at –78 °C for 1 h. Then a solution of anhydrous [benzyloxy(chloro)phosphoryl]oxymethylbenzene (0.366 g, 1.23 mmol) in THF (1 mL) was added dropwise over 4 min. After stirring for an additional 2 h, the excess base was quenched

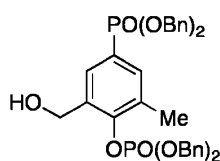
with an ice-cold saturated aqueous NaHCO_3 solution (5 mL). The biphasic mixture was extracted into EtOAc, dried (Na_2SO_4) and evaporated to dryness under reduced pressure. Chromatography (25 g SiO_2 , 30–100% EtOAc in hexanes) to obtain the desired product (82 mg, 18%) as a yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.43 (d, $J = 13.3$ Hz, 1H), 7.35–7.29 (m, 10H), 7.25 (d, $J = 13.7$ Hz, 1H), 5.05 (dd, $J = 11.9, 7.8$ Hz, 4H), 4.79 (s, 2H), 2.15 (s, 3H), 1.54 (s, 6H). ^{31}P NMR (202 MHz, CDCl_3) δ 21.11 (u, $J = 13.9, 7.5$ Hz).

Synthesis of dibenzyl (4-hydroxy-3-(hydroxymethyl)-5-methylphenyl)phosphonate



1M aqueous HCl (10 mL, 10 mmol) was added to a stirring solution of 6-dibenzylphosphoryl-2,2,8-trimethyl-4H-1,3-benzodioxine (1.46 g, 3.35 mmol) in acetone (40 mL) and left to stir at room temperature for 15 hours and then evaporated under reduced pressure to remove the acetone. The remaining aqueous phase was extracted with DCM, dried (MgSO_4) and evaporated to dryness under reduced pressure. Chromatography (25 g SiO_2 , 0–10% methanol/EtOAc) provided the desired product (0.237 g, 14%) as a yellow solid. ^1H NMR (500 MHz, DMSO) δ 9.22 (s, 1H), 7.56 (d, $J = 13.3$ Hz, 1H), 7.40 – 7.29 (m, 11H), 5.36 (s, 1H), 4.98 (dd, $J = 12.1, 8.1$ Hz, 4H), 4.56 (s, 2H), 2.18 (s, 3H). ^{31}P NMR (202 MHz, DMSO) δ 21.15 (dq, $J = 14.2, 6.9$ Hz). LCMS (SQ) $m/z = 399.2$ [$\text{M} + \text{H}$]

20 Synthesis of dibenzyl (4-(bis(benzyloxy)phosphoryl)-2-(hydroxymethyl)-6-methylphenyl) phosphate

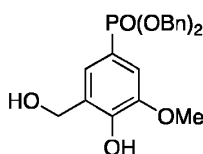


In a round bottom flask containing CCl_4 (0.49 mL, 5.02 mmol), 4-DMAP (0.03 mL, 0.25 mmol), cooled to 5 °C by ice/water, was added 4-dibenzylphosphoryl-2-(hydroxymethyl)-6-methyl-phenol (500 mg, 1.26 mmol) followed by *N,N*-diisopropylethylamine (0.66 mL, 3.77 mmol). After stirring for 5 minutes, a solution of benzyloxyposphonoyloxymethylbenzene (0.36 mL, 1.63 mmol) in MeCN (4.2 mL) was added dropwise over 5 min. The resulting mixture was stirred at room temperature for 16 h

and then diluted with EtOAc, washed with 1 M aqueous HCl solution, brine, dried (MgSO₄), and evaporated to dryness under reduced pressure. Chromatography (0–10 % MeOH in DCM) provided the desired product (105 mg, 11%) as a yellow oil.

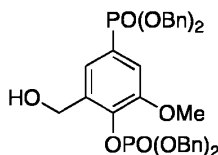
¹H NMR (500 MHz, CDCl₃) δ 7.45–7.22 (m, 22H), 5.12–4.97 (m, 4H), 4.93–4.88 (m, 2H), 4.79 (s, 2H), 4.70 (s, 2H), 2.15 (d, *J* = 0.8 Hz, 3H).

Synthesis of dibenzyl (4-hydroxy-3-(hydroxymethyl)-5-methoxyphenyl)phosphonate



1M aqueous HCl solution (40 mL) was added to a solution of 6-dibenzylphosphoryl-8-methoxy-2,2-dimethyl-4H-1,3-benzodioxine (2.3 g, 5.06 mmol) dissolved in acetone (40 mL). After stirring at room temperature for 12 h, the reaction mixture was evaporated under reduced pressure to remove acetone. Extraction of the aqueous phase with EtOAc (250 ml) followed by washing with brine solution, dried (Na₂SO₄) and evaporated to dryness under reduced pressure gave the desired product (2.1 g, 100%) as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.36 – 7.28 (m, 10H), 7.18 (dt, *J* = 14.4, 1.8 Hz, 1H), 5.08 (dd, *J* = 11.8, 7.8 Hz, 2H), 5.01 (dd, *J* = 11.8, 8.1 Hz, 2H), 4.72 (s, 2H), 3.83 (d, *J* = 1.7 Hz, 3H). MS (ESI) *m/z* = 415.1 [M+H]⁺.

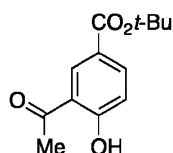
Synthesis of dibenzyl (4-(bis(benzyloxy)phosphoryl)-2-(hydroxymethyl)-6-methoxyphenyl) phosphate



A solution of 4-dibenzylphosphoryl-2-(hydroxymethyl)-6-methoxy-phenol (1.87 g, 4.51 mmol) in MeCN (18 mL) was added dropwise to a cooled (5 °C) solution of CCl₄ (1.75 mL, 18.05 mmol), dibenzyl phosphonate (1.3 mL, 5.87 mmol) and DIPEA (2.35 mL, 13.54 mmol). The reaction mixture was stirred at room temperature for 12 h and then extracted into EtOAc, washed with 1M aq. HCl solution, brine, dried (Na₂SO₄) and evaporated to dryness under reduced pressure. Chromatography (50–100% EtOAc in hexanes) provided the desired product (312 mg, 10%) as a yellow oil. ¹H NMR (500 MHz,

CDCl₃) δ 7.46 (dd, J = 13.6, 1.7 Hz, 1H), 7.36–7.27 (m, 20H), 7.22–7.15 (m, 1H), 5.16 (dt, J = 8.1, 3.7 Hz, 4H), 5.12–5.03 (m, 4H), 4.59 (d, J = 4.0 Hz, 2H), 3.63 (s, 3H). MS (ESI) m/z = 675.2 [M+H]⁺

Synthesis of *tert*-butyl 3-acetyl-4-hydroxy-benzoate

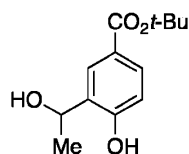


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DCC (601 mg, 2.91 mmol) in THF (34 mL) was added to a mixture of 3-acetyl-4-hydroxy-benzoic acid (500 mg, 2.78 mmol), *tert*-butanol (34 mL) and 4-dimethylaminopyridine (138 mg, 1.13 mmol) in THF and left to stir at room temperature for 12 h. The resulting mixture was filtered and evaporated to dryness under reduced pressure.

10 Chromatography (2–20% EtOAc in hexanes) provided the desired product (352 mg; 53%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 12.62 (s, 1H), 8.44 (d, J = 2.1 Hz, 1H), 8.07 (dd, J = 8.8, 2.1 Hz, 1H), 6.98 (d, J = 8.7 Hz, 1H), 2.69 (s, 3H) and 1.60 (s, 9H).

Synthesis of *tert*-butyl 4-hydroxy-3-(1-hydroxyethyl)benzoate

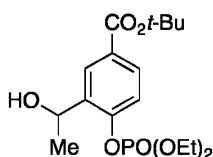


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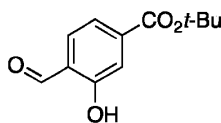
Sodium borohydride (1.97 g, 52.03 mmol) was slowly added to a solution of *tert*-butyl 3-acetyl-4-hydroxy-benzoate (2.46 g, 10.41 mmol) in THF (52 mL). The resulting mixture was heated at 80 °C for 3 hours, cooled and then evaporated to dryness under reduced pressure. The residue was dissolved in water, acidified with 4N HCl solution and then

20 extracted into EtOAc, washed with brine, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (20%–60% EtOAc in hexanes) provide the desired product (1.76 g; 70%) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 8.52 (s, 1H), 7.81 (dd, J = 8.4, 2.1 Hz, 1H), 7.64 (dd, J = 2.1, 0.6 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 5.14 (qd, J = 6.6, 3.6 Hz, 1H), 2.54 (d, J = 3.9 Hz, 1H), 1.61 (d, J = 6.6 Hz, 3H), 1.57 (s, 9H).

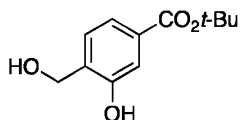
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Synthesis tert-butyl 4-diethoxyphosphoryloxy-3-(1-hydroxyethyl)benzoate

Triethylamine (0.32 mL, 2.28 mmol) was added to a stirred mixture of *tert*-butyl 4-hydroxy-3-(1-hydroxyethyl)benzoate (181 mg, 0.76 mmol) and diethyl chlorophosphate (1.2 mL, 6.61 mmol) in CH₂Cl₂ (2.5 mL). The reaction was left to stir at room temperature for 12 h and then diluted with EtOAc and washed with aq. 1M HCl solution, brine solution, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (40–80% EtOAc in hexanes) provided the desired product (2.76 g, 48%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 8.20 (dd, *J* = 2.2, 1.2 Hz, 1H), 7.88 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.33–7.24 (m, 1H), 5.24 (q, *J* = 6.5 Hz, 1H), 4.33–4.14 (m, 4H), 1.59 (s, 9H), 1.53 (d, *J* = 6.5 Hz, 3H), 1.38 (td, *J* = 7.1, 1.1 Hz, 3H), 1.34 (td, *J* = 7.1, 1.1 Hz, 3H).

Synthesis of tert-butyl 3-formyl-4-(hydroxymethyl)benzoate

A mixture of 4-formyl-3-hydroxy-benzoic acid (3.0 g, 18.06 mmol) and 1,1-di-*tert*-butoxy-*N,N*-dimethyl-methanamine (13.89 mL, 60.19 mmol) in DMF (5 mL) was heated in a microwave at 120 °C for 2 h and left to stir at room temp for 72 h. The resulting mixture was filtered and evaporated to dryness under reduced pressure. Chromatography (5–50% EtOAc in hexanes) provided the desired product (1.98 g; 49%) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 10.94 (s, 2H), 9.98 (s, 2H), 7.64–7.46 (m, 3H), 1.60 (s, 11H).

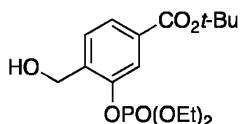
Synthesis of tert-butyl 3-hydroxy-4-(hydroxymethyl)benzoate

Sodium borohydride (206 mg, 5.44 mmol) was added to a solution of *tert*-butyl 4-formyl-3-hydroxy-benzoate (1.21 g, 5.44 mmol) in THF (20 mL) and then heated at 70 °C for 2h. The cooled reaction mixture was evaporated to dryness under reduced pressure, diluted with water and acidified with 4N HCl solution, extracted with EtOAc, washed with brine,

dried (MgSO_4) and evaporated to dryness under reduced pressure. Chromatography (5–50% EtOAc in hexanes) provided the title product (1.1 g; 90%) as a white solid. ^1H NMR (500 MHz, CDCl_3) δ 7.48 (d, J = 7.5 Hz, 2H), 7.41 (s, 1H), 7.08 (d, J = 7.6 Hz, 1H), 4.92 (d, J = 5.5 Hz, 2H), 2.31 (t, J = 5.7 Hz, 1H), 1.58 (s, 9H).

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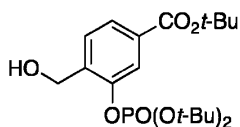
Synthesis of *tert*-butyl 3-diethoxyphosphoryloxy-4-(hydroxymethyl)benzoate



Diethyl chlorophosphate (1.4 mL, 9.7 mmol) was added to a solution of *tert*-butyl 3-hydroxy-4-(hydroxymethyl)benzoate (1.1 g, 4.9 mmol) and DIPEA (2.5 mL, 14.6 mmol) in CH_2Cl_2 (24 mL) at 0 °C. The reaction was allowed to warm up to room temperature and stirred for 15 hours and then quenched by water, extracted into CH_2Cl_2 and evaporated to dryness under reduced pressure. Chromatography (10–50% EtOAc in hexanes) provided the desired product (2.77 g; 88%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.83 (dd, J = 8.0, 1.4 Hz, 1H), 7.79 (t, J = 1.5 Hz, 1H), 7.53 (dd, J = 8.0, 0.9 Hz, 1H), 4.70 (d, J = 6.2 Hz, 2H), 4.28–4.23 (m, 4H), 1.59 (s, 9H) and 1.38 (m, J = 7.1, 1.2 Hz, 6H).

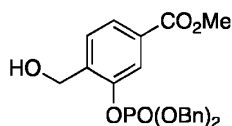
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Synthesis of *tert*-butyl 3-di-*tert*-butoxyphosphoryloxy-4-(hydroxymethyl)benzoate

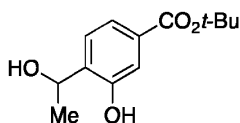


Di-*tert*-butoxyphosphine (1.0 mL; 4.95 mmol) was added to a cooled (5 °C) solution of *tert*-butyl 3-hydroxy-4-(hydroxymethyl)benzoate (1.11 g; 4.95 mmol), DIPEA (2.53 mL; 14.58 mmol) and carbon tetrabromide (8.21 g; 24.75 mmol) and DMAP (100 mg; 0.81 mmol) in CH_3CN (25 mL). After 2 h, the reaction mixture was quenched with water and extracted into EtOAc. The organic phase was washed with brine, dried (MgSO_4) and evaporated to dryness under reduced pressure. Chromatography (5–50% EtOAc in hexanes) provide the desired product (0.69 g; 33%) as a colorless solid. ^1H NMR (500 MHz, CDCl_3) δ 7.82 (dd, J = 7.6, 1.4 Hz, 2H), 7.51–7.45 (m, 1H), 4.65 (s, 2H), 1.59 (s, 9H) and 1.53 (s, 18H).

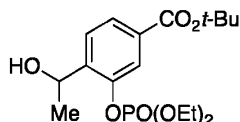
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Synthesis of methyl 3-dibenzyloxyposphoryloxy-4-(hydroxymethyl)benzoate

Benzyloxyposphonoyloxymethylbenzene;methane (513 mg, 1.84 mmol), carbon tetrabromide (3.06 g, 9.22 mmol), and DIPEA (0.96 mL, 5.53 mmol) were added to a cooled (0 °C) solution of methyl 3-hydroxy-4-(hydroxymethyl)benzoate (336 mg, 1.84 mmol) was dissolved in acetonitrile (10 mL). The reaction was stirred at 0 °C for 12 h and then diluted with EtOAc and quenched with 1M HCl solution. The organic phase was separated, washed with brine, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (10–50% EtOAc in hexanes) provided the desired product (0.304 g; 37%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.86 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.76 (d, *J* = 1.6 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.37–7.28 (m, 10H), 5.13 (dd, *J* = 8.9, 1.8 Hz, 4H), 4.61 (s, 2H), 3.89 (s, 3H).

Synthesis of *tert*-butyl 3-hydroxy-4-(1-hydroxyethyl)benzoate

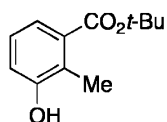
Bromo(methyl)magnesium (9.26 mL, 27.81 mmol) solution in THF was slowly added to a cooled (0 °C) solution of *tert*-butyl 4-formyl-3-hydroxy-benzoate (3.09 g, 13.90 mmol) in THF (13.5 mL) and Et₂O (13.5 mL). The reaction was stirred for 12 h and then quenched by the addition of sat'd aq. NH₄Cl solution and extracted with EtOAc. The organic phase was separated, washed with brine solution, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (10–80% EtOAc in hexanes) provided the desired product (0.77 g, 23%) as a colorless oil. ¹H NMR (500 MHz, DMSO) δ 7.44 (d, *J* = 8.4 Hz, 1H), 7.38–7.32 (m, 2H), 4.99 (q, *J* = 6.4 Hz, 1H), 1.52 (s, 9H), 1.27 (d, *J* = 6.3 Hz, 3H).

Synthesis of *tert*-butyl 4-diethoxyphosphoryloxy-3-(1-hydroxyethyl)benzoate

Diethyl chlorophosphate (1.41 mL, 9.73 mmol) was added to a solution of *tert*-butyl 3-hydroxy-4-(hydroxymethyl)benzoate (1.09 g, 4.87 mmol) and DIPEA (2.54 mL, 14.60 mmol) in DCM (24 mL) cooled by an ice-bath. The reaction was left to stir for 15 h, and then quenched by the addition of water. The organic phase was extracted with further DCM, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (10–60% EtOAc in hexanes) gave the desired product (864 mg, 71%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.87–7.78 (m, 2H), 7.60 (dd, *J* = 8.1, 1.0 Hz, 1H), 5.26 (q, *J* = 6.6 Hz, 1H), 4.35–4.08 (m, 4H), 1.58 (s, 9H), 1.52 (d, *J* = 6.5 Hz, 3H), 1.39 (dtd, *J* = 29.0, 7.0, 1.1 Hz, 6H).

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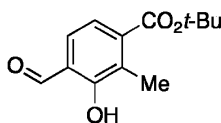
Synthesis of *tert*-butyl 3-hydroxy-2-methyl-benzoate



1,1-Di-*tert*-butoxy-N,N-dimethyl-methanamine (59.6 mL, 262.9 mmol) was added dropwise, via addition funnel, to a mixture of 3-hydroxy-2-methyl benzoic acid (10 g; 65.72 mmol) in toluene (130 mL) heated to 100 °C. The reaction was allowed to stir for another 15 minutes, cooled to room temperature and then quenched with water and extracted into EtOAc. The organic phase was washed with water, brine, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (0–40% EtOAc in hexanes) provided the desired product (6.5 g, 47%) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.32 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 6.89 (dd, *J* = 8.0, 1.2 Hz, 1H), 2.42 (s, 3H), 1.59 (s, 9H).

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Synthesis of *tert*-butyl-formyl-3-hydroxy-2-methylbenzoate



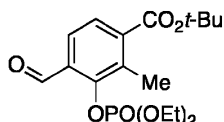
A solution of *tert*-butyl 3-hydroxy-2-methyl-benzoate (6.5 g, 31.21 mmol) in THF (20 mL) was added dropwise to a mixture of MgCl₂ (5.94 g, 62.42 mmol), paraformaldehyde (2.8 g, 93.63 mmol), Et₃N (8.7 mL, 62.42 mmol) and THF (84 mL). The resulting mixture was heated at 65°C for 12 h, cooled to room temperature and diluted with EtOAc (150 mL), washed with aqueous 1M HCl solution, then water and brine solution. The organic phase was

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dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (10–40% EtOAc in hexanes) afforded the desired product (5.1 g, 69%) as off-white crystals. ¹H NMR (500 MHz, CDCl₃) δ 11.39 (s, 1H), 9.91 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 2.40 (s, 3H), 1.61 (s, 9H).

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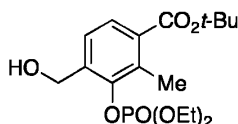
Synthesis of *tert*-butyl 3-diethoxyphosphoryloxy-4-formyl-2-methyl-benzoate



DIPEA (7.5 mL, 43.17 mmol) was added to a solution of *tert*-butyl-formyl-3-hydroxy-2-methylbenzoate (5.1 g, 21.58 mmol) DCM (108 mL) cooled to 0° C. Diethyl phosphochloridate (3.8 mL, 25.90 mmol) was added dropwise and the reaction mixture was allowed to stir for 72 hours. The reaction mixture was washed with water, sat'd aq. NH₄Cl solution, and brine, then the organic phase was dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (10–80% EtOAc in hexanes) provided the desired product (5.89 g, 73%) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 10.37 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 4.30–4.14 (m, 4H), 2.56 (s, 3H), 1.60 (s, 9H), 1.33 (td, *J* = 7.1, 1.1 Hz, 6H).

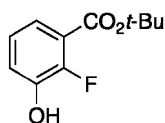
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Synthesis of *tert*-butyl 3-diethoxyphosphoryloxy-4-(hydroxymethyl)-2-methyl-benzoate

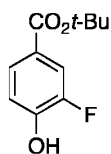


NaBH₄ (513 mg, 13.56 mmol) was added to a solution of *tert*-butyl 3-diethoxyphosphoryloxy-4-formyl-2-methyl-benzoate (5.05 g, 13.56 mmol) in EtOH (27 mL). After 15 minutes, the reaction was quenched with sat'd aq. NH₄Cl solution and extracted in EtOAc, the organic phase was washed with water, dried (MgSO₄) and evaporated to dryness under reduced pressure to afford the desired product (4.90 g, 96%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.61 (d, *J* = 7.9, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 4.61 (s, 2H), 4.30–4.15 (m, 4H), 2.49 (s, 3H), 1.59 (s, 9H), 1.34 (td, *J* = 7.1, 1.2 Hz, 6H).

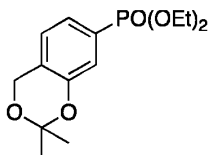
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Synthesis of *tert*-butyl 3-hydroxy-2-fluoro-benzoate

- 1,1-Di-*tert*-butoxy-*N,N*-dimethyl-methanamine (0.61 mL, 2.56 mmol) was added drop-wise via syringe to a suspension of 2-fluoro-3-hydroxybenzoic acid (100 mg, 0.64 mmol) in toluene (3.84 mL) heated at 90 °C and under an atmosphere of argon. The mixture was then stirred at 90 °C for another 45 minutes, cooled to room temperature and quenched by the addition of water. The organic phase was extracted into EtOAc, washed with brine solution, dried (Na₂SO₄) and evaporated to dryness under reduced pressure. Chromatography (0–40% EtOAc in hexanes) provided the desired product (53 mg, 39%) as an off-white solid.
- ¹H NMR (500 MHz, CDCl₃) δ 7.37 (ddd, *J* = 8.1, 6.5, 1.8 Hz, 1H), 7.15 (td, *J* = 7.9, 1.8 Hz, 1H), 7.04 (td, *J* = 8.0, 1.3 Hz, 1H), 1.59 (s, 9H).

Synthesis of *tert*-butyl 3-fluoro-4-hydroxy-benzoate

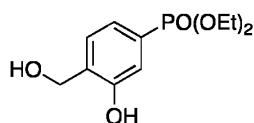
- 1,1-Di-*tert*-butoxy-*N,N*-dimethyl-methanamine (5.81 mL, 25.62 mmol) was slowly added to a heated (90 °C) mixture of 3-fluoro-4-hydroxy-benzoic acid (2.0 g, 12.81 mmol) in toluene (25.62 mL). Heating continued for 4 h and then cooled to room temperature and evaporated to dryness under reduced pressure. Chromatography (0–20% EtOAc in hexanes) provided the desired product (0.27 g, 9%) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.83–7.65 (m, 2H), 7.03 (t, *J* = 8.6 Hz, 1H), 1.60 (s, 9H).

Synthesis of 7-di-ethoxyphosphoryl-2,2-dimethyl-4H-1,3-benzodioxine

- n*-BuLi solution (2.5 M in hexanes, 2.15 mL) was added to a cooled (–78 °C) solution of 7-bromo-2,2-dimethyl-4H-1,3-benzodioxine (1.18 g, 4.88 mmol) in THF (24 mL). The mixture was stirred at –78 °C for 1.5 h before the dropwise addition of a solution of diethoxy

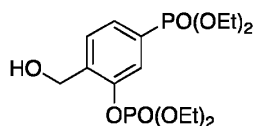
- chlorophosphonate (1.26 g, 7.32 mmol) in THF (3.0 mL). The reaction mixture was allowed to warm to room temperature over 2 h and then quenched by the addition of sat. aq. NH_4Cl solution. The mixture was diluted with water and extracted into diethyl ether, dried (Na_2SO_4) and evaporated to dryness under reduced pressure. Chromatography (30% EtOAc in hexanes) provided the desired product (1.08 g; 73%) as a colorless oil. ^1H NMR (CDCl_3 , 500 MHz) δ 7.57 (ddd, $J = 12.4, 8.4, 3.2$, 1H), 7.48 (dd, $J = 13.3, 3.0$, 1H), 6.88 (dt, $J = 8.4, 3.3$ Hz, 1H), 4.86 (s, 2H), 4.15–4.05 (m, 4H), 1.55 (s, 6H), 1.33–1.30 (m, 6H).

Synthesis of 5-diethoxyphosphoryl-2-(hydroxymethyl)phenol



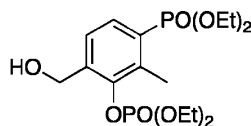
- A mixture of 4-methylbenzenesulfonate;pyridin-1-ium (256 mg, 1.03 mmol) and 7-diethoxyphosphoryl-2,2-dimethyl-4H-1,3-benzodioxine (3.09 g, 10.29 mmol) in MeCN - H_2O (4:1, 248 mL) was stirred at 60 °C overnight. The mixture was quenched with sat. aq. NaHCO_3 . And extracted into EtOAc, washed with brine, dried (Na_2SO_4) and evaporated to dryness under reduced pressure. Chromatography (10% MeOH in EtOAc) afforded the desired product (1.96 g, 73% yield) as a pale-yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.50 (ddd, $J = 13.0, 8.3, 2.0$ Hz, 1H), 7.40 (dd, $J = 13.2, 1.9$ Hz, 1H), 6.93 (dd, $J = 8.3, 3.8$ Hz, 1H), 4.78 (s, 2H), 4.06–3.93 (m, 4H), 1.28 (t, $J = 7.1$ Hz, 6H).

Synthesis of [5-diethoxyphosphoryl-2-(hydroxymethyl)phenyl] diethyl phosphate



- 1-[chloro(ethoxy)phosphoryl]oxyethane (6.7 mL, 46.115 mmol) dropwise was slowly added to a cooled (0 °C) solution of 5-diethoxyphosphoryl-2-(hydroxymethyl)phenol (6.00 g, 23.057 mmol) and DIPEA (12.0 mL, 69.172 mmol) in CH_2Cl_2 (115 mL) under argon. The reaction mixture was stirred for 12 h and then quenched by the addition of water. The organic phase was extracted, dried (Na_2SO_4) and evaporated to dryness under reduced pressure. Chromatography (0–10% MeOH in CH_2Cl_2) provide the desired product as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.67–7.61 (m, 1H), 7.60–7.57 (m, 2H), 4.69 (s, 2H), 4.27–4.20 (m, 4H), 4.15–4.06 (m, 4H), 1.38–1.34 (m, 6H), 1.33–1.27 (m, 6H).

Synthesis of [5-diethoxyphosphoryl-2-(hydroxymethyl)-6-methyl-phenyl] diethyl phosphate

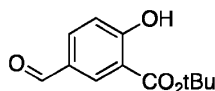


- 5 Experimental procedure as [5-diethoxyphosphoryl-2-(hydroxymethyl)phenyl] diethyl phosphate but starting with 6-methyl derivative.

¹H NMR (500 MHz, MeOD) δ 7.77 (ddd, J = 13.9, 8.0, 1.3 Hz, 1H), 7.56 (dd, J = 8.0, 5.0 Hz, 1H), 4.80 (s, 2H), 4.24 (hept, J = 7.2 Hz, 4H), 4.17–4.09 (m, 4H), 2.55 (s, 3H), 1.36–1.31 (m, 12H).

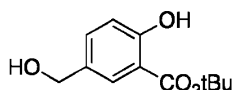
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Synthesis of *tert*-butyl 5-formyl-2-hydroxy-benzoate



- A mixture of 5-formyl-2-hydroxy-benzoic acid (3.5 g, 21.07 mmol) and 1,1-di-*tert*-butoxy-*N,N*-dimethyl-methanamine (10.1 mL, 42.14 mmol) was heated at 100 °C in a microwave for 4h. The resulting mixture was filtered and evaporated to dryness under reduced pressure. Chromatography (2–20% EtOAc in hexanes) provided the desired product (1.35 g; 28%) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 11.71 (s, 1H), 9.88 (s, 1H), 8.30 (d, J = 2.1 Hz, 1H), 7.97 (dd, J = 8.6, 2.1 Hz, 1H), 7.07 (d, J = 8.6 Hz, 1H), 1.65 (s, 9H).
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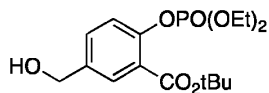
- 20 **Synthesis of *tert*-butyl 2-hydroxy-5-(hydroxymethyl)benzoate**



- Sodium borohydride (0.82 g; 21.8 mmol) was slowly added to a stirred solution of *tert*-butyl 5-formyl-2-hydroxy-benzoate (2.42 g; 10.9 mmol) THF (20 mL). The resulting mixture was stirred at 70 °C for 1h, cooled to room temperature and then evaporated to dryness under reduced pressure. The residue was dissolved in water, acidified with 2N HCl and extracted into EtOAc. The organic phase was separated, washed with brine, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (2–20% EtOAc
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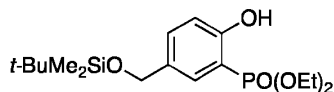
in hexanes). ^1H NMR (500 MHz, CDCl_3) δ 11.04 (s, 1H), 7.77 (d, $J = 2.3$ Hz, 1H), 7.43 (dd, $J = 8.5, 2.3$ Hz, 1H), 6.95 (d, $J = 8.5$ Hz, 1H), 4.61 (s, 2H), 1.62 (s, 9H).

Synthesis of *tert*-butyl 2-diethoxyphosphoryloxy-5-(hydroxymethyl)benzoate



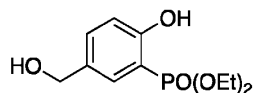
DIPEA (1.31 mL, 7.53 mmol) was added to a stirred solution of *tert*-butyl 2-hydroxy-5-(hydroxymethyl)benzoate (844 mg, 3.76 mmol) and diethyl chlorophosphate (0.82 mL, 4.52 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred under argon for 12 h and then quenched with water. The organic phase was separated, washed with 1N HCl solution, brine, dried (MgSO_4) and evaporated to dryness under reduced pressure. Chromatography (5–50% EtOAc in hexanes) have the desired product (0.901 g; 30%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.73 (dd, $J = 2.2, 1.1$ Hz, 1H), 7.58–7.31 (m, 2H), 4.68 (s, 2H), 4.38 – 4.16 (m, 4H), 1.59 (s, 9H), 1.34 (td, $J = 7.1, 1.1$ Hz, 6H).

Synthesis of 4-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2-diethoxyphosphoryl-phenol



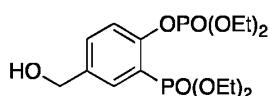
$n\text{-BuLi}$ [2.5M in hexanes (5.47 mL, 13.68 mmol)] was added dropwise to a solution of [2-bromo-4-[[*tert*-butyl(dimethyl)silyl]oxymethyl]phenyl] diethyl phosphate (4.77 g, 10.52 mmol) in THF (35 mL) cooled to -78°C under argon. The resulting mixture was allowed to warm to room temperature over 12 h and then quenched with 1N HCl solution and extracted into EtOAc. The organic phase was washed with brine, dried (MgSO_4) and evaporated to dryness under reduced pressure. Chromatography (2–20% EtOAc in hexanes) provided the desired product (2.57 g; 65%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 10.06 (d, $J = 1.0$ Hz, 1H), 7.33–7.27 (m, 1H), 7.27–7.21 (m, 1H), 6.85 (dd, $J = 8.5, 6.7$ Hz, 1H), 4.56 (d, $J = 0.8$ Hz, 2H), 4.13–4.00 (m, 2H), 3.95 (ddq, $J = 10.1, 8.1, 7.0$ Hz, 2H), 1.24 (td, $J = 7.0, 0.6$ Hz, 6H), 0.84 (s, 9H) 0.02 (s, 3H) and 0.01 (s, 3H).

Synthesis of 2-diethoxyphosphoryl-4-(hydroxymethyl)phenol



Tetrabutylammonium fluoride (2.29 mL, 6.86 mmol) was added to a stirred solution of 4-[[tert-butyl(dimethyl)silyl]oxymethyl]-2-diethoxyphosphoryl-phenol (2.57 g, 6.86 mmol) in THF (17 mL). The reaction mixture was left to stir for 12 h and then evaporated to dryness under reduced pressure. Chromatography (30–80% EtOAc in hexanes) provided the desired product (1.18 g; 66%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 10.23 (s, 1H), 7.45 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.37 (dd, *J* = 14.6, 2.2 Hz, 1H), 6.96 (dd, *J* = 8.6, 6.6 Hz, 1H), 4.62 (d, *J* = 3.9 Hz, 2H), 4.23–4.00 (m, 4H) and 1.33 (t, *J* = 7.0 Hz, 6H).

Synthesis of [2-diethoxyphosphoryl-4-(hydroxymethyl)phenyl] diethyl phosphate

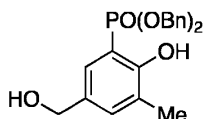


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Triethylamine (1.9 mL, 13.6 mmol) was added to a stirred solution of 2-diethoxyphosphoryl-4-(hydroxymethyl)phenol (1.18 g, 4.53 mmol) and diethyl chlorophosphate (0.98 mL, 6.8 mmol) in CH₂Cl₂ (15 mL). The resulting mixture was allowed to stir at room temperature for 16 h, diluted with EtOAc, washed with sat'd aq. Na₂HCO₃ solution, 1M HCl solution, brine, dried (MgSO₄) and evaporated to dryness. Chromatography (50% EtOAc in hexanes) provided the desired product as a colorless oil. LCMS *m/z* = 397.1 [M+H]⁺

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Synthesis of dibenzyl (2-hydroxy-5-(hydroxymethyl)-3-methylphenyl)phosphonate

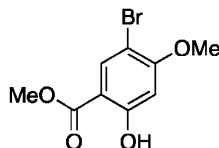


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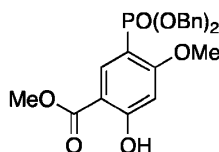
To a stirred solution of ethyl 3-dibenzylphosphoryl-4-hydroxy-5-methyl-benzoate (1.8 g, 4.09 mmol) in dichloromethane (40 mL) cooled –40 °C was added DIBAL-H in 1M THF (19.4 mL). The resulting mixture was allowed to warm to room temperature over 5 h and the excess base quenched by the addition of saturated aqueous NH₄Cl solution, filtered through celite[®] and the organic phase extracted into EtOAc, dried (Na₂SO₄) and evaporated to dryness under reduced pressure. Chromatography (SiO₂; EtOAc in hexanes) gave the desired product (640 mg, 39%) as pale-yellow gum. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.04 (s, 1H), 7.36–7.24 (m, 12H), 5.14–5.00 (m, 5H) 4.35 (d, *J* = 5.6 Hz, 2H), 2.18 (s, 3H).

25

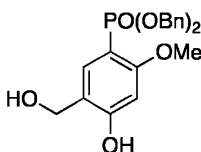
30

Synthesis of methyl 5-bromo-2-hydroxy-4-methoxybenzoate

Br₂ (3.1 mL, 60 mmol) was added dropwise to a stirred solution of methyl 2-hydroxy-4-methoxy-benzoate (10 g, 55 mmol) in dichloromethane (100 mL) at 0 °C. The resulting
 5 reaction was stirred at RT for 2h. The reaction mixture was quenched with sodium thiosulfate solution (300 ml) and extracted with dichloromethane. The combined organic layers were washed with brine solution, dried (Na₂SO₄), filtered and then evaporated to dryness under reduced pressure. Chromatography (SiO₂; EtOAc in hexanes) provided the desired product (14 g, 97%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.74 (s, 1H), 7.88 (s, 1H), 6.72 (s, 1H), 3.90
 10 (s, 3H), 3.87 (s, 3H).

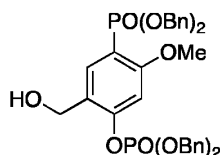
Synthesis of methyl 5-(bis(benzyloxy)phosphoryl)-2-hydroxy-4-methoxybenzoate

Tetrakis(triphenylphosphine)palladium(0) (2.21 g, 1.92 mmol) was added to stirred a
 15 solution of methyl 5-bromo-2-hydroxy-4-methoxy-benzoate (10 g, 38 mmol), benzyloxyposphonyloxymethylbenzene (10.96 mL, 45.96 mmol), and DIPEA (10 mL, 57.46 mmol) in toluene (3 mL). The reaction was heated under microwave irradiation at 80 °C for 16h. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried (Na₂SO₄) and evaporated to dryness under
 20 reduced pressure. Chromatography (SiO₂, EtOAc in hexanes) provided the desired compound (7 g, 41%) as a yellow gum. LCMS *m/z* = 443.9 [M+H]⁺.

Synthesis of dibenzyl (4-hydroxy-5-(hydroxymethyl)-2-methoxyphenyl)phosphonate

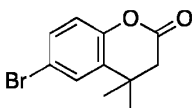
2N lithium aluminum hydride in THF (0.33 mL, 0.17 mmol) was added to stirred solution of methyl 5-dibenzoyloxyphosphoryl-2-hydroxy-4-methoxy-benzoate (300 mg, 0.68 mmol) in THF (8 mL) at 0 °C and allowed to stir for 1h. The reaction mixture was quenched with wet sodium sulphate, filtered through celite, and evaporated to dryness under reduced pressure. Chromatography (SiO₂, methanol in dichloromethane) provides the desired product (60 mg, 21%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.28 (br. s, 1H), 7.68 (d, *J* = 15.6, 1H), 7.32–7.34 (m, 10H), 6.48 (d, *J* = 6H, 1H), 4.78–5.03 (m, 4H), 4.41 (s, 2H), 3.68 (s, 3H). LCMS *m/z* = 415.39 [M+H]⁺.

Synthesis of dibenzyl (4-(bis(benzyloxy)phosphoryl)-2-(hydroxymethyl)-5-methoxyphenyl) phosphate



DMAP (65 mg, 0.53 mmol) was added to a cooled (−10 °C) solution of benzyloxyposphonoyloxymethylbenzene (0.77 mL, 3.45 mmol), carbon tetrachloride (1.03 mL, 10.6 mmol), DIPEA (1.4 mL, 7.96 mmol) in acetonitrile (5.8 mL). The reaction solution was allowed to stir for 15 min at this temperature and then 4-dibenzoyloxyphosphoryl-2-(hydroxymethyl)-5-methoxy-phenol (1.1 g, 2.65 mmol) in acetonitrile (3 mL) was added slowly as a suspension to the reaction solution. After stirring at room temperature for 7.5 hours the reaction mixture was evaporated to dryness. Chromatography (SiO₂; EtOAc in hexanes) gave the desired product (0.76 g, 42%) as clear brown oil. ¹H NMR (500 MHz, CDCl₃) δ 7.75 (dd, *J* = 15.2, 1.0 Hz, 1H), 7.31–7.22 (m, 20H), 6.55 (dd, *J* = 6.1, 1.2 Hz, 1H), 5.13–4.98 (m, 8H), 4.42 (d, *J* = 6.1 Hz, 2H), 3.46 (s, 3H). LCMS *m/z* = 675.1 [M+H]⁺.

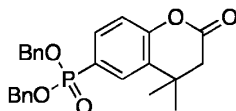
Synthesis of 6-bromo-4,4-dimethylchroman-2-one



3-Methylbut-2-enoic acid (32 g, 318 mmol) was added to a stirred solution of 4-bromophenol (50 g, 289 mmol) in methane sulfonic acid (500 mL). The resulting mixture was heated to 90° C for 12 h, cooled to room temperature and then poured onto ice water and then quenched by saturated aqueous NaHCO₃ and then extracted with EtOAc, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (SiO₂; EtOAc in

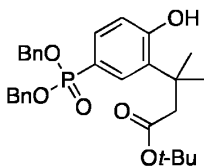
hexanes) provided 6-bromo-4,4-dimethyl-chroman-2-one (30 g, 40%). MS (ESI) m/z = 257.0 $[M + H]^+$.

Synthesis of 6-dibenzyloxyphosphoryl-4,4-dimethyl-chroman-2-one



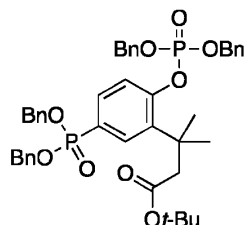
5 Tetrakis (3.62 g, 3.14 mmol) was added to a mixture containing benzyloxyposphonoyloxymethylbenzee (13.46 mL, 56.45 mmol), 6-bromo-4,4-dimethyl-chroman-2-one (16 g, 62.72 mmol) Cs_2CO_3 (30.88 mL, 68.99 mmol) in toluene (80 mL) was heated in a microwave at 120 °C at 30 min. Reaction mixture quenched with water (500 mL) and extracted with EtOAc. Organic layer washed with brine solution and dried for Na_2SO_4 filter it and concentrate to under reduced pressure. Chromatography (EtOAc in hexanes) afforded 6-dibenzyloxyphosphoryl-4,4-dimethyl-chroman-2-one (3.8 g, 14%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.69 (m, 2H), 7.35 (s, 10H), 7.21 (dd, J = 3.6, 8 Hz, 1H), 5.07 (d, J = 8 Hz, 4H), 2.77 (s, 2H), and 1.24 (s, 6H). MS (ESI) m/z = 437.2 $[M + H]^+$.

Synthesis of tert-butyl 3-(5-dibenzyloxyphosphoryl-2-hydroxy-phenyl)-3-methyl-butanoate



Potassium tert-butoxide (0.34 g, 3.02 mmol) was added to a solution of 6-dibenzyloxyphosphoryl-4,4-dimethyl-chroman-2-one (0.88 g, 2.01 mmol) in THF (13 mL). after stirring at room temperature for 2 h, the excess base was quenched by the addition of 1N HCl (10 mL). The organic phase was extracted with EtOAc (75 mL), washed with and brine, dried (Na_2SO_4) and evaporated to dryness under reduced pressure. Chromatography (SiO_2 ; 20–70% EtOAc in hexanes) provided the desired product (528 mg, 51%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.70–7.59 (m, 1H), 7.55 (ddt, J = 13.0, 8.2, 2.1 Hz, 1H), 7.35 – 7.27 (m, 10H), 6.91 – 6.86 (m, 1H), 5.19–4.95 (m, 4H), 2.83 (d, J = 6.6 Hz, 2H), 1.44 (d, J = 1.9 Hz, 6H), 1.14 (d, J = 3.3 Hz, 9H). LRMS (ESI) m/z = 511.2 $[M+H]^+$

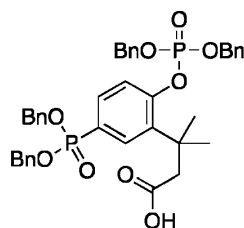
Synthesis of tert-butyl 3-(5-dibenzyloxyphosphoryl-2-dibenzyloxyphosphoryloxy-phenyl)-3-methyl-butanoate



DIPEA (0.61 mL, 3.53 mmol) was dropwise to a cooled (5 °C) solution of dibenzyl
 5 phosphonate (0.34 mL, 1.53 mmol) and DMAP (28 mg, 0.24 mmol) in carbon tetrachloride
 (0.46 mL, 4.71 mmol) under an argon atmosphere. After stirring for 10 min, a solution of
 tert-butyl 3-(5-dibenzyloxyphosphoryl-2-hydroxy-phenyl)-3-methyl-butanoate (0.6 g, 1.18
 mmol) was added dropwise. After stirring for 1.5 h the reaction was diluted with EtOAc (75
 mL), washed with 1N HCl (15 mL) and brine (15 mL), dried (Na₂SO₄) and evaporated to
 10 dryness under reduced pressure. Chromatography (25 g SiO₂; 10-60% EtOAc in hexanes) to
 give the desired product (0.62 g, 68%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.71
 (dt, *J* = 14.3, 1.8 Hz, 1H), 7.62 (ddd, *J* = 12.8, 8.4, 1.9 Hz, 1H), 7.53 (dd, *J* = 8.4, 4.1 Hz,
 1H), 7.36–7.29 (m, 21H), 5.15 (d, *J* = 8.5 Hz, 4H), 5.12–4.99 (m, 5H), 2.66 (s, 2H), 1.40 (s,
 6H), 1.09 (s, 9H). **LRMS (ESI)** *m/z* = 715.2 [*M* – *t*-butyl + H]⁺

15

Synthesis of 3-(5-dibenzyloxyphosphoryl-2-dibenzyloxyphosphoryloxy-phenyl)-3-methyl-butanoic acid



Tert-butyl 3-(5-dibenzyloxyphosphoryl-2-dibenzyloxyphosphoryloxy-phenyl)-3-
 20 methyl-butanoate (187 mg, 0.24 mmol) was dissolved in 1,1,1,3,3,3-Hexafluoroisopropanol
 (HFIP) and heated in microwave at 60 °C for 30 min and then evaporated to dryness under
 reduced pressure. Chromatography (10 g SiO₂; 0–10% methanol in dichloromethane) gave
 the desired product (60 mg, 34%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.78–7.70
 (m, 1H), 7.53 (ddd, *J* = 12.7, 8.4, 1.9 Hz, 1H), 7.48–7.40 (m, 1H), 7.34–7.26 (m, 20H), 5.18–
 25 5.06 (m, 5H), 5.06–4.94 (m, 4H), 1.39 (s, 6H). **LRMS (ESI)** *m/z* = 713.1 [*M*–H][–]

Example 2: Synthesis of Prodrug Building Blocks

General synthetic procedure for substituted [2 or 4-

bisalkoxyl(phosphoryloxy)]benzyl(4-nitrophenyl)carbonates: DIPEA (1.1 mol. equiv.)

5 was added to a stirred solution of the substituted dialkyl[2-(hydroxymethyl)phenyl]phosphates (prepared as in Example 1) (1 mol. equiv.) and bis(4-nitrophenyl) carbonate or 4-nitrophenylchloroformate (1 mol. equiv.) in CH₂Cl₂ (0.05 M). The reaction mixture was left overnight and then evaporated to dryness under reduced pressure. Chromatography (SiO₂ 20–80% EtOAc in hexanes) provided the desired
10 carbonates.

General synthetic procedure for substituted [2 or 4-

bisalkoxyl(phosphoryloxy)]benzyl carbonchloridates: Triphosgene (1.1 mol. equiv.) in a solution in 1 mL of THF was added slowly to a cooled (0 °C) solution of substituted dialkyl[2-(hydroxymethyl)phenyl]phosphates (prepared as in Example 1) (1 mol. equiv.) in
15 THF (0.2 M). DIPEA (1.2 mol. equiv.) was added and the reaction mixture stirred for 1 h and then quenched with water, extracted into EtOAc, washed with brine, dried (MgSO₄) and evaporated to dryness under reduced pressure to give the desired chloroformate.

General synthetic procedure for [bisalkoxyl (2-(chloromethoxy)methyl)-4 or 5-substituted] phenyl phosphates or [bisalkoxyl (4-(chloromethoxy)methyl)-2 or 3-

20 **substituted] phenyl phosphates:** A solution of substituted dialkyl[2-(hydroxymethyl)phenyl]phosphates (prepared as in Example 1) (1.0 mol. equiv.) and paraformaldehyde (1.0 mol. equiv.) in TMSCl (4 mol. equiv.) was stirred at room temperature for 6 h and then evaporated to dryness under reduced pressure to give the desired chloromethyl ether that was used without purification.

