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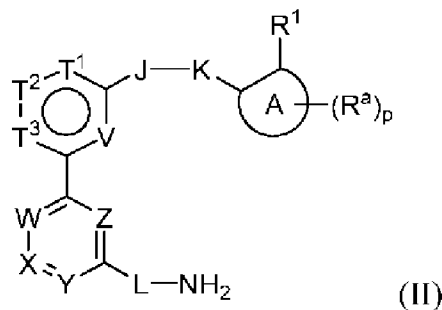
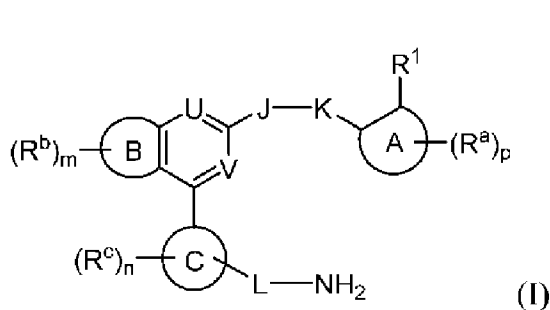
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(54) Titre : BENZOFURANE, BENZOPYRROLE, BENZOTHIOPHENE SUBSTITUES ET INHIBITEURS DU
COMPLEMENT STRUCTURELLEMENT APPARENTES
(54) Title: SUBSTITUTED BENZOFURAN, BENZOPYRROLE, BENZOTHIOPHENE, AND STRUCTURALLY RELATED
COMPLEMENT INHIBITORS



(57) **Abrégé/Abstract:**

Disclosed are compounds of formulae I and II, and pharmaceutically acceptable salts and prodrugs thereof, which are inhibitors of the complement system. Also provided are pharmaceutical compositions comprising such a compound, and methods of using the compounds and compositions in the treatment or prevention of a disease or condition characterized by aberrant complement system activity.

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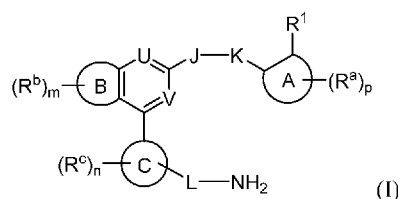
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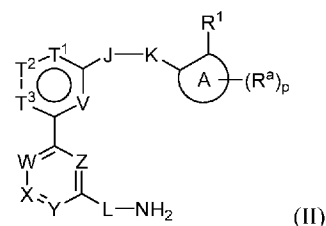
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(54) Title: SUBSTITUTED BENZOFURAN, BENZOPYRROLE, BENZOTHIOPHENE, AND STRUCTURALLY RELATED COMPLEMENT INHIBITORS



(I)



(II)

(57) Abstract: Disclosed are compounds of formulae I and II, and pharmaceutically acceptable salts and prodrugs thereof, which are inhibitors of the complement system. Also provided are pharmaceutical compositions comprising such a compound, and methods of using the compounds and compositions in the treatment or prevention of a disease or condition characterized by aberrant complement system activity.



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DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 4
CONTENANT LES PAGES 1 À 333

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 4
CONTAINING PAGES 1 TO 333

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***SUBSTITUTED BENZOFURAN, BENZOPYRROLE,
BENZOTHIOPHENE, AND STRUCTURALLY RELATED
COMPLEMENT INHIBITORS***

RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Patent Application serial number 62/654,108, filed April 6, 2018.