25 **General synthetic procedure for substituted [2 or 4-bisalkoxyl(phosphoryloxy)]-benzylbromides:** Triphenylphosphine(2.5 mol. equiv.) was added to a stirred solution of the benzyl alcohol (1 mol. equiv.) in DCM (0.25 M). This was followed by the addition of CBr₄ (2.5 mol. equiv.). The reaction mixture was allowed to stir at room temperature for 45 min. and then diluted with water. The organic phase was extracted into DCM, washed with
30 brine, dried (Na₂SO₄) and evaporated to dryness under reduced pressure. Chromatography (SiO₂; EtOAc in Hexanes) provided the desired products.

General synthetic procedure for substituted [2 or 4-bisalkoxyl(phosphoryloxy)]-benzyl mesylates: Triethylamine (0.26 mL, 1.87 mmol 2 mol. equiv.) is added to a solution

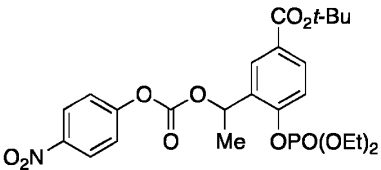
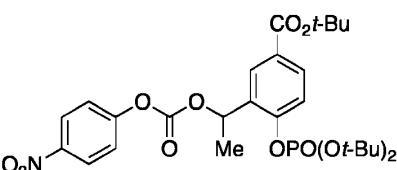
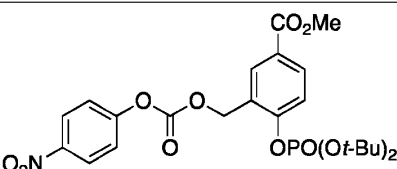
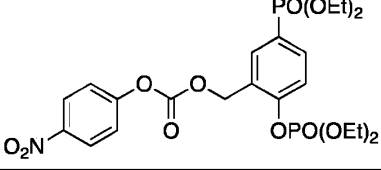
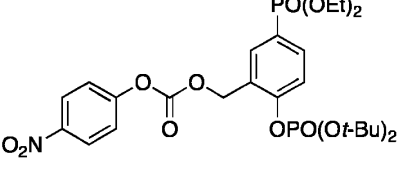
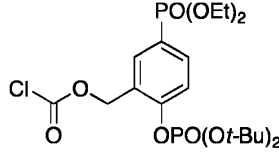
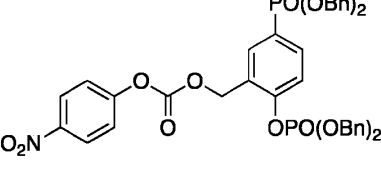
of the benzyl Alcohol (1 mol. equiv.) in anhydrous DCM (0.2 M) at -10°C under an atmosphere of nitrogen gas. Methanesulfonyl chloride (1.5 mol. equiv.) is then added dropwise and the reaction allowed to stir for 1 hour and then warmed to room temperature.

- The reaction mixture is diluted with EtOAc and then washed with aqueous saturated ammonium chloride, brine solution, dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The desired product is isolated by column chromatography (0–10% methanol in DCM).

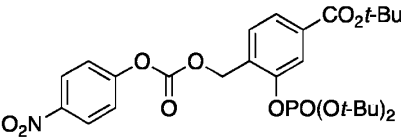
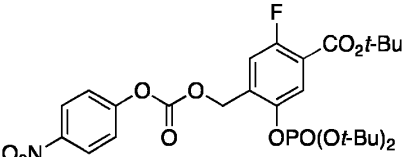
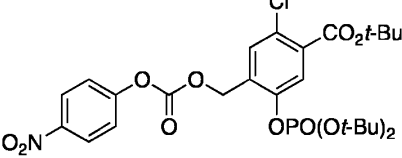
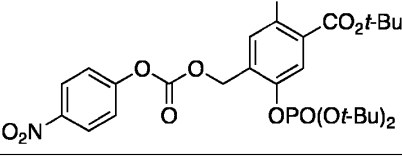
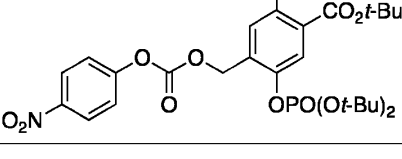
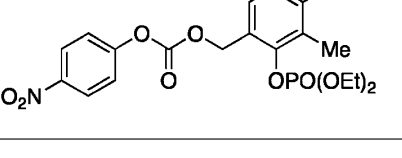
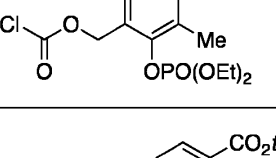
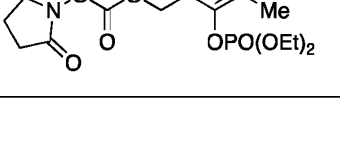
Structures of products and characterization data are provided in Table 1.

10 **Table 1.** Building Block Compounds and Characterization Data

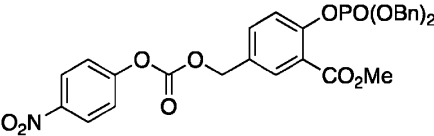
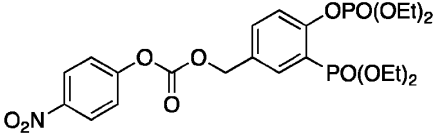
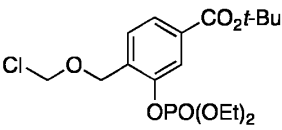
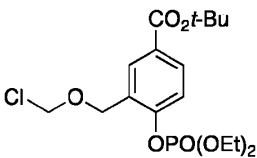
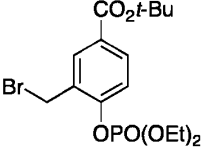
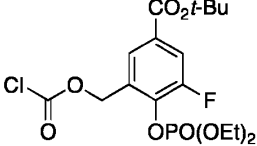
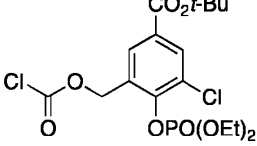
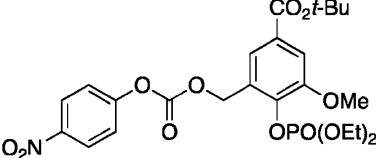
Entry	Structure	Mass/NMR
I		^1H NMR (500 MHz, CDCl_3) δ 8.29 (d, $J = 9.1$ Hz, 2H), 8.11 (dd, $J = 2.2, 1.0$ Hz, 1H), 8.01 (dd, $J = 8.6, 2.2$ Hz, 1H), 7.5 (dd, $J = 8.6, 1.0$ Hz, 1H), 7.41 (d, $J = 9.1$ Hz, 2H), 4.26 (dq, $J = 8.5, 7.0, 4.3$ Hz, 4H), 1.60 (s, 9H), 1.37 (td, $J = 7.1, 1.0$ Hz, 6H).
II		
III		^1H NMR (500 MHz, CDCl_3) δ 8.10–7.83 (m, 2H), 7.45 (dd, $J = 8.6, 0.9$ Hz, 1H), 5.34 (s, 2H), 4.17 (dpt, $J = 8.4, 7.0, 3.5$ Hz, 4H), 1.53 (s, 9H), 1.29 (td, $J = 7.1, 1.1$ Hz, 6H).
IV		^1H NMR (500 MHz, CDCl_3) δ 8.32–8.25 (m, 2H), 8.09 (t, $J = 1.8$ Hz, 1H), 7.99 (dd, $J = 8.6, 2.2$ Hz, 1H), 7.53 (dd, $J = 8.7, 0.8$ Hz, 1H), 7.44–7.37 (m, 2H), 5.42 (s, 2H), 1.59 (d, $J = 1.6$ Hz, 9H), 1.52 (d, $J = 0.7$ Hz, 18H).

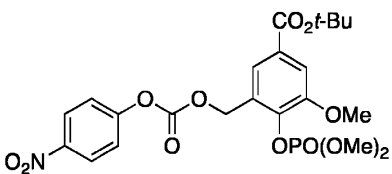
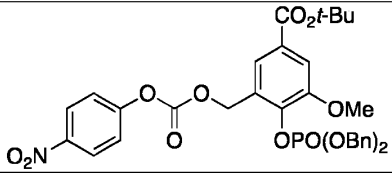
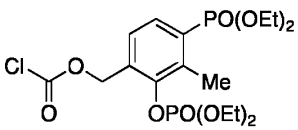
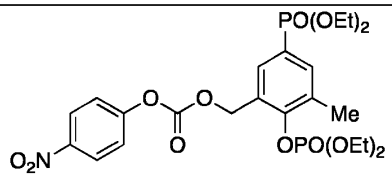
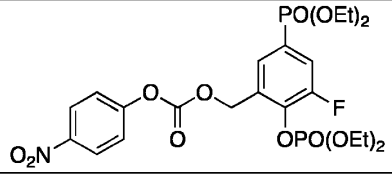
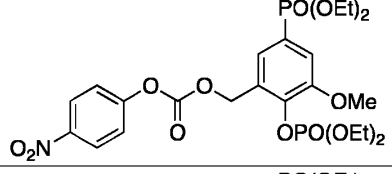
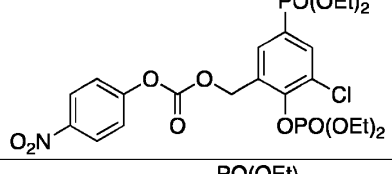
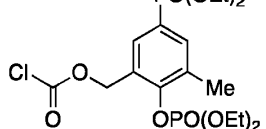
V		¹ H NMR (500 MHz, CDCl ₃) δ 8.31–8.21 (m, 2H), 8.15 (t, <i>J</i> = 1.8 Hz, 1H), 7.95 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.54–7.45 (m, 1H), 7.43–7.35 (m, 2H), 6.20 (q, <i>J</i> = 6.6 Hz, 1H), 4.32–4.20 (m, 4H), 1.72 (d, <i>J</i> = 6.6 Hz, 2H), 1.59 (s, 9H), 1.37–1.34 (m, 6H).
VI		¹ H NMR (500 MHz, CDCl ₃) δ 8.32–8.19 (m, 2H), 8.05 (t, <i>J</i> = 1.2 Hz, 1H), 7.87 (dd, <i>J</i> = 8.1, 1.6 Hz, 1H), 7.59 (dd, <i>J</i> = 8.1, 1.3 Hz, 1H), 7.43–7.35 (m, 2H), 6.25 (q, <i>J</i> = 6.6 Hz, 1H), 1.69 (d, <i>J</i> = 6.6 Hz, 3H), 1.59 (d, <i>J</i> = 7.0 Hz, 27H).
VII		¹ H NMR (500 MHz, CDCl ₃) δ 8.32–8.24 (m, 2H), 8.17 (t, <i>J</i> = 1.8 Hz, 1H), 8.13–8.03 (m, 1H), 7.58–7.48 (m, 1H), 7.46–7.36 (m, 2H), 5.42 (s, 2H), 3.93 (s, 3H), 1.53 (s, 18H).
VIII		562.1 [M+H] ⁺
IX		¹ H NMR (500 MHz, CDCl ₃) δ 8.29 (d, <i>J</i> = 9.1 Hz, 2H), 7.93 (d, <i>J</i> = 13.1 Hz, 1H), 7.81 (ddd, <i>J</i> = 13.1, 8.5, 2.0 Hz, 1H), 7.60 (dd, <i>J</i> = 8.5, 3.5 Hz, 1H), 7.41 (d, <i>J</i> = 9.1 Hz, 2H), 5.42 (s, 2H), 4.20–4.05 (m, 4H), 1.58 (s, 18H), 1.36–1.31 (m, 6H).
X		¹ H NMR (500 MHz, CDCl ₃) δ 7.90–7.82 (m, 2H), 7.63 (dd, <i>J</i> = 8.5, 3.5 Hz, 1H), 5.43 (s, 2H), 4.22–4.07 (m, 4H), 1.54 (s, 18H), 1.36 (t, <i>J</i> = 7.0 Hz, 6H).
XI		¹ H NMR (500 MHz, CDCl ₃) δ 8.31–8.04 (m, 2H), 7.85 (dt, <i>J</i> = 13.4, 1.7 Hz, 1H), 7.74 (ddd, <i>J</i> = 13.0, 8.4, 2.0 Hz, 1H), 7.44 (ddd, <i>J</i> = 8.5, 3.6, 0.9 Hz, 1H), 7.37–7.22 (m, 22H), 5.24 (s, 2H), 5.15 (d, <i>J</i> = 8.9 Hz, 4H), 5.13–4.96 (m, 4H).

XII		¹ H NMR (500 MHz, CDCl ₃) δ 7.72 (ddd, <i>J</i> = 13.0, 6.8, 2.0 Hz, 2H), 7.42 (dd, <i>J</i> = 9.0, 3.5 Hz, 1H), 7.38–7.29 (m, 20H), 5.17 (s, 2H), 5.13 (d, <i>J</i> = 9.3 Hz, 4H), 5.11–5.01 (m, 6H).
XIII		¹ H NMR (500 MHz, CDCl ₃) δ 7.78 (d, <i>J</i> = 1.9 Hz, 1H), 7.73 (dd, <i>J</i> = 10.3, 2.0 Hz, 1H), 5.42 (s, 2H), 4.29–4.13 (m, 4H), 1.52 (s, 10H), 1.32 (td, <i>J</i> = 7.1, 1.2 Hz, 6H).
XIV		¹ H NMR (500 MHz, CDCl ₃) δ 8.40–8.23 (m, 2H), 7.95 (s, 1H), 7.89–7.75 (m, 1H), 7.58–7.32 (m, 2H), 5.51 (s, 2H), 4.39–4.25 (m, 4H), 1.62 (s, 9H), 1.41 (td, <i>J</i> = 7.0, 1.2 Hz, 6H).
XV		
XVI		¹ H NMR (500 MHz, CDCl ₃) δ 7.87 (s, 2H), 5.51 (s, 2H), 4.32–4.16 (m, 4H), 2.43 (s, 3H), 1.59 (s, 9H), 1.35 (t, <i>J</i> = 7.1 Hz, 6H).
XVII		526.1 [M+H] ⁺
XVIII		¹ H NMR (500 MHz, CDCl ₃) δ 7.89 (dt, <i>J</i> = 13.1, 1.7 Hz, 1H), 7.86–7.82 (m, 1H), 7.60–7.56 (m, 1H), 5.42 (s, 2H), 4.26 (dq, <i>J</i> = 8.4, 7.1, 2.6 Hz, 4H), 4.18–4.06 (m, 4H), 2.85 (s, 4H), 1.40–1.31 (m, 12H).
XIX		

XX		¹ H NMR (500 MHz, CDCl ₃) δ 8.32–8.24 (m, 2H), 8.03 (t, <i>J</i> = 1.3 Hz, 1H), 7.83 (dd, <i>J</i> = 7.9, 1.6 Hz, 1H), 7.55–7.46 (m, 1H), 7.43–7.36 (m, 2H), 5.46 (s, 2H), 1.59 (s, 9H), 1.55 (d, <i>J</i> = 0.7 Hz, 18H).
XXI		
XXII		
XXIII		
XXIV		
XXV		¹ H NMR (500 MHz, CDCl ₃) δ 8.31–8.24 (m, 2H), 7.63 (d, <i>J</i> = 8.0 Hz, 1H), 7.41–7.37 (m, 2H), 7.36 (d, <i>J</i> = 8.1 Hz, 1H), 5.54 (s, 2H), 4.23 (m, 4H), 2.55 (s, 3H), 1.59 (s, 9H), 1.35 (td, <i>J</i> = 7.1, 1.1 Hz, 6H).
XXVI		¹ H NMR (500 MHz, CDCl ₃) δ 7.61 (dd, <i>J</i> = 8.1, 1.3 Hz, 1H), 7.28 (d, <i>J</i> = 8.1 Hz, 1H), 5.47 (s, 2H), 4.30–4.15 (m, 4H), 2.53 (s, 3H), 1.58 (s, 9H), 1.35 (td, <i>J</i> = 7.1, 1.2 Hz, 6H).
XXVIII		516.1 [M+H] ⁺

XXIX		585.1 [M+H] ⁺ ¹ H NMR (500 MHz, CDCl ₃) δ 7.63 (dd, <i>J</i> = 8.1, 1.3 Hz, 1H), 7.33 (d, <i>J</i> = 8.1 Hz, 1H), 5.56 (s, 2H), 4.31 – 4.16 (m, 4H), 2.54 (s, 3H), 2.05 (s, 2H), 1.59 (s, 9H), 1.36 (td, <i>J</i> = 7.0, 1.1 Hz, 6H).
XXX		
XXXI		¹ H NMR (500 MHz, CDCl ₃) δ 8.32–8.22 (m, 2H), 7.95 (dd, <i>J</i> = 8.7, 2.2 Hz, 1H), 7.60–7.46 (m, 2H), 7.45 – 7.36 (m, 2H), 6.24 (q, <i>J</i> = 6.5 Hz, 1H), 1.71 (d, <i>J</i> = 6.5 Hz, 3H), 1.62 (s, 9H), 1.54 (s, 18H).
XXXII		
XXXIII		¹ H NMR (500 MHz, CDCl ₃) δ 7.97–7.82 (m, 1H), 7.71–7.47 (m, 2H), 5.45 (s, 2H), 4.20–4.10 (m, 4H), 1.52 (s, 18H), 1.36–1.27 (m, 6H).
XXXIV		¹ H NMR (500 MHz, MeOD) δ 7.81 (ddd, <i>J</i> = 13.9, 7.9, 1.3 Hz, 1H), 7.50 (dd, <i>J</i> = 8.0, 4.8 Hz, 1H), 5.56 (s, 2H), 4.34–4.20 (m, 4H), 4.18–4.10 (m, 4H), 2.59 (s, 3H), 1.38–1.33 (m, 12H).
XXXV		526.1 [M+H] ⁺ ¹ H NMR (500 MHz, CDCl ₃) δ 8.56–8.17 (m, 2H), 7.83 (dd, <i>J</i> = 2.4, 1.0 Hz, 1H), 7.69–7.44 (m, 2H), 7.44 – 7.32 (m, 2H), 5.27 (s, 2H), 4.25 (dq, <i>J</i> = 8.3, 7.1, 3.9 Hz, 4H), 1.60 (s, 9H), 1.35 (td, <i>J</i> = 7.1, 1.1 Hz, 6H).

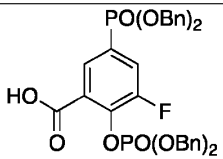
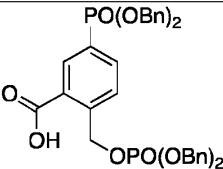
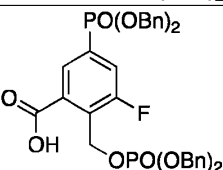
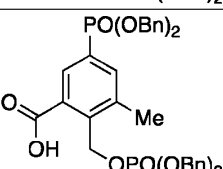
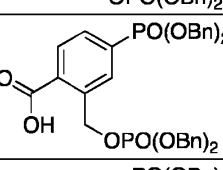
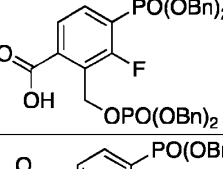
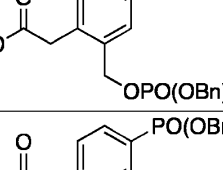
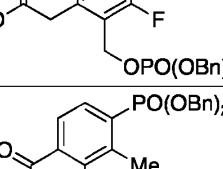
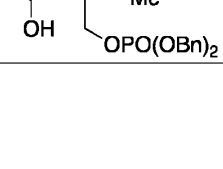
XXXVI		^1H NMR (500 MHz, CDCl_3) δ 8.29 (d, $J = 9.2$ Hz, 2H), 7.96 (dd, $J = 2.4, 1.0$ Hz, 1H), 7.40 (m, 3H), 5.27 (s, 2H), 5.19 (s, 2H), 5.17 (s, 2H), 3.85 (s, 3H).
XXXVII		562.1 $[\text{M}+\text{H}]^+$
XXXIX		
XL		^1H NMR (500 MHz, CDCl_3) δ 8.05 (t, $J = 1.7$ Hz, 1H), 7.95 (dt, $J = 8.4, 2.8$ Hz, 1H), 7.45 (dd, $J = 8.7, 1.0$ Hz, 1H), 5.57 (s, 2H), 4.84 (s, 2H), 4.29–4.22 (m, 4H), 1.59 (s, 9H), 1.38–1.35 (m, 6H).
XLI		^1H NMR (500 MHz, CDCl_3) δ 8.06 (dt, $J = 15.2, 1.8$ Hz, 1H), 7.96 (ddd, $J = 10.8, 8.6, 2.2$ Hz, 1H), 7.49 (dt, $J = 8.6, 1.3$ Hz, 1H), 4.57 (s, 2H), 4.37–4.22 (m, 4H), 1.61 (s, 9H), 1.39 (tdd, $J = 7.1, 4.2, 1.1$ Hz, 6H).
XLII		^1H NMR (500 MHz, CDCl_3) δ 7.78 (d, $J = 1.9$ Hz, 1H), 7.73 (dd, $J = 10.3, 2.0$ Hz, 1H), 5.42 (s, 2H), 4.29–4.13 (m, 4H), 1.52 (s, 10H), 1.32 (td, $J = 7.1, 1.2$ Hz, 6H).
XLIII		^1H NMR (500 MHz, MeOD) δ 8.07 (d, $J = 2.1$ Hz, 1H), 8.03 (d, $J = 2.1$ Hz, 1H), 5.54 (s, 2H), 4.34–4.28 (m, 4H), 1.60 (s, 9H), 1.38 (td, $J = 7.1, 1.2$ Hz, 6H).
XLIV		^1H NMR (500 MHz, CDCl_3) δ 8.28 (d, $J = 9.2$ Hz, 2H), 7.71 (d, $J = 1.9$ Hz, 1H), 7.63 (d, $J = 2.1$ Hz, 1H), 7.41 (d, $J = 9.1$ Hz, 2H), 5.47 (s, 2H), 4.35–4.25 (m, 4H), 3.95 (s, 3H), 1.60 (s, 9H), 1.38 (td, $J = 7.1, 1.2$ Hz, 6H).

XLV		¹ H NMR (500 MHz, CDCl ₃) δ 8.28 (d, <i>J</i> = 9.2 Hz, 2H), 7.77–7.69 (m, 1H), 7.64 (d, <i>J</i> = 1.9 Hz, 1H), 7.40 (d, <i>J</i> = 9.1 Hz, 2H), 5.44 (s, 3H), 3.96 (s, 3H), 3.93 (d, <i>J</i> = 11.5 Hz, 6H), 1.60 (s, 9H).
XLVI		¹ H NMR (500 MHz, CDCl ₃) δ 8.23 (d, <i>J</i> = 9.1 Hz, 2H), 7.68 (m, 1H), 7.58 (d, <i>J</i> = 1.9 Hz, 1H), 7.38–7.21 (m, 12H), 5.41 (s, 2H), 5.19 (d, <i>J</i> = 7.9 Hz, 4H), 3.83 (s, 3H), 1.60 (s, 9H).
XLVII		¹ H NMR (500 MHz, MeOD) δ 7.81 (ddd, <i>J</i> = 13.9, 7.9, 1.3 Hz, 1H), 7.50 (dd, <i>J</i> = 8.0, 4.8 Hz, 1H), 5.56 (s, 2H), 4.34–4.20 (m, 4H), 4.18–4.10 (m, 4H), 2.59 (s, 3H), 1.38–1.33 (m, 12H).
XLVIII		
XLIX		
L		
LI		
LII		

LIII		
LIV		
LV		¹ H NMR (500 MHz, CDCl ₃) δ 7.45–7.27 (m, 22H), 5.31 (s, 2H), 5.16 (d, <i>J</i> = 8.2 Hz, 5H), 5.08 (qd, <i>J</i> = 11.8, 8.2 Hz, 5H), 3.72 (s, 3H).
LVI		
LVII		
LVIII		
LIX		
LX		¹ H NMR (500 MHz, CDCl ₃) δ 7.65–7.50 (m, 3H), 4.57 (s, 2H), 4.40–4.26 (m, 4H), 4.26–4.02 (m, 4H), 1.39 (td, <i>J</i> = 7.1, 1.0 Hz, 6H), 1.33 (t, <i>J</i> = 7.1 Hz, 6H).

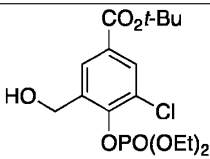
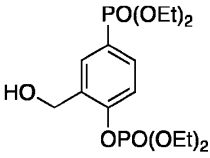
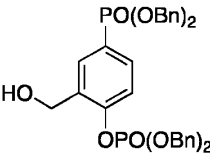
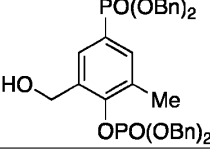
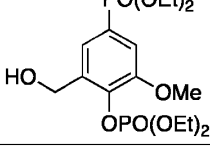
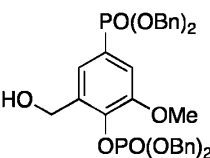
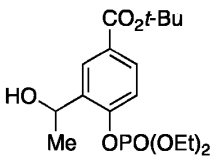
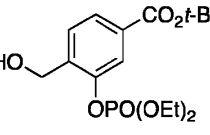
LXI		
LXII		¹ H NMR (500 MHz, CDCl ₃) δ 8.03 (t, <i>J</i> = 1.8 Hz, 1H), 7.94–7.92 (m, 1H), 7.47 (d, <i>J</i> = 1.4 Hz, 1H), 4.55 (s, 2H), 4.34–4.20 (m, 4H), 1.59 (s, 9H), 1.41–1.30 (m, 6H).
LXIII		
LXIV		¹ H NMR (500 MHz, CDCl ₃) δ 7.87 (d, <i>J</i> = 2.3 Hz, 1H), 7.80 (d, <i>J</i> = 2.1 Hz, 1H), 4.73 (s, 2H), 4.31–4.19 (m, 4H), 2.41 (s, 3H), 1.58 (s, 9H), 1.36 (td, <i>J</i> = 7.1, 1.1 Hz, 6H).
LXV		¹ H NMR (500 MHz, CDCl ₃) δ 7.90–7.82 (m, 1H), 7.72 (dd, <i>J</i> = 10.4, 2.1 Hz, 1H), 4.64 (s, 2H), 4.39–4.20 (m, 4H), 1.59 (s, 9H), 1.39 (tdd, <i>J</i> = 7.2, 3.8, 1.2 Hz, 6H).
LXVI		¹ H NMR (500 MHz, CDCl ₃) δ 7.96 (dd, <i>J</i> = 17.2, 2.1 Hz, 1H), 4.71 (s, 2H), 4.38–4.23 (m, 4H), 1.58 (s, 9H), 1.38 (td, <i>J</i> = 7.1, 1.2 Hz, 6H).
LXVII		
LXVIII		
LXIX		

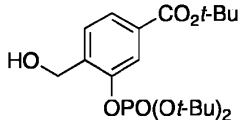
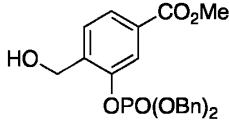
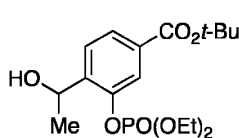
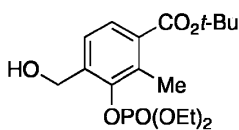
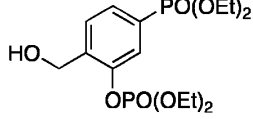
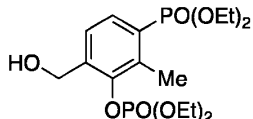
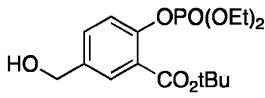
LXX		
LXXI		
LXXII		¹ H NMR (500 MHz, CDCl ₃) δ 8.03 (t, <i>J</i> = 1.8 Hz, 1H), 7.98 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.45 (d, <i>J</i> = 8.6 Hz, 1H), 5.28 (s, 2H), 4.31–4.16 (m, 4H), 2.98 (s, 3H), 1.55 (s, 9H), 1.14–0.97 (m, 4H), 0.00 (s, 18H).
LXXIII		
LXXIV		
LXXV		¹ H NMR (500 MHz, DMSO) δ 7.73 (dd, <i>J</i> = 13.7, 6.6 Hz, 1H), 7.52 (dd, <i>J</i> = 8.0, 4.6 Hz, 1H), 5.43 (s, 2H), 4.25–4.10 (m, 4H), 4.11–3.97 (m, 4H), 3.27 (s, 3H), 2.49 (s, 3H), 1.25 (q, <i>J</i> = 6.8 Hz, 12H). MS <i>m/z</i> = 489.4 [M+H] ⁺
LXXVI		
LXXVII		

LXXVIII		
LXXIX		
LXXX		
LXXXI		
LXXXII		
LXXXII		
LXXXIV		
LXXXV		
LXXXVI		

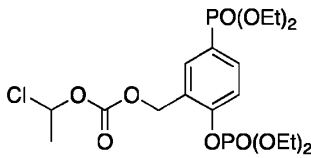
LXXXVII		
LXXXVIII		
LXXXIX		
XC		
XCI		¹ H NMR (500 MHz, CDCl ₃) δ 7.78–7.70 (m, 1H), 7.53 (ddd, <i>J</i> = 12.7, 8.4, 1.9 Hz, 1H), 7.48–7.40 (m, 1H), 7.34–7.26 (m, 20H), 5.18–5.06 (m, 5H), 5.06–4.94 (m, 4H), 1.39 (s, 6H).
XCII		
XCIII		
XCIV		
XCV		

XCVI		
XCVII		¹ H NMR (500 MHz, CDCl ₃) δ 8.32–8.25 (m, 2H), 8.09 (t, <i>J</i> = 1.8 Hz, 1H), 7.99 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 7.53 (dd, <i>J</i> = 8.7, 0.8 Hz, 1H), 7.44–7.37 (m, 2H), 5.42 (s, 2H), 1.59 (d, <i>J</i> = 1.6 Hz, 9H), 1.52 (d, <i>J</i> = 0.7 Hz, 18H).
XCVIII		¹ H NMR (500 MHz, CDCl ₃) δ 8.14–8.08 (m, 1H), 7.95 (dd, <i>J</i> = 8.5, 2.3 Hz, 1H), 7.28–7.23 (m, 2H), 4.69 (s, 2H), 4.32–4.14 (m, 4H), 1.59 (s, 9H), 1.37 (td, <i>J</i> = 7.1, 1.1 Hz, 6H).
XCIX		¹ H NMR (500 MHz, CDCl ₃) δ 8.17 (dd, <i>J</i> = 2.4, 1.0 Hz, 1H), 7.94 (dd, <i>J</i> = 8.5, 2.2 Hz, 1H), 7.49–7.25 (m, 16H), 7.25–7.06 (m, 2H), 5.38 (s, 2H), 5.15 (d, <i>J</i> = 9.0 Hz, 4H), 4.62 (s, 2H).
C		¹ H NMR (500 MHz, CDCl ₃) δ 7.71–7.70 (m, 1H), 7.52 (d, <i>J</i> = 2.1 Hz, 1H), 4.9 (s, 2H), 2.5 (s, 3H), 1.58 (s, 9H), 1.57 (s, 18H).
CII		¹ H NMR (500 MHz, CDCl ₃) δ 7.93 (d, <i>J</i> = 2.3 Hz, 1H), 7.81 (d, <i>J</i> = 2.1 Hz, 1H), 4.63 (s, 2H), 4.33–4.15 (m, 4H), 2.37 (s, 3H), 1.58 (s, 9H), 1.34 (td, <i>J</i> = 7.1, 1.2 Hz, 6H).
CIII		¹ H NMR (500 MHz, CDCl ₃) δ 7.90 (t, <i>J</i> = 1.9 Hz, 1H), 7.73 (dd, <i>J</i> = 10.3, 2.1 Hz, 1H), 4.67 (s, 2H), 4.36–4.16 (m, 4H), 1.58 (s, 9H), 1.38 (td, <i>J</i> = 7.0, 1.2 Hz, 6H).
CIV		¹ H NMR (500 MHz, CDCl ₃) δ 7.71 (d, <i>J</i> = 1.8 Hz, 1H), 7.57 (d, <i>J</i> = 2.0 Hz, 1H), 4.66 (d, <i>J</i> = 7.0 Hz, 2H), 4.07 (t, <i>J</i> = 7.0 Hz, 1H), 3.93 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 1.59 (s, 9H).

CV		¹ H NMR (500 MHz, CDCl ₃) δ 8.01 (s, 2H), 4.66 (s, 2H), 4.36–4.19 (m, 4H), 1.59 (s, 9H), 1.36 (td, <i>J</i> = 7.0, 1.2 Hz, 6H).
CVI		¹ H NMR (500 MHz, CDCl ₃) δ 7.98 (td, <i>J</i> = 13.1, 1.2 Hz, 1H), 7.73 (ddd, <i>J</i> = 13.1, 8.3, 2.7 Hz, 1H), 7.35 (ddd, <i>J</i> = 8.4, 32.7, 1.8 Hz, 1H), 4.73 (s, 2H), 4.28–4.21 (m, 4H), 4.16–4.04 (m, 4H), 1.37 (td, <i>J</i> = 7.1, 1.14, 6H), 1.31 (t, <i>J</i> = 7.1 Hz, 6H).
CVII		¹ H NMR (500 MHz, MeOD) δ 7.90 (dt, <i>J</i> = 13.6, 1.6 Hz, 1H), 7.60 (ddd, <i>J</i> = 13.2, 8.3, 2.0 Hz, 1H), 7.35–7.30 (m, 21 H), 5.48 (s, 4H), 5.16 (d, <i>J</i> = 9.5 Hz, 2H), 5.09–5.03 (m, 4H).
CVIII		¹ H NMR (500 MHz, CDCl ₃) δ 7.45–7.22 (m, 22H), 5.12–4.97 (m, 4H), 4.93–4.88 (m, 2H), 4.79 (s, 2H), 4.70 (s, 2H), 2.15 (d, <i>J</i> = 0.8 Hz, 3H).
CIX		¹ H NMR (500 MHz, CDCl ₃) δ 7.46 (dd, <i>J</i> = 13.5, 1.2 Hz, 1H), 7.36 (dd, <i>J</i> = 14.5, 1.3 Hz, 1H), 4.66 (s, 2H), 4.35–4.18 (m, 4H), 4.18–4.02 (m, 4H), 3.90 (s, 3H), 1.37–1.30 (m, 12H).
CX		¹ H NMR (500 MHz, CDCl ₃) δ 7.46 (dd, <i>J</i> = 13.6, 1.7 Hz, 1H), 7.36–7.27 (m, 20H), 7.22–7.15 (m, 1H), 5.16 (dt, <i>J</i> = 8.1, 3.7 Hz, 4H), 5.12–5.03 (m, 4H), 4.59 (d, <i>J</i> = 4.0 Hz, 2H), 3.63 (s, 3H). MS (ESI) <i>m/z</i> = 675.2 [M+H] ⁺
CXI		¹ H NMR (500 MHz, CDCl ₃) δ 8.20 (dd, <i>J</i> = 2.2, 1.2 Hz, 1H), 7.88 (dd, <i>J</i> = 8.5, 2.2 Hz, 1H), 7.33–7.24 (m, 1H), 5.24 (q, <i>J</i> = 6.5 Hz, 1H), 4.33–4.14 (m, 4H), 1.59 (s, 9H), 1.53 (d, <i>J</i> = 6.5 Hz, 3H), 1.38 (td, <i>J</i> = 7.1, 1.1 Hz, 3H), 1.34 (td, <i>J</i> = 7.1, 1.1 Hz, 3H).
CXII		¹ H NMR (500 MHz, CDCl ₃) δ 7.83 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 7.79 (t, <i>J</i> = 1.5 Hz, 1H), 7.53 (dd, <i>J</i> = 8.0, 0.9 Hz, 1H), 4.70 (d, <i>J</i> = 6.2 Hz, 2H), 4.28–4.23

		(m, 4H), 1.59 (s, 9H) and 1.38 (m, $J = 7.1, 1.2$ Hz, 6H).
CXIII		^1H NMR (500 MHz, CDCl_3) δ 7.82 (dd, $J = 7.6, 1.4$ Hz, 2H), 7.51–7.45 (m, 1H), 4.65 (s, 2H), 1.59 (s, 9H) and 1.53 (s, 18H).
CXIV		^1H NMR (500 MHz, CDCl_3) δ 7.86 (dt, $J = 7.8, 1.4$ Hz, 1H), 7.76 (d, $J = 1.6$ Hz, 1H), 7.52 (d, $J = 7.9$ Hz, 1H), 7.37–7.28 (m, 10H), 5.13 (dd, $J = 8.9, 1.8$ Hz, 4H), 4.61 (s, 2H), 3.89 (s, 3H).
CV		^1H NMR (500 MHz, CDCl_3) δ 7.87–7.78 (m, 2H), 7.60 (dd, $J = 8.1, 1.0$ Hz, 1H), 5.26 (q, $J = 6.6$ Hz, 1H), 4.35–4.08 (m, 4H), 1.58 (s, 9H), 1.52 (d, $J = 6.5$ Hz, 3H), 1.39 (dtd, $J = 29.0, 7.0, 1.1$ Hz, 6H).
CVI		^1H NMR (500 MHz, CDCl_3) δ 7.61 (d, $J = 7.9$ Hz, 1H), 7.34 (d, $J = 7.9$ Hz, 1H), 4.61 (s, 2H), 4.30–4.15 (m, 4H), 2.49 (s, 3H), 1.59 (s, 9H), 1.34 (td, $J = 7.1, 1.2$ Hz, 6H).
CVII		^1H NMR (500 MHz, CDCl_3) δ 7.67–7.61 (m, 1H), 7.60–7.57 (m, 2H), 4.69 (s, 2H), 4.27–4.20 (m, 4H), 4.15–4.06 (m, 4H), 1.38–1.34 (m, 6H), 1.33–1.27 (m, 6H).
CVIII		^1H NMR (500 MHz, MeOD) δ 7.77 (ddd, $J = 13.9, 8.0, 1.3$ Hz, 1H), 7.56 (dd, $J = 8.0, 5.0$ Hz, 1H), 4.80 (s, 2H), 4.24 (hept, $J = 7.2$ Hz, 4H), 4.17–4.09 (m, 4H), 2.55 (s, 3H), 1.36–1.31 (m, 12H).
CIX		^1H NMR (500 MHz, CDCl_3) δ 7.73 (dd, $J = 2.2, 1.1$ Hz, 1H), 7.58–7.31 (m, 2H), 4.68 (s, 2H), 4.38–4.16 (m, 4H), 1.59 (s, 9H), 1.34 (td, $J = 7.1, 1.1$ Hz, 6H).

CX		MS (ESI) $m/z = 397.1$ $[M+H]^+$
CXI		
CXII		
CXIII		
CXIV		
CXV		
CXVI		
CXVII		^1H NMR (500 MHz, CDCl_3) δ 7.88 (dt, $J = 13.2, 1.7$ Hz, 1H), 7.86–7.79 (m, 1H), 7.55 (ddd, $J = 8.4, 3.5, 0.9$ Hz, 1H), 5.75 (s, 2H), 5.35 (s, 2H), 4.25 (dq, $J = 8.4, 7.0, 3.5$ Hz, 4H), 4.19–3.92 (m, 4H), 1.40–1.30 (m, 12H).
CXVIII		^1H NMR (500 MHz, CDCl_3) δ 7.77 (dt, $J = 13.4, 1.6$ Hz, 1H), 7.74–7.67 (m, 1H), 7.41 (ddd, $J = 8.5, 3.6, 1.0$ Hz, 1H), 7.31 (dddd, $J = 6.6, 4.6, 3.2, 1.5$ Hz, 20H), 5.67 (s, 2H), 5.15–5.10 (m, 4H), 5.10–5.00 (m, 4H).

CXIX		¹ H NMR (500 MHz, CDCl ₃) δ 7.91 (dt, <i>J</i> = 13.6, 1.7 Hz, 1H), 7.79–7.71 (m, 1H), 7.54 (ddd, <i>J</i> = 8.4, 3.5, 0.9 Hz, 1H), 6.15 (qd, <i>J</i> = 6.6, 1.3 Hz, 1H), 5.71 (d, <i>J</i> = 0.7 Hz, 2H), 4.26 (dddt, <i>J</i> = 10.2, 8.7, 5.1, 1.9 Hz, 4H), 4.16–4.04 (m, 4H), 1.64 (d, <i>J</i> = 6.6 Hz, 3H), 1.41– 1.35 (m, 6H), 1.33 (t, <i>J</i> = 7.0 Hz, 6H).
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Example 3: Synthesis of Prodrug Compounds

General synthetic procedures for attaching building blocks to pharmaceutical compounds

5 **Method A (attachment to an amide):** LiHMDS 1M in THF (0.22 g, 1.29 mmol) was added to a stirred solution of the carbonate or chloroformate building Block (1.1 mol. equiv.) and the drug compound (e.g., enzalutamide, apalutamide) (1 mol. equiv.) in THF (0.05 M) cooled to 5 °C. After stirring for 12 h, the reaction mixture is quenched by the addition of 1M HCl solution, washed with sat'd aq. NaHCO₃ solution, brine, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (10–80% EtOAc in hexanes).

10 **Method B (attachment to an amide, aniline, or amine):** Sodium hydride (1.5 mol. equiv.) was added to a stirred solution of the drug (e.g., nilotinib, apixaban, rivaroxaban) (1 mol. equiv.) in DMF (0.25 M). A solution of the carbonate or chloroformate building Block (1.1 mol. equiv.) in DMF was added. The reaction is monitored by TLC and, upon
15 completion, is evaporated to dryness under reduced pressure. The residue is dissolved in EtOAc, washed with 1M HCl solution, brine, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (10–80% EtOAc in hexanes).

20 **Method C (attachment to a sulfonamide):** DMAP (0.1 mol. equiv.) was added to a stirred solution of the drug compound (e.g., vemurafenib, dabrafenib) (1 mol. equiv.) and DIPEA (3 mol. equiv.) and the carbonate or chloroformate building Block (1.5 mol. equiv.) in 1,4-dioxane (0.2 M). The reaction mixture was then heated in a microwave at 100 °C for 3 h, quenched with water, extracted into EtOAc, washed with brine, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (50–70% EtOAc in hexanes).

25 **Method D (benzylation of amine):** A mixture of the drug compound (e.g., Palbociclib) (1 mol. equiv.) and the benzyl bromide prodrug analog (1.1 mol. equiv.) in a solvent such as acetonitrile (0.05 M) was heated at 100 °C for 1 h, cooled, evaporated to dryness. The Crude material was dissolved in EtOAc, washed with sat'd ammonium chloride

solution, water, brine solution, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (50–70% EtOAc in hexanes).

Method E (attachment to hydroxyl group): A solution of the chloroformate (1.1 mol. equiv.) in dichloromethane (0.05 M) was added to stirred solution of drug (1 mol. equiv.) and DIPEA (2 mol. equiv.) in dichloromethane (0.05 M) cooled to 0 °C. The reaction is stirred at ambient temperature over 6 hours and then diluted with water. The organic phase is extracted with dichloromethane, washed with brine, dried (MgSO₄) and evaporated to dryness under reduced pressure. Chromatography (SiO₂; ethyl acetate in hexanes) was used to isolate the desired products.

10

General synthetic procedure to deprotect prodrug compounds after synthesis

***Tert*-Butyl deprotection.** TFA was added to a solution of the protected prodrug compound in CH₂Cl₂ (0.2 M). After 15 minutes, the reaction mixture was evaporated to dryness under reduced pressure. Chromatography (C-18 25–90% acetonitrile in water) provided the desired product.

15

Ethyl and *tert*-Butyl protecting groups. TMSBr (3–20 mol. equiv.) was added dropwise to a solution of the protected prodrug compound (1 mol. equiv.) in THF, DCM or MeCN (0.2 M). The reaction was allowed to warm up to room temperature over 12 hours. The reaction was placed in an ice bath (0 °C) and quenched with MeOH. The solution was then evaporated to dryness under reduced pressure. Chromatography (C18 25–90% acetonitrile in water) provided the desired products.

20

Benzyl groups. A mixture containing Pd/C and the protected prodrug compound in EtOH was placed under an atmosphere of hydrogen and stirred for 12 h, filtered and evaporated to dryness.

25

General synthetic procedure for sodium salt formation.

To a solution of the deprotected Prodrug (1 mol. equiv.) in THF (0.2 M) is added sodium bicarbonate (2–4 mol. equiv.). The mixture is stirred for 4 hours and then evaporated to dryness under reduced pressure. If needed, the product can be purified by reverse phase chromatography (30–70% MeCN in water).

30

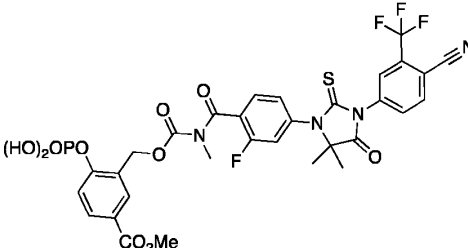
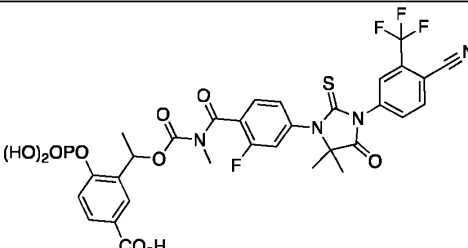
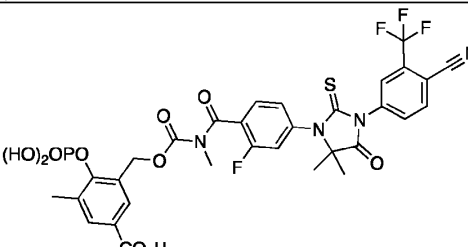
Structures of products and characterization data are provided in Table 2.

Table 2. Prodrug Compounds and Characterization Data

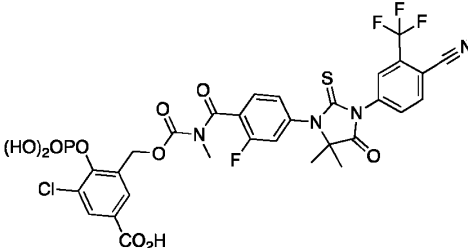
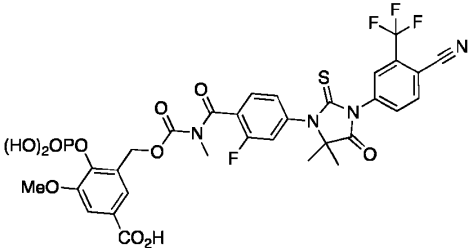
Cpd. No.		
1	Structure	
	Name	4-(((4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluorobenzoyl)(methyl)carbamoyl)oxy)methyl)-3-(phosphonooxy)benzoic acid
	Mass spec	(ES) $m/z = 739.1$ $[M+H]^+$ and 737.1 $[M-H]^-$
	NMR	1H NMR (500 MHz, DMSO- d_6) δ 8.39 (d, $J = 8.3$ Hz, 1H), 8.28 (d, $J = 1.9$ Hz, 1H), 8.07 (dd, $J = 8.3, 1.9$ Hz, 1H), 7.88 (d, $J = 1.4$ Hz, 1H), 7.74 (t, $J = 8.0$ Hz, 1H), 7.66 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.39–7.27 (m, 2H), 5.21 (s, 2H), 3.35 (s, 3H), 1.42 (s, 6H).
2	Structure	
	Name	4-(((4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluorobenzoyl)(methyl)carbamoyl)oxy)methyl)-2-methyl-3-(phosphonooxy)benzoic acid
	Mass spec	(ES) $m/z = 753.1$ $[M+H]^+$
	NMR	1H NMR (500 MHz, DMSO- d_6 /D $_2$ O) 8.34 (d, $J = 8.3$ Hz, 1H), 8.25 (d, $J = 1.9$ Hz, 1H), 8.04 (dd, $J = 8.1, 2.0$ Hz, 1H), 7.70 (t, $J = 8.0$ Hz, 1H), 7.36 (d, $J = 8.1$ Hz, 1H), 7.34 (dd, $J = 10.6, 1.9$ Hz, 1H), 7.28 (dd, $J = 8.2, 1.9$ Hz, 1H), 6.92 (d, $J = 8.1$ Hz, 1H), 5.32 (s, 2H), 3.33 (s, 3H), 2.38 (s, 3H), 1.37 (s, 6H). As sodium salt: 1H NMR (500 MHz, D $_2$ O) δ 8.24 (d, $J = 8.3$ Hz, 1H), 8.12 (s, 1H), 7.99 (d, $J = 8.6$ Hz, 1H), 7.73 (t, $J = 8.0$ Hz, 1H), 7.36 (t, $J = 8.2$ Hz, 2H), 7.07–6.98 (m, 2H), 5.45 (s, 2H), 3.44 (s, 3H), 2.34 (s, 3H), 1.56 (s, 6H).

3	Structure	
	Name	4-(((4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluorobenzoyl)(methyl)carbamoyl)oxy)methyl)-2-fluoro-3-(phosphonooxy)benzoic acid
4	Structure	
	Name	methyl 4-[[[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]-2-fluorobenzoyl]-methylcarbamoyl]oxymethyl]-3-phosphonooxybenzoate
	NMR	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.40 (d, <i>J</i> = 8.2 Hz, 1H), 8.29 (d, <i>J</i> = 1.9 Hz, 1H), 8.08 (dd, <i>J</i> = 8.2, 1.9 Hz, 1H), 7.90 (t, <i>J</i> = 1.5 Hz, 1H), 7.75 (t, <i>J</i> = 8.0 Hz, 1H), 7.70 (dd, <i>J</i> = 8.1, 1.7 Hz, 1H), 7.42–7.29 (m, 3H), 5.22 (s, 2H), 3.86 (s, 3H), 3.36 (s, 3H) and 1.44 (s, 6H).
5	Structure	
	Name	(4-(((4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluorobenzoyl)(methyl)carbamoyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
	Mass spec	(ES) <i>m/z</i> = 775.1 [M+H] ⁺
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 8.14 (d, <i>J</i> = 8.3 Hz, 1H), 8.04 (d, <i>J</i> = 2.1 Hz, 1H), 7.90 (dd, <i>J</i> = 8.3, 2.0 Hz, 1H), 7.65 (t, <i>J</i> = 7.9 Hz, 1H), 7.52 (d, <i>J</i> = 12.7 Hz, 1H), 7.34 – 7.26 (m, 3H), 7.16 (dd, <i>J</i> = 7.7, 3.7 Hz, 1H), 5.26 (s, 2H), 3.35 (s, 3H), 1.53 (s, 6H).

6	Structure	
	Name	[4-[[[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]-2-fluoro-benzoyl]-methyl-carbamoyl]oxymethyl]-2-methyl-3-phosphonooxy-phenyl]phosphonic acid
	Mass spec	787.1 [M-H] ⁻
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 8.15 (d, <i>J</i> = 8.3 Hz, 1H), 8.04 (d, <i>J</i> = 2.0 Hz, 1H), 7.90 (dd, <i>J</i> = 8.2, 2.0 Hz, 1H), 7.65 (t, <i>J</i> = 7.9 Hz, 1H), 7.45 (dd, <i>J</i> = 12.2, 7.7 Hz, 1H), 7.33–7.27 (m, 2H), 6.97 (dd, <i>J</i> = 7.9, 3.7 Hz, 1H), 5.39 (s, 2H), 3.35 (s, 3H), 2.48 (s, 3H), 1.50 (d, <i>J</i> = 5.4 Hz, 6H).
7	Structure	
	Name	3-(((4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluorobenzoyl)(methyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)benzoic acid
	Mass spec	HRMS (ESI): <i>m/z</i> : [M + H] ⁺ calcd for C ₃₀ H ₂₃ F ₄ N ₄ O ₁₀ PS, 739.0881; found, 739.0890
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 7.69 (d, <i>J</i> = 8.2 Hz, 1H), 7.57 (s, 1H), 7.43 (d, <i>J</i> = 10.5 Hz, 1H), 7.28–7.18 (m, 2H), 7.12 (s, 1H), 6.86 (d, <i>J</i> = 8.7 Hz, 1H), 6.79–6.76 (m, 2H), 4.79 (s, 2H), 2.92 (s, 3H), 0.91 (s, 6H). ¹³ C NMR (125 MHz, methanol- <i>d</i> ₄) δ 181.60, 176.63, 174.87, 168.81, 159.91 (d, <i>J</i> = 250.2 Hz), 155.72 (d, <i>J</i> = 5.8 Hz), 155.56, 139.87 (d, <i>J</i> = 10.2 Hz), 139.45, 136.80, 134.50, 133.85 (q, <i>J</i> = 33.1 Hz), 131.57, 130.98 (d, <i>J</i> = 4.0 Hz), 130.52, 128.92 (q, <i>J</i> = 4.7 Hz), 128.42 (d, <i>J</i> = 15.9 Hz), 127.28 (d, <i>J</i> = 3.3 Hz), 126.03 (d, <i>J</i> = 6.8 Hz), 123.69 (q, <i>J</i> = 273.8 Hz), 122.70, 120.04 (d, <i>J</i> = 2.1 Hz), 118.61 (d, <i>J</i> = 23.8 Hz), 116.00, 110.76 (d, <i>J</i> = 2.4 Hz), 68.09, 66.27, 32.37, 23.73 (2C). ³¹ P NMR (202 MHz, methanol- <i>d</i> ₄) δ -1.34.

8	Structure	
	Name	methyl 3-[[[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]-2-fluoro-benzoyl]-methyl-carbamoyl]oxymethyl]-4-phosphonooxy-benzoate
	Mass spec	(ES) $m/z = 753.0$ $[M+H]^+$ and 751.0 $[M-H]^-$
	NMR	1H NMR (500 MHz, DMSO- d_6) δ 8.40 (d, $J = 8.3$ Hz, 1H), 8.28 (d, $J = 1.9$ Hz, 1H), 8.07 (dd, $J = 8.2, 2.0$ Hz, 1H), 7.96 (dd, $J = 8.6, 2.3$ Hz, 1H), 7.86 (dd, $J = 2.2, 1.0$ Hz, 1H), 7.75 (t, $J = 8.0$ Hz, 1H), 7.46 (dd, $J = 8.6, 1.0$ Hz, 1H), 7.34 (dd, $J = 10.6, 1.9$ Hz, 1H), 7.29 (dd, $J = 8.1, 1.8$ Hz, 1H), 5.20 (s, 2H), 3.86 (s, 3H), 3.34 (s, 3H), 1.42 (s, 6H).
9	Structure	
	Name	3-[1-[[[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]-2-fluoro-benzoyl]-methyl-carbamoyl]oxyethyl]-4-phosphonooxy-benzoic acid
	Mass spec	(ES) $m/z = 776.1$ $[M+Na]^+$ and 751.0 $[M-H]^-$
	NMR	1H NMR (500 MHz, DMSO- d_6) δ 8.39 (d, $J = 8.3$ Hz, 1H), 8.28 (d, $J = 1.9$ Hz, 1H), 8.07 (dd, $J = 8.3, 1.9$ Hz, 1H), 7.88 (d, $J = 1.4$ Hz, 1H), 7.74 (t, $J = 8.0$ Hz, 1H), 7.66 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.39–7.27 (m, 2H), 5.21 (s, 2H), 3.35 (s, 3H), 1.42 (s, 6H).
10	Structure	

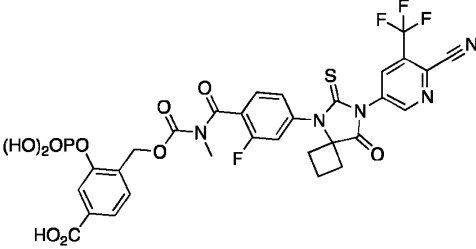
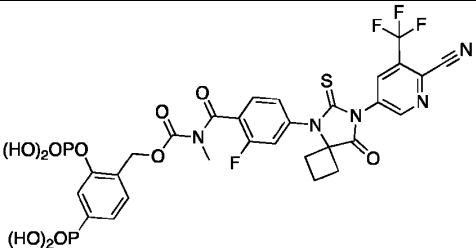
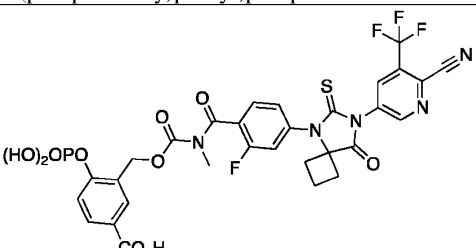
	Name	3-((((4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluorobenzoyl)(methyl)carbamoyl)oxy)methyl)-5-methyl-4-(phosphonooxy)benzoic acid
	Mass spec	HRMS (ESI) calcd C ₃₁ H ₂₅ F ₄ N ₄ O ₁₀ PSNa [M + Na] ⁺ 775.0857; found 775.0858
	NMR	δ 8.15 (s, 1H), 8.14 (d, J = 4.6 Hz, 1H), 7.97 (dd, J = 8.2, 2.1 Hz, 1H), 7.79 (d, J = 2.4 Hz, 1H), 7.69 (br d, J = 2.4 Hz, 1H), 7.66 (t, J = 7.9 Hz, 1H), 7.24 (dd, J = 8.1, 2.0 Hz, 1H), 7.21 (dd, J = 10.4, 1.8 Hz, 1H), 5.47 (s, 2H), 3.43 (s, 3H), 2.43 (s, 3H), 1.46 (s, 6H). ¹³ C NMR (125 MHz, methanol- <i>d</i> ₄) δ 181.58, 176.55, 169.90, 168.65, 159.93 (d, J = 250.5 Hz), 155.41, 154.76 (d, J = 8.2 Hz), 140.00 (d, J = 10.2 Hz), 139.38, 136.80, 134.45, 133.85 (q, J = 33.4 Hz), 133.44, 133.32, 130.94, 129.84, 128.88 (d, J = 5.1 Hz), 128.57, 128.34, 128.22, 127.38 (d, J = 22.1 Hz), 123.67 (q, J = 273.0 Hz), 118.68 (d, J = 23.7 Hz), 115.98, 110.79, 67.98, 66.09, 32.39, 23.65 (2C), 17.61. ³¹ P NMR (202 MHz, methanol- <i>d</i> ₄) δ -4.07.
11	Structure	
	Name	3-((((4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluorobenzoyl)(methyl)carbamoyl)oxy)methyl)-5-fluoro-4-(phosphonooxy)benzoic acid
	Mass spec	HRMS (ESI) calcd for C ₃₀ H ₂₂ F ₅ N ₄ O ₁₀ PSNa [M + Na] ⁺ 779.0607; found 779.0608
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 8.22 (d, J = 8.3 Hz, 1H), 8.10 (d, J = 2.1 Hz, 1H), 7.96 (dd, J = 8.2, 2.0 Hz, 1H), 7.76 (dd, J = 8.0, 8.0 Hz, 1H), 7.56 (dd, J = 10.9, 2.1 Hz, 1H), 7.49 (s, 1H), 7.30–7.26 (m, 2H), 5.42 (s, 2H), 3.47 (s, 3H), 1.46 (s, 6H). ¹³ C NMR (125 MHz, acetonitrile- <i>d</i> ₃) δ 180.04, 176.41, 172.49, 168.15, 157.96 (d, J = 251.2 Hz), 154.53, 153.91 (d, J = 245.3 Hz), 141.55, 137.57 (d, J = 10.2 Hz), 136.77, 135.95, 132.74, 132.56 (q, J = 32.2 Hz), 131.83, 129.66, 129.13, 127.16, 126.09 (d, J = 14.7 Hz), 125.68, 123.67, 121.59 (d, J = 272.9 Hz), 116.99 (d, J = 23.2 Hz), 116.50 (d, J = 19.7 Hz), 115.16, 109.23, 67.25, 64.39, 31.68, 21.89 (2C). ³¹ P NMR (202 MHz, acetonitrile- <i>d</i> ₃) δ -2.35.

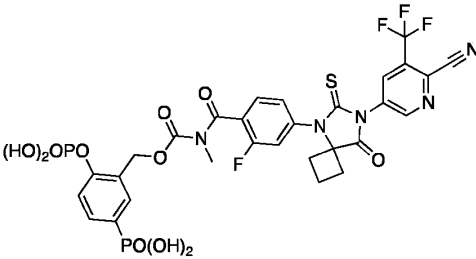
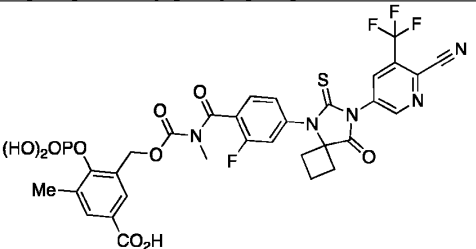
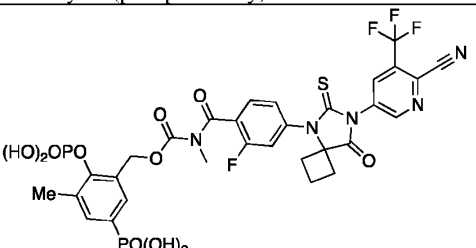
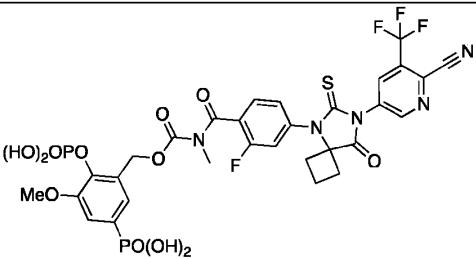
12	Structure	
	Name	3-chloro-5-[[[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]-2-fluoro-benzoyl]-methyl-carbamoyl]oxymethyl]-4-phosphonooxy-benzoic acid
	Mass spec	(ES) $m/z = 773.1$ $[M+H]^+$ and 771.1 $[M-H]^-$
	NMR	1H NMR (500 MHz, D_2O) δ 8.23 (d, $J = 8.3$ Hz, 1H), 8.10 (d, $J = 2.0$ Hz, 1H), 7.96 (dd, $J = 8.2$, 2.0 Hz, 1H), 7.82 (d, $J = 2.1$ Hz, 1H), 7.75 (t, $J = 8.0$ Hz, 1H), 7.59 (d, $J = 2.2$ Hz, 1H), 7.28–7.21 (m, 2H), 5.45 (s, 2H), 3.47 (s, 3H), 1.42 (s, 6H).
13	Structure	
	Name	3-Methoxy-5-[[[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]-2-fluoro-benzoyl]-methyl-carbamoyl]oxymethyl]-4-phosphonooxy-benzoic acid
	Mass spec	HRMS (ESI) calcd for $C_{31}H_{25}F_4N_4O_{11}PS$ $[M + H]^+$ 769.0986; found 769.0989
	NMR	1H NMR (500 MHz, D_2O) δ 8.14 (d, $J = 8.2$ Hz, 1H), 8.01 (d, $J = 2.3$ Hz, 1H), 7.87 (dd, $J = 8.2$, 2.1 Hz, 1H), 7.68 (dd, $J = 8.0$, 8.0 Hz, 1H), 7.36 (d, $J = 2.3$ Hz, 1H), 7.21 (d, $J = 2.1$ Hz, 1H), 7.19–7.14 (m, 2H), 5.34 (s, 2H), 3.76 (s, 3H), 3.38 (s, 3H), 1.32 (s, 6H). ^{13}C NMR (125 MHz, D_2O) δ 180.52, 177.09, 173.99, 168.91, 158.43 (d, $J = 251.5$ Hz), 155.08, 151.16, 142.15 (d, $J = 7.3$ Hz), 137.85 (d, $J = 8.9$ Hz), 136.85, 136.29, 133.42 (q, $J = 32.3$ Hz), 132.98, 132.24, 130.15, 127.78, 127.48, 126.37 (d, $J = 14.6$ Hz), 125.95, 121.91 (q, $J = 272.7$ Hz), 120.71, 117.35 (d, $J = 23.8$ Hz), 115.74, 113.12, 109.82, 67.69, 65.16, 55.75, 32.14, 22.13 (2C). ^{31}P NMR (202 MHz, D_2O) δ 0.35.

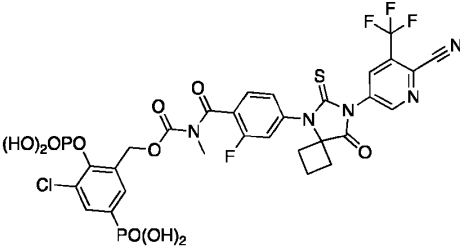
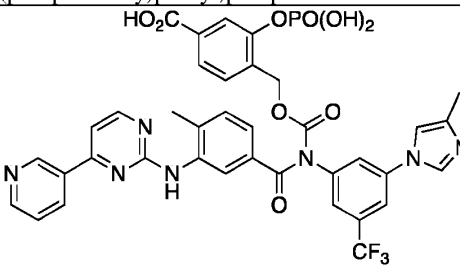
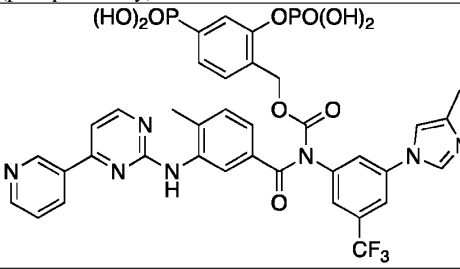
14	Structure	
	Name	(3-((((4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluorobenzoyl)(methyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
	Mass spec	(ES) $m/z = 775.1$ $[M+H]^+$
	NMR	As sodium salt: ^1H NMR (500 MHz, D_2O) δ 8.12 (d, $J = 8.3$ Hz, 1H), 8.01 (d, $J = 1.9$ Hz, 1H), 7.87 (dd, $J = 8.3$, 2.0 Hz, 1H), 7.64 (t, $J = 7.9$ Hz, 1H), 7.60–7.54 (m, 2H), 7.36 (dd, $J = 8.6$, 2.9 Hz, 1H), 7.29–7.23 (m, 2H), 5.25 (s, 2H), 3.36 (s, 3H), 1.50 (s, 6H)
15	Structure	
	Name	Methyl 5-[[[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]-2-fluoro-benzoyl]-methyl-carbamoyl]oxymethyl]-2-phosphonooxybenzoate
	Mass spec	(ES) $m/z = 753.0$ $[M+H]^+$
	NMR	^1H NMR (500 MHz, CDCl_3) δ 8.17 (d, $J = 8.2$ Hz, 2H), 8.02 (d, $J = 8.3$ Hz, 1H), 7.74 (s, 1H), 7.63 (t, $J = 7.7$ Hz, 1H), 7.48–7.38 (m, 2H), 7.31 (d, $J = 8.3$ Hz, 1H), 7.22 (d, $J = 10.5$ Hz, 1H), 5.12 (d, $J = 4.4$ Hz, 2H), 3.89 (dd, $J = 4.5$, 1.6 Hz, 3H), 3.39 (t, $J = 2.7$ Hz, 3H), 1.52 (s, 3H) and 1.51 (s, 3H).
16	Structure	
	Name	3-[[[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]-2-fluoro-benzoyl]-methyl-carbamoyl]oxymethyl]-2-phosphonooxybenzoic acid

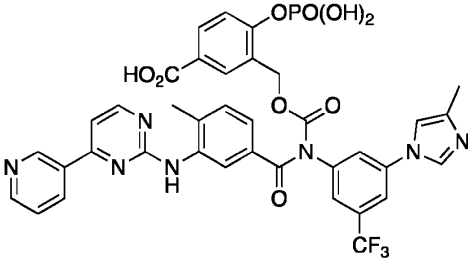
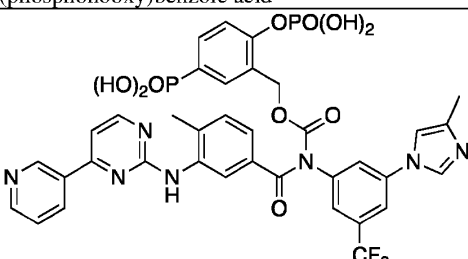
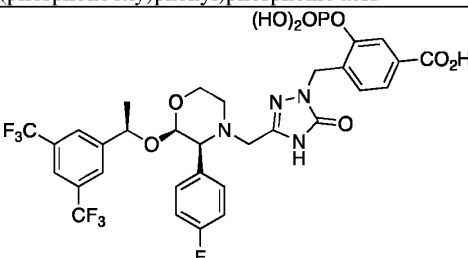
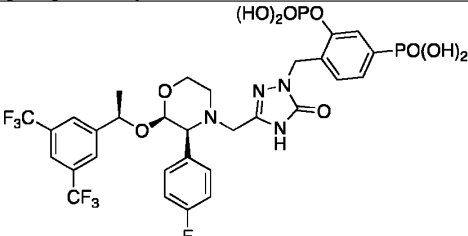
		fluoro-benzoyl]-methyl-amino]methyl]-4-phosphonooxy-benzoic acid
	Mass spec	(ES) $m/z = 693.0$ $[M-H]^-$
	NMR	
17	Structure	
	Name	4-((4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamido)methyl)-3-(phosphonooxy)benzoic acid sodium salt
	Mass spec	(ES) $m/z = 695.1$ $[M+H]^+$
18	Structure	
	Name	(3-((4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamido)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
19	Structure	
	Name	4-((4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamido)methyl)-3-(phosphonooxy)phenyl)phosphonic acid sodium salt
	Mass spec	(ES) $m/z = 731.1$ $[M+H]^+$
	NMR	1H NMR (500 MHz, D_2O) δ 8.17 (t, $J = 7.5$ Hz, 1H), 8.07 (d, $J = 9.4$ Hz, 1H), 7.93 (t, $J = 8.6$ Hz, 1H), 7.70–7.50 (m, 2H), 7.46–7.28 (m, 4H), 7.23 (dd, $J = 7.9, 3.7$ Hz, 1H), 7.07 (dd, $J = 7.8, 3.7$ Hz, 1H), 4.67 (s, 2H), 3.03–2.99 (m, 3H), 1.60 (s, 3H), 1.56 (s, 3H).

20	Structure	
	Name	[4-[[[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]-2-fluoro-benzoyl]-methyl-amino]methyl]-2-methyl-3-phosphonooxy-phenyl]phosphonic acid
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 8.15 (d, <i>J</i> = 8.3 Hz, 1H), 8.04 (d, <i>J</i> = 2.0 Hz, 1H), 7.90 (dd, <i>J</i> = 8.2, 2.0 Hz, 1H), 7.65 (t, <i>J</i> = 7.9 Hz, 1H), 7.45 (dd, <i>J</i> = 12.2, 7.7 Hz, 1H), 7.33–7.27 (m, 2H), 6.97 (dd, <i>J</i> = 7.9, 3.7 Hz, 1H), 5.39 (s, 2H), 3.35 (s, 3H), 2.48 (s, 3H), 1.50 (d, <i>J</i> = 5.4 Hz, 6H).
21	Structure	
	Name	3-((4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro- <i>N</i> -methylbenzamido)methyl)-5-fluoro-4-(phosphonooxy)benzoic acid
22	Structure	
	Name	3-((4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro- <i>N</i> -methylbenzamido)methyl)-5-methoxy-4-(phosphonooxy)benzoic acid
23	Structure	
	Name	3-chloro-5-((4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro- <i>N</i> -methylbenzamido)methyl)-4-(phosphonooxy)benzoic acid

	Mass spec	(ES) $m/z = 729.1$ $[M+H]^+$
24	Structure	
	Name	4-((((4-(7-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)-2-fluorobenzoyl)(methyl)carbamoyl)oxy)methyl)-3-(phosphonooxy)benzoic acid
25	Structure	
	Name	4-((((4-(7-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)-2-fluorobenzoyl)(methyl)carbamoyl)oxy)methyl)-3-(phosphonooxy)phenylphosphonic acid
26	Structure	
	Name	3-((((4-(7-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)-2-fluorobenzoyl)(methyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)benzoic acid
	Mass spec	(ES) $m/z = 750.0$ $[M+H]^+$
	NMR	^1H NMR (500 MHz, D_2O) δ 9.00 (d, $J = 2.2$ Hz, 1H), 8.51 (d, $J = 2.1$ Hz, 1H), 7.76 (t, $J = 7.9$ Hz, 1H), 7.69 (dd, $J = 8.5, 2.3$ Hz, 1H), 7.59 (d, $J = 2.2$ Hz, 1H), 7.37–7.26 (m, 3H), 7.18 (s, 1H), 5.27 (s, 3H), 3.39 (s, 3H), 2.65 (s, 1H), 2.54 (tt, $J = 11.5, 3.9$ Hz, 2H), 2.38 (dt, $J = 13.8, 10.5$ Hz, 2H), 1.88 (dp, $J = 11.3, 9.1$ Hz, 2H), 1.40–1.28 (m, 1H).

27	Structure	
	Name	(3-((((4-(7-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)-2-fluorobenzoyl)(methyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
28	Structure	
	Name	3-((((4-(7-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)-2-fluorobenzoyl)(methyl)carbamoyl)oxy)methyl)-5-methyl-4-(phosphonooxy)benzoic acid
29	Structure	
	Name	(3-((((4-(7-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)-2-fluorobenzoyl)(methyl)carbamoyl)oxy)methyl)-5-methyl-4-(phosphonooxy)phenyl)phosphonic acid
30	Structure	
	Name	(3-((((4-(7-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)-2-fluorobenzoyl)(methyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid

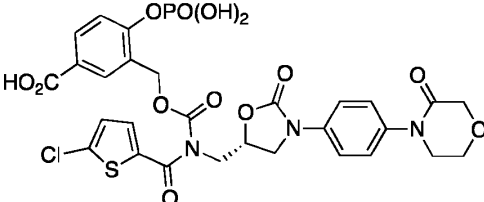
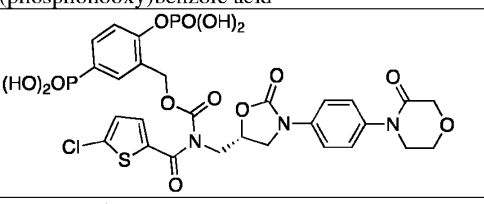
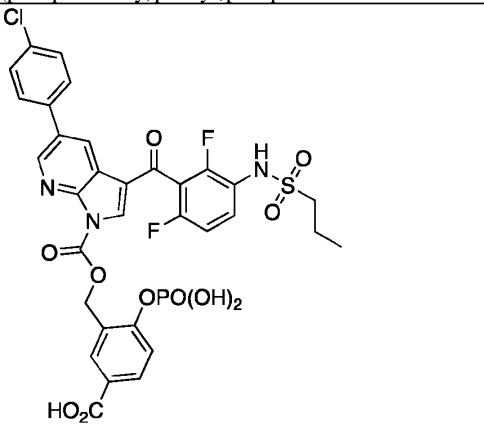
		5-methoxy-4-(phosphonooxy)phenyl)phosphonic acid
31	Structure	
	Name	(3-chloro-5-(((4-(7-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)-2-fluorobenzoyl)(methyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
32	Structure	
	Name	4-(((3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)benzoyl)carbamoyl)oxy)methyl)-3-(phosphonooxy)benzoic acid
33	Structure	
	Name	4-(((3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)benzoyl)carbamoyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid

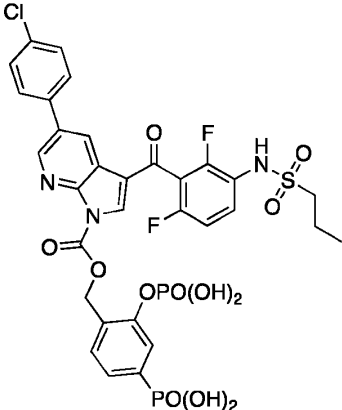
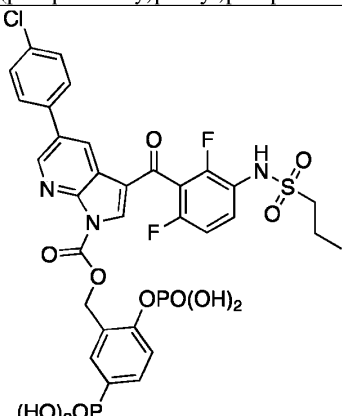
34	Structure	
	Name	3-(((3-(4-methyl-1 <i>H</i> -imidazol-1-yl)-5-(trifluoromethyl)phenyl)(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)benzoyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)benzoic acid
35	Structure	
	Name	(3-(((3-(4-methyl-1 <i>H</i> -imidazol-1-yl)-5-(trifluoromethyl)phenyl)(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)benzoyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
36	Structure	
	Name	4-((3-(((2 <i>R</i> ,3 <i>S</i>)-2-((<i>R</i>)-1-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(4-fluorophenyl)morpholino)methyl)-5-oxo-4,5-dihydro-1 <i>H</i> -1,2,4-triazol-1-yl)methyl)-3-(phosphonooxy)benzoic acid
37	Structure	

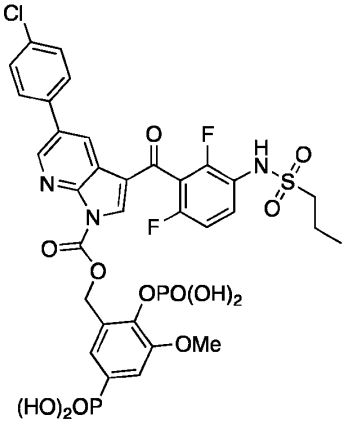
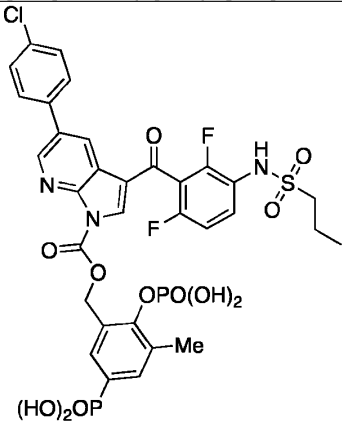
	Name	(4-(((3-(((2 <i>R</i> ,3 <i>S</i>)-2-((<i>R</i>)-1-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(4-fluorophenyl)morpholino)methyl)-5-oxo-4,5-dihydro-1 <i>H</i> -1,2,4-triazol-1-yl)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
38	Structure	
	Name	(3-(((3-(((2 <i>R</i> ,3 <i>S</i>)-2-((<i>R</i>)-1-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(4-fluorophenyl)morpholino)methyl)-5-oxo-4,5-dihydro-1 <i>H</i> -1,2,4-triazol-1-yl)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
39	Structure	
	Name	(4-(((3-(((2 <i>R</i> ,3 <i>S</i>)-2-((<i>R</i>)-1-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(4-fluorophenyl)morpholino)methyl)-5-oxo-4,5-dihydro-1 <i>H</i> -1,2,4-triazole-1-carbonyl)oxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
40	Structure	
	Name	(3-(((3-(((2 <i>R</i> ,3 <i>S</i>)-2-((<i>R</i>)-1-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(4-fluorophenyl)morpholino)methyl)-5-oxo-4,5-dihydro-1 <i>H</i> -1,2,4-triazole-1-carbonyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid

41	Structure	
	Name	3-(((1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carbonyl)carbamoyloxy)methyl)-4-(phosphonoxy)benzoic acid sodium salt
	Mass spec	HRMS (ESI) calcd for $C_{34}H_{32}N_5O_{12}P [M-H]^-$ 732.1712; found 732.1705
	NMR	δ 7.95 (d, J = 2.9 Hz, 1H), 7.85 (dd, J = 8.5, 2.3 Hz, 1H), 7.53–7.46 (m, 3H), 7.39 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 5.42 (s, 2H), 4.13 (t, J = 6.8 Hz, 2H), 3.86 (s, 3H), 3.65–3.59 (m, 2H), 3.28 (t, J = 6.8 Hz, 2H), 2.52 (t, J = 6.1 Hz, 2H), 1.95–1.88 (m, 4H). (125 MHz, D_2O) δ 175.66, 174.83, 162.46, 160.19, 159.26, 155.51 (d, J = 6.2 Hz), 153.19, 141.85, 140.98, 140.53, 133.84, 132.75, 131.38, 131.15, 130.59, 128.66, 128.00 (2C), 127.85 (2C), 127.24 (2C), 126.22 (d, J = 6.2 Hz), 119.83 (d, J = 2.9 Hz), 114.67 (2C), 64.50, 56.28, 52.87, 52.06, 32.26, 22.97, 21.09, 20.81. ^{31}P NMR (202 MHz, D_2O) δ –0.38.
42	Structure	
	Name	(4-((1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamido)methyl)-2-methyl-3-(phosphonoxy)phenyl)phosphonic acid

43	Structure	
	Name	(3-((1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamido)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
44	Structure	
	Name	(4-((1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamido)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
45	Structure	
	Name	(R)-4-((((5-chlorothiophene-2-carbonyl)((2-oxo-3-(4-(3-oxomorpholino)phenyl)oxazolidin-5-yl)methyl)carbamoyl)oxy)methyl)-3-(phosphonooxy)benzoic acid
46	Structure	
	Name	(R)-4-((((5-chlorothiophene-2-carbonyl)((2-oxo-3-(4-(3-oxomorpholino)phenyl)oxazolidin-5-yl)methyl)carbamoyl)oxy)methyl)-3-(phosphonooxy)benzoic acid

		yl)methyl)carbamoyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
47	Structure	
	Name	(R)-3-(((5-chlorothiophene-2-carbonyl)((2-oxo-3-(4-(3-oxomorpholino)phenyl)oxazolidin-5-yl)methyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)benzoic acid
48	Structure	
	Name	(R)-3-(((5-chlorothiophene-2-carbonyl)((2-oxo-3-(4-(3-oxomorpholino)phenyl)oxazolidin-5-yl)methyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)benzoic acid
49	Structure	
	Name	3-(((5-(4-chlorophenyl)-3-(2,6-difluoro-3-(propylsulfonamido)benzoyl)-1H-pyrrolo[2,3-b]pyridine-1-carbonyl)oxy)methyl)-4-(phosphonooxy)benzoic acid
	Mass spec	HRMS (ESI) calcd for C ₃₂ H ₂₅ ClF ₂ N ₃ O ₁₁ PS [M – H] [–] 762.0531; found 762.0525.
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 8.56 (d, J = 2.1 Hz, 1H), 7.94–7.86 (m, 4H), 7.58 (d, J = 9.3 Hz, 1H), 7.55–7.51 (m, 2H), 7.46–7.34 (m, 4H), 5.58 (s, 2H), 4.08–3.87 (m, 2H), 2.07–1.92 (m, 2H), 1.14 (t, J = 7.5 Hz, 3H). ¹³ C NMR (125 MHz, methanol- <i>d</i> ₄) δ 182.11, 175.05, 161.03 (dd, J = 253.7, 7.0 Hz), 157.08 (d, J = 5.8 Hz), 156.57 (dd, J = 252.0, 8.7 Hz), 153.66, 150.51, 144.74,

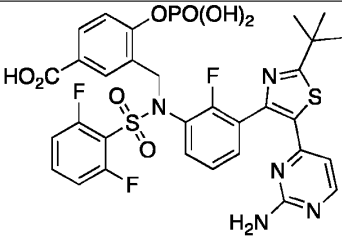
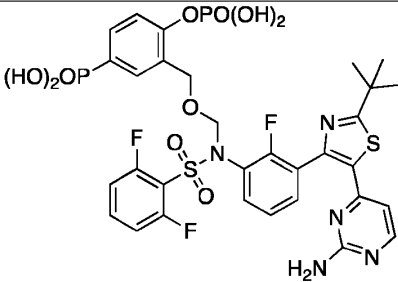
		141.00, 139.78, 138.80, 134.87 (d, $J = 9.9$ Hz), 134.74, 133.19, 132.42, 132.00, 130.22 (2C), 129.91 (2C), 129.44, 125.19 (d, $J = 6.7$ Hz), 121.38 (dd, $J = 15.0, 4.0$ Hz), 120.26 (d, $J = 2.5$ Hz), 119.69, 119.46 (dd, $J = 23.1, 23.1$ Hz), 116.99, 113.61 (dd, $J = 22.9, 3.5$ Hz), 66.37, 56.82, 17.99, 13.11. ^{31}P NMR (202 MHz, D_2O) δ -0.26 .
50	Structure	
	Name	4-(((5-(4-chlorophenyl)-3-(2,6-difluoro-3-(propylsulfonamido)benzoyl)-1H-pyrrolo[2,3-b]pyridine-1-carbonyl)oxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
51	Structure	
	Name	3-(((5-(4-chlorophenyl)-3-(2,6-difluoro-3-(propylsulfonamido)benzoyl)-1H-pyrrolo[2,3-b]pyridine-1-carbonyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
	Mass spec	HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{26}\text{ClF}_2\text{N}_3\text{O}_{12}\text{P}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 800.0442; found, 800.0429.
	NMR	^1H NMR (500 MHz, D_2O) δ 8.39 (s, 1H), 7.69 (s, 1H), 7.66–7.59 (m, 1H), 7.59–7.45 (m, 3H), 7.41 (d, $J = 8.5$ Hz, 2H), 7.35–7.24 (m, 3H), 7.15 (t, $J = 8.6$ Hz, 1H), 5.36 (d, $J = 11.4$ Hz, 1H), 5.30 (d, $J = 11.7$ Hz, 1H), 3.77 (m, $J = 14.8, 7.9$ Hz, 1H),

		3.67 (m, $J = 14.8, 7.7$ Hz, 1H), 1.83–1.73 (m, 2H), 0.91 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (125 MHz, methanol- d_4) δ 182.15, 160.67 (dd, $J = 253.6, 7.5$ Hz), 156.49 (dd, $J = 252.1, 9.0$ Hz), 156.35 (dd, $J = 5.7, 3.4$ Hz), 153.83, 150.88, 144.66, 141.23, 138.83, 134.89 (d, $J = 20.3$ Hz), 134.89, 134.71, 134.33 (d, $J = 9.6$ Hz), 133.45, 132.31, 130.22 (2C), 129.89 (2C), 129.41, 124.58 (dd, $J = 13.8, 7.1$ Hz), 121.24 (dd, $J = 15.0, 4.2$ Hz), 120.32 (d, $J = 13.6$ Hz), 119.79, 119.40 (t, $J = 23.5$ Hz) 116.88, 113.71 (dd, $J = 23.2, 4.0$ Hz), 67.43, 56.81, 17.93, 13.13. ^{31}P NMR (202 MHz, D_2O) δ 11.84, -0.09 .
52	Structure	
	Name	(3-(((5-(4-chlorophenyl)-3-(2,6-difluoro-3-(propylsulfonamido)benzoyl)-1H-pyrrolo[2,3-b]pyridine-1-carbonyl)oxy)methyl)-5-methoxy-4-(phosphonoxy)phenyl)phosphonic acid
53	Structure	
	Name	(3-(((5-(4-chlorophenyl)-3-(2,6-difluoro-3-(propylsulfonamido)benzoyl)-1H-pyrrolo[2,3-b]pyridine-1-carbonyl)oxy)methyl)-5-methyl-4-(phosphonoxy)phenyl)phosphonic acid

54	Structure	(HO)₂OP
	Name	(3-(((5-(4-chlorophenyl)-3-(2,6-difluoro-3-(propylsulfonamido)benzoyl)-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine-1-carbonyl)oxy)methyl)-5-chloro-4-(phosphonooxy)phenyl)phosphonic acid
55	Structure	PO(OH)₂
	Name	(4-(((5-(4-chlorophenyl)-3-(2,6-difluoro-3-(propylsulfonamido)benzoyl)-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine-1-carbonyl)oxy)methyl)-2-methyl-3-(phosphonooxy)phenyl)phosphonic acid
56	Structure	HO₂C

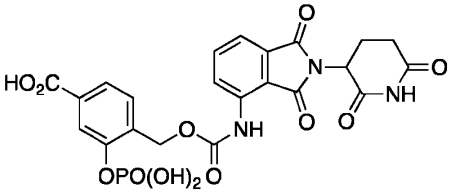
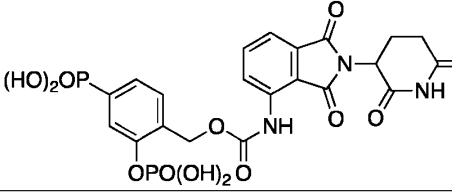
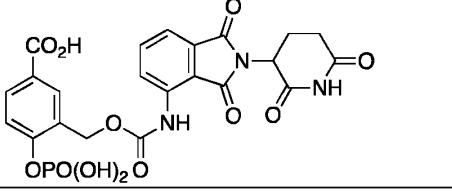
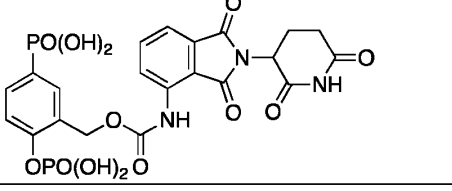
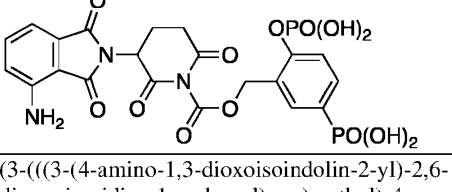
	Name	3-(((5-(4-chlorophenyl)-3-(2,6-difluoro-3-(propylsulfonamido)benzoyl)-1H-pyrrolo[2,3-b]pyridine-1-carbonyl)oxy)methyl)-5-methyl-4-(phosphonooxy)benzoic acid
	Mass Spec	(ES) $m/z = 778.1$ [M+H] ⁺
57	Structure	
	Name	3-((5-(4-chlorophenyl)-3-(2,6-difluoro-3-(propylsulfonamido)benzoyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl)-4-(phosphonooxy)benzoic acid
	Mass spec	(ES) $m/z = 721.10$ [M+H] ⁺
	NMR	¹ H NMR (500 MHz, DMSO) δ 8.70 (d, $J = 2.3$ Hz, 1H), 8.05 (d, $J = 2.3$ Hz, 1H), 7.97 (s, 1H), 7.81 (d, $J = 8.6$ Hz, 2H), 7.75 (dd, $J = 8.6, 2.3$ Hz, 1H), 7.57 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.6$ Hz, 1H), 7.44 (t, $J = 7.8$ Hz, 1H), 7.18 (t, $J = 8.7$ Hz, 1H), 4.88 (s, 2H), 3.34 (dd, $J = 9.0, 6.4$ Hz, 2H), 1.77 (h, $J = 7.5$ Hz, 2H), 0.98 (t, $J = 7.4$ Hz, 3H).
58	Structure	
	Name	4-((5-(4-chlorophenyl)-3-(2,6-difluoro-3-(propylsulfonamido)benzoyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl)-3-(phosphonooxy)phenylphosphonic acid sodium salt
	Mass spec	(ES) $m/z = 756.10$ [M+H] ⁺
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 8.69 (s, 1H), 8.56 (d, $J = 2.2$ Hz, 1H), 7.92–7.80 (m, 1H), 7.66 (d, $J = 8.3$ Hz, 2H), 7.49 (d, $J = 8.7$ Hz, 3H), 7.38–7.27 (m, 2H), 7.16 (t, $J = 8.7$ Hz, 1H), 6.65 (s, 1H),

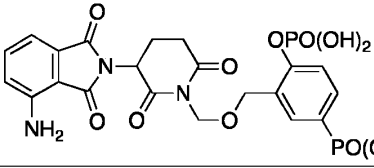
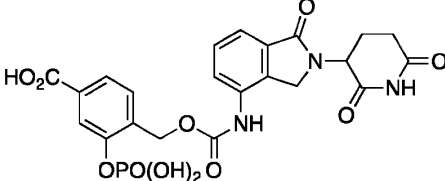
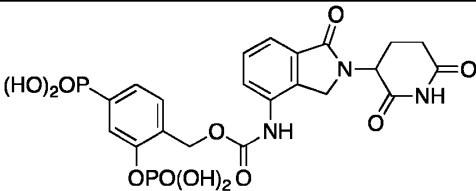
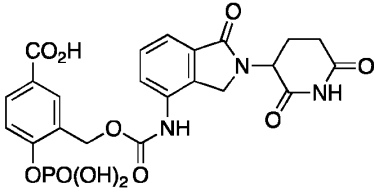
		4.93 (s, 2H), 3.79–3.33 (m, 2H), 1.86 (q, $J = 7.7$ Hz, 2H), 1.00 (t, $J = 7.4$ Hz, 3H).
59	Structure	
	Name	3-[[3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-N-propylsulfonyl-anilino]methyl]-4-phosphonoxybenzoic acid
	Mass spec	(ES) $m/z = 721.10$ [M+H] ⁺
	NMR	As sodium salt: ¹ H NMR (500 MHz, D ₂ O) δ 8.62 (d, $J = 2.0$ Hz, 1H), 8.37 (s, 1H), 7.77 (dd, $J = 8.8$, 2.2 Hz, 1H), 7.67 (t, $J = 10.6$ Hz, 3H), 7.51 (dd, $J = 15.4$, 8.4 Hz, 3H), 7.26–7.19 (m, 2H), 5.69 (s, 2H), 3.13 (d, $J = 8.8$ Hz, 2H), 1.73 (p, $J = 7.6$ Hz, 2H), 0.85 (t, $J = 7.4$ Hz, 3H).
60	Structure	
	Name	(3-(((N-(3-(5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)propylsulfonamido)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
61	Structure	
	Name	(3-(((N-(3-(5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)propylsulfonamido)methoxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 8.42 (s, 1H), 7.99 (s, 1H), 7.78 (td, $J = 8.9$, 5.8 Hz, 1H), 7.61 (d, $J = 13.0$ Hz, 1H), 7.58–7.51 (m, 1H), 7.42 (s, 2H),