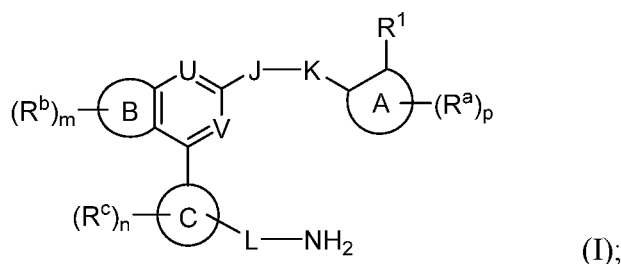
BACKGROUND OF THE INVENTION

The complement system is a branch of an organism's immune system that enhances the ability of antibodies and phagocytic cells to destroy and remove foreign particles (e.g., pathogens) from the organism. The complement system comprises a set of plasma proteins that act together to attack extracellular forms of pathogens and induce a series of inflammatory responses to help fight infection. Complement activation can occur through several pathways. For example, complement activation can occur spontaneously in response to certain pathogens or by antibody binding to a pathogen. When complement proteins are activated a cascade is triggered by which one complement protein induces the activation of the next protein in the sequence. The activation of a small number of complement proteins at the start of the pathway is hugely amplified by each successive enzymatic reaction, resulting in the rapid generation of a disproportionately large complement response. (Marrides, S. *Pharmacological Reviews* 1998, Vol. 50, pages 59-88). In healthy organisms there are regulatory mechanisms to prevent uncontrolled complement activation.

When activated, complement proteins can bind to a pathogen, opsonizing them for engulfment by phagocytes bearing receptors for complement. Then, small fragments of some complement proteins act as chemoattractants to recruit more phagocytes to the site of complement activation, and also to activate these phagocytes. Next, the complement proteins create holes or pores in the invading organisms, leading to their destruction. While complement plays an important role in protecting the body from foreign organisms, it can also destroy healthy cells and tissue. The inappropriate activation of complement is implicated in a long list of disease pathologies (Morgan, B. *Eur J Clin Invest* 1994, Vol. 24, pages 219-228) affecting the immune, renal, cardiovascular, and neurological systems. Accordingly, there exists a need to develop further complement inhibitors, which have therapeutic potential in the treatment of numerous disorders.

SUMMARY OF THE INVENTION

In certain aspects, the invention provides compounds having the structure of formula (I), and pharmaceutically acceptable salts and prodrugs thereof:



wherein:

ring $\textcircled{\text{A}}$ is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

ring $\textcircled{\text{B}}$ is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

ring $\textcircled{\text{C}}$ is aryl or heteroaryl;

R^{a} , independently for each occurrence, is halogen, cyano, hydroxy, $-\text{NH}_2$, $-\text{NH}(\text{Ac})$, $-\text{NH}(\text{alkyl})$, $-\text{NH}(\text{cycloalkyl})$, $-\text{NH}(\text{heterocycloalkyl})$, $-\text{NH}(\text{aryl})$, $-\text{NH}(\text{heteroaryl})$, $-\text{N}(\text{alkyl})_2$, $-\text{NHC}(\text{O})(\text{alkyl})$, $-\text{CH}(\text{alkyl})\text{NH}_2$, $-\text{CH}(\text{hydroxyalkyl})\text{NH}_2$, $-\text{CH}(\text{haloalkyl})\text{NH}_2$, $-\text{CH}(\text{cycloalkyl})\text{NH}_2$, $-\text{CH}(\text{heterocycloalkyl})\text{NH}_2$, $-\text{CH}(\text{aryl})\text{NH}_2$, $-\text{CH}(\text{heteroaryl})\text{NH}_2$, $-\text{CH}_2\text{NHC}(\text{O})(\text{alkyl})$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})(\text{alkyl})$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2(\text{cycloalkyl})$, $-\text{SO}_2(\text{heterocycloalkyl})$, $-\text{SO}_2(\text{alkyl})$, $-\text{SO}_2(\text{aryl})$, or $-\text{SO}_2(\text{heteroaryl})$; or is selected from the group consisting of substituted or unsubstituted aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl;

R^{b} , independently for each occurrence, is halogen, cyano, $-\text{CH}_2(\text{OCH}_2\text{CH}_2)_q\text{OCH}_3$, $-\text{alkylene}-(\text{branched or unbranched polyethylene glycol})$, $-\text{alkylene-O}-(\text{branched or unbranched polyethylene glycol})$, or $-\text{NR}^{\text{j}}\text{R}^{\text{k}}$; or is selected from the group consisting of substituted or unsubstituted alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, (hydroxy)haloalkyl, hydroxy(cycloalkyl)alkyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, arylalkyl, heteroarylalkyl, (heteroarylalkoxy)alkyl, (arylalkoxy)alkyl, (aryloxy)alkyl,