		7.38 (dd, $J = 8.5, 3.0$ Hz, 1H), 7.31 (d, $J = 8.3$ Hz, 2H), 7.24 (t, $J = 8.7$ Hz, 1H), 7.17 (d, $J = 1.2$ Hz, 1H), 5.17 (s, 2H), 4.77 (s, 2H), 3.30 (t, $J = 7.8$ Hz, 2H), 1.77 (q, $J = 7.3$ Hz, 2H), 0.94 (t, $J = 7.4$ Hz, 3H).
62	Structure	
	Name	3-(((N-(3-(5-(2-aminopyrimidin-4-yl)-2-(tert-butyl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorophenyl)sulfonamido)methyl)-4-(phosphonoxy)benzoic acid
	Mass spec	HRMS (ESI) calcd for $C_{31}H_{27}F_3N_5O_8PS_2$ $[M + H]^+$ 750.1063; found, 750.1065.
	NMR	1H NMR (500 MHz, D_2O) δ 8.00 (d, $J = 5.4$ Hz, 1H), 7.90 (s, 1H), 7.73–7.61 (m, 3H), 7.53–7.47 (m, 1H), 7.35–7.27 (m, 2H), 7.13 (t, $J = 9.0$ Hz, 2H), 6.12 (d, $J = 5.5$ Hz, 1H), 5.08 (s, 2H), 1.48 (s, 9H). ^{13}C NMR (125 MHz, methanol- d_4) δ 182.67, 174.07, 163.08, 159.76 (dd, $J = 258.8, 3.9$ Hz, 2C), 158.69, 158.58, 157.07 (d, $J = 255.5$ Hz), 155.12 (d, $J = 5.6$ Hz), 146.08, 135.28 (t, $J = 11.1$ Hz), 134.05, 133.39, 131.66 (d, $J = 2.7$ Hz), 130.08, 129.86, 129.40, 126.67 (d, $J = 12.4$ Hz), 124.38–124.18 (m, 2C), 118.11 (d, $J = 2.8$ Hz), 116.84 (t, $J = 16.4$ Hz), 112.97 (dd, $J = 24.0, 3.5$ Hz, 2C), 106.59, 89.71, 49.80, 37.59, 29.59 (3C). ^{31}P NMR (202 MHz, D_2O) δ -0.34.
63	Structure	
	Name	(3-(((N-(3-(5-(2-aminopyrimidin-4-yl)-2-(tert-butyl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorophenyl)sulfonamido)methoxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid

64	Structure	
	Name	3-(((N-(3-(5-(2-aminopyrimidin-4-yl)-2-(tert-butyl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorophenyl)sulfonamido)methoxy)methyl)-4-(phosphonoxy)benzoic acid
65	Structure	
	Name	(3-(((N-(3-(5-(2-aminopyrimidin-4-yl)-2-(tert-butyl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorophenyl)sulfonamido)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
66	Structure	
	Name	4-(((4-(2-(tert-butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)pyrimidin-2-yl)carbamoyloxy)methyl)-3-(phosphonoxy)benzoic acid

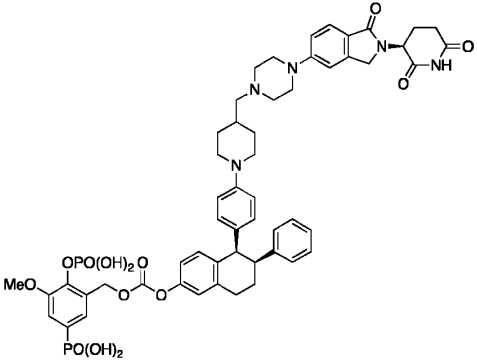
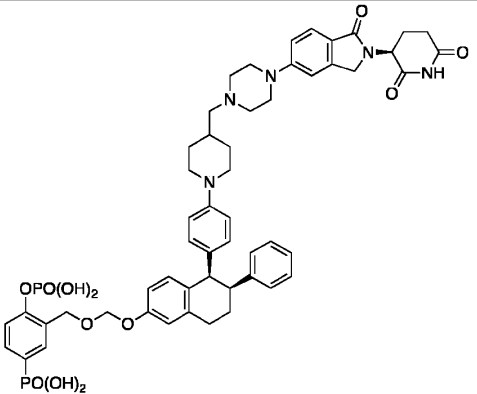
67	Structure	
	Name	(4-((((4-(2-(<i>tert</i> -butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)pyrimidin-2-yl)carbamoyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
68	Structure	
	Name	3-((((4-(2-(<i>tert</i> -butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)pyrimidin-2-yl)carbamoyl)oxy)methyl)-4-(phosphonooxy)benzoic acid
69	Structure	
	Name	(3-((((4-(2-(<i>tert</i> -butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)pyrimidin-2-yl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid

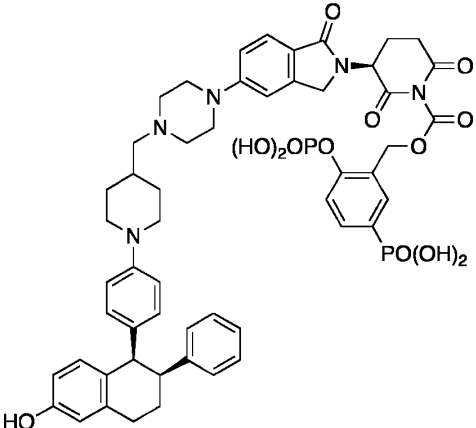
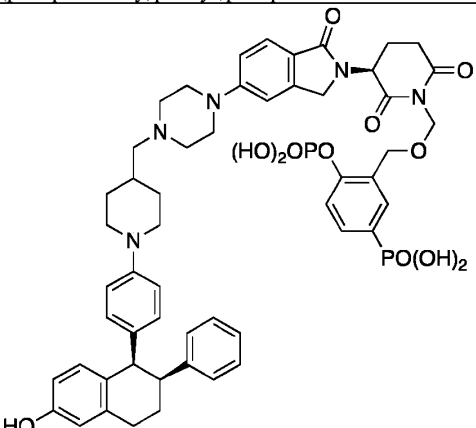
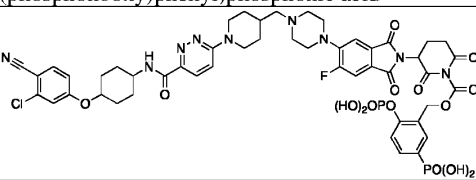
70	Structure	
	Name	4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)carbamoyl)oxy)methyl)-3-(phosphonoxy)benzoic acid
71	Structure	
	Name	(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)carbamoyl)oxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
72	Structure	
	Name	3-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)carbamoyl)oxy)methyl)-3-(phosphonoxy)benzoic acid
73	Structure	
	Name	(3-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)carbamoyl)oxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
74	Structure	
	Name	(3-(((3-(4-amino-1,3-dioxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid

75	Structure	
	Name	(3-(((3-(4-amino-1,3-dioxoisindolin-2-yl)-2,6-dioxopiperidin-1-yl)methoxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
76	Structure	
	Name	4-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)carbamoyl)oxy)methyl)-3-(phosphonoxy)benzoic acid
77	Structure	
	Name	(4-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)carbamoyl)oxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
78	Structure	
	Name	3-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)carbamoyl)oxy)methyl)-3-(phosphonoxy)benzoic acid
	Mass Spec	HRMS (ESI) calcd for C ₂₂ H ₂₀ N ₃ O ₁₁ PNa [M + Na] ⁺ 556.0728; found 556.0736
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 7.94 (d, <i>J</i> = 2.6 Hz, 1H), 7.84 (dd, <i>J</i> = 8.6, 2.4 Hz, 1H), 7.73 (d, <i>J</i> = 7.9 Hz, 1H), 7.65–7.60 (m, 1H), 7.58–7.53 (m, 1H), 7.49 (d, <i>J</i> = 8.5 Hz, 1H), 5.37 (s, 2H), 5.11 (dd, <i>J</i> = 13.4, 5.3 Hz, 1H), 4.48 (d, <i>J</i> = 17.5 Hz, 1H), 4.41 (d, <i>J</i> = 17.5 Hz, 1H), 2.94–2.84 (m, 2H), 2.50–2.41 (m, 1H), 2.29–2.18 (m, 1H). ¹³ C NMR (125 MHz, DMSO- <i>d</i> ₆) δ 172.83, 170.97, 167.79, 167.21, 156.65, 153.84, 133.94, 133.19, 132.79, 129.97, 129.83, 128.73, 126.47, 124.36, 123.28, 119.79, 118.43, 61.80, 51.62, 46.42, 31.19

		and 22.53. ^{31}P NMR (202 MHz, DMSO- d_6) δ – 5.28..
79	Structure	
	Name	3-[[[2-(2,6-dioxo-3-piperidyl)-1-oxo-isoindolin-4-yl]amino]methyl]-4-phosphonoxy-benzoic acid
	Mass spec	(ES) m/z = 490.1 $[\text{M}+\text{H}]^+$
	NMR	^1H NMR (500 MHz, DMSO) δ 11.01 (s, 1H), 7.90 (d, J = 2.2 Hz, 1H), 7.81 (dd, J = 8.5, 2.2 Hz, 1H), 7.41 (dd, J = 8.6, 1.1 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 6.94 (d, J = 7.4 Hz, 1H), 6.62 (d, J = 8.1 Hz, 1H), 5.12 (dd, J = 13.3, 5.1 Hz, 1H), 4.44 (s, 2H), 4.34 (d, J = 17.2 Hz, 1H), 4.22 (d, J = 17.1 Hz, 1H), 2.93 (ddd, J = 17.2, 13.5, 5.4 Hz, 1H), 2.61 (d, J = 3.5 Hz, 1H), 2.39–2.27 (m, 1H), 2.10 – 2.01 (m, 1H).
80	Structure	
	Name	3-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)carbamoyl)oxy)methyl)-3-(phosphonoxy)phenylphosphonic acid
81	Structure	
	Name	(3-(((3-(4-amino-1-oxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
82	Structure	
	Names	(3-(((3-(4-amino-1-oxoisindolin-2-yl)-2,6-dioxopiperidin-1-yl)methoxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid

83	Structure	
	Name	4-(((5-acrylamido-4-((2-(dimethylamino)ethyl)(methylamino)-2-methoxyphenyl)(4-(1-methyl-1H-indol-3-yl)pyrimidin-2-yl)carbamoyl)oxy)methyl)-3-(phosphonoxy)benzoic acid
84	Structure	
	Name	(3-((((((5R,6S)-5-(4-(4-((4-(2-((S)-2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy)carbonyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
85	Structure	
	Name	(3-((((((5R,6S)-5-(4-(4-((4-(2-((S)-2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy)carbonyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid

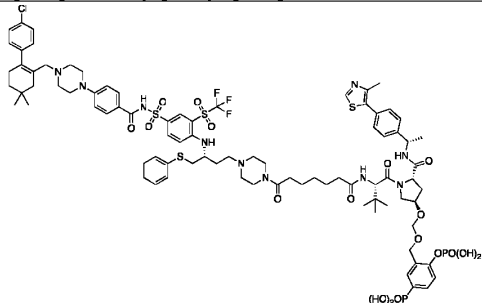
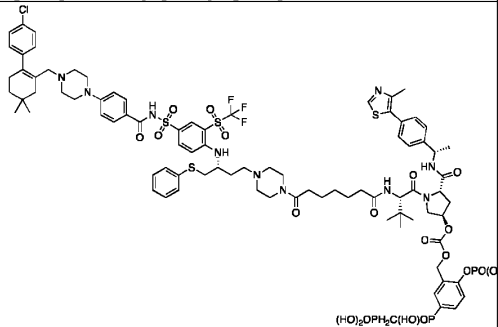
		yl)oxy)carbonyl)oxy)methyl)-5-methyl-4-(phosphonoxy)phenyl)phosphonic acid
86	Structure	
	Name	(3-((((((5 <i>R</i> ,6 <i>S</i>)-5-(4-(4-((4-(2-((<i>S</i>)-2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy)carbonyl)oxy)methyl)-5-methoxy-4-(phosphonoxy)phenyl)phosphonic acid
87	Structure	
	Name	(3-((((((5 <i>R</i> ,6 <i>S</i>)-5-(4-(4-((4-(2-((<i>S</i>)-2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy)methoxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid

88	Structure	
	Name	(3-(((S)-3-(5-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
89	Structure	
	Name	(3-(((S)-3-(5-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisindolin-2-yl)-2,6-dioxopiperidine-1-yl)methoxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
90	Structure	
	Name	(3-(((3-(5-(4-((1-(6-((4-(3-chloro-4-cyanophenoxy)cyclohexyl)carbamoyl)pyridazin-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)-6-fluoro-1,3-dioxoisindolin-2-yl)-2,6-

		dioxopiperidine-1-carbonyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
91	Structure	
	Name	(3-(((3-(5-(4-((1-(6-((4-(3-chloro-4-cyanophenoxy)cyclohexyl)carbamoyl)pyridazin-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)-6-fluoro-1,3-dioxoisindolin-2-yl)-2,6-dioxopiperidin-1-yl)methoxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
92	Structure	
	Name	(3-(((4-(3-chloro-4-cyanophenoxy)cyclohexyl)(6-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1,3-dioxoisindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)pyridazine-3-carbonyl)carbamoyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
93	Structure	
	Name	(3-(((N-(4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1,3-dioxoisindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)pyridazine-3-carboxamido)methoxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
94	Structure	
	Name	(3-(((3-(5-((S)-3-((4-(4-((3-carbamoyl-6-(piperidin-1-yl)pyrazin-2-yl)amino)phenyl)piperidin-1-yl)methyl)pyrrolidin-1-yl)-1,3-dioxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid

95	Structure	
	Name	(3-(((3-(5-((<i>S</i>)-3-((4-(4-((3-carbamoyl-6-(piperidin-1-yl)pyrazin-2-yl)amino)phenyl)piperidin-1-yl)methyl)pyrrolidin-1-yl)-1,3-dioxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl)-5-methyl-4-(phosphonooxy)phenyl)phosphonic acid
96	Structure	
	Name	(3-(((3-(5-((<i>S</i>)-3-((4-(4-((3-carbamoyl-6-(piperidin-1-yl)pyrazin-2-yl)amino)phenyl)piperidin-1-yl)methyl)pyrrolidin-1-yl)-1,3-dioxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl)-5-methoxy-4-(phosphonooxy)phenyl)phosphonic acid
97	Structure	
	Name	(3-(((3-(5-((<i>S</i>)-3-((4-(4-((3-carbamoyl-6-(piperidin-1-yl)pyrazin-2-yl)amino)phenyl)piperidin-1-yl)methyl)pyrrolidin-1-yl)-1,3-dioxoisindolin-2-yl)-2,6-dioxopiperidine-1-yl)methoxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid

98	Structure	
	Name	(3-((((3-((4-(1-(((3 <i>S</i>)-1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)pyrrolidin-3-yl)methyl)piperidin-4-yl)phenyl)amino)-5-(piperidin-1-yl)pyrazine-2-carbonyl)carbamoyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
100	Structure	
	Name	(3-((((3-((4-(1-(((3 <i>S</i>)-1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)pyrrolidin-3-yl)methyl)piperidin-4-yl)phenyl)amino)-5-(piperidin-1-yl)pyrazine-2-carboxamido)methoxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
101	Structure	
	Name	(3-((((((3 <i>R</i> ,5 <i>S</i>)-1-((<i>S</i>)-2-(7-(4-((<i>R</i>)-3-((4-(<i>N</i> -(4-(4-(4'-chloro-4,4-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-5-((<i>S</i>)-

		1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-3-yl)oxy)carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
102	Structure	
	Name	(3-((((((3 <i>R</i> ,5 <i>S</i>)-1-((<i>S</i>)-2-(7-(4-((<i>R</i>)-3-((4-(<i>N</i> -(4-(4-((4'-chloro-4,4-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-5-(((<i>S</i>)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-3-yl)oxy)methoxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
103	Structure	
	Name	((((3-((((((3 <i>R</i> ,5 <i>S</i>)-1-((<i>S</i>)-2-(7-(4-((<i>R</i>)-3-((4-(<i>N</i> -(4-(4-((4'-chloro-4,4-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-((trifluoromethyl)sulfonyl)phenyl)amino)-4-(phenylthio)butyl)piperazin-1-yl)-7-oxoheptanamido)-3,3-dimethylbutanoyl)-5-(((<i>S</i>)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-3-yl)oxy)carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)(hydroxy)phosphoryl)methyl)phosphonic acid

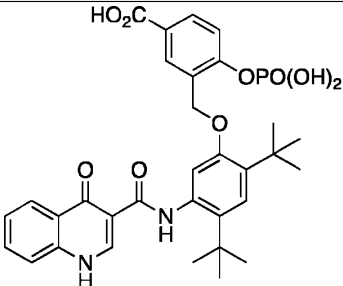
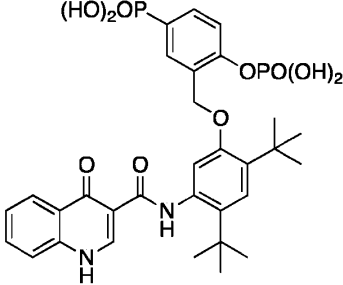
104	Structure	
	Name	(S)-((3-(((3-(4-(4-((1-(4-((3-(4-cyano-3-methoxyphenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-2-fluorobenzamido)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
105	Structure	
	Name	(S)-((3-(((3-(4-(4-((1-(4-((3-(4-cyano-3-methoxyphenoxy)-2,2,4,4-tetramethylcyclobutyl)carbamoyl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-2-fluorobenzamido)-2,6-dioxopiperidine-1-yl)methoxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
106	Structure	
	Name	(S)-((3-(((3-(6-(7-((1-(4-(6-(azetidin-1-yl)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)piperidin-4-yl)methyl)-2,7-diazaspiro[3.5]nonan-2-yl)-1-oxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl)-4-((dihydroxyphosphanyl)oxy)phenyl)phosphonic acid
107	Structure	
	Name	(S)-((3-(((3-(6-(7-((1-(4-(6-(azetidin-1-yl)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)piperidin-4-yl)methyl)-2,7-diazaspiro[3.5]nonan-2-yl)-1-oxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid

		((dihydroxyphosphaneyl)oxy)-5-methylphenylphosphonic acid
108	Structure	
	Name	(S)-3-(((3-(6-(7-((1-(4-(6-(azetidin-1-yl)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)piperidin-4-yl)methyl)-2,7-diazaspiro[3.5]nonan-2-yl)-1-oxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl)-4-((dihydroxyphosphaneyl)oxy)-5-methoxyphenyl)phosphonic acid
109	Structure	
	Name	4-((((5-acrylamido-4-((2-(dimethylamino)ethyl)(methyl)amino)-2-methoxyphenyl)(4-(1-methyl-1H-indol-3-yl)pyrimidin-2-yl)carbamoyl)oxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
110	Structure	
	Name	3-((((5-acrylamido-4-((2-(dimethylamino)ethyl)(methyl)amino)-2-methoxyphenyl)(4-(1-methyl-1H-indol-3-yl)pyrimidin-2-yl)carbamoyl)oxy)methyl)-4-(phosphonoxy)benzoic acid

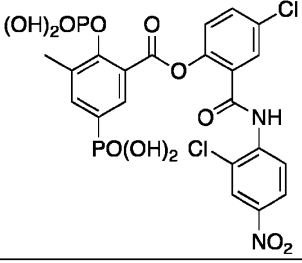
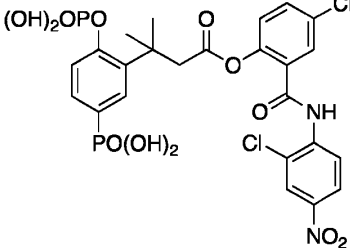
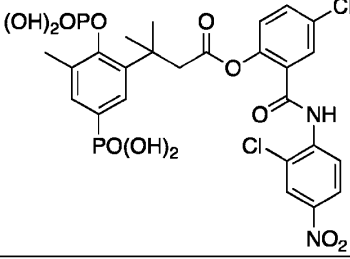
111	Structure	
	Name	(3-(((5-acrylamido-4-((2-(dimethylamino)ethyl)(methyl)amino)-2-methoxyphenyl)(4-(1-methyl-1H-indol-3-yl)pyrimidin-2-yl)carbamoyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
112	Structure	
	Name	(R)-4-(((1-(1-acryloylpiperidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)carbamoyl)oxy)methyl)-3-(phosphonoxy)benzoic acid
113	Structure	
	Name	(R)-4-(((1-(1-acryloylpiperidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)carbamoyl)oxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid

114	Structure	
	Name	(R)-3-((((1-(1-acryloylpiperidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)carbamoyl)oxy)methyl)-4-(phosphonoxy)benzoic acid
115	Structure	
	Name	(R)-3-((((1-(1-acryloylpiperidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)carbamoyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
116	Structure	
	Name	(4-(((4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
117	Structure	
	Name	(3-(((4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-

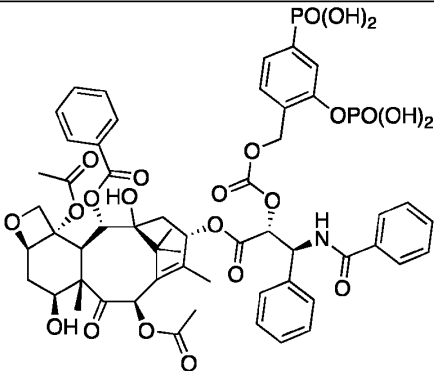
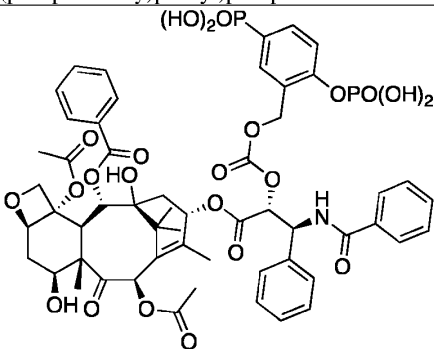
		yl)amino)pyridin-3-yl)piperazin-1-yl)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
	NMR	¹ H NMR (500 MHz, DMSO) δ 10.26 (s, 1H), 8.97 (s, 1H), 8.10 (d, <i>J</i> = 3.0 Hz, 1H), 7.90 (d, <i>J</i> = 9.1 Hz, 1H), 7.58–7.42 (m, 4H), 5.88–5.76 (m, 1H), 4.22 (s, 2H), 3.23 (s, 4H), 2.63 (t, <i>J</i> = 2.0 Hz, 4H), 2.42 (s, 3H), 2.38–2.34 (m, 3H), 2.31 (s, 2H), 1.89 (s, 2H), 1.78 (s, 2H), 1.58 (d, <i>J</i> = 4.7 Hz, 2H).
118	Structure	
	Name	4-((4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3- <i>d</i>]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)methyl)-3-(phosphonooxy)benzoic acid
119	Structure	
	Name	3-((4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3- <i>d</i>]pyrimidin-2-yl)amino)pyridin-3-yl)piperazin-1-yl)methyl)-4-(phosphonooxy)benzoic acid
	Mass spec	(ES) <i>m/z</i> = 678.3 [M+H] ⁺
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 8.74 (s, 1H), 7.97 (d, <i>J</i> = 2.9 Hz, 1H), 7.89–7.77 (m, 2H), 7.59 (d, <i>J</i> = 9.0 Hz, 1H), 7.47 (d, <i>J</i> = 8.7 Hz, 1H), 7.36 (d, <i>J</i> = 8.4 Hz, 1H), 5.59 (q, <i>J</i> = 8.6 Hz, 1H), 4.08 (s, 2H), 3.23 (d, <i>J</i> = 70.2 Hz, 8H), 2.43 (s, 3H), 2.23 (s, 3H), 2.09–1.88 (m, 2H), 1.70 (s, 4H), 1.52 (d, <i>J</i> = 9.3 Hz, 2H).
120	Structure	

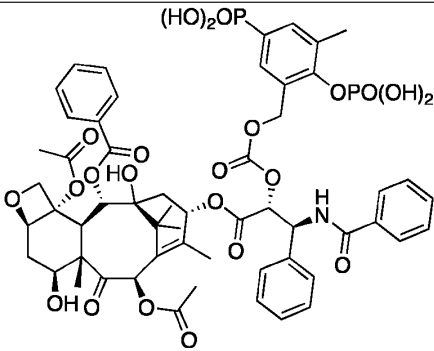
	Name	3-[[2,4-ditert-butyl-5-[(4-oxo-1H-quinoline-3-carbonyl)amino]phenoxy]carbonyloxymethyl]-4-phosphonooxy-benzoic acid
	NMR	¹ H NMR (500 MHz, DMSO) δ 12.06 (s, 1H), 8.88 (d, J = 6.6 Hz, 1H), 8.34 (dd, J = 8.2, 1.4 Hz, 1H), 8.04 (d, J = 2.2 Hz, 1H), 7.92 (dd, J = 8.5, 2.2 Hz, 1H), 7.82 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.61 (s, 1H), 7.59 – 7.48 (m, 2H), 7.39 (s, 1H), 5.36 (s, 2H), 1.46 (s, 9H), 1.31 (s, 9H).
121	Structure	
	Name	3-[[2,4-ditert-butyl-5-[(4-oxo-1H-quinoline-3-carbonyl)amino]phenoxy]methyl]-4-phosphonooxy-benzoic acid
	Mass spec	(ES) m/z = 623.2 [M+H] ⁺
	NMR	¹ H NMR (500 MHz, DMSO) δ 11.75 (s, 1H), 9.20 (s, 1H), 9.19 (s, 1H), 8.42 (dd, J = 8.1, 1.6 Hz, 1H), 7.86 (dd, J = 8.5, 2.2 Hz, 1H), 7.81 (d, J = 8.7 Hz, 1H), 7.76–7.72 (m, 1H), 7.72 (d, J = 1.6 Hz, 1H), 7.59–7.50 (m, 2H), 7.32–7.28 (m, 1H), 7.16 (d, J = 17.8 Hz, 2H), 5.83 (s, 2H), 1.40 (s, 9H), 1.36 (s, 9H).
122	Structure	
	Name	(3-((2,4-di-tert-butyl-5-(4-oxo-1,4-dihydroquinoline-3-carboxamido)phenoxy)methyl)-(phosphonooxy)phenyl)phosphonic acid

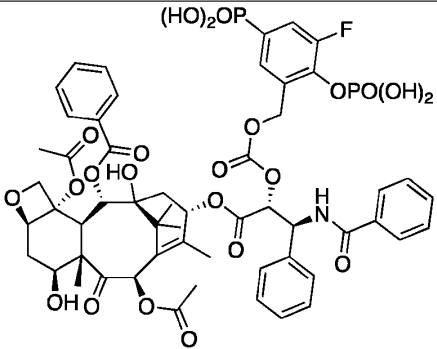
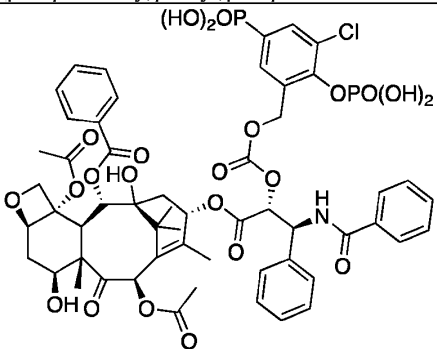
123	Structure	
	Name	(4-((2,4-di- <i>tert</i> -butyl-5-(4-oxo-1,4-dihydroquinoline-3-carboxamido)phenoxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
124	Structure	
	Name	3-[[4-chloro-2-[(2-chloro-4-nitrophenyl)carbamoyl]phenoxy]methyl]-4-phosphonoxybenzoic acid
	Mass spec	(ES) $m/z = 558.8$ $[M+H]^+$
	NMR	^1H NMR (500 MHz, DMSO) δ 10.48 (s, 1H), 8.63 (d, $J = 9.2$ Hz, 1H), 8.30–8.21 (m, 2H), 8.09 (d, $J = 2.2$ Hz, 1H), 8.00 – 7.93 (m, 2H), 7.67 (dd, $J = 9.0, 2.9$ Hz, 1H), 7.49 (dd, $J = 8.5, 1.0$ Hz, 1H), 7.43 (d, $J = 9.0$ Hz, 1H), 5.47 (s, 2H).
125	Structure	
	Name	3-((4-chloro-2-((2-chloro-4-nitrophenyl)carbamoyl)phenoxy)carbonyl)-4-(phosphonoxy)benzoic acid
126	Structure	

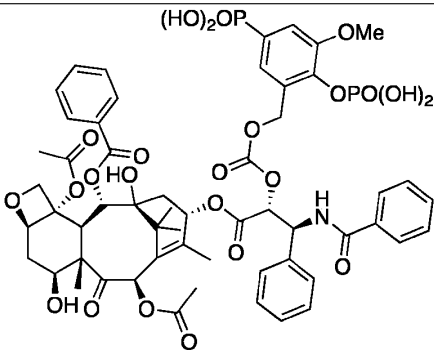
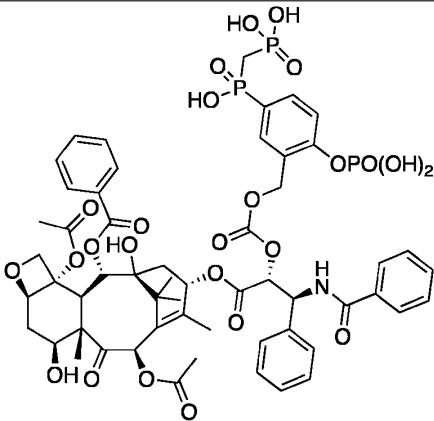
	Name	(3-((4-chloro-2-((2-chloro-4-nitrophenyl)carbamoyl)phenoxy)carbonyl)-4-(phosphonoxy)phenyl)phosphonic acid
127	Structure	
	Name	(3-((4-chloro-2-((2-chloro-4-nitrophenyl)carbamoyl)phenoxy)carbonyl)-5-methyl-4-(phosphonoxy)phenyl)phosphonic acid
128	Structure	
	Name	(3-(4-(4-chloro-2-((2-chloro-4-nitrophenyl)carbamoyl)phenoxy)-2-methyl-4-oxobutan-2-yl)-4-(phosphonoxy)phenyl)phosphonic acid
129	Structure	
	Name	(3-(4-(4-chloro-2-((2-chloro-4-nitrophenyl)carbamoyl)phenoxy)-2-methyl-4-oxobutan-2-yl)-5-methyl-4-(phosphonoxy)phenyl)phosphonic acid

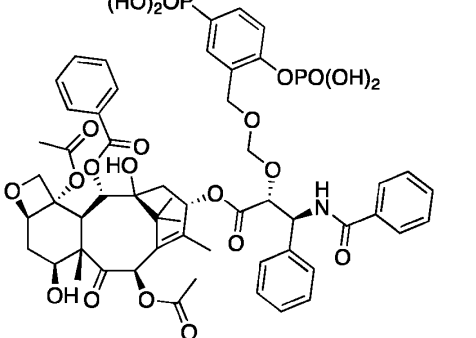
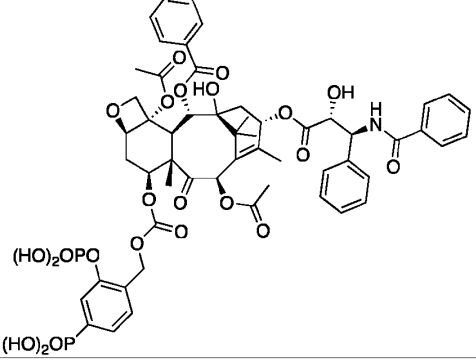
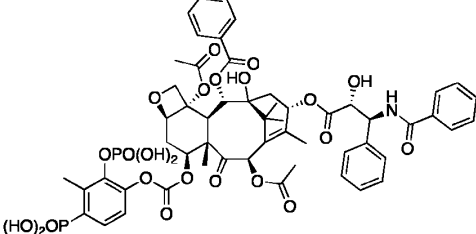
130	Structure	
	Name	4-((((((1 <i>S</i> ,2 <i>R</i>)-1-benzamido-3-(((2 <i>aR</i> ,4 <i>S</i> ,4 <i>aS</i> ,6 <i>R</i> ,9 <i>S</i> ,11 <i>S</i> ,12 <i>S</i> ,12 <i>aR</i> ,12 <i>bS</i>)-6,12b-diacetoxyl-12-(benzoyloxy)-4,11-dihydroxy-4 <i>a</i> ,8,13,13-tetramethyl-5-oxo-2 <i>a</i> ,3,4,4 <i>a</i> ,5,6,9,10,11,12,12 <i>a</i> ,12 <i>b</i> -dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-9-yl)oxy)-3-oxo-1-phenylpropan-2-yl)oxy)carbonyl)oxy)methyl)-3-(phosphonooxy)benzoic acid
131	Structure	
	Name	3-((((((1 <i>S</i> ,2 <i>R</i>)-1-benzamido-3-(((2 <i>aR</i> ,4 <i>S</i> ,4 <i>aS</i> ,6 <i>R</i> ,9 <i>S</i> ,11 <i>S</i> ,12 <i>S</i> ,12 <i>aR</i> ,12 <i>bS</i>)-6,12b-diacetoxyl-12-(benzoyloxy)-4,11-dihydroxy-4 <i>a</i> ,8,13,13-tetramethyl-5-oxo-2 <i>a</i> ,3,4,4 <i>a</i> ,5,6,9,10,11,12,12 <i>a</i> ,12 <i>b</i> -dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-9-yl)oxy)-3-oxo-1-phenylpropan-2-yl)oxy)carbonyl)oxy)methyl)-4-(phosphonooxy)benzoic acid
	Mass spec	HRMS (ESI) calcd for C ₃₆ H ₅₈ NO ₂₃ P [M + H] ⁺ calcd 1128.3261; found, 1128.3252.
	NMR	¹ H NMR (500 MHz, MeOD) δ 8.11 (d, <i>J</i> = 7.6 Hz, 2H), 8.06 (s, 1H), 7.96 (d, <i>J</i> = 7.9 Hz, 1H), 7.81 (d, <i>J</i> = 7.5 Hz, 2H), 7.66 (dd, <i>J</i> = 7.4, 7.4 Hz, 1H), 7.59–7.54 (m, 3H), 7.54–7.49 (m, 3H), 7.47–7.40 (m, 4H), 7.27 (dd, <i>J</i> = 7.4, 7.4 Hz, 1H), 6.45 (s, 1H), 6.10 (t, <i>J</i> = 9.2 Hz, 1H), 5.85 (d, <i>J</i> = 6.3 Hz, 1H), 5.64 (d, <i>J</i> = 7.2 Hz, 1H), 5.52 (d, <i>J</i> = 6.3

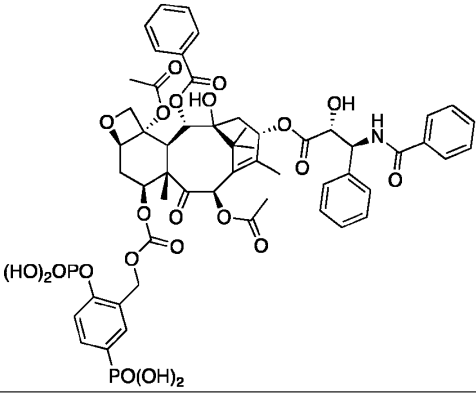
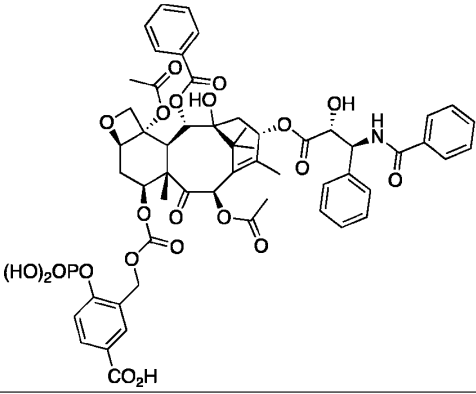
		Hz, 1H), 5.44 (d, $J = 13.3$ Hz, 1H), 5.36 (d, $J = 13.0$ Hz, 1H), 5.00 (d, $J = 9.6$ Hz, 1H), 4.35 (dd, $J = 11.0, 6.6$ Hz, 1H), 4.19 (s, 2H), 3.82 (d, $J = 7.2$ Hz, 1H), 2.53–2.44 (m, 1H), 2.41 (s, 3H), 2.22 (dd, $J = 15.4, 9.5$ Hz, 1H), 2.18 (s, 3H), 1.91 (s, 3H), 1.89–1.76 (m, 2H), 1.65 (s, 3H), 1.14 (s, 6H). ^{13}C NMR (125 MHz, methanol-d_4) δ 205.24, 171.66, 171.29, 170.64, 170.21, 169.21, 167.69, 156.31 (d, $J = 3.1$ Hz), 155.71, 142.34, 138.22, 135.46, 134.85, 132.84, 132.33, 131.72, 131.40, 131.20 (2C), 130.09 (2C), 129.71 (2C), 129.65, 129.55 (2C), 128.67 (2C), 128.63 (2C), 127.78 (d, $J = 4.6$ Hz), 126.60, 120.97, 120.48, 85.96, 82.24, 79.02, 78.58, 77.47, 76.82, 76.28, 73.21, 72.27, 66.68, 59.20, 55.38, 47.87, 44.59, 37.53, 36.46, 26.95, 23.22, 22.41, 20.78, 14.95, 10.46. ^{31}P NMR (202 MHz, methanol-d_4) δ -4.98.
132	Structure	
	Name	(4-((((1<i>S</i>,2<i>R</i>)-1-benzamido-3-(((2<i>aR</i>,4<i>S</i>,4<i>aS</i>,6<i>R</i>,9<i>S</i>,11<i>S</i>,12<i>S</i>,12<i>aR</i>,12<i>bS</i>)-6,12b-diacetoxy-12-(benzoyloxy)-4,11-dihydroxy-4<i>a</i>,8,13,13-tetramethyl-5-oxo-2<i>a</i>,3,4,4<i>a</i>,5,6,9,10,11,12,12<i>a</i>,12<i>b</i>-dodecahydro-1<i>H</i>-7,11-methanocyclodeca[3,4]benzo[1,2-<i>b</i>]oxet-9-yl)oxy)-3-oxo-1-phenylpropan-2-yl)oxy)carbonyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
133	Structure	
	Name	(3-((((1<i>S</i>,2<i>R</i>)-1-benzamido-3-(((2<i>aR</i>,4<i>S</i>,4<i>aS</i>,6<i>R</i>,9<i>S</i>,11<i>S</i>,12<i>S</i>,12<i>aR</i>,12<i>bS</i>)-6,12b-

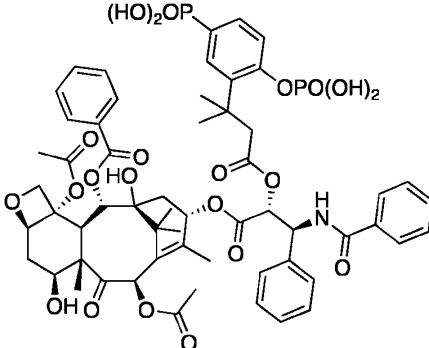
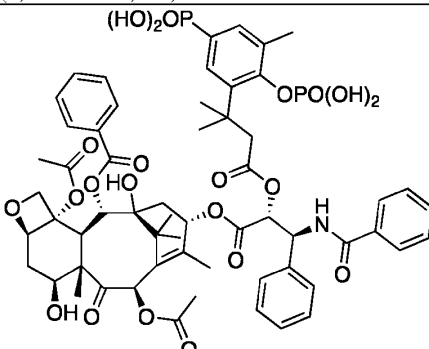
		diacetoxy-12-(benzoyloxy)-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-9-yl)oxy)-3-oxo-1-phenylpropan-2-yl)oxy)carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
	Mass spec	HRMS (ESI) calcd for C ₅₅ H ₅₉ NO ₂₃ P ₂ Na [M + Na] ⁺ 1186.2845; found 1186.2843.
	NMR	¹ H NMR (500 MHz, D ₂ O) ¹ H NMR (500 MHz, methanol- <i>d</i> ₄) δ 8.17–8.11 (m, 2H), 7.94 (d, <i>J</i> = 13.4 Hz, 1H), 7.86–7.77 (m, 3H), 7.72–7.65 (m, 1H), 7.62–7.56 (m, 2H), 7.54–7.49 (m, 4H), 7.48–7.41 (m, 4H), 7.29 (dd, <i>J</i> = 7.3, 7.3 Hz, 1H), 6.48 (s, 1H), 6.13 (t, <i>J</i> = 8.4 Hz, 1H), 5.87 (d, <i>J</i> = 6.1 Hz, 1H), 5.67 (d, <i>J</i> = 7.3 Hz, 1H), 5.53 (d, <i>J</i> = 6.1 Hz, 1H), 5.43 (d, <i>J</i> = 12.8 Hz, 1H), 5.36 (d, <i>J</i> = 12.8 Hz, 1H), 5.02 (dd, <i>J</i> = 9.7, 2.4 Hz, 1H), 4.37 (dd, <i>J</i> = 11.1, 6.6 Hz, 1H), 4.21 (s, 2H), 3.84 (d, <i>J</i> = 7.2 Hz, 1H), 2.50 (ddd, <i>J</i> = 14.3, 9.7, 6.6 Hz, 1H), 2.43 (s, 3H), 2.23 (dd, <i>J</i> = 15.6, 9.6 Hz, 1H), 2.19 (s, 3H), 1.97 (d, <i>J</i> = 1.5 Hz, 3H), 1.89 (dd, <i>J</i> = 15.3, 9.1 Hz, 1H), 1.83 (ddd, <i>J</i> = 14.3, 11.1, 2.4 Hz, 1H), 1.68 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H). ¹³ C NMR (125 MHz, methanol- <i>d</i> ₄) δ 205.16, 171.65, 171.30, 170.58, 170.20, 167.65, 155.65, 153.49 (dd, <i>J</i> = 6.5, 3.7 Hz), 142.29, 138.11, 135.38, 134.89, 134.61, 133.84 (d, <i>J</i> = 11.0 Hz), 133.58 (d, <i>J</i> = 11.8 Hz), 132.88, 131.36, 131.19 (2C), 130.38, 130.12 (2C), 129.71 (2C), 129.56 (2C), 128.87, 128.62 (2C), 128.57 (2C), 128.06 (dd, <i>J</i> = 15.6, 6.6 Hz), 121.19 (dd, <i>J</i> = 15.8, 2.8 Hz), 85.88, 82.26, 79.01, 78.59, 77.45, 76.81, 76.23, 73.21, 72.31, 66.27, 59.21, 55.31, 47.86, 44.57, 37.48, 36.41, 26.93, 23.24, 22.39, 20.78, 14.95, 10.45. ³¹ P NMR (202 MHz, methanol- <i>d</i> ₄) δ 14.78, −5.76.
134	Structure	
	Name	(3-((((((1 <i>S</i> ,2 <i>R</i>)-1-benzamido-3-(((2 <i>aR</i> ,4 <i>S</i> ,4 <i>aS</i> ,6 <i>R</i> ,9 <i>S</i> ,11 <i>S</i> ,12 <i>S</i> ,12 <i>aR</i> ,12 <i>bS</i>)-6,12b-diacetoxy-12-(benzoyloxy)-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-

		962a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-9-yl)oxy)-3-oxo-1-phenylpropan-2-yl)oxy)carbonyl)oxy)methyl)-5-methyl-4-(phosphonoxy)phenyl)phosphonic acid
135	Structure	
	Name	(3-((((((1 <i>S</i> ,2 <i>R</i>)-1-benzamido-3-(((2 <i>aR</i> ,4 <i>S</i> ,4 <i>aS</i> ,6 <i>R</i> ,9 <i>S</i> ,11 <i>S</i> ,12 <i>S</i> ,12 <i>aR</i> ,12 <i>bS</i>)-6,12b-diacetoxy-12-(benzoyloxy)-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-9-yl)oxy)-3-oxo-1-phenylpropan-2-yl)oxy)carbonyl)oxy)methyl)-5-fluoro-4-(phosphonoxy)phenyl)phosphonic acid
136	Structure	
	Name	(3-((((((1 <i>S</i> ,2 <i>R</i>)-1-benzamido-3-(((2 <i>aR</i> ,4 <i>S</i> ,4 <i>aS</i> ,6 <i>R</i> ,9 <i>S</i> ,11 <i>S</i> ,12 <i>S</i> ,12 <i>aR</i> ,12 <i>bS</i>)-6,12b-diacetoxy-12-(benzoyloxy)-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-9-yl)oxy)-3-oxo-1-phenylpropan-2-yl)oxy)carbonyl)oxy)methyl)-5-chloro-4-(phosphonoxy)phenyl)phosphonic acid

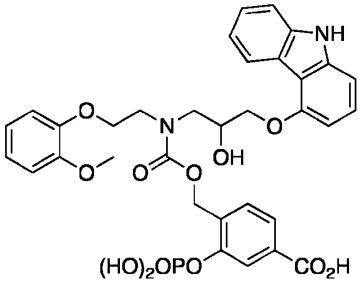
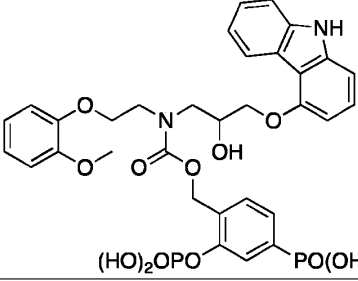
137	Structure	
	Name	(3-((((((1 <i>S</i> ,2 <i>R</i>)-1-benzamido-3-(((2 <i>aR</i> ,4 <i>S</i> ,4 <i>aS</i> ,6 <i>R</i> ,9 <i>S</i> ,11 <i>S</i> ,12 <i>S</i> ,12 <i>aR</i> ,12 <i>bS</i>)-6,12b-diacetoxy-12-(benzoyloxy)-4,11-dihydroxy-4 <i>a</i> ,8,13,13-tetramethyl-5-oxo-2 <i>a</i> ,3,4,4 <i>a</i> ,5,6,9,10,11,12,12 <i>a</i> ,12 <i>b</i> -dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-9-yl)oxy)-3-oxo-1-phenylpropan-2-yl)oxy)carbonyl)oxy)methyl)-5-methoxy-4-(phosphonooxy)phenyl)phosphonic acid
	Mass spec	(ES) $m/z = 1195.3$ $[M+H]^+$
138	Structure	
	Name	((3-((((((1 <i>S</i> ,2 <i>R</i>)-1-benzamido-3-(((2 <i>aR</i> ,4 <i>S</i> ,4 <i>aS</i> ,6 <i>R</i> ,9 <i>S</i> ,11 <i>S</i> ,12 <i>S</i> ,12 <i>aR</i> ,12 <i>bS</i>)-6,12b-diacetoxy-12-(benzoyloxy)-4,11-dihydroxy-4 <i>a</i> ,8,13,13-tetramethyl-5-oxo-2 <i>a</i> ,3,4,4 <i>a</i> ,5,6,9,10,11,12,12 <i>a</i> ,12 <i>b</i> -dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-9-yl)oxy)-3-oxo-1-phenylpropan-2-yl)oxy)carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)(hydroxy)phosphoryl)methyl)phosphonic acid

139	Structure	
	Name	(3-((((1<i>S</i>,2<i>R</i>)-1-benzamido-3-(((2<i>aR</i>,4<i>S</i>,4<i>aS</i>,6<i>R</i>,9<i>S</i>,11<i>S</i>,12<i>S</i>,12<i>aR</i>,12<i>bS</i>)-6,12b-diacetoxy-12-(benzyloxy)-4,11-dihydroxy-4<i>a</i>,8,13,13-tetramethyl-5-oxo-2<i>a</i>,3,4,4<i>a</i>,5,6,9,10,11,12,12<i>a</i>,12<i>b</i>-dodecahydro-1<i>H</i>-7,11-methanocyclodeca[3,4]benzo[1,2-<i>b</i>]oxet-9-yl)oxy)-3-oxo-1-phenylpropan-2-yl)oxy)methoxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
140	Structure	
	Name	(4-((((((2<i>aR</i>,4<i>S</i>,4<i>aS</i>,6<i>R</i>,9<i>S</i>,11<i>S</i>,12<i>S</i>,12<i>aR</i>,12<i>bS</i>)-6,12b-diacetoxy-9-(((2<i>R</i>,3<i>S</i>)-3-benzamido-2-hydroxy-3-phenylpropanoyl)oxy)-12-(benzyloxy)-11-hydroxy-4<i>a</i>,8,13,13-tetramethyl-5-oxo-2<i>a</i>,3,4,4<i>a</i>,5,6,9,10,11,12,12<i>a</i>,12<i>b</i>-dodecahydro-1<i>H</i>-7,11-methanocyclodeca[3,4]benzo[1,2-<i>b</i>]oxet-4-yl)oxy)carbonyl)oxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
141	Structure	