((cycloalkyl)alkoxy)alkyl, ((heterocycloalkyl)alkoxy)alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -alkylene-NR^jR^k, tosyl, -SO₂(alkyl), -SO₂(cycloalkyl), -CO(alkyl), -CO(aryl), -CO(heteroaryl), -CO(cycloalkyl), -CO(heterocycloalkyl), -CONH(alkyl), -CONH(arylalkyl), -CONH(heteroarylalkyl), -CON(alkyl)₂, -CONH(heterocycloalkyl), and -CONH(cycloalkyl);

R^c, independently for each occurrence, is selected from the group consisting of halogen, -OH, -NR^jR^k, alkoxy, alkyl, cycloalkyl, and heterocycloalkyl;

R¹ is selected from the group consisting of -NH₂, -COOH, -CH₂COOH, -CH(NH(CO)(alkyl))COOH, -CH(NH(CO)(arylalkyl))COOH, -CH(NH(CO)(cycloalkyl))COOH, -CH(NH(CO)(aryl substituted cycloalkyl))COOH, -CH(NH(CO)(heteroaryl substituted cycloalkyl))COOH, -CH(S(alkyl))COOH, -CO(NH)CH₂(substituted or unsubstituted aryl), -CO(NH)CH₂(substituted or unsubstituted heteroaryl), -CO(NH)(substituted or unsubstituted aryl), -CO(NH)(substituted or unsubstituted heteroaryl), and -CH₂(tetrazolyl);

n is 0, 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

p is 0, 1, 2, 3, or 4;

q is an integer from 1-20;

J is -C(O)-, -NH-, -CH₂-, -O-, -S-, -S(O)-, -SO₂-, -N(alkyl)-, -CH(alkyl)-, -CH(cycloalkyl)-, -N((C(O)O)arylalkyl)-, -N((C(O)O)heteroarylalkyl)-, or -N(C(O)arylalkyl)-;

K is -C(O)-, -NH-, -CH₂-, -O-, -S-, -S(O)-, -SO₂-, -N(alkyl)-, -CH(alkyl)-, -CH(cycloalkyl)-, -N((C(O)O)arylalkyl)-, -N((C(O)O)heteroarylalkyl)-, or -N(C(O)arylalkyl)-;

wherein at least one of J and K is -C(O)-, -CH₂-, or -CH(alkyl)-;

L is selected from the group consisting of a bond, -CH₂-, -CH₂CH₂-, -CHR²-, -CF₂-, -CFR²-, -C(O)-, -C(=NR^L)-, -C(=CHR^L)-, -S(O)₂-, and -S(O)-; wherein R^L is H or alkyl;

or wherein R^L and an occurrence of R^c taken together with the intervening atoms form a substituted or unsubstituted heteroaryl ring;

R² is alkyl, cycloalkyl, hydroxyalkyl, or haloalkyl;

R^j and R^k are each independently H or are selected from the group consisting of substituted or unsubstituted alkyl, aminoalkyl, (heterocycloalkyl)alkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, -CO(aryl), -CO(arylalkyl), -CO(heteroarylalkyl), and -CO((heterocycloalkyl)alkyl);

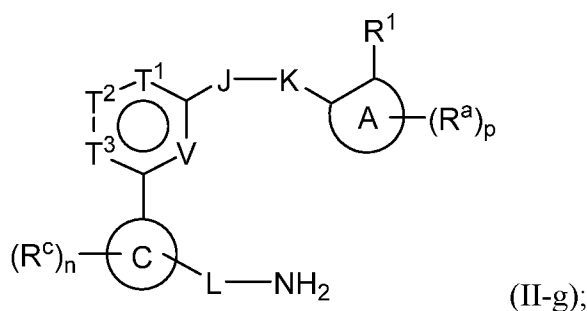
U is N or CR^3 ;

R^3 is H, halogen, alkyl, cycloalkyl, aryl, heteroaryl, alkoxy, haloalkyl, -CN, -CONH₂, -CO₂H, -CH₂CO₂H, -NH₂, hydroxyalkyl, aminoalkyl, -OH, -NH(alkyl), -N(alkyl)₂, thioalkyl, or -S(alkyl);

V is N, CH, C(halogen), or C(alkyl); and

the stereochemical configuration at any chiral center is *R*, *S*, or a mixture of *R* and *S*.