	Name	(4-((((2a <i>R</i> ,4 <i>S</i> ,4a <i>S</i> ,6 <i>R</i> ,9 <i>S</i> ,11 <i>S</i> ,12 <i>S</i> ,12a <i>R</i> ,12b <i>S</i>)-6,12b-diacetoxy-9-(((2 <i>R</i> ,3 <i>S</i>)-3-benzamido-2-hydroxy-3-phenylpropanoyl)oxy)-12-(benzoyloxy)-11-hydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-4-yl)oxy)carbonyl)oxy)-2-methyl-3-(phosphonoxy)phenyl)phosphonic acid
142	Structure	
	Name	(3-((((2a <i>R</i> ,4 <i>S</i> ,4a <i>S</i> ,6 <i>R</i> ,9 <i>S</i> ,11 <i>S</i> ,12 <i>S</i> ,12a <i>R</i> ,12b <i>S</i>)-6,12b-diacetoxy-9-(((2 <i>R</i> ,3 <i>S</i>)-3-benzamido-2-hydroxy-3-phenylpropanoyl)oxy)-12-(benzoyloxy)-11-hydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-4-yl)oxy)carbonyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
143	Structure	
	Name	3-((((2a <i>R</i> ,4 <i>S</i> ,4a <i>S</i> ,6 <i>R</i> ,9 <i>S</i> ,11 <i>S</i> ,12 <i>S</i> ,12a <i>R</i> ,12b <i>S</i>)-6,12b-diacetoxy-9-(((2 <i>R</i> ,3 <i>S</i>)-3-benzamido-2-hydroxy-3-phenylpropanoyl)oxy)-12-(benzoyloxy)-11-hydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-4-

		yl)oxy)carbonyl)oxy)methyl)-4-(phosphonooxy)benzoic acid
144	Structure	
	Name	(3-(4-(((1 <i>S</i> ,2 <i>R</i>)-1-benzamido-3-(((2 <i>aR</i> ,4 <i>S</i> ,4 <i>aS</i> ,6 <i>R</i> ,9 <i>S</i> ,11 <i>S</i> ,12 <i>S</i> ,12 <i>aR</i> ,12 <i>bS</i>)-6,12b-diacetoxy-12-(benzoyloxy)-4,11-dihydroxy-4 <i>a</i> ,8,13,13-tetramethyl-5-oxo-2 <i>a</i> ,3,4,4 <i>a</i> ,5,6,9,10,11,12,12 <i>a</i> ,12 <i>b</i> -dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-9-yl)oxy)-3-oxo-1-phenylpropan-2-yl)oxy)-2-methyl-4-oxobutan-2-yl)-4-(phosphonooxy)phenyl)phosphonic acid
	Mass spec	(ES) m/z = 1190.1 [M+H] ⁺
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 8.53 (s, 1H), 8.15–7.89 (m, 2H), 7.78–7.66 (m, 3H), 7.66–7.60 (m, 3H), 7.60–7.53 (m, 1H), 7.53–7.45 (m, 2H), 7.45–7.31 (m, 6H), 7.26 (dd, J = 8.4, 3.4 Hz, 1H), 7.11 (tt, J = 6.9, 1.8 Hz, 1H), 6.31 (s, 1H), 5.84–5.74 (m, 1H), 5.46 (d, J = 7.3 Hz, 1H), 5.38–5.21 (m, 2H), 5.04 (dd, J = 9.4, 2.1 Hz, 1H), 4.31–4.21 (m, 1H), 4.21–4.14 (m, 1H), 4.13 (d, J = 8.7 Hz, 1H), 3.61 (d, J = 7.3 Hz, 1H), 3.22 (d, J = 14.2 Hz, 1H), 3.00 (d, J = 14.2 Hz, 1H), 2.47 (ddd, J = 14.6, 9.8, 6.5 Hz, 1H), 2.26 (s, 3H), 2.16 (s, 3H), 1.75 (dd, J = 15.4, 9.4 Hz, 2H), 1.69 (d, J = 1.5 Hz, 3H), 1.53 (s, 3H), 1.44–1.29 (m, 7H), 1.02 (d, J = 6.1 Hz, 6H).
145	Structure	

		(3-(4-(((1<i>S</i>,2<i>R</i>)-1-benzamido-3-(((2<i>aR</i>,4<i>S</i>,4<i>aS</i>,6<i>R</i>,9<i>S</i>,11<i>S</i>,12<i>S</i>,12<i>aR</i>,12<i>bS</i>)-6,12b-diacetoxy-12-(benzoyloxy)-4,11-dihydroxy-4<i>a</i>,8,13,13-tetramethyl-5-oxo-2<i>a</i>,3,4,4<i>a</i>,5,6,9,10,11,12,12<i>a</i>,12<i>b</i>-dodecahydro-1<i>H</i>-7,11-methanocyclodeca[3,4]benzo[1,2-<i>b</i>]oxet-9-yl)oxy)-3-oxo-1-phenylpropan-2-yl)oxy)-2-methyl-4-oxobutan-2-yl)-5-methyl-4-(phosphonooxy)phenyl)phosphonic acid
146	Structure	
	Name	(3-(4-(((1<i>S</i>,2<i>R</i>)-1-benzamido-3-(((2<i>aR</i>,4<i>S</i>,4<i>aS</i>,6<i>R</i>,9<i>S</i>,11<i>S</i>,12<i>S</i>,12<i>aR</i>,12<i>bS</i>)-6,12b-diacetoxy-12-(benzoyloxy)-4,11-dihydroxy-4<i>a</i>,8,13,13-tetramethyl-5-oxo-2<i>a</i>,3,4,4<i>a</i>,5,6,9,10,11,12,12<i>a</i>,12<i>b</i>-dodecahydro-1<i>H</i>-7,11-methanocyclodeca[3,4]benzo[1,2-<i>b</i>]oxet-9-yl)oxy)-3-oxo-1-phenylpropan-2-yl)oxy)carbonyl)-4-(phosphonooxy)phenyl)phosphonic acid
147	Structure	
	Name	(3-(4-(((1<i>S</i>,2<i>R</i>)-1-benzamido-3-(((2<i>aR</i>,4<i>S</i>,4<i>aS</i>,6<i>R</i>,9<i>S</i>,11<i>S</i>,12<i>S</i>,12<i>aR</i>,12<i>bS</i>)-6,12b-diacetoxy-12-(benzoyloxy)-4,11-dihydroxy-4<i>a</i>,8,13,13-tetramethyl-5-oxo-2<i>a</i>,3,4,4<i>a</i>,5,6,9,10,11,12,12<i>a</i>,12<i>b</i>-dodecahydro-1<i>H</i>-7,11-methanocyclodeca[3,4]benzo[1,2-<i>b</i>]oxet-9-yl)oxy)-3-oxo-1-phenylpropan-2-yl)oxy)carbonyl)-5-methyl-4-(phosphonooxy)phenyl)phosphonic acid

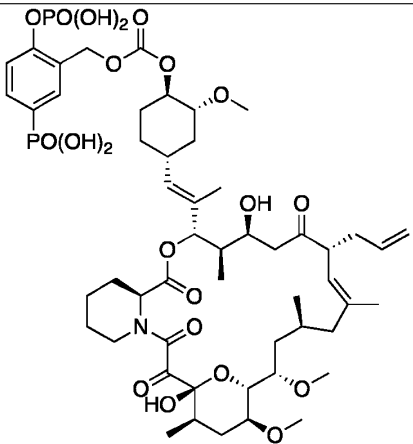
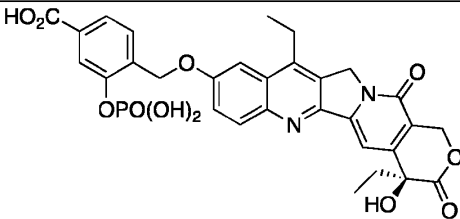
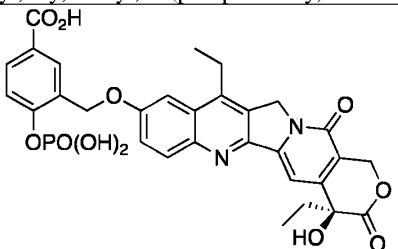
148	Structure	
	Name	4-((((3-((9 <i>H</i> -carbazol-4-yl)oxy)-2-hydroxypropyl)(2-(2-methoxyphenoxy)ethyl)carbamoyl)oxy)methyl)-3-(phosphonoxy)benzoic acid
	Mass spec	HRMS (ESI) calcd for C ₃₃ H ₃₃ N ₂ O ₁₂ PNa [M + Na] ⁺ 703.1663; found 703.1670.
	NMR	¹ H NMR (500 MHz, DMSO) δ 8.78 (br s, 1H), 8.41 (br s, 2H), 8.11 (br s, 1H), 8.06 (br s, 1H), 8.00 (br s, 1H), 7.95 (br s, 1H), 7.75 (br s, 2H), 7.39 (br s, 2H), 7.31 (br s, 3H), 5.83 (br s, 2H), 5.04 (br s, 1H), 4.88 (br s, 2H), 4.75 (br s, 2H), 4.31 (br s, 4H), 4.15 (br s, 3H). ¹³ C NMR (125 MHz, methanol- <i>d</i> ₄) δ 175.52, 158.87 (d, <i>J</i> = 38.4 Hz), 156.54, 150.92, 149.60, 142.91, 140.66, 131.60, 131.30, 130.86, 127.44, 127.38, 125.51, 124.20, 123.57, 122.60 (d, <i>J</i> = 17.6 Hz), 122.13, 120.05, 119.86, 115.05 (d, <i>J</i> = 15.8 Hz), 113.63, 113.41, 113.28, 110.90, 104.93, 101.51, 71.15*, 69.76*, 68.86*, 64.92, 56.36, 53.29*, 49.79 (*split peaks due to rotamers). ³¹ P NMR (202 MHz, D ₂ O) δ -0.30.
149	Structure	
	Name	4-((((3-((9 <i>H</i> -carbazol-4-yl)oxy)-2-hydroxypropyl)(2-(2-methoxyphenoxy)ethyl)carbamoyl)oxy)methyl)-3-(phosphonoxy)phenylphosphonic acid

150	Structure	
	Name	3-((((3-((9H-carbazol-4-yl)oxy)-2-hydroxypropyl)(2-(2-methoxyphenoxy)ethyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)benzoic acid
151	Structure	
	Name	(3-((((3-((9H-carbazol-4-yl)oxy)-2-hydroxypropyl)(2-(2-methoxyphenoxy)ethyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
152	Structure	
	Name	(6R,7R)-7-(((Z)-2-(2-((((5-carboxy-2-(phosphonooxy)benzyl)oxy)carbonyl)amino)thiazol-4-yl)-2-(hydroxyimino)acetamido)-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

153	Structure	
	Name	4-(((4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carbonyl)oxy)methyl)-3-(phosphonooxy)benzoic acid
154	Structure	
	Name	3-(((4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carbonyl)oxy)methyl)-4-(phosphonooxy)benzoic acid
155	Structure	
	Name	3-[[4-(13-chloro-4-azatricyclo[9.4.0.03,8]pentadec-1(15),3(8),4,6,11,13-hexaen-2-ylidene)-1-piperidyl]methyl]-4-phosphonooxy-benzoic acid
	Mass spec	HRMS (ESI) calcd for C ₂₇ H ₂₆ ClN ₂ O ₆ PNa [M + Na] ⁺ 563.1109; found 563.1104
	NMR	As sodium salt. ¹ H NMR (500 MHz, MeOD) δ 8.36 (d, J = 4.9 Hz, 1H), 8.12 (dd, J = 8.6, 1.8 Hz, 2H), 7.67 (dd, J = 7.8, 1.5 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.28 (dd, J = 7.8, 4.9 Hz, 1H), 7.26 (d, J = 2.0 Hz, 1H), 7.21 (dd, J = 8.2, 2.1 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H), 4.32 (s, 2H), 3.39 (br s, 6H), 2.97–2.79 (m, 2H), 2.76–2.63 (m, 2H), 2.45 (br s, 2H). ¹³ C NMR (125 MHz,

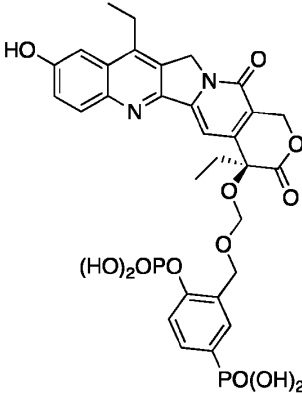
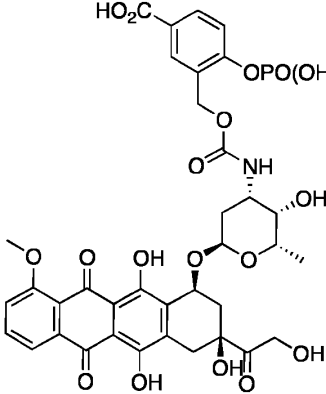
		methanol- <i>d</i> ₄) δ 168.63, 157.54 (d, $J = 7.4$ Hz), 157.33, 147.27, 141.40, 139.98, 137.87, 136.83, 136.00, 135.93, 134.72, 134.38, 133.80, 131.31, 130.45, 128.57, 127.35, 124.64, 124.51, 124.15, 56.63, 53.59, 53.55, 32.38, 31.97, 28.76, 28.55. ³¹ P NMR (202 MHz, methanol- <i>d</i> ₄) δ -3.62
156	Structure	
	Name	(3-((4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2- <i>b</i>]pyridin-11-ylidene)piperidin-1-yl)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
157	Structure	
	Name	(4-((4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2- <i>b</i>]pyridin-11-ylidene)piperidin-1-yl)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
158	Structure	
	Name	4-((4-(6-hydroxy-3-(4-(2-(piperidin-1-yl)ethoxy)benzoyl)benzo[<i>b</i>]thiophen-2-yl)phenoxy)methyl)-3-(phosphonooxy)benzoic acid
159	Structure	

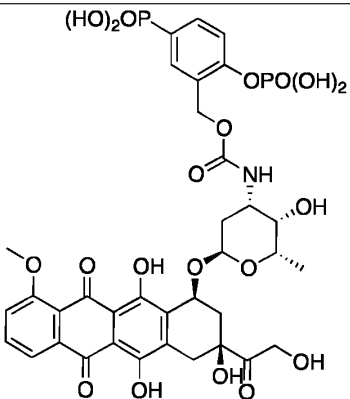
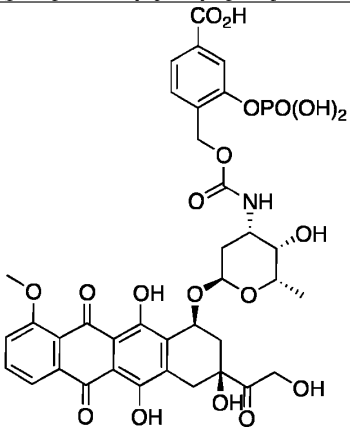
	Name	3-((4-(6-hydroxy-3-(4-(2-(piperidin-1-yl)ethoxy)benzoyl)benzo[<i>b</i>]thiophen-2-yl)phenoxy)methyl)-4-(phosphonooxy)benzoic acid
160	Structure	
	Name	(3-((4-(6-hydroxy-3-(4-(2-(piperidin-1-yl)ethoxy)benzoyl)benzo[<i>b</i>]thiophen-2-yl)phenoxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
161	Structure	
	Name	(4-((4-(6-hydroxy-3-(4-(2-(piperidin-1-yl)ethoxy)benzoyl)benzo[<i>b</i>]thiophen-2-yl)phenoxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
162	Structure	
	Name	(4-((((((1 <i>R</i> ,2 <i>R</i> ,4 <i>R</i>)-4-((<i>E</i>)-2-((3 <i>S</i> ,4 <i>R</i> ,5 <i>S</i> ,8 <i>R</i> ,12 <i>S</i> ,14 <i>S</i> ,15 <i>R</i> ,16 <i>S</i> ,18 <i>R</i> ,19 <i>R</i> ,26 <i>aS</i> , <i>E</i>)-8-allyl-5,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-1,7,20,21-tetraoxo-1,4,5,6,7,8,11,12,13,14,15,16,17,18,19,20,21,23,24,25,26,26 <i>a</i> -docosahydro-3 <i>H</i> -15,19-epoxypyrido[2,1- <i>c</i>][1]oxa[4]azacyclotricosin-3-yl)prop-1-en-1-yl)-2-methoxycyclohexyl)oxy)carbonyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid

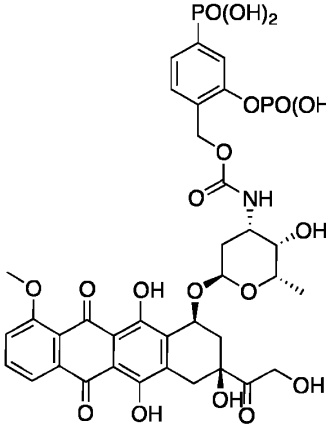
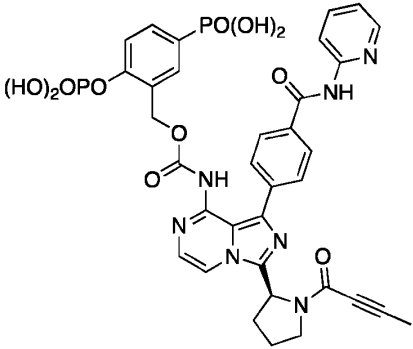
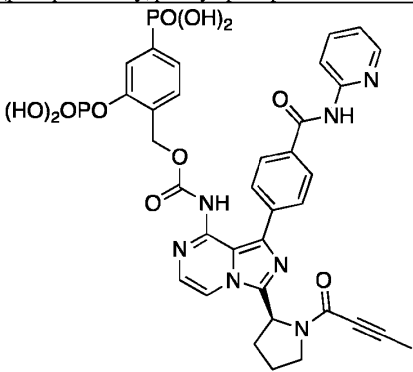
163	Structure	
	Name	(3-((((((1 <i>R</i> ,2 <i>R</i> ,4 <i>R</i>)-4-((<i>E</i>)-2-((3 <i>S</i> ,4 <i>R</i> ,5 <i>S</i> ,8 <i>R</i> ,12 <i>S</i> ,14 <i>S</i> ,15 <i>R</i> ,16 <i>S</i> ,18 <i>R</i> ,19 <i>R</i> ,26 <i>aS</i> , <i>E</i>)-8-allyl-5,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-1,7,20,21-tetraoxo-1,4,5,6,7,8,11,12,13,14,15,16,17,18,19,20,21,23,24,25,26,26 <i>a</i> -docosahydro-3 <i>H</i> -15,19-epoxypyrido[2,1- <i>c</i>][1]oxa[4]azacyclotricosin-3-yl)prop-1-en-1-yl)-2-methoxycyclohexyl)oxy)carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
164	Structure	
	Name	(<i>S</i>)-4-((((4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1 <i>H</i> -pyrano[3',4':6,7]indolizino[1,2- <i>b</i>]quinolin-9-yl)oxy)methyl)-3-(phosphonooxy)benzoic acid
165	Structure	
	Name	(<i>S</i>)-3-((((4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1 <i>H</i> -pyrano[3',4':6,7]indolizino[1,2- <i>b</i>]quinolin-9-yl)oxy)methyl)-4-(phosphonooxy)benzoic acid

166	Structure	
	Name	(S)-4-(((4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl)oxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
167	Structure	
	Name	(S)-3-(((4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
168	Structure	
	Name	(S)-4-(((4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl)oxy)methyl)-3-methoxy-5-(phosphonoxy)phenyl)phosphonic acid
169	Structure	
	Name	(S)-3-(((4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl)oxy)methoxymethyl)-4-(phosphonoxy)benzoic acid

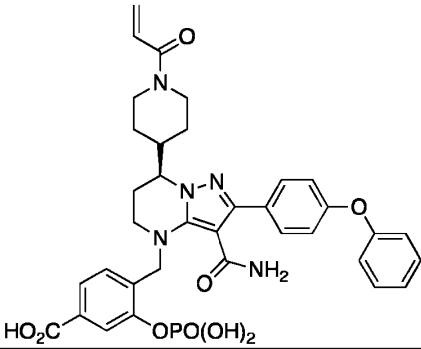
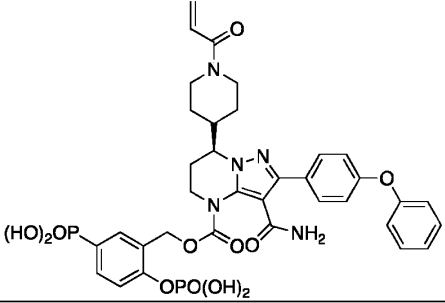
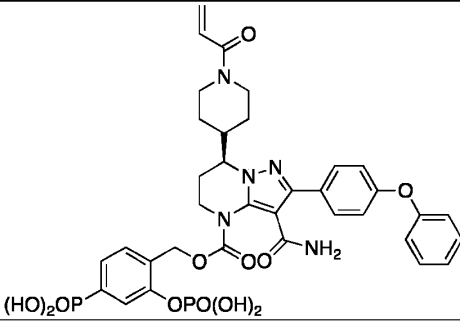
170	Structure	
	Name	(S)-3-((((4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl)oxy)carbonyl)-4-(phosphonoxy)phenyl)phosphonic acid
171	Structure	
	Name	(S)-3-((((4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl)oxy)carbonyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
172	Structure	
	Name	(S)-3-((((4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl)oxy)carbonyl)oxy)methyl)-4-(phosphonoxy)benzoic acid
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 7.96 (s, 1H), 7.66 (s, 1H), 7.45–7.36 (m, 1H), 7.25 (d, <i>J</i> = 8.5 Hz, 1H), 7.20 (s, 2H), 7.11 (s, 1H), 5.73 (d, <i>J</i> = 16.3 Hz, 1H), 5.51 (d, <i>J</i> = 16.3 Hz, 1H), 5.43 (d, <i>J</i> = 11.9 Hz, 1H), 5.30 (d, <i>J</i> = 11.9 Hz, 1H), 4.76–4.72 (m, 2H), 2.92 (d, <i>J</i> = 7.8 Hz, 2H), 2.28 (dp, <i>J</i> = 22.1, 7.4 Hz, 2H), 1.25 (t, <i>J</i> = 7.7 Hz, 3H), 1.08 (t, <i>J</i> = 7.4 Hz, 3H).

173	Structure	
	Name	(S)-(3-((((4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl)oxy)methoxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
174	Structure	
	Name	3-((((((2S,3S,4S,6R)-3-hydroxy-2-methyl-6-(((1S,3S)-3,5,12-trihydroxy-3-(2-hydroxyacetyl)-10-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yl)oxy)tetrahydro-2H-pyran-4-yl)carbamoyl)oxy)methyl)-4-(phosphonooxy)benzoic acid

175	Structure	
	Name	(3-((((2<i>S</i>,3<i>S</i>,4<i>S</i>,6<i>R</i>)-3-hydroxy-2-methyl-6-(((1<i>S</i>,3<i>S</i>)-3,5,12-trihydroxy-3-(2-hydroxyacetyl)-10-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yl)oxy)tetrahydro-2<i>H</i>-pyran-4-yl)carbamoyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
176	Structure	
	Name	4-((((2<i>S</i>,3<i>S</i>,4<i>S</i>,6<i>R</i>)-3-hydroxy-2-methyl-6-(((1<i>S</i>,3<i>S</i>)-3,5,12-trihydroxy-3-(2-hydroxyacetyl)-10-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yl)oxy)tetrahydro-2<i>H</i>-pyran-4-yl)carbamoyl)oxy)methyl)-3-(phosphonoxy)benzoic acid

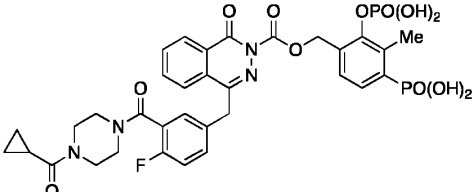
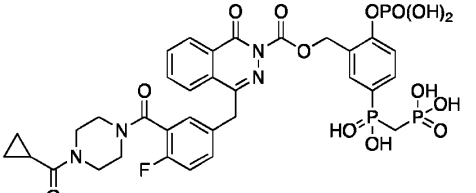
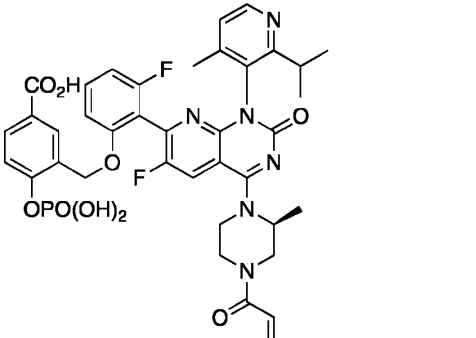
177	Structure	
	Name	(4-((((2 <i>S</i> ,3 <i>S</i> ,4 <i>S</i> ,6 <i>R</i>)-3-hydroxy-2-methyl-6-(((1 <i>S</i> ,3 <i>S</i>)-3,5,12-trihydroxy-3-(2-hydroxyacetyl)-10-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yl)oxy)tetrahydro-2 <i>H</i> -pyran-4-yl)carbamoyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
178	Structure	
	Name	(<i>S</i>)-(3-((((3-(1-(but-2-ynyl)pyrrolidin-2-yl)-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5- <i>a</i>]pyrazin-8-yl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
179	Structure	
	Name	(<i>S</i>)-(4-((((3-(1-(but-2-ynyl)pyrrolidin-2-yl)-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-

		<i>a</i>]pyrazin-8-yl)carbamoyl)oxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
180	Structure	
	Name	(<i>S</i>)-3-((7-(1-acryloylpiperidin-4-yl)-3-carbamoyl-2-(4-phenoxyphenyl)-6,7-dihydropyrazolo[1,5- <i>a</i>]pyrimidin-4(<i>5H</i>)-yl)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
181	Structure	
	Name	(<i>S</i>)-3-((7-(1-acryloylpiperidin-4-yl)-3-carbamoyl-2-(4-phenoxyphenyl)-6,7-dihydropyrazolo[1,5- <i>a</i>]pyrimidin-4(<i>5H</i>)-yl)methyl)-4-(phosphonoxy)benzoic acid
182	Structure	
	Name	(<i>S</i>)-4-((7-(1-acryloylpiperidin-4-yl)-3-carbamoyl-2-(4-phenoxyphenyl)-6,7-dihydropyrazolo[1,5- <i>a</i>]pyrimidin-4(<i>5H</i>)-yl)methyl)-3-(phosphonoxy)phenyl)phosphonic acid

183	Structure	
	Name	(S)-4-(((7-(1-acryloylpiperidin-4-yl)-3-carbamoyl-2-(4-phenoxyphenyl)-6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)methyl)-3-(phosphonoxy)benzoic acid
184	Structure	
	Name	(S)-3-(((7-(1-acryloylpiperidin-4-yl)-3-carbamoyl-2-(4-phenoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-4-carbonyl)oxy)methyl)-4-(phosphonoxy)phenylphosphonic acid
185	Structure	
	Name	(S)-3-(((7-(1-acryloylpiperidin-4-yl)-3-carbamoyl-2-(4-phenoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-4-carbonyl)oxy)methyl)-3-(phosphonoxy)phenylphosphonic acid

186	Structure	
	Name	(3-(((4-(3-(4-(cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzyl)-1-oxo-1,2-dihydrophthalazine-2-carbonyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
187	Structure	
	Name	3-(((4-(3-(4-(cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzyl)-1-oxo-1,2-dihydrophthalazine-2-carbonyl)oxy)methyl)-4-(phosphonoxy)benzoic acid
188	Structure	
	Name	(4-(((4-(3-(4-(cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzyl)-1-oxo-1,2-dihydrophthalazine-2-carbonyl)oxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 8.33 (d, <i>J</i> = 7.1 Hz, 1H), 7.90 – 7.79 (m, 3H), 7.59 (d, <i>J</i> = 12.8 Hz, 1H), 7.37 (s, 1H), 7.28 (dd, <i>J</i> = 15.5, 6.2 Hz, 1H), 7.19 (dd, <i>J</i> = 11.4, 7.8 Hz, 1H), 7.12 (t, <i>J</i> = 9.0 Hz, 2H), 6.72 (dd, <i>J</i> = 7.8, 3.7 Hz, 1H), 5.55 (s, 2H), 4.39 (s, 2H), 3.80 (d, <i>J</i> = 39.1 Hz, 2H), 3.70–3.53 (m, 3H), 3.28 (d, <i>J</i> = 56.3 Hz, 3H), 1.86 (dd, <i>J</i> = 62.5, 5.3 Hz, 1H), 0.81 (d, <i>J</i> = 17.3 Hz, 4H).
189	Structure	
	Name	4-(((4-(3-(4-(cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzyl)-1-oxo-1,2-

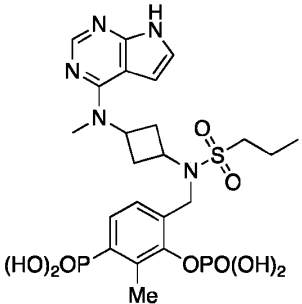
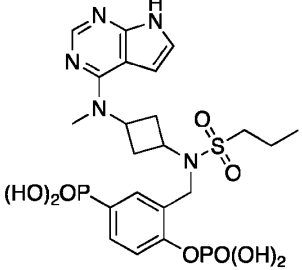
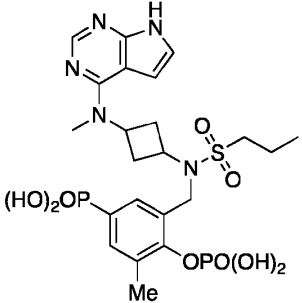
		dihydrophthalazine-2-carbonyl)oxy)methyl)-3-(phosphonoxy)benzoic acid
190	Structure	
	Name	(3-(((4-(3-(4-(cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzyl)-1-oxo-1,2-dihydrophthalazine-2-carbonyl)oxy)methyl)-5-methyl-4-(phosphonoxy)phenyl)phosphonic acid
191	Structure	
	Name	(3-(((4-(3-(4-(cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzyl)-1-oxo-1,2-dihydrophthalazine-2-carbonyl)oxy)methyl)-5-fluoro-4-(phosphonoxy)phenyl)phosphonic acid
192	Structure	
	Name	(3-(((4-(3-(4-(cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzyl)-1-oxo-1,2-dihydrophthalazine-2-carbonyl)oxy)methyl)-5-chloro-4-(phosphonoxy)phenyl)phosphonic acid
193	Structure	
	Name	(3-(((4-(3-(4-(cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzyl)-1-oxo-1,2-dihydrophthalazine-2-carbonyl)oxy)methyl)-5-methoxy-4-(phosphonoxy)phenyl)phosphonic acid

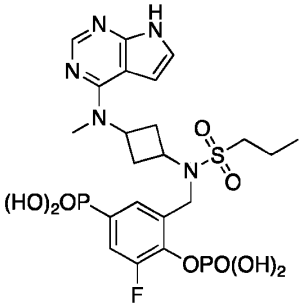
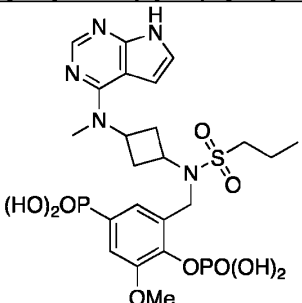
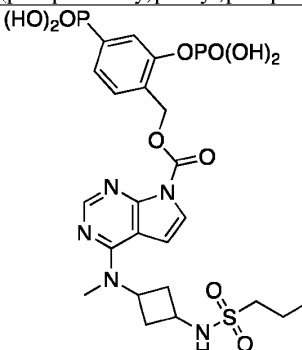
194	Structure	
	Name	(4-(((4-(3-(4-(cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzyl)-1-oxo-1,2-dihydrophthalazine-2-carbonyl)oxy)methyl)-2-methyl-3-(phosphonooxy)phenyl)phosphonic acid
195	Structure	
	Name	((3-(((4-(3-(4-(cyclopropanecarbonyl)piperazine-1-carbonyl)-4-fluorobenzyl)-1-oxo-1,2-dihydrophthalazine-2-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)(hydroxy)phosphoryl)methyl)phosphonic acid
196	Structure	
	Name	3-((2-(4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3-d]pyrimidin-7-yl)-3-fluorophenoxy)methyl)-4-(phosphonooxy)benzoic acid

197	Structure	
	Name	(3-((2-(4-((<i>S</i>)-4-acryloyl-2-methylpiperazin-1-yl)-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3- <i>d</i>]pyrimidin-7-yl)-3-fluorophenoxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
198	Structure	
	Name	(4-((2-(4-((<i>S</i>)-4-acryloyl-2-methylpiperazin-1-yl)-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3- <i>d</i>]pyrimidin-7-yl)-3-fluorophenoxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
199	Structure	
	Name	4-((2-(4-((<i>S</i>)-4-acryloyl-2-methylpiperazin-1-yl)-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3- <i>d</i>]pyrimidin-7-yl)-3-fluorophenoxy)methyl)-3-(phosphonooxy)benzoic acid

200	Structure	
	Name	(3-((((2-(4-((<i>S</i>)-4-acryloyl-2-methylpiperazin-1-yl)-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3- <i>d</i>]pyrimidin-7-yl)-3-fluorophenoxy)carbonyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
201	Structure	
	Name	(4-((((2-(4-((<i>S</i>)-4-acryloyl-2-methylpiperazin-1-yl)-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3- <i>d</i>]pyrimidin-7-yl)-3-fluorophenoxy)carbonyl)oxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
202	Structure	
	Name	(3-((((2-(4-((<i>S</i>)-4-acryloyl-2-methylpiperazin-1-yl)-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3- <i>d</i>]pyrimidin-7-yl)-3-fluorophenoxy)carbonyl)oxy)methyl)-5-methyl-4-(phosphonoxy)phenyl)phosphonic acid

203	Structure	
	Name	(3-((((2-(4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3-d]pyrimidin-7-yl)-3-fluorophenoxy)carbonyl)oxy)methyl)-5-chloro-4-(phosphonooxy)phenyl)phosphonic acid
204	Structure	
	Name	(3-((((2-(4-((S)-4-acryloyl-2-methylpiperazin-1-yl)-6-fluoro-1-(2-isopropyl-4-methylpyridin-3-yl)-2-oxo-1,2-dihydropyrido[2,3-d]pyrimidin-7-yl)-3-fluorophenoxy)carbonyl)oxy)methyl)-5-methoxy-4-(phosphonooxy)phenyl)phosphonic acid
205	Structure	
	Name	(4-((N-(3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propylsulfonamido)methyl)-3-(phosphonooxy)phenyl)phosphonic acid

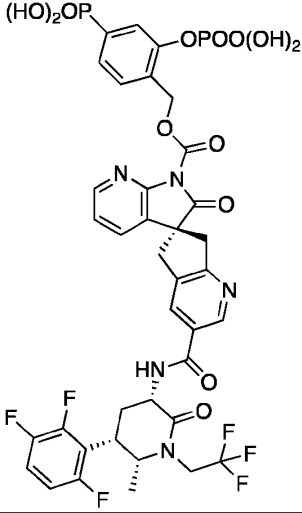
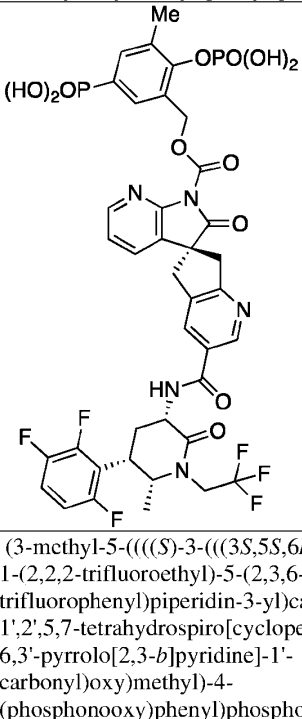
206	Structure	
	Name	(2-methyl-4-((N-(3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propylsulfonamido)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
207	Structure	
	Name	(3-((N-(3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propylsulfonamido)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
208	Structure	
	Name	(3-methyl-5-((N-(3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propylsulfonamido)methyl)-4-(phosphonooxy)phenyl)phosphonic acid

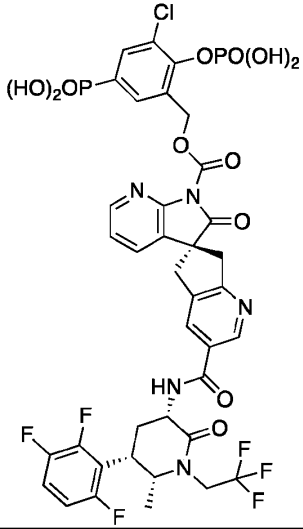
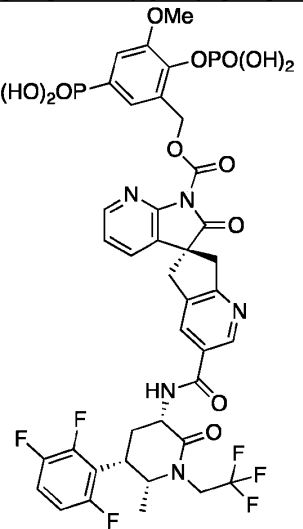
209	Structure	
	Name	(3-fluoro-5-((N-(3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propylsulfonamido)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
210	Structure	
	Name	(3-methoxy-5-((N-(3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propylsulfonamido)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
211	Structure	
	Name	(4-(((4-(methyl(3-(propylsulfonamido)cyclobutyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-7-carbonyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid

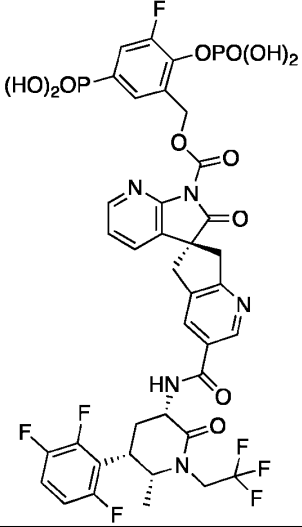
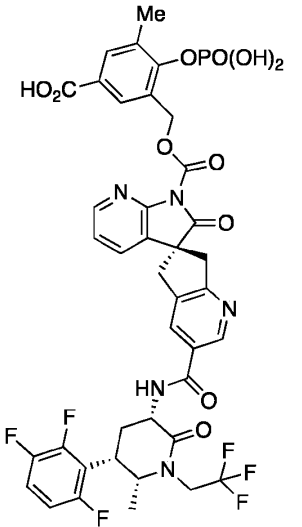
212	Structure	
	Name	(3-(((4-(methyl(3-(propylsulfonamido)cyclobutyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-7-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
213	Structure	
	Name	(4-(((4-(((1-ethylpyrrolidin-2-yl)methyl)carbamoyl)-2-(ethylsulfonyl)-5-methoxyphenyl)carbamoyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
214	Structure	
	Name	(3-(((4-(((1-ethylpyrrolidin-2-yl)methyl)carbamoyl)-2-(ethylsulfonyl)-5-methoxyphenyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
215	Structure	
	Name	(R)-(4-((((1-(5-((4-(chlorodifluoromethoxy)phenyl)carbamoyl)-3-(1H-pyrazol-5-yl)pyridin-2-yl)pyrrolidin-3-yl)methyl)carbamoyl)oxy)methyl)-3-(1H-pyrazol-5-yl)pyridin-2-yl)pyrrolidin-3-yl)methyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid

		yl)oxy)carbonyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
216	Structure	
	Name	(R)-3-((((1-(5-((4-(chlorodifluoromethoxy)phenyl)carbamoyl)-3-(1H-pyrazol-5-yl)pyridin-2-yl)pyrrolidin-3-yl)oxy)carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
217	Structure	
	Name	(R)-3-((((5-(5-((4-(chlorodifluoromethoxy)phenyl)carbamoyl)-2-(3-hydroxypyrrolidin-1-yl)pyridin-3-yl)-1H-pyrazole-1-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
218	Structure	
	Name	(R)-3-((((5-(5-((4-(chlorodifluoromethoxy)phenyl)carbamoyl)-2-(3-hydroxypyrrolidin-1-yl)pyridin-3-yl)-1H-pyrazole-1-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid

219	Structure	
	Name	(<i>R</i>)-3-((((4-(chlorodifluoromethoxy)phenyl)(6-(3-hydroxypyrrolidin-1-yl)-5-(1 <i>H</i> -pyrazol-5-yl)nicotinoyl)carbamoyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
220	Structure	
	Name	(<i>R</i>)-3-((((4-(chlorodifluoromethoxy)phenyl)(6-(3-hydroxypyrrolidin-1-yl)-5-(1 <i>H</i> -pyrazol-5-yl)nicotinoyl)carbamoyl)oxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
221	Structure	
	Name	(4-((hydroperoxy(hydroxy)phosphoryl)oxy)-3-((((<i>S</i>)-3-((((3 <i>S</i> ,5 <i>S</i> ,6 <i>R</i>)-6-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-5-(2,3,6-trifluorophenyl)piperidin-3-yl)carbamoyl)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[<i>b</i>]pyridine-6,3'-pyrrolo[2,3- <i>b</i>]pyridine]-1'-carbonyl)oxy)methyl)phenyl)phosphonic acid

222	Structure	
	Name	(3-((hydroperoxy(hydroxy)phosphoryl)oxy)-4-(((<i>S</i>)-3-(((3<i>S</i>,5<i>S</i>,6<i>R</i>)-6-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-5-(2,3,6-trifluorophenyl)piperidin-3-yl)carbamoyl)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[<i>b</i>]pyridine-6,3'-pyrrolo[2,3-<i>b</i>]pyridine]-1'-carbonyl)oxy)methyl)phenyl)phosphonic acid
223	Structure	
	Name	(3-methyl-5-(((<i>S</i>)-3-(((3<i>S</i>,5<i>S</i>,6<i>R</i>)-6-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-5-(2,3,6-trifluorophenyl)piperidin-3-yl)carbamoyl)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[<i>b</i>]pyridine-6,3'-pyrrolo[2,3-<i>b</i>]pyridine]-1'-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid

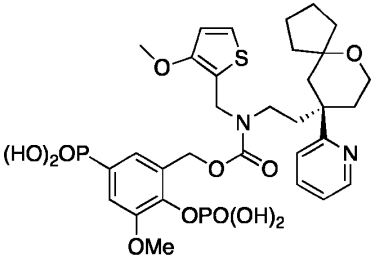
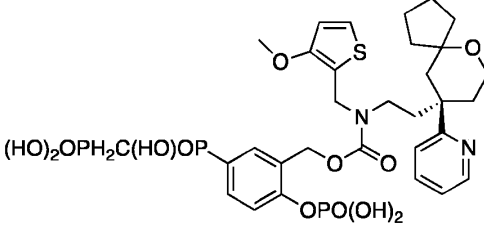
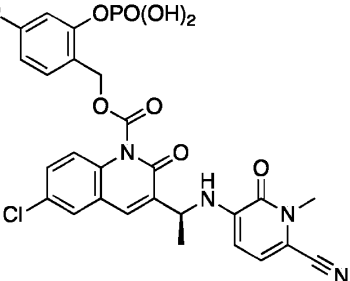
224	Structure	
	Name	(3-chloro-5-((((<i>S</i>)-3-(((3<i>S</i>,5<i>S</i>,6<i>R</i>)-6-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-5-(2,3,6-trifluorophenyl)piperidin-3-yl)carbamoyl)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[<i>b</i>]pyridine-6,3'-pyrrolo[2,3-<i>b</i>]pyridine]-1'-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
225	Structure	
	Name	(3-methoxy-5-((((<i>S</i>)-3-(((3<i>S</i>,5<i>S</i>,6<i>R</i>)-6-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-5-(2,3,6-trifluorophenyl)piperidin-3-yl)carbamoyl)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[<i>b</i>]pyridine-6,3'-pyrrolo[2,3-<i>b</i>]pyridine]-1'-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid

226	Structure	
	Name	(3-fluoro-5-(((<i>S</i>)-3-(((3 <i>S</i> ,5 <i>S</i> ,6 <i>R</i>)-6-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-5-(2,3,6-trifluorophenyl)piperidin-3-yl)carbamoyl)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[<i>b</i>]pyridine-6,3'-pyrrolo[2,3- <i>b</i>]pyridine]-1'-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
227	Structure	
	Name	3-methyl-5-(((<i>S</i>)-3-(((3 <i>S</i> ,5 <i>S</i> ,6 <i>R</i>)-6-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-5-(2,3,6-trifluorophenyl)piperidin-3-yl)carbamoyl)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[<i>b</i>]pyridine-6,3'-pyrrolo[2,3- <i>b</i>]pyridine]-1'-carbonyl)oxy)methyl)-4-(phosphonooxy)benzoic acid

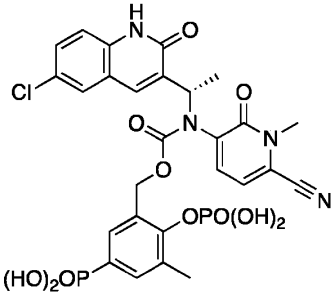
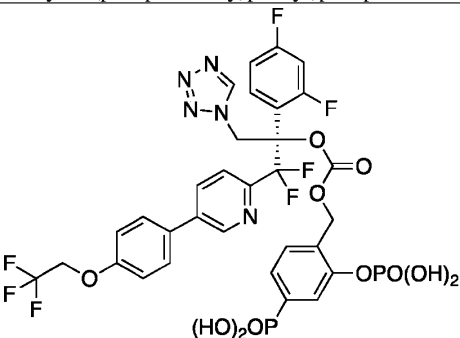
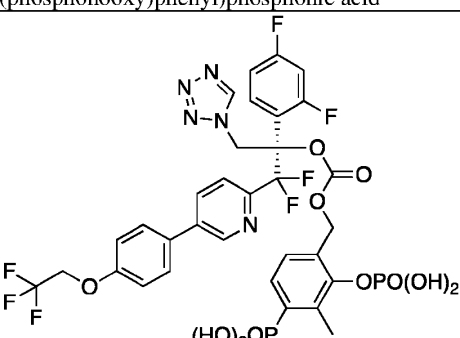
228	Structure	
	Name	(3-(((cyclopentyl(4-((2 <i>R</i> ,3 <i>S</i>)-1-(2-fluoro-6-methylbenzoyl)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)piperidin-2-yl)phenyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
229	Structure	
	Name	(3-(((cyclopentyl(4-((2 <i>R</i> ,3 <i>S</i>)-1-(2-fluoro-6-methylbenzoyl)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)piperidin-2-yl)phenyl)carbamoyl)oxy)methyl)-5-(phosphonooxy)phenyl)phosphonic acid
230	Structure	
	Name	(<i>S</i>)-(3-(((1-(4-fluorophenyl)-1-(2-(4-(6-(1-methyl-1 <i>H</i> -pyrazol-4-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-yl) group at position 3, and a (4-(phosphonooxy)phenyl)methyl group at position 4. The phosphonooxy group is further substituted with a (cyclopentyl) and a (2-fluoro-6-methylbenzoyl) group."/>

		yl)piperazin-1-yl)pyrimidin-5-yl)ethyl)carbamoyloxy)methyl)-4-(phosphonooxy)phenyl)phosphonodiperoxoic acid
231	Structure	
	Name	(S)-(4-((((1-(4-fluorophenyl)-1-(2-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)piperazin-1-yl)pyrimidin-5-yl)ethyl)carbamoyloxy)methyl)-3-(phosphonooxy)phenyl)phosphonodiperoxoic acid
232	Structure	
	Name	(R)-(4-((((3-methoxythiophen-2-yl)methyl)(2-(9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl)ethyl)carbamoyloxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
233	Structure	
	Name	(R)-(4-((((3-methoxythiophen-2-yl)methyl)(2-(9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl)ethyl)carbamoyloxy)methyl)-2-methyl-3-(phosphonooxy)phenyl)phosphonic acid