In certain aspects, the invention provides compounds having the structure of formula (II-g), and pharmaceutically acceptable salts and prodrugs thereof:



wherein:

ring is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

ring is aryl or heteroaryl;

R^a , independently for each occurrence, is halogen, cyano, hydroxy, -NH₂, -NH(Ac), -NH(alkyl), -NH(cycloalkyl), -NH(heterocycloalkyl), -NH(aryl), -NH(heteroaryl), -N(alkyl)₂, -NHC(O)(alkyl), -CH(alkyl)NH₂, -CH(hydroxyalkyl)NH₂, -CH(haloalkyl)NH₂, -CH(cycloalkyl)NH₂, -CH(heterocycloalkyl)NH₂, -CH(aryl)NH₂, -CH(heteroaryl)NH₂, -CH₂NHC(O)(alkyl), -C(O)NH₂, -C(O)(alkyl), -SO₂NH₂, -SO₂(cycloalkyl), -SO₂(heterocycloalkyl), -SO₂(alkyl), -SO₂(aryl), or -SO₂(heteroaryl); or is selected from the group consisting of substituted or unsubstituted aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl;

T^1 is N, CH, NR^{T1} , or CR^{T1} ;

T^2 is NR^{T2} or CR^{T2} ;

T^3 is N, CH, NR^{T3} , or CR^{T3} ;

wherein:

(a) T^1 is CR^{T1} or NR^{T1} , wherein R^{T1} and R^{T2} , taken together with the intervening atoms, form an optionally substituted cycloalkyl, aryl, or heteroaryl ring; and

T^3 is N or CH; or

(b) T^3 is CR^{T3} or NR^{T3} ; wherein R^{T3} and R^{T2} , taken together with the intervening atoms, form an optionally substituted heteroaryl ring; and

T^1 is N or CH; and

at least one of (a) T^2 is NR^{T2} , (b) T^3 is N, or (c) T^1 is NR^{T1} ;

R^1 is selected from the group consisting of $-NH_2$, $-COOH$, $-CH_2COOH$, $-CH(NH(CO)(alkyl))COOH$, $-CH(NH(CO)(arylalkyl))COOH$, $-CH(NH(CO)(cycloalkyl))COOH$, $-CH(NH(CO)(aryl substituted cycloalkyl))COOH$, $-CH(NH(CO)(heteroaryl substituted cycloalkyl))COOH$, $-CH(S(alkyl))COOH$, $-CO(NH)CH_2(substituted or unsubstituted aryl)$, $-CO(NH)CH_2(substituted or unsubstituted heteroaryl)$, $-CO(NH)(substituted or unsubstituted aryl)$, $-CO(NH)(substituted or unsubstituted heteroaryl)$, and $-CH_2(tetrazolyl)$;

n is 0, 1, 2, 3, or 4;

p is 0, 1, 2, 3, or 4;

J is $-C(O)-$, $-NH-$, $-CH_2-$, $-O-$, $-S-$, $-S(O)-$, $-SO_2-$, $-N(alkyl)-$, $-CH(alkyl)-$, $-CH(cycloalkyl)-$, $-N((C(O)O)arylalkyl)-$, $-N((C(O)O)heteroarylalkyl)-$, or $-N(C(O)arylalkyl)-$;

K is $-C(O)-$, $-NH-$, $-CH_2-$, $-O-$, $-S-$, $-S(O)-$, $-SO_2-$, $-N(alkyl)-$, $-CH(alkyl)-$, $-CH(cycloalkyl)-$, $-N((C(O)O)arylalkyl)-$, $-N((C(O)O)heteroarylalkyl)-$, or $-N(C(O)arylalkyl)-$;

R^c , independently for each occurrence, is selected from the group consisting of halogen, $-OH$, $-NR^jR^k$, alkoxy, alkyl, cycloalkyl, and heterocycloalkyl;