234	Structure	
	Name	(R)-3-((((3-methoxythiophen-2-yl)methyl)(2-(9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl)ethyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
235	Structure	
	Name	(R)-3-((((3-methoxythiophen-2-yl)methyl)(2-(9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl)ethyl)carbamoyl)oxy)methyl)-5-methyl-4-(phosphonooxy)phenyl)phosphonic acid
236	Structure	
	Name	(R)-3-fluoro-5-((((3-methoxythiophen-2-yl)methyl)(2-(9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl)ethyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
237	Structure	
	Name	(R)-3-chloro-5-((((3-methoxythiophen-2-yl)methyl)(2-(9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl)ethyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid

		yl)ethyl)carbamoyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
238	Structure	
	Name	(<i>R</i>)-(3-methoxy-5-((((3-methoxythiophen-2-yl)methyl)(2-(9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl)ethyl)carbamoyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
239	Structure	
	Name	((hydroxy(3-((((3-methoxythiophen-2-yl)methyl)(2-((<i>R</i>)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl)ethyl)carbamoyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphoryl)methyl)phosphonic acid
240	Structure	
	Name	(<i>S</i>)-(4-((((6-chloro-3-(1-((6-cyano-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)amino)ethyl)-2-oxo-1,2-dihydroquinoline-1-carbonyl)oxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid

241	Structure	
	Name	(S)-3-(((6-chloro-3-(1-((6-cyano-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)amino)ethyl)-2-oxo-1,2-dihydroquinoline-1-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
242	Structure	
	Name	(S)-4-(((1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)(6-cyano-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)carbamoyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
243	Structure	
	Name	(S)-4-(((1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)(6-cyano-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid

244	Structure	
	Name	(S)-3-((((1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)(6-cyano-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)carbamoyl)oxy)methyl)-5-methyl-4-(phosphonoxy)phenyl)phosphonic acid
245	Structure	
	Name	(R)-4-((((2-(2,4-difluorophenyl)-1,1-difluoro-3-(1H-tetrazol-1-yl)-1-(5-(4-(2,2,2-trifluoroethoxy)phenyl)pyridin-2-yl)propan-2-yl)oxy)carbonyl)oxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
246	Structure	
	Name	(R)-4-((((2-(2,4-difluorophenyl)-1,1-difluoro-3-(1H-tetrazol-1-yl)-1-(5-(4-(2,2,2-trifluoroethoxy)phenyl)pyridin-2-yl)propan-2-yl)oxy)carbonyl)oxy)methyl)-2-methyl-3-(phosphonoxy)phenyl)phosphonic acid

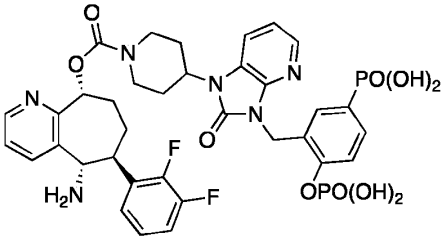
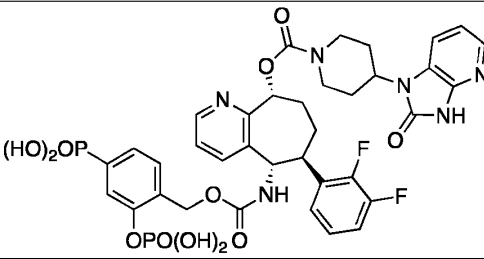
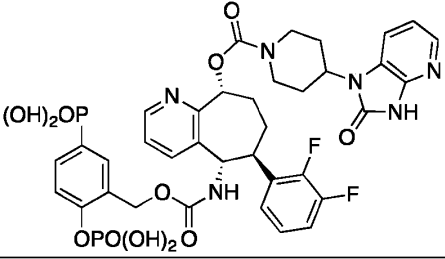
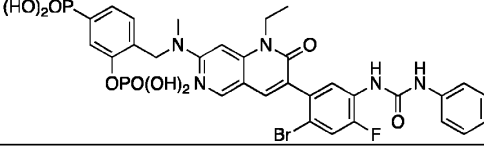
247	Structure	
	Name	(R)-3-((((2-(2,4-difluorophenyl)-1,1-difluoro-3-(1H-tetrazol-1-yl)-1-(5-(4-(2,2,2-trifluoroethoxy)phenyl)pyridin-2-yl)propan-2-yl)oxy)carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
248	Structure	
	Name	(R)-3-((((2-(2,4-difluorophenyl)-1,1-difluoro-3-(1H-tetrazol-1-yl)-1-(5-(4-(2,2,2-trifluoroethoxy)phenyl)pyridin-2-yl)propan-2-yl)oxy)carbonyl)oxy)methyl)-5-methyl-4-(phosphonooxy)phenyl)phosphonic acid
249	Structure	
	Name	(R)-3-chloro-5-((((2-(2,4-difluorophenyl)-1,1-difluoro-3-(1H-tetrazol-1-yl)-1-(5-(4-(2,2,2-trifluoroethoxy)phenyl)pyridin-2-yl)propan-2-yl)oxy)carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid

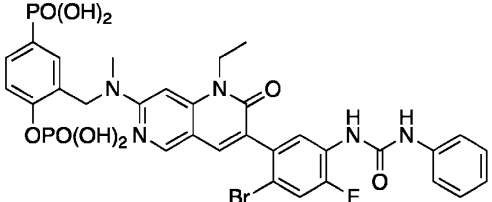
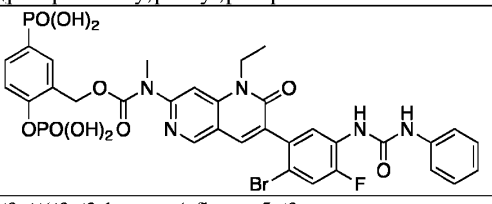
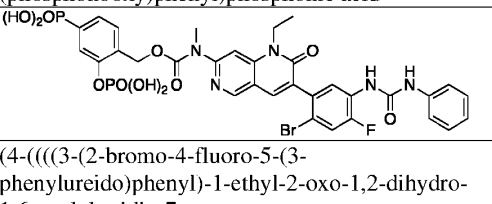
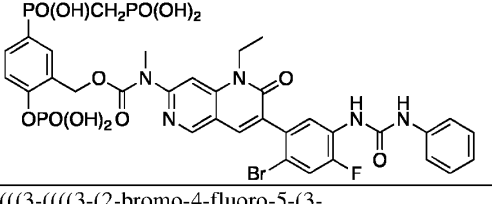
250	Structure	
	Name	(R)-(3-((((2-(2,4-difluorophenyl)-1,1-difluoro-3-(1H-tetrazol-1-yl)-1-(5-(4-(2,2,2-trifluoroethoxy)phenyl)pyridin-2-yl)propan-2-yl)oxy)carbonyl)oxy)methyl)-5-methoxy-4-(phosphonooxy)phenyl)phosphonic acid
251	Structure	
	Name	(E)-(3-(phosphonooxy)-4-(((4-(2-(pyrrolidin-1-yl)ethoxy)-6,11-dioxo-3-aza-2(4,2)-pyrimidina-1,4(1,3)-dibenzenacyclododecaphan-8-en-3-yl)methyl)phenyl)phosphonic acid
252	Structure	
	Name	(E)-(3-(phosphonooxy)-4-(((4-(2-(pyrrolidin-1-yl)ethoxy)-6,11-dioxo-3-aza-2(4,2)-pyrimidina-1,4(1,3)-dibenzenacyclododecaphan-8-ene-3-carbonyl)oxy)methyl)phenyl)phosphonic acid

253	Structure	
	Name	(E)-(4-(phosphonooxy)-3-(((4 ⁴ -(2-(pyrrolidin-1-yl)ethoxy)-6,11-dioxo-3-aza-2(4,2)-pyrimidina-1,4(1,3)-dibenzenacyclododecaphan-8-ene-3-carbonyl)oxy)methyl)phenyl)phosphonic acid
254	Structure	
	Name	(E)-(3-methyl-4-(phosphonooxy)-5-(((4 ⁴ -(2-(pyrrolidin-1-yl)ethoxy)-6,11-dioxo-3-aza-2(4,2)-pyrimidina-1,4(1,3)-dibenzenacyclododecaphan-8-ene-3-carbonyl)oxy)methyl)phenyl)phosphonic acid
255	Structure	
	Name	(E)-(3-methoxy-4-(phosphonooxy)-5-(((4 ⁴ -(2-(pyrrolidin-1-yl)ethoxy)-6,11-dioxo-3-aza-2(4,2)-pyrimidina-1,4(1,3)-dibenzenacyclododecaphan-8-ene-3-carbonyl)oxy)methyl)phenyl)phosphonic acid

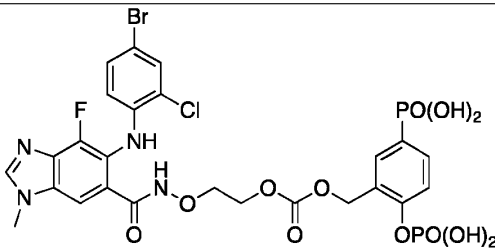
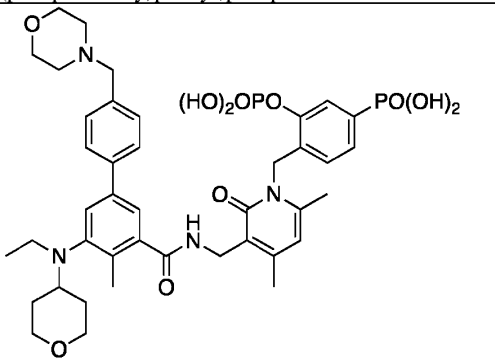
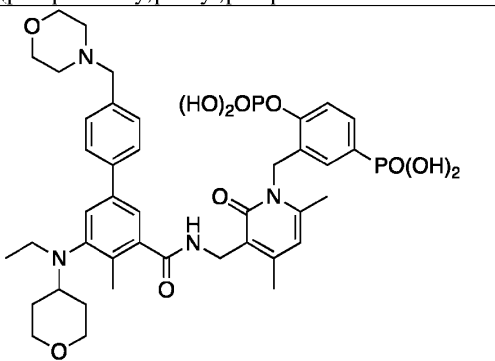
256	Structure	
	Name	(<i>E</i>)-((hydroxy(4-(phosphonooxy)-3-(((4-(2-(pyrrolidin-1-yl)ethoxy)-6,11-dioxo-3-aza-2(4,2)-pyrimidina-1,4(1,3)-dibenzenacyclododecaphan-8-ene-3-carbonyl)oxy)methyl)phenyl)phosphoryl)methyl)phosphonic acid
257	Structure	
	Name	(<i>S</i>)-3-(((3-((2-(4-((1-(6-(4-fluoro-1 <i>H</i> -pyrazol-1-yl)pyridin-3-yl)ethyl)carbamoyl)-4-methoxycyclohexyl)-6-methylpyrimidin-4-yl)amino)-5-methyl-1 <i>H</i> -pyrazole-1-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
258	Structure	
	Name	(<i>S</i>)-4-(((3-((2-(4-((1-(6-(4-fluoro-1 <i>H</i> -pyrazol-1-yl)pyridin-3-yl)ethyl)carbamoyl)-4-methoxycyclohexyl)-6-methylpyrimidin-4-yl)amino)-5-methyl-1 <i>H</i> -pyrazole-1-carbonyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
259	Structure	
	Name	(<i>S</i>)-4-((((2-(4-((1-(6-(4-fluoro-1 <i>H</i> -pyrazol-1-yl)pyridin-3-yl)ethyl)carbamoyl)-4-methoxycyclohexyl)-6-methylpyrimidin-4-yl)(5-methyl-1 <i>H</i> -pyrazol-1-yl)amino)-5-methyl-1 <i>H</i> -pyrazole-1-carbonyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid

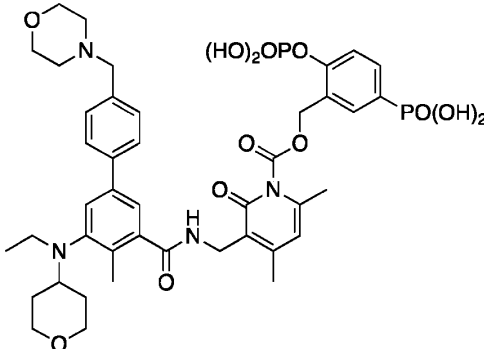
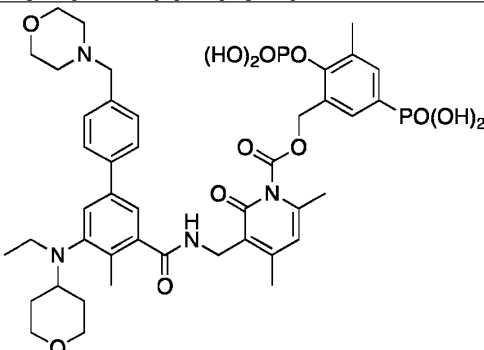
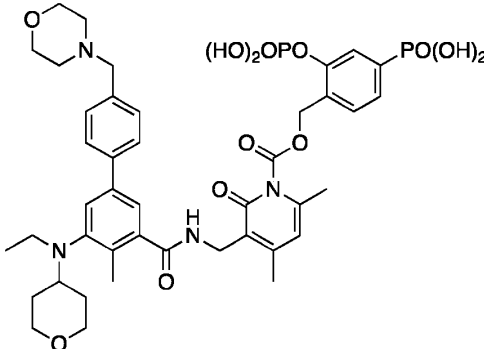
		methyl-1 <i>H</i> -pyrazol-3-yl)carbamoyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
260	Structure	
	Name	(<i>S</i>)-(3-(((2-(4-((1-(6-(4-fluoro-1 <i>H</i> -pyrazol-1-yl)pyridin-3-yl)ethyl)carbamoyl)-4-methoxycyclohexyl)-6-methylpyrimidin-4-yl)(5-methyl-1 <i>H</i> -pyrazol-3-yl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
261	Structure	
	Name	(<i>S</i>)-(3-(((2-(4-((1-(6-(4-fluoro-1 <i>H</i> -pyrazol-1-yl)pyridin-3-yl)ethyl)carbamoyl)-4-methoxycyclohexyl)-6-methylpyrimidin-4-yl)(5-methyl-1 <i>H</i> -pyrazol-3-yl)carbamoyl)oxy)methyl)-5-methyl-4-(phosphonooxy)phenyl)phosphonic acid
262	Structure	
	Name	(4-((1-(1-(((5 <i>S</i> ,6 <i>S</i> ,9 <i>R</i>)-5-amino-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5 <i>H</i> -cyclohepta[<i>b</i>]pyridin-9-yl)oxy)carbonyl)piperidin-4-yl)-2-oxo-1,2-dihydro-3 <i>H</i> -imidazo[4,5- <i>b</i>]pyridin-3-yl)methyl)-3-(phosphonooxy)phenyl)phosphonic acid

263	Structure	
	Name	(3-((1-(1-(((5 <i>S</i> ,6 <i>S</i> ,9 <i>R</i>)-5-amino-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5 <i>H</i> -cyclohepta[<i>b</i>]pyridin-9-yl)oxy)carbonyl)piperidin-4-yl)-2-oxo-1,2-dihydro-3 <i>H</i> -imidazo[4,5- <i>b</i>]pyridin-3-yl)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
264	Structure	
	Name	(4-((((5 <i>S</i> ,6 <i>S</i> ,9 <i>R</i>)-6-(2,3-difluorophenyl)-9-((4-(2-oxo-2,3-dihydro-1 <i>H</i> -imidazo[4,5- <i>b</i>]pyridin-1-yl)piperidine-1-carbonyl)oxy)-6,7,8,9-tetrahydro-5 <i>H</i> -cyclohepta[<i>b</i>]pyridin-5-yl)carbamoyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
265	Structure	
	Name	(3-((((5 <i>S</i> ,6 <i>S</i> ,9 <i>R</i>)-6-(2,3-difluorophenyl)-9-((4-(2-oxo-2,3-dihydro-1 <i>H</i> -imidazo[4,5- <i>b</i>]pyridin-1-yl)piperidine-1-carbonyl)oxy)-6,7,8,9-tetrahydro-5 <i>H</i> -cyclohepta[<i>b</i>]pyridin-5-yl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
266	Structure	
	Name	(4-(((3-(2-bromo-4-fluoro-5-(3-phenylureido)phenyl)-1-ethyl-2-oxo-1,2-dihydro-

		1,6-naphthyridin-7-yl)(methylamino)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
267	Structure	
	Name	(3-(((3-(2-bromo-4-fluoro-5-(3-phenylureido)phenyl)-1-ethyl-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl)(methylamino)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
268	Structure	
	Name	(3-(((3-(2-bromo-4-fluoro-5-(3-phenylureido)phenyl)-1-ethyl-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl)(methylcarbamoyloxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
269	Structure	
	Name	(4-(((3-(2-bromo-4-fluoro-5-(3-phenylureido)phenyl)-1-ethyl-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl)(methylcarbamoyloxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
270	Structure	
	Name	((3-(((3-(2-bromo-4-fluoro-5-(3-phenylureido)phenyl)-1-ethyl-2-oxo-1,2-dihydro-1,6-naphthyridin-7-yl)(methylcarbamoyloxy)methyl)-4-(phosphonooxy)phenyl)(hydroxy)phosphoryl)methyl)phosphonic acid

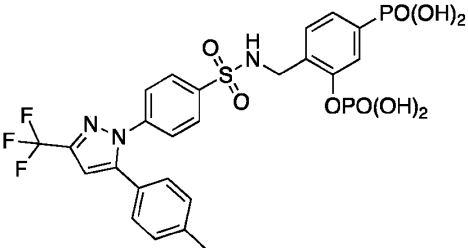
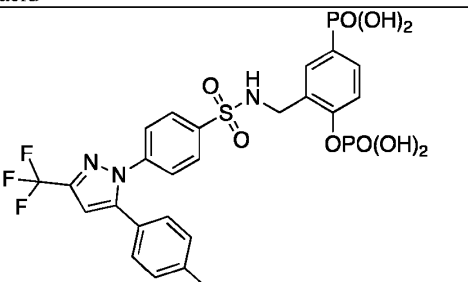
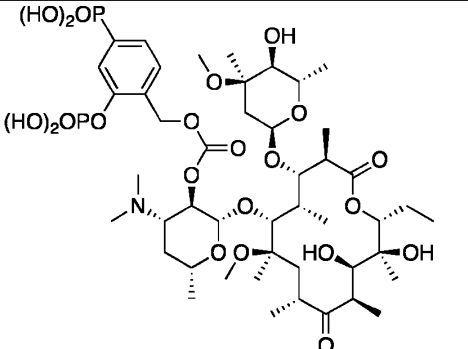
271	Structure	
	Name	(4-((((1-((3-cyano-4-(6-(6-(6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)-2-methylpropan-2-yl)oxy)carbonyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
272	Structure	
	Name	(3-((((1-((3-cyano-4-(6-(6-(6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)-2-methylpropan-2-yl)oxy)carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
273	Structure	
	Name	(4-(1-(5-((4-bromo-2-chlorophenyl)amino)-4-fluoro-1-methyl-1H-benzo[d]imidazol-6-yl)-1,7-dioxo-3,6,8-trioxa-2-azanonan-9-yl)-3-(phosphonooxy)phenyl)phosphonic acid

274	Structure	
	Name	(3-(1-(5-((4-bromo-2-chlorophenyl)amino)-4-fluoro-1-methyl-1 <i>H</i> -benzo[<i>d</i>]imidazol-6-yl)-1,7-dioxo-3,6,8-trioxa-2-azanonan-9-yl)-4-(phosphonoxy)phenyl)phosphonic acid
275	Structure	
	Name	(4-((3-((5-(ethyl(tetrahydro-2 <i>H</i> -pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamido)methyl)-4,6-dimethyl-2-oxopyridin-1(2 <i>H</i>)-yl)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
276	Structure	
	Name	(3-((3-((5-(ethyl(tetrahydro-2 <i>H</i> -pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamido)methyl)-4,6-dimethyl-2-oxopyridin-1(2 <i>H</i>)-yl)methyl)-4-(phosphonoxy)phenyl)phosphonic acid

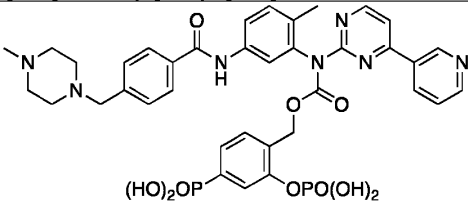
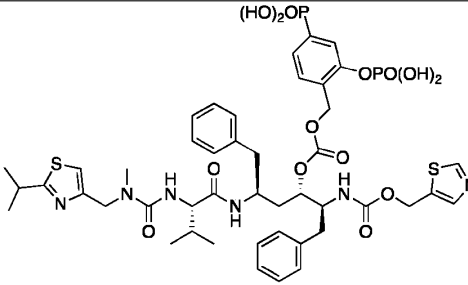
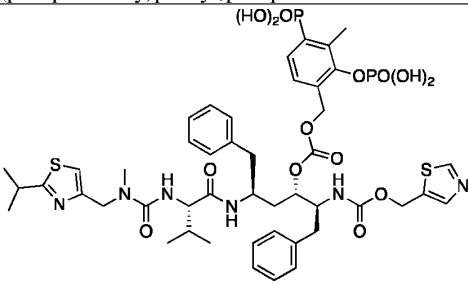
277	Structure	
	Name	(3-(((3-((5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamido)methyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-1-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
278	Structure	
	Name	(3-(((3-((5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamido)methyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-1-carbonyl)oxy)methyl)-5-methyl-4-(phosphonooxy)phenyl)phosphonic acid
279	Structure	
	Name	(4-(((3-((5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamido)methyl)-4,6-dimethyl-2-

		oxo-1,2-dihydropyridine-1-carbonyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
280	Structure	
	Name	(3-(((benzyl(2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
281	Structure	
	Name	(4-(((benzyl(2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetyl)carbamoyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
282	Structure	
	Name	(3-(((2'-((5-(4-methylpiperazin-1-yl)pyridin-2-yl)amino)-6'-oxo-7',8'-dihydro-6'H-spiro[cyclohexane-1,9'-pyrazino[1',2':1,5]pyrrolo[2,3-d]pyrimidine)-7'-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
283	Structure	
	Name	(4-(((2'-((5-(4-methylpiperazin-1-yl)pyridin-2-yl)amino)-6'-oxo-7',8'-dihydro-6'H-spiro[cyclohexane-1,9'-pyrazino[1',2':1,5]pyrrolo[2,3-d]pyrimidine)-7'-carbonyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid

284	Structure	
	Name	(3-((((5-(4-methylpiperazin-1-yl)pyridin-2-yl)(6'-oxo-7',8'-dihydro-6'H-spiro[cyclohexane-1,9'-pyrazino[1',2':1,5]pyrrolo[2,3-d]pyrimidin]-2'-yl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
285	Structure	
	Name	(4-((((5-(4-methylpiperazin-1-yl)pyridin-2-yl)(6'-oxo-7',8'-dihydro-6'H-spiro[cyclohexane-1,9'-pyrazino[1',2':1,5]pyrrolo[2,3-d]pyrimidin]-2'-yl)carbamoyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
286	Structure	
	Name	(3-((((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)(6-((4,4-dimethyl-4,5-dihydrooxazol-2-yl)amino)quinazolin-4-yl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
287	Structure	
	Name	(4-((((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)(6-((4,4-dimethyl-4,5-dihydrooxazol-2-yl)amino)quinazolin-4-yl)carbamoyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid

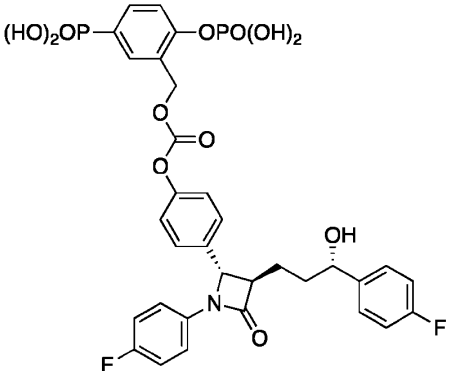
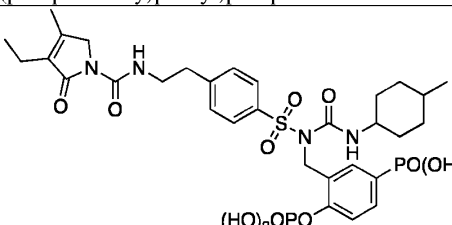
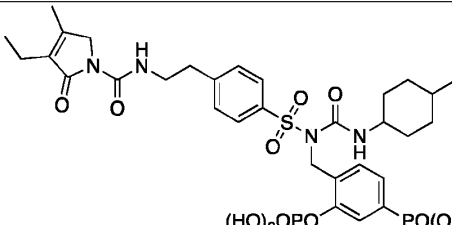
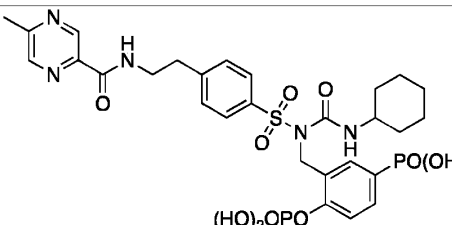
288	Structure	
	Name	(3-(phosphonooxy)-4-(((4-(5-(<i>p</i> -tolyl)-3-(trifluoromethyl)-1 <i>H</i> -pyrazol-1-yl)phenyl)sulfonamido)methyl)phenyl)phosphonic acid
289	Structure	
	Name	(4-(phosphonooxy)-3-(((4-(5-(<i>p</i> -tolyl)-3-(trifluoromethyl)-1 <i>H</i> -pyrazol-1-yl)phenyl)sulfonamido)methyl)phenyl)phosphonic acid
290	Structure	
	Name	(4-((((((2 <i>S</i> ,3 <i>R</i> ,4 <i>S</i> ,6 <i>R</i>)-4-(dimethylamino)-2-(((3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i> ,6 <i>R</i> ,7 <i>R</i> ,9 <i>R</i> ,11 <i>R</i> ,12 <i>R</i> ,13 <i>S</i> ,14 <i>R</i>)-14-ethyl-12,13-dihydroxy-4-(((2 <i>R</i> ,4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i>)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2 <i>H</i> -pyran-2-yl)oxy)-7-methoxy-3,5,7,9,11,13-hexamethyl-2,10-dioxoacetyl)oxy)-6-methyltetrahydro-2 <i>H</i> -pyran-3-yl)oxy)carbonyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid

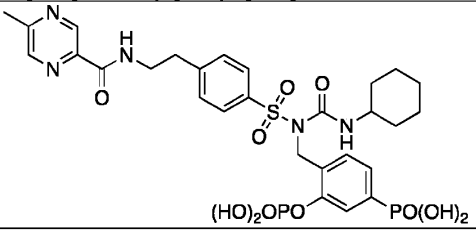
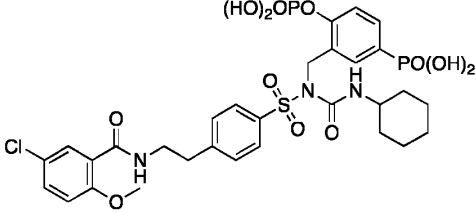
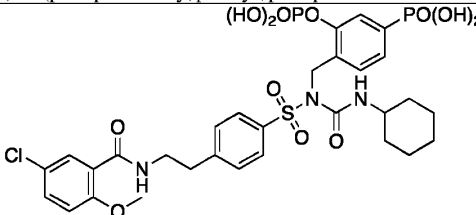
291	Structure	
	Name	(3-((((((2 <i>S</i> ,3 <i>R</i> ,4 <i>S</i> ,6 <i>R</i>)-4-(dimethylamino)-2-(((3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i> ,6 <i>R</i> ,7 <i>R</i> ,9 <i>R</i> ,11 <i>R</i> ,12 <i>R</i> ,13 <i>S</i> ,14 <i>R</i>)-14-ethyl-12,13-dihydroxy-4-(((2 <i>R</i> ,4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i>)-5-hydroxy-4-methoxy-4,6-dimethyltetrahydro-2 <i>H</i> -pyran-2-yl)oxy)-7-methoxy-3,5,7,9,11,13-hexamethyl-2,10-dioxooxacyclotetradecan-6-yl)oxy)-6-methyltetrahydro-2 <i>H</i> -pyran-3-yl)oxy)carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
292	Structure	
	Name	(4-((((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)(4-((4-methylpiperazin-1-yl)methyl)benzoyl)carbamoyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
293	Structure	
	Name	(4-((((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)(4-((4-methylpiperazin-1-yl)methyl)benzoyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
294	Structure	

	Name	(3-((((2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)benzamido)phenyl)(4-(pyridin-3-yl)pyrimidin-2-yl)carbamoyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
295	Structure	
	Name	(4-((((2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)benzamido)phenyl)(4-(pyridin-3-yl)pyrimidin-2-yl)carbamoyl)oxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
296	Structure	
	Name	(4-((((5S,8S,10S)-8-benzyl-5-isopropyl-1-(2-isopropylthiazol-4-yl)-2-methyl-3,6,12-trioxo-10-((S)-2-phenyl-1-(((thiazol-5-ylmethoxy)carbonyl)amino)ethyl)-11,13-dioxo-2,4,7-triazatetradecan-14-yl)-3-(phosphonoxy)phenyl)phosphonic acid
297	Structure	
	Name	(4-((((5S,8S,10S)-8-benzyl-5-isopropyl-1-(2-isopropylthiazol-4-yl)-2-methyl-3,6,12-trioxo-10-((S)-2-phenyl-1-(((thiazol-5-ylmethoxy)carbonyl)amino)ethyl)-11,13-dioxo-2,4,7-triazatetradecan-14-yl)-2-methyl-3-(phosphonoxy)phenyl)phosphonic acid

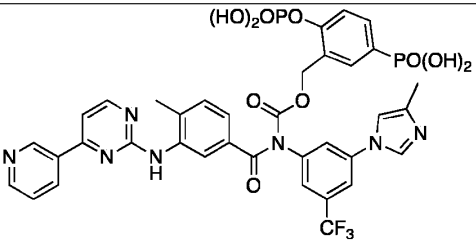
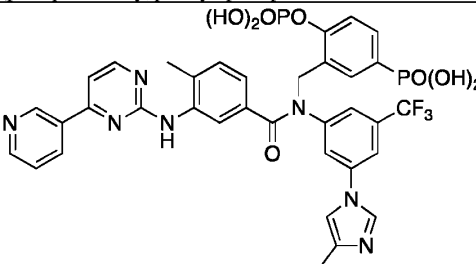
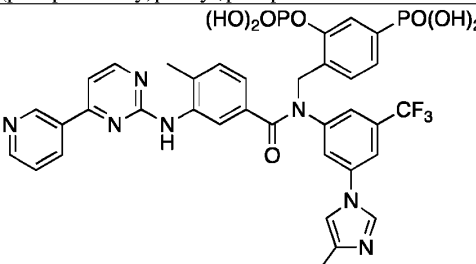
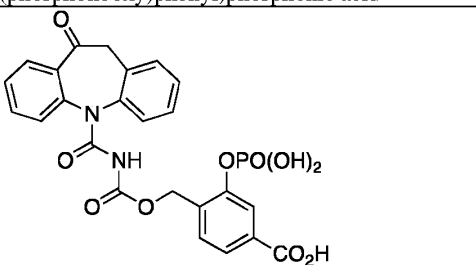
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	Name	(3-((5 <i>S</i> ,8 <i>S</i> ,10 <i>S</i>)-8-benzyl-5-isopropyl-1-(2-isopropylthiazol-4-yl)-2-methyl-3,6,12-trioxo-10-((<i>S</i>)-2-phenyl-1-(((thiazol-5-ylmethoxy)carbonyl)amino)ethyl)-11,13-dioxo-2,4,7-triazatetradecan-14-yl)-5-chloro-4-(phosphonooxy)phenyl)phosphonic acid
299	Structure	
	Name	(3-((5 <i>S</i> ,8 <i>S</i> ,10 <i>S</i>)-8-benzyl-5-isopropyl-1-(2-isopropylthiazol-4-yl)-2-methyl-3,6,12-trioxo-10-((<i>S</i>)-2-phenyl-1-(((thiazol-5-ylmethoxy)carbonyl)amino)ethyl)-11,13-dioxo-2,4,7-triazatetradecan-14-yl)-5-methoxy-4-(phosphonooxy)phenyl)phosphonic acid
300	Structure	
	Name	(3-(((3-((3-(3-chloro-5-cyanophenoxy)-2-oxo-4-(trifluoromethyl)pyridin-1(2 <i>H</i>)-yl)methyl)-4-methyl-5-oxo-4,5-dihydro-1 <i>H</i> -1,2,4-triazole-1-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
301	Structure	
	Name	(3-(((3-((3-(3-chloro-5-cyanophenoxy)-2-oxo-4-(trifluoromethyl)pyridin-1(2 <i>H</i>)-yl)methyl)-4-methyl-5-oxo-4,5-dihydro-1 <i>H</i> -1,2,4-triazole-1-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid

		methyl-5-oxo-4,5-dihydro-1 <i>H</i> -1,2,4-triazole-1-carbonyloxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
302	Structure	
	Name	(3-((((<i>S</i>)-1-(4-fluorophenyl)-3-((2 <i>S</i> ,3 <i>R</i>)-1-(4-fluorophenyl)-2-(4-hydroxyphenyl)-4-oxoazetidin-3-yl)propoxy)carbonyloxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
303	Structure	
	Name	(4-((((<i>S</i>)-1-(4-fluorophenyl)-3-((2 <i>S</i> ,3 <i>R</i>)-1-(4-fluorophenyl)-2-(4-hydroxyphenyl)-4-oxoazetidin-3-yl)propoxy)carbonyloxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
304	Structure	
	Name	(4-((((4-((2 <i>S</i> ,3 <i>R</i>)-1-(4-fluorophenyl)-3-((<i>S</i>)-3-(4-fluorophenyl)-3-hydroxypropyl)-4-oxoazetidin-2-yl)phenoxy)carbonyloxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid

305	Structure	
	Name	(3-((((4-((2 <i>S</i> ,3 <i>R</i>)-1-(4-fluorophenyl)-3-((<i>S</i>)-3-(4-fluorophenyl)-3-hydroxypropyl)-4-oxoazetidin-2-yl)phenoxy)carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
306	Structure	
	Name	(3-((((4-(2-(3-ethyl-4-methyl-2-oxo-2,5-dihydro-1 <i>H</i> -pyrrole-1-carboxamido)ethyl)- <i>N</i> -((4-methylcyclohexyl)carbamoyl)phenyl)sulfonamido)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
307	Structure	
	Name	(4-((((4-(2-(3-ethyl-4-methyl-2-oxo-2,5-dihydro-1 <i>H</i> -pyrrole-1-carboxamido)ethyl)- <i>N</i> -((4-methylcyclohexyl)carbamoyl)phenyl)sulfonamido)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
308	Structure	

	Name	(3-(((N-(cyclohexylcarbamoyl)-4-(2-(5-methylpyrazine-2-carboxamido)ethyl)phenyl)sulfonamido)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
309	Structure	 (HO) ₂ OPO
	Name	(4-(((N-(cyclohexylcarbamoyl)-4-(2-(5-methylpyrazine-2-carboxamido)ethyl)phenyl)sulfonamido)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
310	Structure	 (HO) ₂ OPO
	Name	(3-(((4-(2-(5-chloro-2-methoxybenzamido)ethyl)-N-(cyclohexylcarbamoyl)phenyl)sulfonamido)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
311	Structure	 (HO) ₂ OPO
	Name	(4-(((4-(2-(5-chloro-2-methoxybenzamido)ethyl)-N-(cyclohexylcarbamoyl)phenyl)sulfonamido)methyl)-3-(phosphonooxy)phenyl)phosphonic acid

312	Structure	
	Name	(4-((((((2 <i>R</i> ,4 <i>R</i>)-2-(2-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1 <i>H</i> -pyrrol-1-yl)ethyl)-6-oxotetrahydro-2 <i>H</i> -pyran-4-yl)oxy)carbonyl)oxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
313	Structure	
	Name	(3-((((((2 <i>R</i> ,4 <i>R</i>)-2-(2-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1 <i>H</i> -pyrrol-1-yl)ethyl)-6-oxotetrahydro-2 <i>H</i> -pyran-4-yl)oxy)carbonyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
314	Structure	
	Name	(4-((((3-(4-methyl-1 <i>H</i> -imidazol-1-yl)-5-(trifluoromethyl)phenyl)(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)benzoyl)carbonyl)oxy)methyl)-3-(phosphonoxy)phenyl)phosphonic acid

315	Structure	
	Name	(3-(((3-(4-methyl-1 <i>H</i> -imidazol-1-yl)-5-(trifluoromethyl)phenyl)(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)benzoyl)carbamoyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
316	Structure	
	Name	(3-((4-methyl- <i>N</i> -(3-(4-methyl-1 <i>H</i> -imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)benzamido)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
317	Structure	
	Name	(4-((4-methyl- <i>N</i> -(3-(4-methyl-1 <i>H</i> -imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)benzamido)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
318	Structure	
	Name	4-(((10-oxo-10,11-dihydro-5 <i>H</i> -dibenzo[<i>b,f</i>]azepine-5-

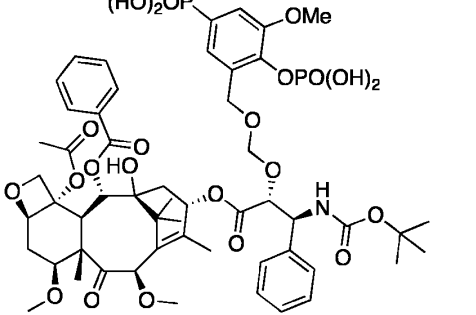
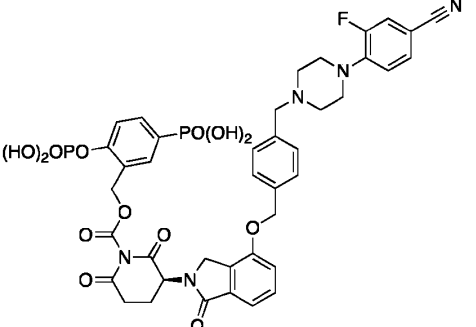
		carbonyl)carbamoyl)oxy)methyl)-3-(phosphonoxy)benzoic acid
319	Structure	
	Name	(3-(((10-oxo-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carbonyl)carbamoyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
320	Structure	
	Name	(4-(((4-(5-methyl-3-phenylisoxazol-4-yl)phenyl)sulfonamido)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
321	Structure	
	Name	(3-(((4-(5-methyl-3-phenylisoxazol-4-yl)phenyl)sulfonamido)methyl)-3-(phosphonoxy)phenyl)phosphonic acid
322	Structure	
	Name	3-((3-(4-chloro-3-(trifluoromethyl)phenyl)-1-(4-((2-(methylcarbamoyl)pyridin-4-yl)oxy)phenyl)ureido)methyl)-4-(phosphonoxy)benzoic acid

	NMR	¹ H NMR (500 MHz, MeOD) δ 8.42 (d, J = 5.6 Hz, 1H), 7.96 (s, 1H), 7.85 (dd, J = 8.5, 2.2 Hz, 1H), 7.83 (d, J = 2.6 Hz, 1H), 7.69 (dd, J = 8.8, 2.7 Hz, 1H), 7.61 (dd, J = 9.5, 2.7 Hz, 2H), 7.59 (d, J = 2.6 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.04–7.00 (m, 2H), 6.96 (dd, J = 5.6, 2.5 Hz, 1H), 5.25 (s, 2H), 2.93 (s, 3H).
	Mass spec	(ES) m/z = 695.1 [M+H] ⁺
323	Structure	
	Name	3-((((4-(4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)phenoxy)picolinoyl)(methyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)benzoic acid
324	Structure	
	Name	3-((((4-(4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)phenoxy)picolinoyl)(methyl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenylphosphonic acid
325	Structure	
	Name	(S)-3-((((6-((1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl)amino)-7H-purine-7-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
326	Structure	

	Name	(S)-(4-(((6-(((1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)propyl)amino)-7H-purine-7-carbonyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
327	Structure	
	Name	(R,E)-(3-(((1-(1-(2-cyano-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-en-1-yl)piperidin-3-yl)-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
328	Structure	
	Name	(R,E)-(3-(((1-(1-(2-cyano-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-en-1-yl)piperidin-3-yl)-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)carbamoyl)oxy)methyl)-5-methyl-4-(phosphonooxy)phenyl)phosphonic acid
329	Structure	
	Name	(3-((5R,6S)-5-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-11-hydroxy-4,6-dimethoxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-

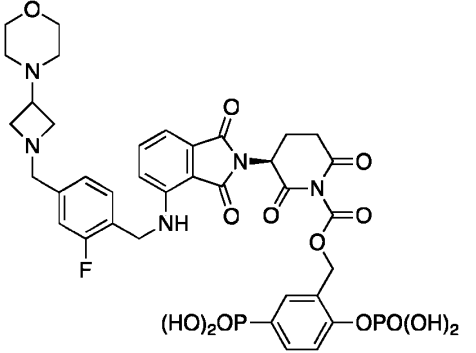
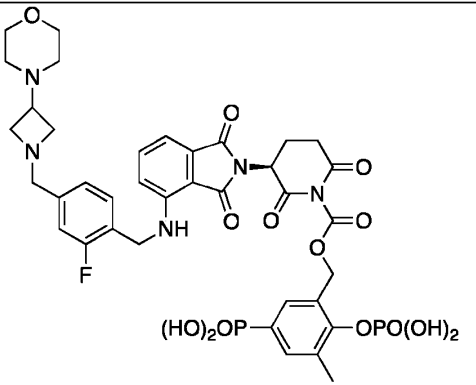
		dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-9-yl)oxy)carbonyl)-10,10-dimethyl-3,8-dioxo-6-phenyl-2,4,9-trioxa-7-azaundecyl)-4-(phosphonoxy)phenyl)phosphonic acid
330	Structure	
	Name	(3-((5 <i>R</i> ,6 <i>S</i>)-5-(((2 <i>aR</i> ,4 <i>S</i> ,4 <i>aS</i> ,6 <i>R</i> ,9 <i>S</i> ,11 <i>S</i> ,12 <i>S</i> ,12 <i>aR</i> ,12 <i>bS</i>)-12 <i>b</i> -acetoxo-12-(benzoyloxy)-11-hydroxy-4,6-dimethoxy-4 <i>a</i> ,8,13,13-tetramethyl-5-oxo-2 <i>a</i> ,3,4,4 <i>a</i> ,5,6,9,10,11,12,12 <i>a</i> ,12 <i>b</i> -dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-9-yl)oxy)carbonyl)-10,10-dimethyl-3,8-dioxo-6-phenyl-2,4,9-trioxa-7-azaundecyl)-5-methyl-4-(phosphonoxy)phenyl)phosphonic acid
331	Structure	
	Name	(3-((5 <i>R</i> ,6 <i>S</i>)-5-(((2 <i>aR</i> ,4 <i>S</i> ,4 <i>aS</i> ,6 <i>R</i> ,9 <i>S</i> ,11 <i>S</i> ,12 <i>S</i> ,12 <i>aR</i> ,12 <i>bS</i>)-12 <i>b</i> -acetoxo-12-(benzoyloxy)-11-hydroxy-4,6-dimethoxy-4 <i>a</i> ,8,13,13-tetramethyl-5-oxo-2 <i>a</i> ,3,4,4 <i>a</i> ,5,6,9,10,11,12,12 <i>a</i> ,12 <i>b</i> -dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-9-yl)oxy)carbonyl)-10,10-dimethyl-3,8-dioxo-6-phenyl-2,4,9-trioxa-7-azaundecyl)-5-methoxy-4-

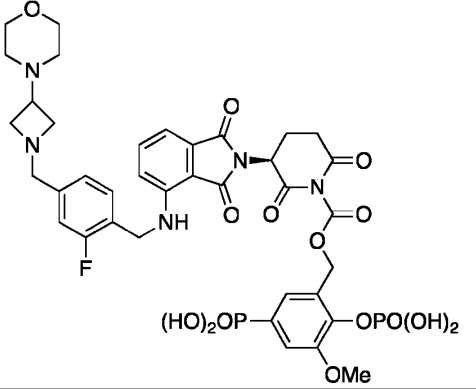
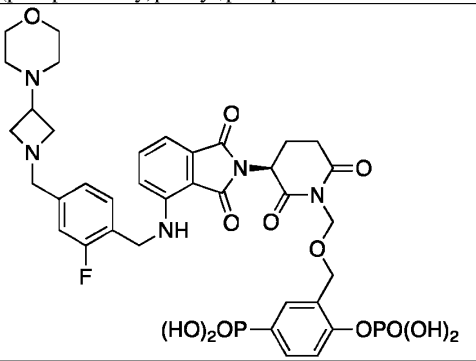
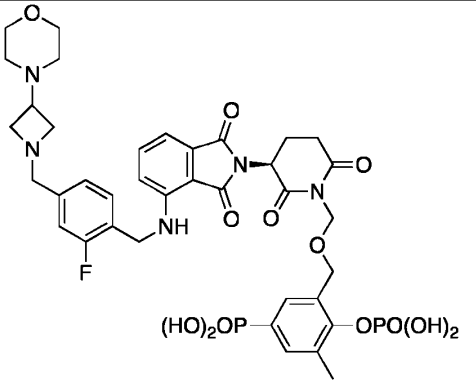
		(phosphonooxy)phenyl)phosphonic acid
332	Structure	
	Name	(3-((5 <i>R</i> ,6 <i>S</i>)-5-(((2 <i>aR</i> ,4 <i>S</i> ,4 <i>aS</i> ,6 <i>R</i> ,9 <i>S</i> ,11 <i>S</i> ,12 <i>S</i> ,12 <i>aR</i> ,12 <i>bS</i>)-12 <i>b</i> -acetoxy-12-(benzoyloxy)-11-hydroxy-4,6-dimethoxy-4 <i>a</i> ,8,13,13-tetramethyl-5-oxo-2 <i>a</i> ,3,4,4 <i>a</i> ,5,6,9,10,11,12,12 <i>a</i> ,12 <i>b</i> -dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-9-yl)oxy)carbonyl)-10,10-dimethyl-8-oxo-6-phenyl-2,4,9-trioxa-7-azaundecyl)-4-(phosphonooxy)phenyl)phosphonic acid
333	Structure	
	Name	(3-((5 <i>R</i> ,6 <i>S</i>)-5-(((2 <i>aR</i> ,4 <i>S</i> ,4 <i>aS</i> ,6 <i>R</i> ,9 <i>S</i> ,11 <i>S</i> ,12 <i>S</i> ,12 <i>aR</i> ,12 <i>bS</i>)-12 <i>b</i> -acetoxy-12-(benzoyloxy)-11-hydroxy-4,6-dimethoxy-4 <i>a</i> ,8,13,13-tetramethyl-5-oxo-2 <i>a</i> ,3,4,4 <i>a</i> ,5,6,9,10,11,12,12 <i>a</i> ,12 <i>b</i> -dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-9-yl)oxy)carbonyl)-10,10-dimethyl-8-oxo-6-phenyl-2,4,9-trioxa-7-azaundecyl)-5-methyl-4-(phosphonooxy)phenyl)phosphonic acid

334	Structure	
	Name	(3-((5<i>R</i>,6<i>S</i>)-5-(((2<i>aR</i>,4<i>S</i>,4<i>aS</i>,6<i>R</i>,9<i>S</i>,11<i>S</i>,12<i>S</i>,12<i>aR</i>,12<i>bS</i>)-12<i>b</i>-acetoxo-12-(benzoyloxy)-11-hydroxy-4,6-dimethoxy-4<i>a</i>,8,13,13-tetramethyl-5-oxo-2<i>a</i>,3,4,4<i>a</i>,5,6,9,10,11,12,12<i>a</i>,12<i>b</i>-dodecahydro-1<i>H</i>-7,11-methanocyclodeca[3,4]benzo[1,2-<i>b</i>]oxet-9-yl)oxy)carbonyl)-10,10-dimethyl-8-oxo-6-phenyl-2,4,9-trioxa-7-azaundecyl)-5-methoxy-4-(phosphonoxy)phenyl)phosphonic acid
335	Structure	
	Name	(<i>S</i>)-(3-(((3-(4-(((4-(4-cyano-2-fluorophenyl)piperazin-1-yl)methyl)benzyl)oxy)-1-oxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid

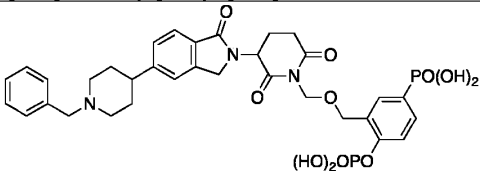
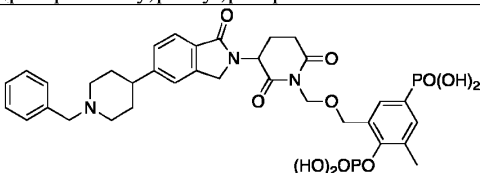
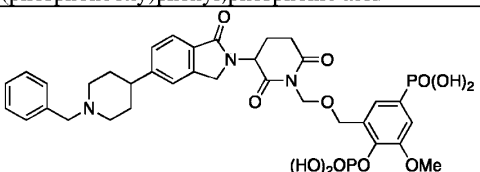
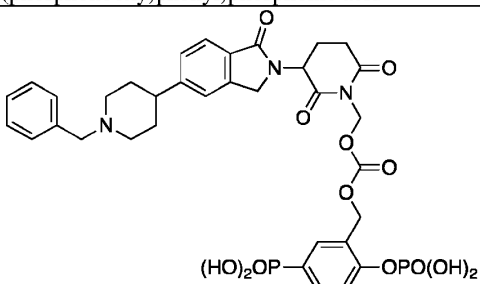
336	Structure	
	Name	(S)-3-(((3-(4-((4-(4-cyano-2-fluorophenyl)piperazin-1-yl)methyl)benzyl)oxy)-1-oxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl-5-methyl-4-(phosphonooxy)phenyl)phosphonic acid
337	Structure	
	Name	(S)-3-(((3-(4-((4-(4-cyano-2-fluorophenyl)piperazin-1-yl)methyl)benzyl)oxy)-1-oxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl-5-methoxy-4-(phosphonooxy)phenyl)phosphonic acid
338	Structure	
	Name	(S)-3-(((3-(4-((4-(4-cyano-2-fluorophenyl)piperazin-1-yl)methyl)benzyl)oxy)-1-oxoisindolin-2-yl)-2,6-dioxopiperidin-1-

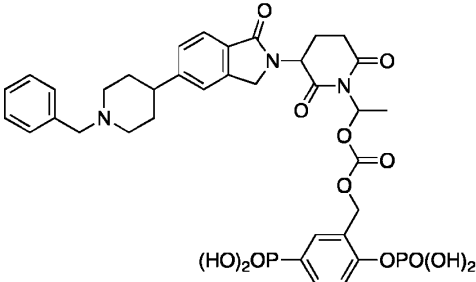
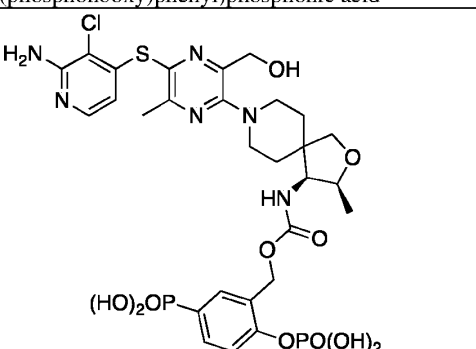
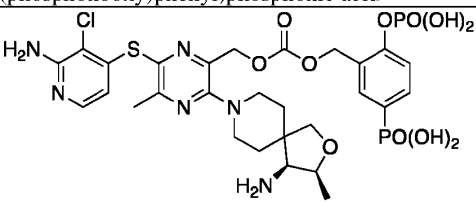
		yl)methoxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
339	Structure	
	Name	(3-(((3-(5-(2-(4-chlorophenyl)-2,2-difluoroacetamido)methyl)-1-oxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
341	Structure	
	Name	(3-(((3-(5-(2-(4-chlorophenyl)-2,2-difluoroacetamido)methyl)-1-oxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl)-5-methyl-4-(phosphonooxy)phenyl)phosphonic acid
342	Structure	
	Name	(3-(((3-(5-(2-(4-chlorophenyl)-2,2-difluoroacetamido)methyl)-1-oxoisindolin-2-yl)-2,6-dioxopiperidin-1-yl)methoxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid

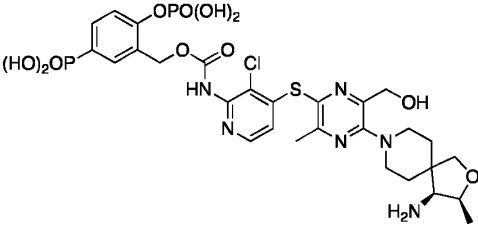
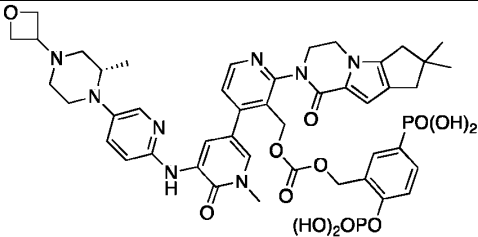
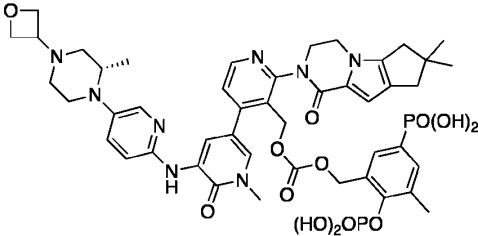
343	Structure	
	Name	(S)-3-(((3-(4-((2-fluoro-4-((3-morpholinoazetidin-1-yl)methyl)benzyl)amino)-1,3-dioxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
344	Structure	
	Name	(S)-3-(((3-(4-((2-fluoro-4-((3-morpholinoazetidin-1-yl)methyl)benzyl)amino)-1,3-dioxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl)-5-methyl-4-(phosphonoxy)phenyl)phosphonic acid

345	Structure	
	Name	(S)-3-(((3-(4-((2-fluoro-4-((3-morpholinoazetidin-1-yl)methyl)benzyl)amino)-1,3-dioxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl)-5-methoxy-4-(phosphonooxy)phenyl)phosphonic acid
346	Structure	
	Name	(S)-3-(((3-(4-((2-fluoro-4-((3-morpholinoazetidin-1-yl)methyl)benzyl)amino)-1,3-dioxoisindolin-2-yl)-2,6-dioxopiperidin-1-yl)methoxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
347	Structure	

	Name	(S)-3-(((3-(4-((2-fluoro-4-((3-morpholinoazetidin-1-yl)methyl)benzyl)amino)-1,3-dioxoisindolin-2-yl)-2,6-dioxopiperidin-1-yl)methoxy)methyl)-5-methyl-4-(phosphonooxy)phenyl)phosphonic acid
348	Structure	
	Name	(S)-3-(((3-(4-((2-fluoro-4-((3-morpholinoazetidin-1-yl)methyl)benzyl)amino)-1,3-dioxoisindolin-2-yl)-2,6-dioxopiperidin-1-yl)methoxy)methyl)-5-methoxy-4-(phosphonooxy)phenyl)phosphonic acid
349	Structure	
	Name	(S)-3-(((3-(5-(1-benzylpiperidin-4-yl)-1-oxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
350	Structure	
	Name	(S)-3-(((3-(5-(1-benzylpiperidin-4-yl)-1-oxoisindolin-2-yl)-2,6-dioxopiperidine-1-carbonyl)oxy)methyl)-5-methyl-4-(phosphonooxy)phenyl)phosphonic acid
351	Structure	

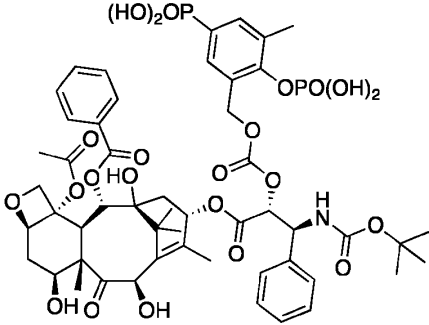
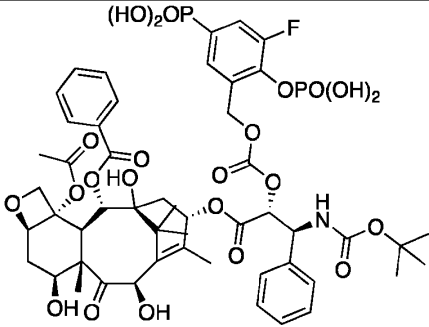
	Name	(3-(((3-(5-(1-benzylpiperidin-4-yl)-1-oxoisindolin-2-yl)-2,6-dioxopiperidin-1-carbonyl)oxy)methyl)-5-methoxy-4-(phosphonoxy)phenyl)phosphonic acid
352	Structure	
	Name	(3-(((3-(5-(1-benzylpiperidin-4-yl)-1-oxoisindolin-2-yl)-2,6-dioxopiperidin-1-yl)methoxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
352	Structure	
	Name	(3-(((3-(5-(1-benzylpiperidin-4-yl)-1-oxoisindolin-2-yl)-2,6-dioxopiperidin-1-yl)methoxy)methyl)-5-methyl-4-(phosphonoxy)phenyl)phosphonic acid
353	Structure	
	Name	(3-(((3-(5-(1-benzylpiperidin-4-yl)-1-oxoisindolin-2-yl)-2,6-dioxopiperidin-1-yl)methoxy)methyl)-5-methoxy-4-(phosphonoxy)phenyl)phosphonic acid
354	Structure	
	Name	(3-((((3-(5-(1-benzylpiperidin-4-yl)-1-oxoisindolin-2-yl)-2,6-dioxopiperidin-1-yl)methoxy)carbonyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid

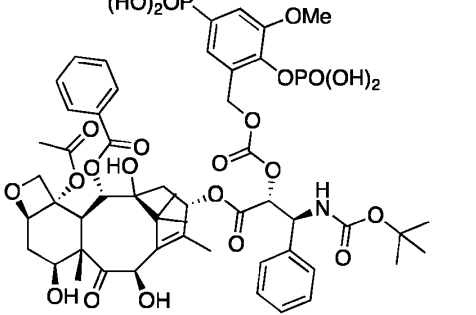
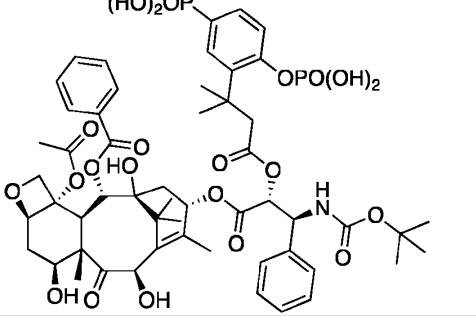
355	Structure	
	Name	(3-((((1-(3-(5-(1-benzylpiperidin-4-yl)-1-oxoisindolin-2-yl)-2,6-dioxopiperidin-1-yl)ethoxy)carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
356	Structure	
	Name	(3-((((((3S,4S)-8-(5-((2-amino-3-chloropyridin-4-yl)thio)-3-(hydroxymethyl)-6-methylpyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-yl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
357	Structure	
	Name	(3-((((((6-((2-amino-3-chloropyridin-4-yl)thio)-3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-methylpyrazin-2-yl)methoxy)carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid

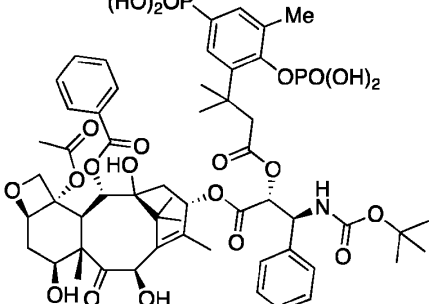
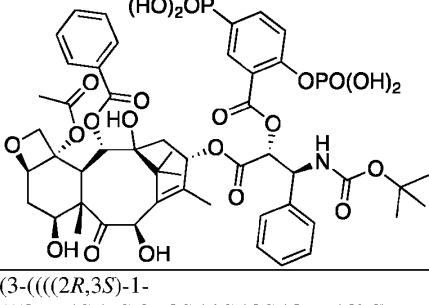
358	Structure	
	Name	(3-((((4-((5-((3 <i>S</i> ,4 <i>S</i>)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(hydroxymethyl)-3-methylpyrazin-2-yl)thio)-3-chloropyridin-2-yl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
359	Structure	
	Name	(<i>S</i>)-3-((((2'-(7,7-dimethyl-1-oxo-1,3,4,6,7,8-hexahydro-2 <i>H</i> -cyclopenta[4,5]pyrrolo[1,2- <i>a</i>]pyrazin-2-yl)-1-methyl-5-((5-(2-methyl-4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-yl)amino)-6-oxo-1,6-dihydro-[3,4'-bipyridin]-3'-yl)methoxy)carbonyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
360	Structure	
	Name	(<i>S</i>)-3-((((2'-(7,7-dimethyl-1-oxo-1,3,4,6,7,8-hexahydro-2 <i>H</i> -cyclopenta[4,5]pyrrolo[1,2- <i>a</i>]pyrazin-2-yl)-1-methyl-5-((5-(2-methyl-4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-yl)amino)-6-oxo-1,6-dihydro-[3,4'-bipyridin]-3'-yl)methoxy)carbonyl)oxy)methyl)-5-methyl-4-(phosphonooxy)phenyl)phosphonic acid

361	Structure	
	Name	(S)-3-((((2'-(7,7-dimethyl-1-oxo-1,3,4,6,7,8-hexahydro-2H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-2-yl)-1-methyl-5-((5-(2-methyl-4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-yl)amino)-6-oxo-1,6-dihydro-[3,4'-bipyridin]-3'-yl)methoxy)carbonyloxy)methyl)-5-methoxy-4-(phosphonoxy)phenyl)phosphonic acid
362	Structure	
	Name	(S)-3-((((2'-(7,7-dimethyl-1-oxo-1,3,4,6,7,8-hexahydro-2H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-2-yl)-1-methyl-5-((5-(2-methyl-4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-yl)amino)-6-oxo-1,6-dihydro-[3,4'-bipyridin]-3'-yl)methoxy)methoxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid
363	Structure	
	Name	(S)-3-((((3-(1-(but-2-ynoyl)pyrrolidin-2-yl)-1-(4-(pyridin-2-yl)carbamoyl)phenyl)imidazo[1,5-a]pyrazin-8-yl)carbamoyloxy)methyl)-4-(phosphonoxy)benzoic acid

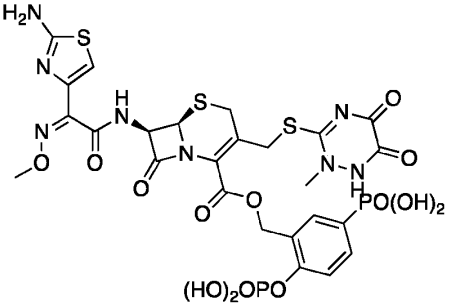
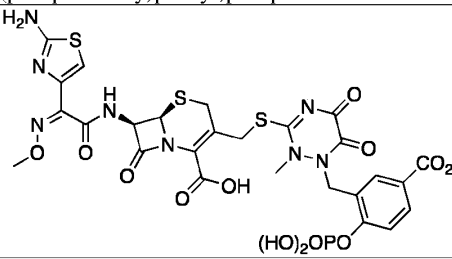
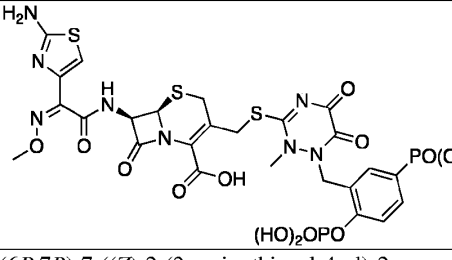
364	Structure	
	Name	(S)-3-((((3-(1-(but-2-ynoyl)pyrrolidin-2-yl)-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-8-yl)carbamoyl)oxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
365	Structure	
	Name	(S)-4-((((3-(1-(but-2-ynoyl)pyrrolidin-2-yl)-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-8-yl)amino)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
	Mass spec	$m/z = 732.2$ [M+H] ⁺
366	Structure	
	Name	(3-((5R,6S)-5-((((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)carbonyl)-10,10-dimethyl-3,8-dioxo-6-phenyl-2,4,9-trioxa-7-

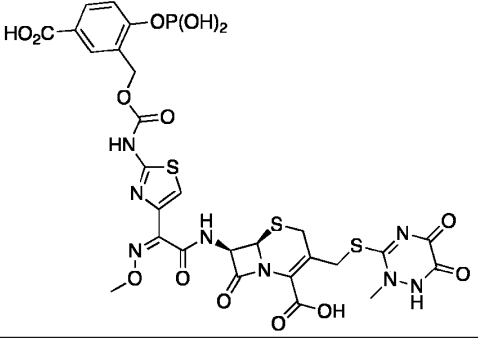
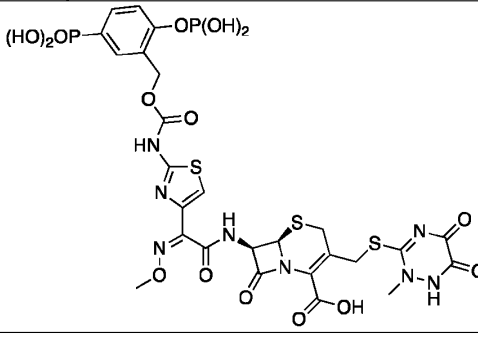
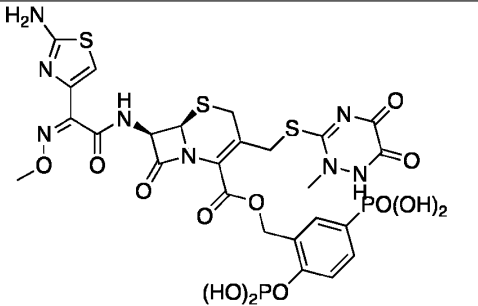
		azaundecyl)-4-(phosphonooxy)phenyl)phosphonic acid
367	Structure	
	Name	(3-((5 <i>R</i> ,6 <i>S</i>)-5-(((2 <i>aR</i> ,4 <i>S</i> ,4 <i>aS</i> ,6 <i>R</i> ,9 <i>S</i> ,11 <i>S</i> ,12 <i>S</i> ,12 <i>aR</i> ,12 <i>bS</i>)-12 <i>b</i> -acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4 <i>a</i> ,8,13,13-tetramethyl-5-oxo-2 <i>a</i> ,3,4,4 <i>a</i> ,5,6,9,10,11,12,12 <i>a</i> ,12 <i>b</i> -dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-9-yl)oxy)carbonyl)-10,10-dimethyl-3,8-dioxo-6-phenyl-2,4,9-trioxa-7-azaundecyl)-5-methyl-4-(phosphonooxy)phenyl)phosphonic acid
368	Structure	
	Name	(3-((5 <i>R</i> ,6 <i>S</i>)-5-(((2 <i>aR</i> ,4 <i>S</i> ,4 <i>aS</i> ,6 <i>R</i> ,9 <i>S</i> ,11 <i>S</i> ,12 <i>S</i> ,12 <i>aR</i> ,12 <i>bS</i>)-12 <i>b</i> -acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4 <i>a</i> ,8,13,13-tetramethyl-5-oxo-2 <i>a</i> ,3,4,4 <i>a</i> ,5,6,9,10,11,12,12 <i>a</i> ,12 <i>b</i> -dodecahydro-1 <i>H</i> -7,11-methanocyclodeca[3,4]benzo[1,2- <i>b</i>]oxet-9-yl)oxy)carbonyl)-10,10-dimethyl-3,8-dioxo-6-phenyl-2,4,9-trioxa-7-azaundecyl)-5-fluoro-4-(phosphonooxy)phenyl)phosphonic acid

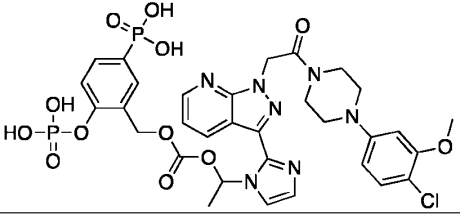
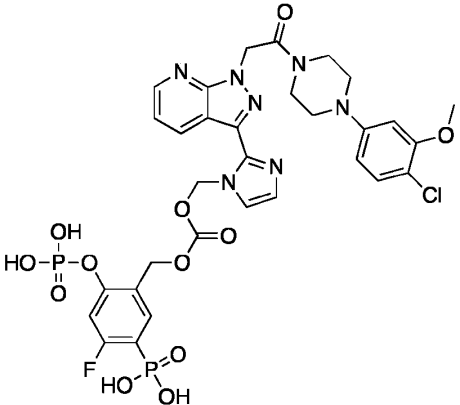
369	Structure	
	Name	(3-((5<i>R</i>,6<i>S</i>)-5-(((2<i>aR</i>,4<i>S</i>,4<i>aS</i>,6<i>R</i>,9<i>S</i>,11<i>S</i>,12<i>S</i>,12<i>aR</i>,12<i>bS</i>)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1<i>H</i>-7,11-methanocyclodeca[3,4]benzo[1,2-<i>b</i>]oxet-9-yl)oxy)carbonyl)-10,10-dimethyl-3,8-dioxo-6-phenyl-2,4,9-trioxa-7-azaundecyl)-5-methoxy-4-(phosphonoxy)phenyl)phosphonic acid
370	Structure	
	Name	(3-(4-(((2<i>R</i>,3<i>S</i>)-1-(((2<i>aR</i>,4<i>S</i>,4<i>aS</i>,6<i>R</i>,9<i>S</i>,11<i>S</i>,12<i>S</i>,12<i>aR</i>,12<i>bS</i>)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1<i>H</i>-7,11-methanocyclodeca[3,4]benzo[1,2-<i>b</i>]oxet-9-yl)oxy)-3-((<i>tert</i>-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl)oxy)-2-methyl-4-oxobutan-2-yl)-4-(phosphonoxy)phenyl)phosphonic acid

371	Structure	
	Name	(3-(4-(((2<i>R</i>,3<i>S</i>)-1-(((2<i>aR</i>,4<i>S</i>,4<i>aS</i>,6<i>R</i>,9<i>S</i>,11<i>S</i>,12<i>S</i>,12<i>aR</i>,12<i>bS</i>)-12<i>b</i>-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4<i>a</i>,8,13,13-tetramethyl-5-oxo-2<i>a</i>,3,4,4<i>a</i>,5,6,9,10,11,12,12<i>a</i>,12<i>b</i>-dodecahydro-1<i>H</i>-7,11-methanocyclodeca[3,4]benzo[1,2-<i>b</i>]oxet-9-yl)oxy)-3-((<i>tert</i>-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl)oxy)-2-methyl-4-oxobutan-2-yl)-5-methyl-4-(phosphonoxy)phenyl)phosphonic acid
372	Structure	
	Name	(3-(((2<i>R</i>,3<i>S</i>)-1-(((2<i>aR</i>,4<i>S</i>,4<i>aS</i>,6<i>R</i>,9<i>S</i>,11<i>S</i>,12<i>S</i>,12<i>aR</i>,12<i>bS</i>)-12<i>b</i>-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4<i>a</i>,8,13,13-tetramethyl-5-oxo-2<i>a</i>,3,4,4<i>a</i>,5,6,9,10,11,12,12<i>a</i>,12<i>b</i>-dodecahydro-1<i>H</i>-7,11-methanocyclodeca[3,4]benzo[1,2-<i>b</i>]oxet-9-yl)oxy)-3-((<i>tert</i>-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl)oxy)carbonyl)-4-(phosphonoxy)phenyl)phosphonic acid

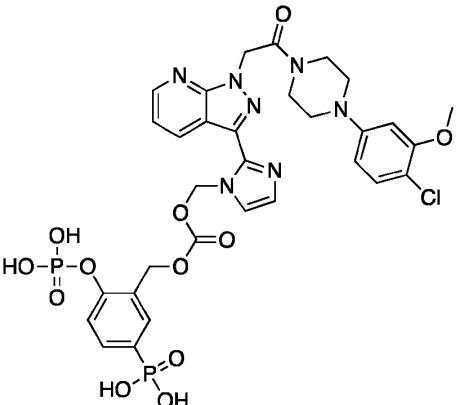
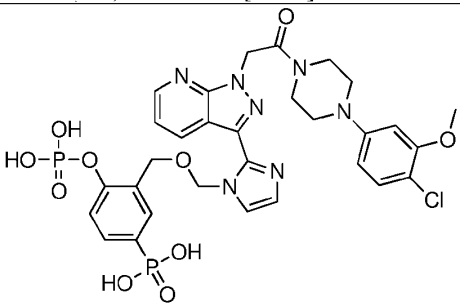
373	Structure	
	Name	(6 <i>R</i> ,7 <i>R</i>)-7-((<i>Z</i>)-2-(2-aminothiazol-4-yl)-2-(((5-carboxy-2-(phosphonooxy)benzyl)oxy)imino)acetamido)-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid
374	Structure	
	Name	(6 <i>R</i> ,7 <i>R</i>)-7-((<i>Z</i>)-2-(2-aminothiazol-4-yl)-2-(((5-phosphono-2-(phosphonooxy)benzyl)oxy)imino)acetamido)-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid
375	Structure	
	Name	3-((((6 <i>R</i> ,7 <i>R</i>)-7-((<i>Z</i>)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido)-3-((2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)thio)methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carbonyl)oxy)methyl)-4-(phosphonooxy)benzoic acid

376	Structure	
	Name	(3-((((6R,7R)-7-((Z)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido)-3-((2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)thio)methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carbonyloxy)methyl)-4-(phosphonooxy)phenyl)phosphonic acid
377	Structure	
	Name	(6R,7R)-7-((Z)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido)-3-((((1-(5-carboxy-2-(phosphonooxy)benzyl)-2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)thio)methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid
378	Structure	
	Name	(6R,7R)-7-((Z)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido)-3-((((2-methyl-5,6-dioxo-1-(5-phosphono-2-(phosphonooxy)benzyl)-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)thio)methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

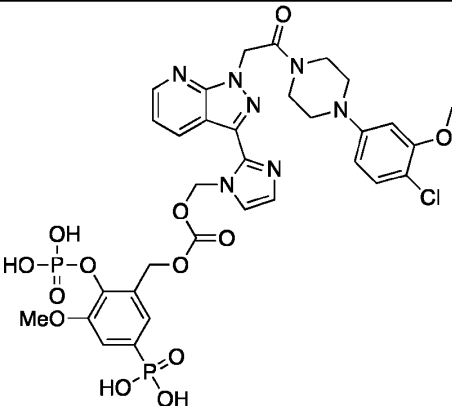
379	Structure	
	Name	(6<i>R</i>,7<i>R</i>)-7-((<i>Z</i>)-2-(2-(((5-carboxy-2-((dihydroxyphosphaneyl)oxy)benzyl)oxy)carbonyl)amino)thiazol-4-yl)-2-(methoxyimino)acetamido)-3-(((2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)thio)methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid
378	Structure	
	Name	(6<i>R</i>,7<i>R</i>)-7-((<i>Z</i>)-2-(2-(((2-((dihydroxyphosphaneyl)oxy)-5-phosphonobenzyl)oxy)carbonyl)amino)thiazol-4-yl)-2-(methoxyimino)acetamido)-3-(((2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)thio)methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid
380	Structure	

	Name	(3-((((6 <i>R</i> ,7 <i>R</i>)-7-((<i>Z</i>)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido)-3-((2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)thio)methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carbonyl)oxy)methyl)-4-((dihydroxyphosphaneyl)oxy)phenyl)phosphonic acid
381	Structure	
	Name	(3-((((1-(2-(1-(2-(4-(4-chloro-3-methoxyphenyl)piperazin-1-yl)-2-oxoethyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl)-1 <i>H</i> -imidazol-1-yl)ethoxy)carbonyl)oxy)methyl)-4-(phosphonoxy)phenyl)phosphonic acid sodium salt
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 8.55 (dt, <i>J</i> = 4.7, 1.1 Hz, 1H), 8.49 (ddd, <i>J</i> = 8.2, 1.6, 0.7 Hz, 1H), 7.58 (d, <i>J</i> = 1.5 Hz, 1H), 7.56–7.45 (m, 2H), 7.38 (dd, <i>J</i> = 8.2, 4.7 Hz, 1H), 7.34–7.25 (m, 3H), 7.24 (d, <i>J</i> = 1.5 Hz, 1H), 6.71 (d, <i>J</i> = 2.6 Hz, 1H), 6.61 (dd, <i>J</i> = 8.8, 2.6 Hz, 1H), 5.66–5.50 (m, 2H), 5.17–4.97 (m, 2H), 3.82 (d, <i>J</i> = 4.0 Hz, 5H), 3.70–3.64 (m, 2H), 3.24 (dd, <i>J</i> = 12.1, 6.4 Hz, 2H), 3.14 (q, <i>J</i> = 5.1 Hz, 2H), 1.83 (d, <i>J</i> = 6.1 Hz, 3H).
	Mass Spec	LRMS (ESI) <i>m/z</i> = 804.1 [M–H] [–] .
382		
	Name	[5-[[[2-[1-[2-[4-(4-chloro-3-methoxyphenyl)piperazin-1-yl]-2-oxoethyl]pyrazolo[3,4- <i>b</i>]pyridin-3-yl]imidazol-1-

383		yl]methoxycarbonyloxymethyl]-2-fluoro-4-phosphonooxy-phenyl]phosphonic acid sodium salt
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 8.56 (dd, <i>J</i> = 4.7, 1.5 Hz, 1H), 8.51 (dd, <i>J</i> = 8.1, 1.5 Hz, 1H), 7.47 (d, <i>J</i> = 1.5 Hz, 1H), 7.42–7.35 (m, 1H), 7.28 (d, <i>J</i> = 8.7 Hz, 1H), 7.24 (dd, <i>J</i> = 12.7, 6.6 Hz, 1H), 7.21 (d, <i>J</i> = 1.5 Hz, 1H), 6.90 (dd, <i>J</i> = 7.8, 2.9 Hz, 1H), 6.72 (d, <i>J</i> = 2.6 Hz, 1H), 6.62 (dd, <i>J</i> = 8.7, 2.7 Hz, 1H), 6.34 (s, 2H), 5.55 (s, 2H), 5.30 (s, 2H), 3.83 (s, 3H), 3.79 (t, <i>J</i> = 5.2 Hz, 2H), 3.68 (t, <i>J</i> = 5.3 Hz, 2H), 3.24 (t, <i>J</i> = 5.2 Hz, 2H), 3.15 (t, <i>J</i> = 5.3 Hz, 2H). LRMS (ESI) <i>m/z</i> = 808.9 [M–H] [–] .
	Structure	
	Name	(4-((((2-(1-(2-(4-(4-chloro-3-methoxyphenyl)piperazin-1-yl)-2-oxoethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-1H-imidazol-1-yl)methoxy)carbonyl)oxy)methyl)-3-(phosphonooxy)phenyl)phosphonic acid
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 8.57–8.52 (m, 2H), 7.60–7.52 (m, 2H), 7.49 (d, <i>J</i> = 1.5 Hz, 1H), 7.38 (dd, <i>J</i> = 8.2, 4.7 Hz, 1H), 7.33 (dd, <i>J</i> = 8.1, 2.9 Hz, 1H), 7.29 (d, <i>J</i> = 8.7 Hz, 1H), 7.21 (d, <i>J</i> = 1.5 Hz, 1H), 7.10 (d, <i>J</i> = 1.2 Hz, 1H), 6.73 (d, <i>J</i> = 2.6 Hz, 1H), 6.64 (dd, <i>J</i> = 8.8, 2.7 Hz, 1H), 6.34 (s, 2H), 5.59 (s, 2H), 5.21 (s, 2H), 3.86–3.79 (m, 6H), 3.68 (dd, <i>J</i> = 6.9, 3.8 Hz, 2H), 3.27 (t, <i>J</i> = 5.2 Hz, 2H), 3.16 (t, <i>J</i> = 5.3 Hz, 2H).
	Mass	LRMS (ESI) <i>m/z</i> = 790.1 [M–H] [–] .

384		
	Name	[3-[[[2-[1-[2-[4-(4-chloro-3-methoxyphenyl)piperazin-1-yl]-2-oxoethyl]pyrazolo[3,4-b]pyridin-3-yl]imidazol-1-yl]methoxycarbonyloxymethyl]-4-phosphonooxy-phenyl]phosphonic acid tetrasodium salt
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 8.59–8.49 (m, 2H), 7.55 (ddd, <i>J</i> = 11.6, 10.1, 2.0 Hz, 2H), 7.49 (d, <i>J</i> = 1.4 Hz, 1H), 7.38 (dd, <i>J</i> = 8.2, 4.6 Hz, 1H), 7.32 (dd, <i>J</i> = 8.3, 2.7 Hz, 1H), 7.29 (d, <i>J</i> = 8.8 Hz, 1H), 7.21 (d, <i>J</i> = 1.4 Hz, 1H), 6.73 (d, <i>J</i> = 2.7 Hz, 1H), 6.63 (dd, <i>J</i> = 8.8, 2.6 Hz, 1H), 6.34 (s, 2H), 5.59 (s, 2H), 5.22 (s, 2H), 3.83 (d, <i>J</i> = 7.2 Hz, 5H), 3.68 (t, <i>J</i> = 5.2 Hz, 2H), 3.27 (t, <i>J</i> = 5.1 Hz, 2H), 3.16 (t, <i>J</i> = 5.3 Hz, 2H).
	Mass spec	LRMS (ESI) <i>m/z</i> = 790.1 [M–H] [–] .
385	Structure	
	Name	[3-[[[2-[1-[2-[4-(4-chloro-3-methoxyphenyl)piperazin-1-yl]-2-oxoethyl]pyrazolo[3,4-b]pyridin-3-yl]imidazol-1-yl]methoxymethyl]-4-phosphonooxy-phenyl]phosphonic acid tetrasodium salt
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 8.57–8.48 (m, 2H), 7.56 (t, <i>J</i> = 1.1 Hz, 1H), 7.51 (td, <i>J</i> = 11.3, 2.7 Hz, 2H), 7.38 (ddd, <i>J</i> =

		8.2, 4.7, 0.9 Hz, 1H), 7.31 (dd, $J = 8.7$, 0.9 Hz, 1H), 7.26 (dd, $J = 8.2$, 2.8 Hz, 1H), 7.22 (t, $J = 1.1$ Hz, 1H), 6.77 (d, $J = 2.6$ Hz, 1H), 6.67 (dd, $J = 8.8$, 2.6 Hz, 1H), 5.83 (s, 2H), 5.60 (s, 2H), 4.65 (s, 2H), 3.86 (d, $J = 0.9$ Hz, 5H), 3.74–3.67 (m, 2H), 3.32 (t, $J = 5.1$ Hz, 2H), 3.19 (t, $J = 5.2$ Hz, 2H).
	Mass spec	LRMS (ESI) $m/z = 746.0$ $[M-H]^-$.
386	Structure	
	Name	(3-((((2-(1-(2-(4-(4-chloro-3-methoxyphenyl)piperazin-1-yl)-2-oxoethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-1H-imidazol-1-yl)methoxy)carbonyl)oxy)methyl)-5-fluoro-4-(phosphonooxy)phenyl)phosphonic acid
	NMR	^1H NMR (500 MHz, D_2O) δ 8.60–8.39 (m, 2H), 7.55–7.41 (m, 1H), 7.41–7.36 (m, 1H), 7.36–7.31 (m, 1H), 7.28 (d, $J = 8.7$ Hz, 1H), 7.24–7.17 (m, 1H), 6.72 (d, $J = 2.6$ Hz, 1H), 6.62 (dd, $J = 8.8$, 2.6 Hz, 1H), 6.34 (s, 2H), 5.59 (s, 2H), 5.30 (s, 2H), 3.83 (s, 5H), 3.68 (t, $J = 5.2$ Hz, 2H), 3.26 (d, $J = 5.3$ Hz, 2H), 3.15 (t, $J = 5.3$ Hz, 2H).
387	Structure	
	Name	(2-((((2-(1-(2-(4-(4-chloro-3-methoxyphenyl)piperazin-1-yl)-2-oxoethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-1H-imidazol-1-

		yl)methoxy)carbonyl)oxy)methyl)-6-methoxy-3-(phosphonoxy)phenyl)phosphonic acid
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 8.63 (dd, <i>J</i> = 4.7, 1.5 Hz, 1H), 8.59 (dd, <i>J</i> = 8.2, 1.5 Hz, 1H), 7.57 (d, <i>J</i> = 14.8 Hz, 1H), 7.55 (d, <i>J</i> = 1.5 Hz, 1H), 7.45 (dd, <i>J</i> = 8.2, 4.7 Hz, 1H), 7.34 (d, <i>J</i> = 8.7 Hz, 1H), 7.28 (d, <i>J</i> = 1.5 Hz, 1H), 6.77 – 6.76 (m, 2H), 6.68 (dd, <i>J</i> = 8.8, 2.7 Hz, 1H), 6.44 (s, 2H), 5.51 (s, 2H), 5.33 (s, 2H), 3.90 (s, 3H), 3.81 (t, <i>J</i> = 5.2 Hz, 2H), 3.72 (t, <i>J</i> = 5.2 Hz, 2H), 3.54 (s, 3H), 3.29 (t, <i>J</i> = 5.2 Hz, 2H), 3.19 (t, <i>J</i> = 5.2 Hz, 2H).
388	Structure	
	Name	(3-((((2-(1-(2-(4-(4-chloro-3-methoxyphenyl)piperazin-1-yl)-2-oxoethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-1H-imidazol-1-yl)methoxy)carbonyl)oxy)methyl)-5-methoxy-4-(phosphonoxy)phenyl)phosphonic acid
	NMR	¹ H NMR (500 MHz, D ₂ O) δ 8.61 (dd, <i>J</i> = 4.6, 1.5 Hz, 1H), 8.57 (dd, <i>J</i> = 8.2, 1.5 Hz, 1H), 7.54 (s, 1H), 7.43 (dd, <i>J</i> = 8.2, 4.6 Hz, 1H), 7.30 (d, <i>J</i> = 8.7 Hz, 1H), 7.26 (s, 2H), 7.24 (s, 1H), 6.71 (d, <i>J</i> = 2.6 Hz, 1H), 6.62 (dd, <i>J</i> = 8.7, 2.6 Hz, 1H), 6.41 (s, 2H), 5.58 (s, 2H), 5.40 (s, 2H), 3.87 (s, 3H), 3.84 (t, <i>J</i> = 5.2 Hz, 2H), 3.79 (s, 3H), 3.71 (t, <i>J</i> = 5.2 Hz, 2H), 3.23 (t, <i>J</i> = 5.2 Hz, 2H), 3.14 (t, <i>J</i> = 5.2 Hz, 2H).

Example 4: Mouse Pharmacokinetic Assay

Compounds were formulated using saline solution and administered via oral gavage.

The compounds were dosed at 0.0107 mmol/kg in male C57BI/6J mice (3 mice per dose study). Plasma samples collected at 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8h and 24 h.

Analysis as performed to determine the concentration of the released active drug. No prodrug was observed in plasma.

Compound No.	C _{max} μ M of released drug	AUC μ M.hr of released drug
5	10.5	65.3
7	11.5	212.7
10	9.25	169.6
11	8.14	153.0
12	7.64	145.7
13	11.2	204.6
14	8.02	66.21
19	0.11	1.87
41	1.34	2.75
51	8.59	74.72
62	0.02	0.08
78	1.89	1.61
119	0.10	0.41
131	0.08	0.27
133	0.30	0.98
124	0.42	0.14
148	0.20	0.87
155	11.4	217.56

5

Example 4: Stability and Solubility Data

Stability in simulated gastric fluid (SGF) and Hank's balanced salt solution

(HBSS). 10 μ M of test compound was placed in 500 μ L of either SGF or HBSS and incubated for 2 hours at 37 °C. Aliquots of 25 μ L were removed at 0, 60, and 120 min. 300 μ L of acetonitrile was added along with an internal standard. The sample was vortexed for 3 minutes and then Sol-moiety-drug conjugate and released drug concentrations were measured by LC-MS/MS. The percentage of compound (Sol-moiety-drug conjugate) remaining as well as released drug was measured for each time point.

10

Table 4. Stability of Sol-moiety-drug conjugates tested in SGF and HBSS.

Compound	SGF (pH 1.2) $t_{1/2}$ min	HBSS (pH 6.5) $t_{1/2}$ min
7	>120	>120
41	>120	>120
49	>120	>120
62	>120	>120
78	>120	>120
131	>120	>120
133	>120	>120
148	>120	>120
155	>120	>120

Solubility study using simulated gastric fluid (SGF) and Hank's balanced salt solution (HBSS). 10 mg/mL samples of each Sol-moiety-drug conjugate were prepared in Hank's balanced salt solution (HBSS) at a pH of 6.5. A series of dilutions were then performed to obtain concentrations of 8, 6, 4, and 2 mg/mL. A standard curve was generated using the peak area at each concentration by HPLC analysis. Amax was measured for each prodrug utilizing UV-spec. Saturated solutions were prepared by dissolved prodrugs (1 mg) in HBSS (20 μ L) or Simulated Gastric Fluid (SGF) (100 μ L). The slurries were sonicated for 30 seconds and then centrifuged at 14,000 RPM for 10 min to pellet the insoluble prodrug. The supernatant was analyzed on HPLC, and the product peaks were integrated and compared to calibration curves to quantify the level of prodrug in solution.

Table 5. Solubility of Sol-moiety-drug conjugates tested in SGF and HBSS.

Compound	Solubility (mg/mL) in SGF (pH 1.2)	Solubility (mg/mL) in HBSS (pH 6.5)
7	0.45	47 ^a
10	0.22	44 ^a
11	0.40	29
13	0.24	>49 ^a
41	0.24	43
49	0.080	29
51	0.66	37
62	0.35	>49 ^a
78	1.7	45

131	0.022	0.1
133	0.66	>49 ^a
148	0.23	>49 ^a
155	1.69	>49 ^a

^a Maximum solubility measurement.

Example 6: Hydrolysis in human placental alkaline phosphatase solution

Human placental ALP (Sigma, 524604) (0.5 unit/mL) was incubated with prodrug
5 (100 μM) in Tris Buffer (50 mM, pH 7.6) at 37 °C in a final volume of 1 mL. The prodrug in
buffer was preincubated at 37 °C for 5 minutes and reactions were initiated with the addition
of 100× enzyme. Aliquots (50 μL) were taken at 0 (immediately after mixing), 2, 4, 8, 16, 32,
and 64 minutes and quenched in an equal volume acetonitrile + 0.1% formic acid.
Disappearance of the prodrug and appearance of the parent drug were monitored utilizing
10 low-resolution mass spectra on an Agilent LCMS iQ instrument and compared to standard
curves for individual parent drugs. The hydrolysis and product formation rates were
calculated from the slope of the linear portion of the plotted regression curve of product and
converted to picomoles of parent drug available versus time. A control sample was incubated
without enzyme and analyzed at the final timepoint.

15

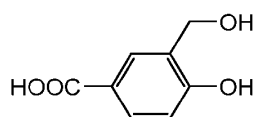
Table 6. Hydrolysis rates of Sol-moiety-drug conjugates using human placental
alkaline phosphatase (0.5 units/mL).

Compound	Drug formation rate (pmol/min)
7	4.16
10	2.97
11	3.43
13	1.81
41	1.65
49	0.64
51	1.15
62	1.26
78	2.24
131	2.13
133	1.44
148	2.11
155	1.53

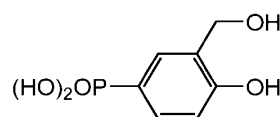
Example 7: Caco-2 permeability assays

Caco-2 cells were maintained in DMEM in an atmosphere of 5% CO₂. For transport experiments 50,000 cells/well were seeded on 12-well plate with polycarbonate filter inserts and allowed to grow and differentiate for 25 ±4 days before the cell monolayers were used for experiments. Apparent permeability coefficients were determined for apical to basolateral and basolateral to apical directions. Test articles and reference compounds were dissolved in HBSS containing 25 mM HEPES to yield a final concentration of 10 μM. The assays were performed in HBSS at pH 7.4 for the basolateral side and pH 6.5 for apical side at 37 °C. Prior to the study, the monolayers were washed in prewarmed HBSS. At the start of the experiments, pre-warmed HBSS containing the test articles was added to the donor side of the monolayer and HBSS without test articles was added to the receiver side. Aliquots of the receiver side were taken over the 2 h incubation period; aliquots of the donor side were taken at 0 h and 2 h. Aliquots were diluted with an equal volume of methanol/water with 0.1% formic acid containing the internal standard. The mixture was analyzed by LCMS/MS. The apparent permeability coefficients (P_{app}) were calculated using the formula: $P_{app} = \frac{1}{A} \left(\frac{dC_{rec}}{dt} \right) / (C_{0,donor}) \times 10^6$ with dC_{rec}/dt being the change in concentration in the receiver compartment with time; C_{0,donor} the concentration in the donor compartment at time 0; and A the area of the cells monolayer (Hidalgo *et al. Gastroenterology* 96, 736–749 (1989)). Data are shown in FIG. 52/

The Caco2 assay is known to display similar levels of alkaline phosphatases as that found in the human intestine due to its derivation from human colorectal adenocarcinoma cancer cells (Heimbach *et al. Int. J. Pharm.* 261, 81–92 (2003); Pinto *et al. Biol. Cell.* 47, 323–330 (1983)). When the Sol-moiety-drug conjugates were applied to the apical side of Caco-2 cells, no cell absorption was observed (FIG. 52, box i) and only released drug was measured in the basolateral chamber (FIG. 52, box ii). The Sol-moiety by-products **X** and **Y** (structures shown below) were poorly absorbed, if at all (P_{app} = 0.1 and 0.0 × 10⁻⁶ cm/s respectively), suggesting these would display limited permeability and potentially avoid any in vivo toxicity concerns that a hydroxybenzyl alcohol might possess.



By-product X



By-product Y

Example 7: *In vivo* pharmacokinetic studies

Methods

Male C57BI/6 mice were administered the Sol-moiety drug prototypes by oral gavage (18/22-gauge gavage needle with a rounded ball at the tip to prevent injury during insertion),
5 directly into the stomach using saline solution (0.9% NaCl) or deionized water as a vehicle (dose of 10 μ l/g body weight). Microbleeds via the tail vein at indicated time points over 24 hours were performed on each mouse.

IV injections were made using a 27/29- or 30-gauge insulin syringe, and the dose was injected into the right or left lateral tail vein or via the retro-orbital route. IV injection of
10 paclitaxel was dosed at a concentration of 0.2 mg/ml (5 μ l/g body weight) using a formulation consisting of DMSO (10%), Tween 80 (10%), and water (80%). Enzalutamide and vemurafenib were formulated in DMSO (10%) and water (90%). Mice were maintained and experiments performed at UF Scripps Institute for Biomedical Innovation & Technology or at Stanford University. Parent drug concentration was analyzed by LC-MS/MS. P values
15 were determined using an ordinary One Way ANOVA in GraphPad Prism.

Results and Discussion

Sol-moiety compounds (**7**, **49**, **62**, **41**, **148**, **78**, **155** and **131**) were dosed via oral gavage using saline solution as the vehicle. Despite known limitations of cassette studies, due
20 to potential inhibition of transporters and metabolizing enzymes, excellent exposure of released drug was observed for Sol-enzalutamide **7** (AUC = 212.7 μ M•hr), Sol-vemurafenib **49** (AUC = 74.7 μ M•hr), and Sol-desloratadine **155** (AUC = 217.5 μ M•hr). Moderate or low exposure was observed for Sol-dabrafenib **62** (AUC = 0.08 μ M•hr), Sol-apixaban **41** (AUC = 2.75 μ M•hr), Sol-carvedilol **148** (AUC = 0.87 μ M•hr), Sol-lenalidomide **78** (AUC = 1.61
25 μ M•hr) and Sol-paclitaxel **131** (AUC = 0.27 μ M•hr) (FIG. 53). These data confirm that Sol-moiety-drug conjugates can be dosed via oral gavage in saline solution and provide good exposure levels, potentially replacing standard organic solvent-based formulations, such as DMSO or PEG, for highly water-insoluble preclinical compounds.

Given the promising oral bioavailability observed for enzalutamide from the cassette
30 PK study, the PK profiles of Sol-enzalutamide **7** (formulated in water) to enzalutamide formulated in carboxymethylcellulose (CMC)/Tween 80 (Tran *et al. Science* 324, 787–790 (2009)) were directly compared. Both compounds were dosed via oral gavage at 0.0215 mmol/kg and 0.107 mmol/kg (10 mg/kg and 50 mg/kg equivalent of enzalutamide)

respectively. Enzalutamide was found to have an oral bioavailability of 45% at the 0.0215 mmol/kg dose, that decreased to 33% upon dose escalation. In contrast, Sol-enzalutamide **7** displayed oral bioavailability of 64% at both dose levels, suggesting that solubility is potentially driving the lack of dose-proportional increase in exposure observed with the standard CMC formulation of enzalutamide (FIG. 54A). Thus, at the 50 mg/kg dose equivalent of enzalutamide, a ~50% improvement in oral bioavailability was achieved using the water-based Sol-moiety technology. Next, attention focused on modifying the electronic and/or steric bulk around the phosphate group, to see if reducing the Sol-moiety hydrolysis rate could enhance the exposure of enzalutamide. Sol-enzalutamide analogs **10**, **11**, and **13** were evaluated in the human placental alkaline phosphatase stability assay. Herein, a decrease in the rate of alkaline phosphatase hydrolysis was observed in accordance with the increase in steric bulk around the phosphate group (FIG. 55). The compounds (**10**, **11**, and **13**) were then dosed at 0.0107 mmol/kg (5 mg/kg equivalent of enzalutamide), via oral gavage in a mouse PK experiment. Unfortunately, enzalutamide drug levels remained high at the 24-hour timepoint, so we were unable to clearly distinguish the differences in the oral bioavailability between the Sol-moiety analogs. However, an extended mouse PK study (72 hours) with the methyl analog **10** at a dose of 0.021 mmol/kg (equivalent to a dose of 10 mg/kg enzalutamide) gave an AUC_{0-72} of 2133 $\mu\text{M}\cdot\text{h}$ that is equivalent to 86% oral bioavailability of enzalutamide (FIG. 54B), a notable improvement relative to **7** (64% F) and almost a 2-fold boost in bioavailability over the standard CMC formulation of enzalutamide at the same dose. This indicates that modifying steric and/or electronic substituents on the Sol-moiety modulates the rate of phosphate hydrolysis and, consequently, oral bioavailability of the released drug.

The highly insoluble and poorly permeable (BCS Class IV) BRAF mutant inhibitor, vemurafenib was then investigated. When Sol-vemurafenib **49** and **51** were dosed at 0.051 mmol/kg (25 mg/kg equivalent of vemurafenib), 96% and 113% oral bioavailability was observed, significantly higher (>10-fold) than a 25 mg/kg dose of vemurafenib, formulated using PEG 400 with vitamin E (emulsifier) in saline. Once again, the concentrations of vemurafenib in plasma at 24 h, following delivery with Sol-vemurafenib **49** and **51**, remained high, preventing pharmacokinetic differences between the two Sol-vemurafenib analogs from being fully distinguishable (FIG. 56). Interestingly, the Sol-vemurafenib analogs **49** and **51** displayed elongated T_{max} and $t_{1/2}$ relative to vemurafenib, suggesting non-linear kinetics. Regardless, the results demonstrate the pharmacokinetic benefits of the water-soluble Sol-

moiety technology over a standard PEG-based formulation and confirmed vemurafenib to be readily absorbed into mouse plasma once soluble.

Paclitaxel is a widely used chemotherapeutic that is highly insoluble in water and poorly absorbed (BCS Class IV), due to first-pass metabolism and efflux; consequently, it is intravenously administered to patients using Cremophor® EL as a formulation vehicle. As shown earlier, Sol-paclitaxel **131** gave low to modest oral bioavailability following a dose of 0.004 mmol/kg (equivalent to 3.5 mg/kg of paclitaxel) (FIG. 52). However, **131** was not particularly soluble (0.1 mg/ml) in its free acid form at pH 6.5 in HBSS. Therefore, to enhance solubility, the Sol-paclitaxel derivative **133** was prepared and found to be soluble at >49 mg/ml in HBSS also in its free acid form. Dosed orally to mice, at 0.004 mmol/kg (3.5 mg/kg equivalent of paclitaxel), **133** displayed a significant improvement in exposure (AUC = 0.98 $\mu\text{M}\cdot\text{hr}$) with bioavailability of ~36%, a >3-fold increase relative to **131** and a 7-fold improvement over a previously described phosphonooxymethyl prodrug of paclitaxel, Compound **Z** (Golik *et al. Bioorg. Med. Chem.* **6**, 1837–1842 (1996)) (FIG. 57). The rate of hydrolysis for **133** was also slightly lower (1.44 pmol/min) than **131** (2.13 pmol/min) and Compound **Z** (2.03 pmol/min). Although a slight decrease in dose proportionality was observed when **133** was administered by oral gavage in mice at 25 mg/kg and 75 mg/kg (18 and 55 mg/kg equivalent of paclitaxel) (FIG. 57), the overall oral bioavailability of **133** remained between 5–7-fold higher than Compound **Z** and clearly demonstrates superiority of the Sol-moiety technology over traditional water-soluble prodrugs.

Example 8: *In vivo* efficacy studies using pancreatic cancer xenograft mouse tumor model

Methods

Female Foxn nu/nu mice (4 weeks old at time of delivery) were procured through Jackson laboratory. Mice were housed in Optimice carousel sterile quarters with filtered air supply in disposable cages from Animal Care Systems, Inc. (Centennial, CO). A 12-hour light/12-hour dark light cycle is observed, with animal handling only taking place during the light cycle. On the day of implantation, BxPC-3 cells were trypsinized and allowed to detach from flasks. Trypsin was then neutralized with complete media and cells were spun at 400 x g. Media was aspirated and cells were resuspended in 50:50 *Cultrex BME, Type 3:DMEM (no supplementation) at a concentration of 3.5×10^7 cells/mL. A volume of 100 μL was injected into the right hind flank of each animal (a total of 3.5×10^6 cells).

When mean tumor volume reached $\sim 95 \text{ mm}^3$, mice were stratified and placed into four treatment groups of eight mice for the efficacy study and four treatment groups of four mice for the plasma and tumor PK study. Treatments were administered by oral gavage (20-gauge 38 mm flexible nylon) or by tail vein injection (adjusted by mouse weight for 10 mL/kg dosing). The PK mice were dosed with a single dose. Tumor volumes were measured by digital caliper by the same technician each time and volume was calculated using the formula $[\text{Width}^2 \times \text{Length}]/2$. Tumor volumes were analyzed in Prism 10.1.1 (GraphPad) using a mixed model and a Dunnett post hoc analysis for repeated measures with multiple comparisons. Mice were maintained and experiments were conducted at RinconBio, Utah. Plasma and tumor concentrations of paclitaxel were analyzed at UF Scripps Institute for Biomedical Innovation & Technology.

All statistical analysis was performed using independent experimental samples..

Results and Discussion

As the 75 mg/kg dose of Sol-paclitaxel (**133**) provided paclitaxel plasma concentrations over an extended time above the $0.05 \mu\text{mol C}_{\text{trough}}$ levels needed for in vivo efficacy (Stage *et al. Clin. Pharmacokinet.* **57**, 7–19 (2018)), a proof-of-concept study was conducted using a BxPC-3 xenograft mouse model for pancreatic cancer, following a similar protocol described for a lipid-based formulation of oral paclitaxel (Jang *et al. PLoS One* **14**(11) e0225095 (2019)). The experiment was conducted using a vehicle arm (saline solution), a paclitaxel positive control dosed IV at 12.5 mg/kg once a week (QWK) in Cremophor[®] EL, and Sol-paclitaxel **133** dosed PO at 25 mg/kg and 75 mg/kg every other day (QOD) in saline solution. Dosing was performed over 21 days and tumor growth monitored for an additional 25 days. Tumor volume and animal weight were monitored on a biweekly basis (FIGS. 58A-B). Following the dosing period, the tumor growth inhibition (TGI) of the 25 mg/kg QOD dose of **133** was -15% , whereas the 75 mg/kg (55 mg/kg equivalent of paclitaxel) dose had a TGI of 91% that reduced to 84% following the 25-day observation period. The IV dose of 12.5 mg/kg paclitaxel had a TGI of 78% following the dosing period that reduced to 51% following the observation period. There was no appreciable toxicity reported during the dosing of Sol-paclitaxel **133**. Tumor and plasma concentrations of paclitaxel, measured at 6 and 24 h post-dose of **133**, confirmed reasonable dose-proportional exposure of paclitaxel. Interestingly, accumulation of paclitaxel in the tumor was observed at both doses of **133** after 24 hours, with the 75 mg/kg dose being almost 10-fold higher than the desired trough level for efficacy (FIG. 58C). This is the first

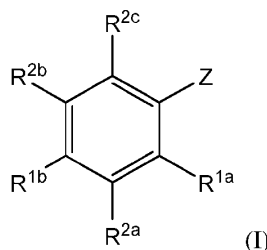
reported efficacy study using an orally bioavailable prodrug of paclitaxel and highlights the ability of the Sol-moiety technology to transform the route of drug administration from intravenous to oral.

5 **Example 9: In vivo exposure of the major sol-moiety by-products, Compounds X and Y**

Compound **X** was detected in mouse plasma following an oral dose of 4 mg/kg ($AUC_{last} = 3.93 \mu M \cdot hr$ and $t_{1/2} = 1.24 h$) whereas compound **Y** was not detectable following a dose of 25 mg/kg (FIG. 53) This data correlates well with the results of the Caco-2 permeability assay (FIG. 52) and supports the development of Sol-moieties possessing a phosphonate group given
10 their superior aqueous solubility and by-product profile.

CLAIMS

1. A compound of formula (I):



5 or a salt thereof, wherein:

Z is $-\text{CR}^{3a}\text{R}^{3b}-\text{O}-\text{CR}^{4a}\text{R}^{4b}-\text{LG}$, $-(\text{CR}^{5a}\text{R}^{5b})_p-\text{CO}-\text{E}$, $-(\text{CR}^{6a}\text{R}^{6b})-\text{LG}$, or $-\text{CR}^{7a}\text{R}^{7b}-\text{O}-\text{CR}^{8a}\text{R}^{8b}-\text{O}-\text{CR}^{9a}\text{R}^{9b}-\text{LG}$;

one of R^{1a} and R^{1b} is $-\text{OPO}(\text{OR}^a)_2$, and the other is selected from hydrogen, alkyl, halo, haloalkyl, and $-(\text{CR}^b\text{R}^c)_m-\text{X}$;

10 R^{2a} , R^{2b} , and R^{2c} are each independently selected from hydrogen, alkyl, halo, haloalkyl, and $-(\text{CR}^d\text{R}^e)_n-\text{Y}$;

wherein, when R^{1a} is $-\text{OPO}(\text{OR}^a)_2$, R^{1b} and R^{2a} , together with the carbon atoms to which they are attached, are optionally taken together to form an optionally substituted ring;

15 X and Y are each independently selected from cyano, nitro, $-\text{OR}^f$, $-\text{NR}^g\text{R}^h$, $-\text{COOR}^i$, $-\text{CONR}^j\text{R}^k$, $-\text{S}(\text{O})_2\text{NR}^l\text{R}^m$, $-\text{PO}(\text{OR}^n)_2$, and $-\text{PO}(\text{OR}^o)\text{CH}_2\text{PO}(\text{OR}^p)_2$;

m, n, and p are each independently 0, 1, or 2;

R^{3a} , R^{3b} , R^{6a} , R^{6b} , R^{7a} , and R^{7b} are each independently selected from hydrogen and alkyl;

R^{4a} and R^{4b} are each hydrogen, or are taken together to form an oxo group;

20 R^{5a} and R^{5b} are each independently selected from hydrogen, alkyl, halo, and alkoxy;

R^{8a} and R^{8b} are each hydrogen, or are taken together to form an oxo group;

R^{9a} and R^{9b} are each selected from hydrogen and alkyl, or are taken together to form an oxo group;

25 R^a , R^f , R^g , R^h , R^i , R^j , R^k , R^l , R^m , R^n , R^o , and R^p are each independently selected from hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, and arylalkyl; wherein R^g and R^h , R^j and R^k , and R^l and R^m , together with the nitrogen atoms to which they are attached, are optionally taken together to form an optionally substituted ring;

R^b , R^c , R^d , and R^e are each independently selected from hydrogen and alkyl;

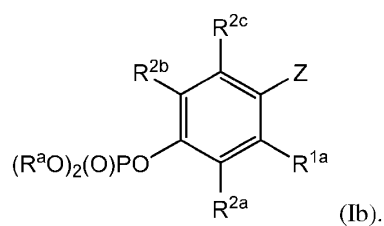
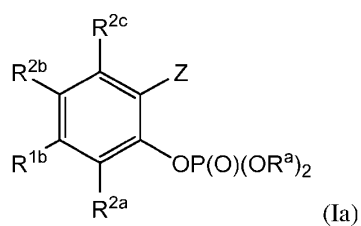
E is halo or $-\text{OH}$; and

LG is selected from -O-Q, halo, and hydroxy, wherein Q is optionally substituted aryl, optionally substituted heterocyclyl, or -SO₂R⁸, wherein R⁸ is selected from alkyl and optionally substituted aryl.

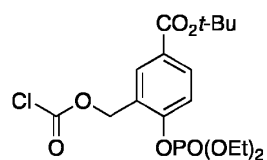
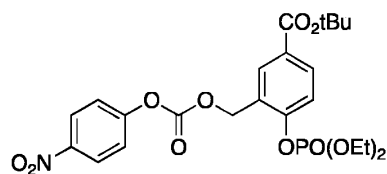
- 5 2. The compound of claim 1, or a salt thereof, wherein, when R^{1a} is -OPO(OR^a)₂, then either: R^{1b} is -(CR^bR^c)_m-X, wherein X is -COORⁱ or -PO(ORⁿ)₂; or at least one of R^{2a}, R^{2b}, and R^{2c} is -(CR^dR^e)_n-Y, wherein Y is -COORⁱ or -PO(ORⁿ)₂.
3. The compound of claim 1, or a salt thereof, wherein, when R^{1b} is -OPO(OR^a)₂, then
10 either: R^{1a} is -(CR^bR^c)_m-X, wherein X is -COORⁱ or -PO(ORⁿ)₂; or at least one of R^{2a}, R^{2b}, and R^{2c} is -(CR^dR^e)_n-Y, wherein Y is -COORⁱ or -PO(ORⁿ)₂.
4. The compound of any one of claims 1-3, or a salt thereof, wherein Z is -CR^{3a}R^{3b}-O-CR^{4a}R^{4b}-LG, -(CR^{5a}R^{5b})_p-CO-E, or -(CR^{6a}R^{6b})-LG.
15
5. The compound of any one of claims 1-4, or a salt thereof, wherein Z is -CR^{3a}R^{3b}-O-CR^{4a}R^{4b}-LG.
6. The compound of claim 5, or a salt thereof, wherein R^{3a} and R^{3b} are each
20 independently selected from hydrogen and methyl.
7. The compound of claim 5 or claim 6, or a salt thereof, wherein R^{4a} and R^{4b} are taken together to form an oxo group.
8. The compound of claim 5 or claim 6, or a salt thereof, wherein R^{4a} and R^{4b} are each
25 hydrogen.
9. The compound of any one of claims 1-4, or a salt thereof, wherein Z is -(CR^{5a}R^{5b})_p-CO-E.
30
10. The compound of claim 9, or a salt thereof, wherein p is 2, each R^{5a} and R^{5b} is independently selected from hydrogen and methyl, and E is selected from chloro and hydroxy.

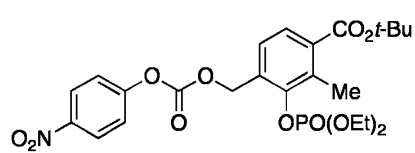
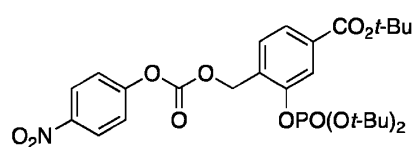
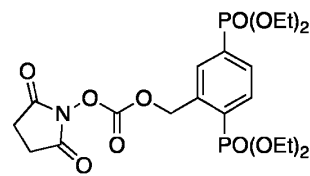
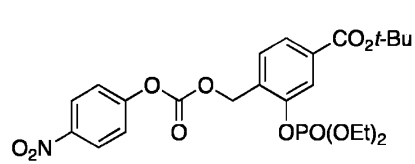
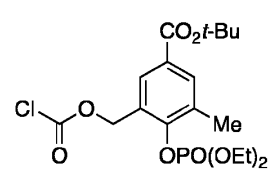
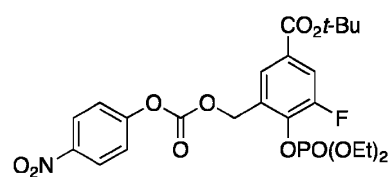
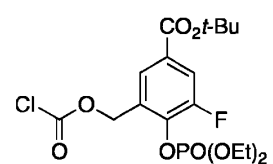
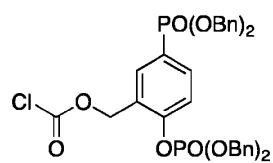
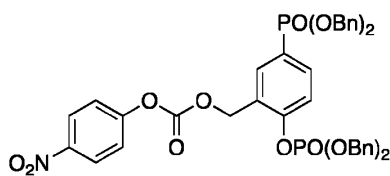
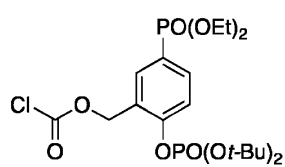
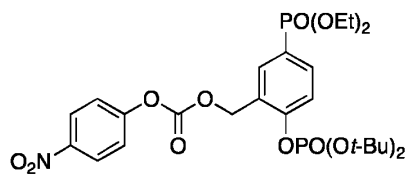
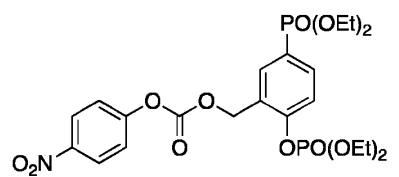
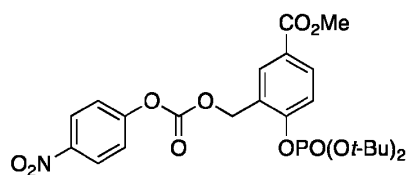
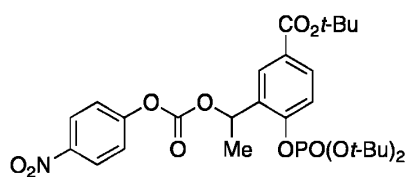
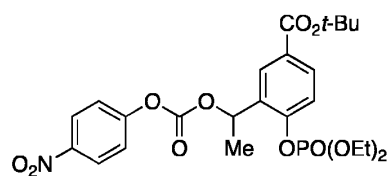
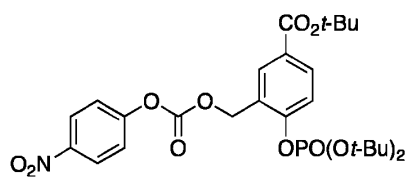
11. The compound of any one of claims 1-4, or a salt thereof, wherein Z is $-(CR^{6a}R^{6b})-$
LG.
12. The compound of claim 11, or a salt thereof, wherein R^{6a} and R^{6b} are each
5 independently selected from hydrogen and methyl, and LG is halo or hydroxy.
13. The compound of claim 12, or a salt thereof, wherein LG is bromo or hydroxy.
14. The compound of any one of claims 1-4, or a salt thereof, wherein Z is $-CR^{7a}R^{7b}-O-$
10 $CR^{8a}R^{8b}-O-CR^{9a}R^{9b}-LG$.
15. The compound of claim 14, or a salt thereof, wherein R^{7a} and R^{7b} are each hydrogen.
16. The compound of claim 14 or claim 15, or a salt thereof, wherein R^{8a} and R^{8b} are each
15 hydrogen, and R^{9a} and R^{9b} are taken together to form an oxo group.
17. The compound of claim 14 or claim 15, or a salt thereof, wherein R^{8a} and R^{8b} taken
together to form an oxo group, and R^{9a} and R^{9b} are each hydrogen.
- 20 18. The compound of any one of claims 1-17, or a salt thereof, wherein R^a , R^f , R^g , R^h , R^i ,
 R^j , R^k , R^l , R^m , R^n , R^o , and R^p are each independently selected from hydrogen, C₁-C₄ alkyl,
phenyl, and phenyl-C₁-C₂-alkyl.
19. The compound of any one of claims 1-18, or a salt thereof, wherein R^b , R^c , R^d , and
25 R^e are each independently selected from hydrogen and methyl.
20. The compound of any one of claims 1-19, or a salt thereof, wherein R^{2a} , R^{2b} , and R^{2c}
are each independently selected from hydrogen, C₁-C₄ alkyl, halo, and $-(CR^dR^e)_n-Y$, wherein
n is 0 or 1, R^d and R^e are each hydrogen, and Y is selected from cyano, $-OR^f$, $-COOR^i$, and -
30 $PO(OR^n)_2$, wherein each R^f , R^i , and R^n is independently selected from hydrogen and C₁-C₄
alkyl.

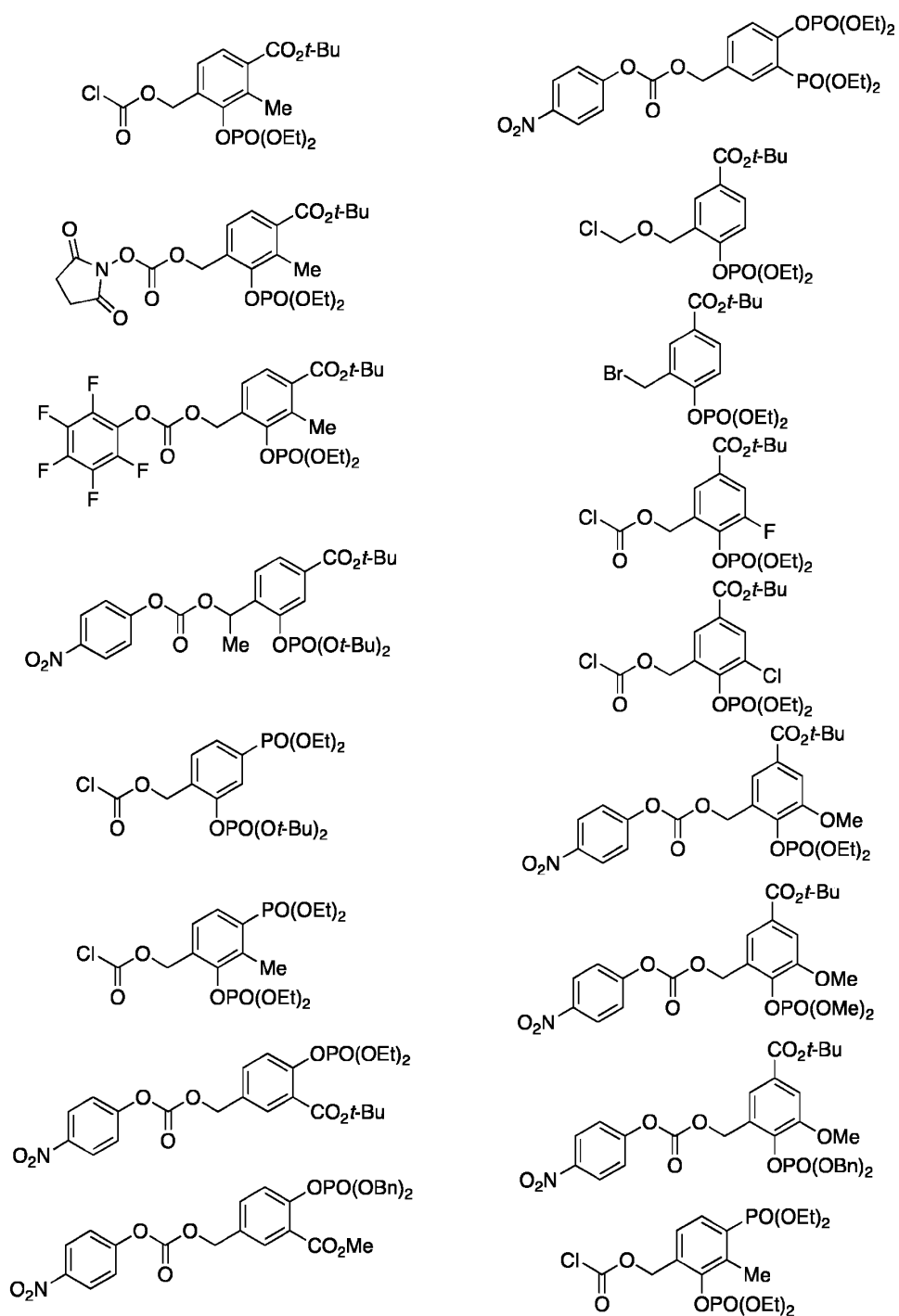
21. The compound of any one of claims 1-20, or a salt thereof, wherein LG is -O-Q, wherein Q is optionally substituted phenyl or an optionally substituted 5- or 6-membered heterocyclyl having 1 or 2 heteroatoms independently selected from N, O, and S.
- 5 22. The compound of claim 21, or a salt thereof, wherein LG is -O-Q, wherein Q is phenyl substituted with 1, 2, 3, 4, or 5 substituents independently selected from nitro and halo.
23. The compound of claim 11, or a salt thereof, wherein LG is -O-(4-nitrophenyl) or -O-
10 pentafluorophenyl.
24. The compound of claim 1, or a salt thereof, wherein LG is -O-Q, wherein Q is an optionally substituted pyrrolidine-2,5-dione.
- 15 25. The compound of any one of claims 1-20, or a salt thereof, wherein LG is -O-Q, wherein Q is -SO₂R⁸, wherein R⁸ is methyl.
26. The compound of any one of claims 1-20, or a salt thereof, wherein LG is halo or hydroxy.
- 20 27. The compound of claim 1, or a salt thereof, wherein the compound has formula (Ia) or (Ib):

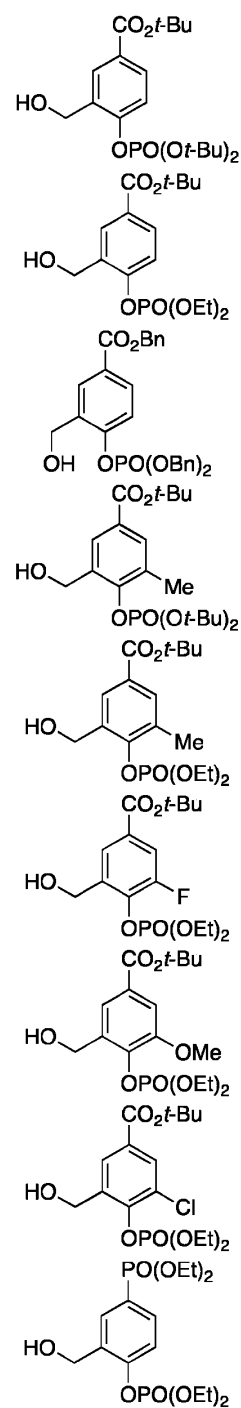
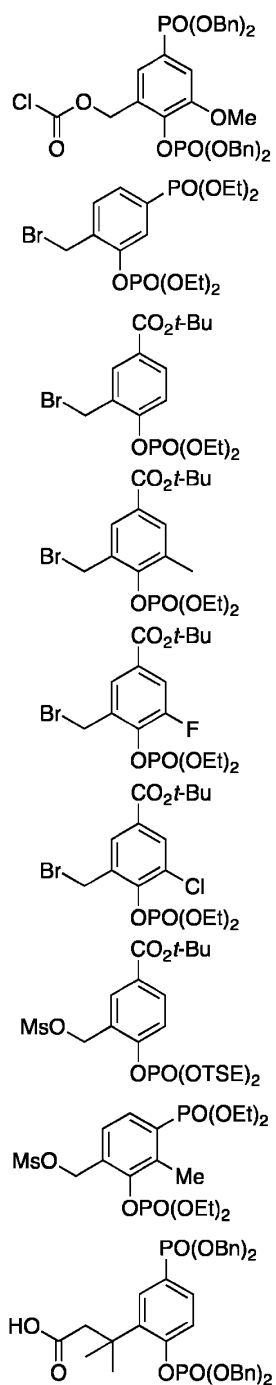


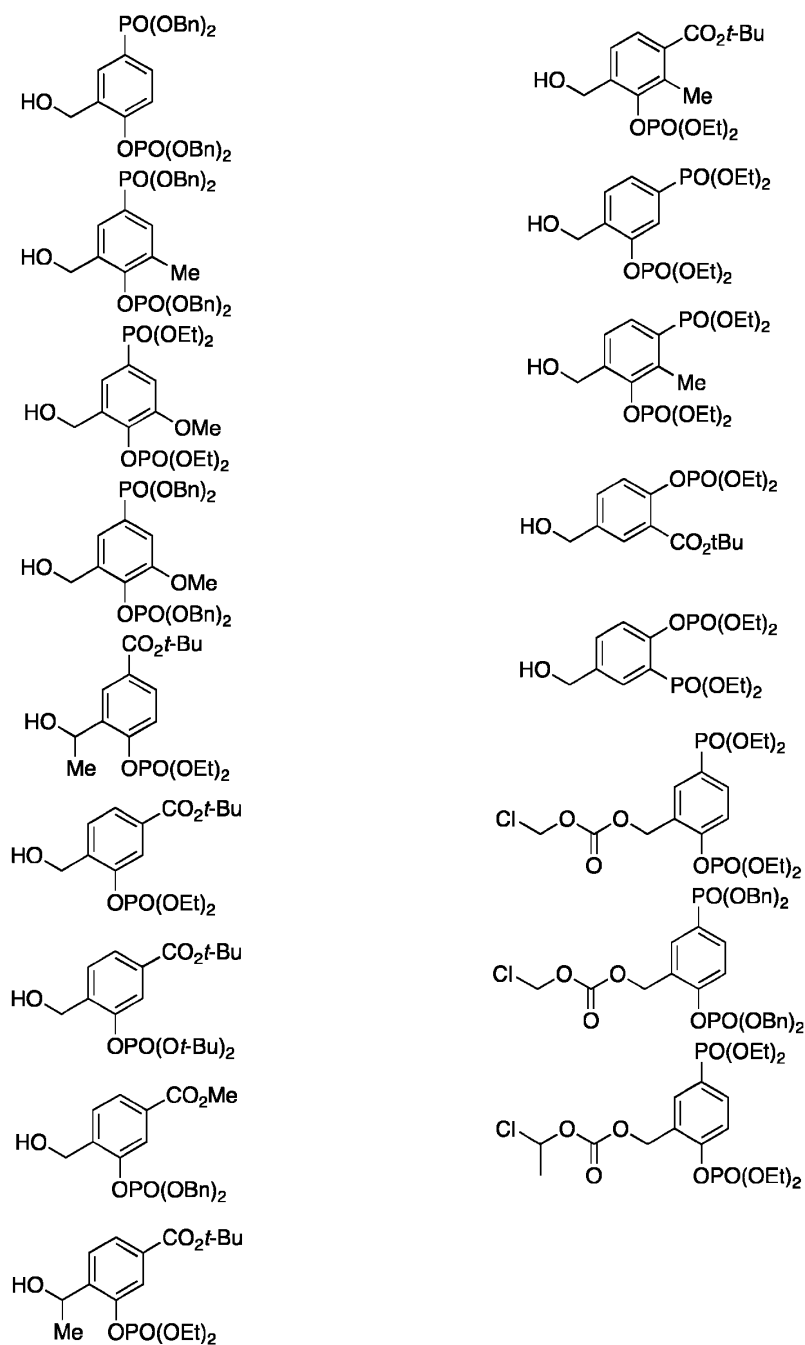
- 25 28. The compound of claim 1, selected from the group consisting of:



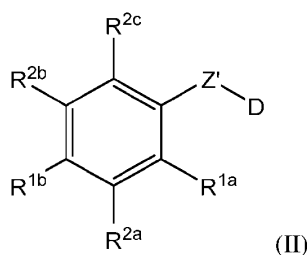








29. A compound of formula (II):



or a pharmaceutically acceptable salt thereof, wherein:

Z' is $-\text{CR}^{3a}\text{R}^{3b}-\text{O}-\text{CR}^{4a}\text{R}^{4b}-$, $-(\text{CR}^{5a}\text{R}^{5b})_p-\text{CO}-$, $-(\text{CR}^{6a}\text{R}^{6b})-$, or $-\text{CR}^{7a}\text{R}^{7b}-\text{O}-\text{CR}^{8a}\text{R}^{8b}-\text{O}-\text{CR}^{9a}\text{R}^{9b}-$;

5 one of R^{1a} and R^{1b} is $-\text{OPO}(\text{OR}^a)_2$, and the other is selected from hydrogen, alkyl, halo, haloalkyl, and $-(\text{CR}^b\text{R}^c)_m-\text{X}$;

R^{2a} , R^{2b} , and R^{2c} are each independently selected from hydrogen, alkyl, halo, haloalkyl, and $-(\text{CR}^d\text{R}^e)_n-\text{Y}$;

10 wherein, when R^{1a} is $-\text{OPO}(\text{OR}^a)_2$, R^{1b} and R^{2a} , together with the carbon atoms to which they are attached, are optionally taken together to form an optionally substituted ring

X and Y are each independently selected from cyano, nitro, $-\text{OR}^f$, $-\text{NR}^g\text{R}^h$, $-\text{COOR}^i$, $-\text{CONR}^j\text{R}^k$, $-\text{S}(\text{O})_2\text{NR}^l\text{R}^m$, $-\text{PO}(\text{OR}^n)_2$, and $-\text{PO}(\text{OR}^o)\text{CH}_2\text{PO}(\text{OR}^p)_2$;

m, n, and p are each independently 0, 1, or 2;

15 R^{3a} , R^{3b} , R^{6a} , R^{6b} , R^{7a} , and R^{7b} are each independently selected from hydrogen and alkyl;

R^{4a} and R^{4b} are each hydrogen, or are taken together to form an oxo group;

R^{5a} and R^{5b} are each independently selected from hydrogen, alkyl, halo, and alkoxy;

R^{8a} and R^{8b} are each hydrogen, or are taken together to form an oxo group;

20 R^{9a} and R^{9b} are each selected from hydrogen and alkyl, or are taken together to form an oxo group;

R^a , R^f , R^g , R^h , R^i , R^j , R^k , R^l , R^m , R^n , R^o , and R^p are each independently selected from hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, and arylalkyl; wherein R^g and R^h , R^j and R^k , and R^l and R^m , together with the nitrogen atoms to which they are attached, are optionally taken together to form an optionally substituted ring;

25 R^b , R^c , R^d , and R^e are each independently selected from hydrogen and alkyl; and D is a pharmaceutically active compound.

30 The compound of claim 29, or a pharmaceutically acceptable salt thereof, wherein, when R^{1a} is $-\text{OPO}(\text{OR}^a)_2$, then either: R^{1b} is $-(\text{CR}^b\text{R}^c)_m-\text{X}$, wherein X is $-\text{COOR}^i$ or -

PO(ORⁿ)₂; or at least one of R^{2a}, R^{2b}, and R^{2c} is -(CR^dR^e)_n-Y, wherein Y is -COORⁱ or -PO(ORⁿ)₂.

31. The compound of claim 29, or a pharmaceutically acceptable salt thereof, wherein,
 5 when R^{1b} is -OPO(OR^a)₂, then either: R^{1a} is -(CR^bR^c)_m-X, wherein X is -COORⁱ or -PO(ORⁿ)₂; or at least one of R^{2a}, R^{2b}, and R^{2c} is -(CR^dR^e)_n-Y, wherein Y is -COORⁱ or -PO(ORⁿ)₂.

32. The compound of any one of claims 29-31, or a pharmaceutically acceptable salt
 10 thereof, wherein Z' is -CR^{3a}R^{3b}-O-CR^{4a}R^{4b}-, -(CR^{5a}R^{5b})_p-CO-, or -(CR^{6a}R^{6b})-

33. The compound of any one of claims 29-32, or a pharmaceutically acceptable salt thereof, wherein Z' is -CR^{3a}R^{3b}-O-CR^{4a}R^{4b}-.

15 34. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein R^{3a} and R^{3b} are each independently selected from hydrogen and methyl.

35. The compound of claim 33 or claim 34, or a pharmaceutically acceptable salt thereof, wherein R^{4a} and R^{4b} are each hydrogen.
 20

36. The compound of claim 33 or claim 34, or a pharmaceutically acceptable salt thereof, wherein R^{4a} and R^{4b} are taken together to form an oxo group.

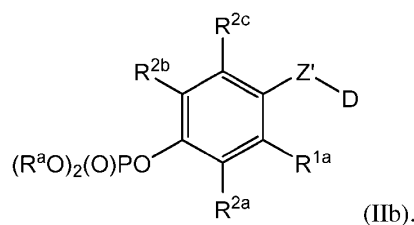
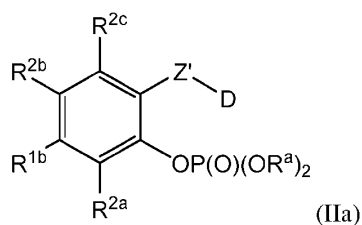
37. The compound of any one of claims 29-32, or a pharmaceutically acceptable salt
 25 thereof, wherein Z' is -(CR^{5a}R^{5b})_p-CO-.

38. The compound of claim 37, wherein p is 2, and R^{5a} and R^{5b} are each independently selected from hydrogen and methyl.

30 39. The compound of any one of claims 29-32, or a pharmaceutically acceptable salt thereof, wherein Z' is -(CR^{6a}R^{6b})-

40. The compound of claim 39, or a pharmaceutically acceptable salt thereof, wherein R^{6a} and R^{6b} are each independently selected from hydrogen and methyl.

41. The compound of any one of claims 29-32 or a salt thereof, wherein Z' is $-\text{CR}^{7a}\text{R}^{7b}-\text{O}-\text{CR}^{8a}\text{R}^{8b}-\text{O}-\text{CR}^{9a}\text{R}^{9b}-\text{LG}$.
- 5 42. The compound of claim 41, or a salt thereof, wherein R^{7a} and R^{7b} are each hydrogen.
43. The compound of claim 41 or claim 42, or a salt thereof, wherein R^{8a} and R^{8b} are each hydrogen, and R^{9a} and R^{9b} are taken together to form an oxo group.
- 10 44. The compound of claim 41 or claim 42, or a salt thereof, wherein R^{8a} and R^{8b} taken together to form an oxo group, and R^{9a} and R^{9b} are each hydrogen.
45. The compound of any one of claims 29-44, or a pharmaceutically acceptable salt thereof, wherein R^a , R^f , R^g , R^h , R^i , R^j , R^k , R^l , R^m , R^n , R^o , and R^p are each independently
15 selected from hydrogen, C_1 - C_4 alkyl, phenyl, and phenyl- C_1 - C_2 -alkyl.
46. The compound of any one of claims 29-45, or a pharmaceutically acceptable salt thereof, wherein R^b , R^c , R^d , and R^e are each independently selected from hydrogen and methyl.
- 20 47. The compound of any one of claims 29-46, or a pharmaceutically acceptable salt thereof, wherein R^{2a} , R^{2b} , and R^{2c} are each independently selected from hydrogen, C_1 - C_4 alkyl, halo, and $-(\text{CR}^d\text{R}^e)_n-\text{Y}$, wherein n is 0 or 1, R^d and R^e are each hydrogen, and Y is selected from cyano, $-\text{OR}^f$, $-\text{COOR}^i$, and $-\text{PO}(\text{OR}^n)_2$, wherein each R^f , R^i , and R^n is
25 independently selected from hydrogen and C_1 - C_4 alkyl.
48. The compound of claim 29, or a pharmaceutically acceptable salt thereof, wherein the compound has formula (IIa) or (IIb):



49. The compound of any one of claims 29-48, or a pharmaceutically acceptable salt thereof, wherein group D is attached to the compound via a nitrogen atom or an oxygen atom.
- 5 50. The compound of any one of claims 29-49, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutically active compound is selected from the group consisting of: analgesics; anesthetics; antibacterials; anticonvulsants; antidementia agents; antidepressants; antiemetics; antifungals; antigout agents; anti-inflammatories; antimigraine agents; antimuscarinic agents; antimycobacterials; antineoplastics; antiparasitics;
- 10 antiparkinson agents; antipsychotics; antispasticity agents; antivirals; anxiolytics; bipolar agents; blood glucose regulators; blood products / modifiers / volume expanders; cardiovascular agents; central nervous system agents; dental and oral agents; dermatological agents; enzyme replacements/modifiers; gastrointestinal agents; genitourinary agents; hormonal agents; immunological agents; inflammatory bowel disease agents; metabolic bone
- 15 disease agents; ophthalmic agents; otic agents; respiratory tract agents; sedatives/hypnotics; and skeletal muscle relaxants.
51. The compound of claim 50, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutically active compound is an antineoplastic agent.
- 20 52. The compound of any one of claims 29-51, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutically active compound is selected from the group consisting of abrocitinib, acalabrutinib, amisulpride, apalutamide, apixaban, aprepitant, ARV-766, asciminib, atorvastatin, avacopan, avapritinib, bavdegalutamide, bicalutamide, cabazitaxel,
- 25 carvedilol, cefdinir, cefprozil, celecoxib, clarithromycin, dabrafenib, desloratadine, docetaxel, doravirine, doxorubicin, DT2216, efavirenz, enzalutamide, eragidomide, etravirine, ezetimibe, FHD-609, glimepiride, glipizide, glyburide, golcadomide, hydrochlorothiazide, hydroxyzine pamoate, ibrutinib, idelalisib, imatinib, ivacaftor, lamotrigine, lenalidomide, linezolid, lopinavir, meloxicam, metaxalone, methylphenidate, mezigdomide, modafinil, N-
- 30 desalkylquetiapine, niclosamide, nilotinib, NX-2127, olanzapine, olaparib, oliceridine, osimertinib, oteseconazole, oxcarbazepine, paclitaxel, pacritinib, palbociclib, pioglitazone, pomalidomide, pralsetinib, quetiapine, raloxifene, rilpivirine, rilzabrutinib, rimegepant, ripretinib, ritonavir, rivaroxaban, selpercatinib, selumetinib, simvastatin, SN-38, sorafenib,

sotorasib, tacrolimus, tazemetostat, tucatinib, valdecoxib, vemurafenib, vepdegestrant, vociprotafib, and zanubrutinib.

53. The compound of any one of claims 29-52, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutically active compound is selected from the group consisting of apixaban, carvedilol, dabrafenib, desloratadine, enzalutamide, lenalidomide, paclitaxel, and vemurafenib.

54. The compound of any one of claims 29-53, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutically active compound is paclitaxel.

55. The compound of claim 29, or a pharmaceutically acceptable salt thereof, selected from compounds shown in FIGS. 1-51 and Table 2.

56. A method of preparing a prodrug of a pharmaceutically active compound, comprising:
15 reacting a compound of any one of claims 1-28 with a pharmaceutically active compound in the presence of a base to form a protected prodrug compound; and removing protecting groups from the protected prodrug compound, to thereby provide the prodrug of the pharmaceutically active compound.

20 57. The method of claim 44, wherein the reacting step comprises:
(a) combining the compound of any one of claims 1-28 and the pharmaceutically active compound to form a mixture; and
(b) adding the base to the mixture.

25 58. The method of claim 45, wherein the reacting step comprises:
(a) reacting the pharmaceutically active compound with a base to form a mixture; and
(b) adding the compound of any one of claims 1-28 to the mixture.

59. A method of treating a disorder in a subject in need of treatment, comprising
30 administering to the subject a therapeutically effective amount of a compound of any one of claims 29-55, or a pharmaceutically acceptable salt thereof.

60. A system or kit comprising a compound of any one of claims 1-28, or a salt thereof, and a pharmaceutically active compound.

61. A compound of any one of claims 1-28, or a salt thereof, for use in preparing a prodrug compound.
- 5 62. A compound of any one of claims 29-55, or a pharmaceutically acceptable salt thereof, for use as a medicament.