L is selected from the group consisting of a bond, $-CH_2-$, $-CH_2CH_2-$, $-CHR^2-$, $-CF_2-$, $-CFR^2-$, $-C(O)-$, $-C(=NR^L)-$, $-C(=CHR^L)-$, $-S(O)_2-$, and $-S(O)-$; wherein R^L is H or alkyl;

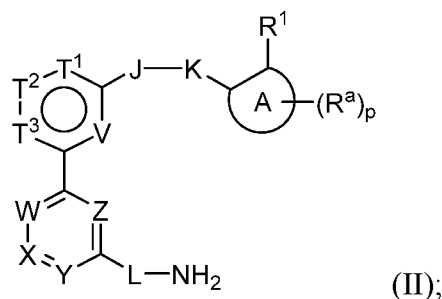
or wherein R^L and an occurrence of R^c taken together with the intervening atoms form a substituted or unsubstituted heteroaryl ring;

R^2 is alkyl, cycloalkyl, hydroxyalkyl, or haloalkyl;

V is N or CH; and

the stereochemical configuration at any chiral center is *R*, *S*, or a mixture of *R* and *S*.

In further aspects, the invention provides compounds having the structure of formula (II), and pharmaceutically acceptable salts and prodrugs thereof:



wherein:

ring $\textcircled{A}$ is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^a , independently for each occurrence, is selected from the group consisting of halogen, cyano, hydroxy, $-\text{NH}_2$, $-\text{NH}(\text{Ac})$, $-\text{NH}(\text{alkyl})$, $-\text{N}(\text{alkyl})_2$, $-\text{NHC}(\text{O})(\text{alkyl})$, $-\text{CH}_2\text{NHC}(\text{O})(\text{alkyl})$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})(\text{alkyl})$, optionally substituted aryl, optionally substituted heteroaryl, cycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl;

T^1 is N, CH, NR^{T1} , or CR^{T1} ;

T^2 is NR^{T2} or CR^{T2} ;

T^3 is N, CH, NR^{T3} , or CR^{T3} ;

wherein:

(a) T^1 is CR^{T1} or NR^{T1} , wherein R^{T1} and R^{T2} , taken together with the intervening atoms, form an optionally substituted cycloalkyl, aryl, or heteroaryl ring; and

T^3 is N or CH; or

(b) T^3 is CR^{T3} or NR^{T3} ; wherein R^{T3} and R^{T2} , taken together with the intervening atoms, form an optionally substituted heteroaryl ring; and

T^1 is N or CH; and

at least one of (a) T^2 is NR^{T2} , (b) T^3 is N, or (c) T^1 is NR^{T1} ;

R^1 is selected from the group consisting of $-NH_2$, $-CH_2COOH$,
 $-CH(NH(CO)(alkyl))COOH$, $-CH(NH(CO)(cycloalkyl))COOH$,
 $-CO(NH)CH_2aryl$, $-CO(NH)CH_2heteroaryl$, $-CO(NH)aryl$, and
 $-CO(NH)heteroaryl$;

p is 0, 1, or 2;

J is $-C(O)-$, $-NH-$, $-CH_2-$, $-O-$, $-S-$, $-S(O)-$, $-SO_2-$, $-N(alkyl)-$, or $-CH(alkyl)-$;

K is $-C(O)-$, $-NH-$, $-O-$, $-CH_2-$, $-S-$, $-S(O)-$, $-SO_2-$, $-N(alkyl)-$, or $-CH(alkyl)-$;

wherein at least one of J and K is $-C(O)-$, $-CH_2-$, or $-CH(alkyl)-$;

W is N , CH , or CR^c ;

X is N , CH , or CR^c ;

Y is N , CH , or CR^c ;

Z is N , CH , or CR^c ;

R^c , independently for each occurrence, is selected from the group consisting of
halogen, $-OH$, $-NR^jR^k$, alkoxy, and alkyl;

L is selected from the group consisting of a bond, $-CH_2-$, $-CH_2CH_2-$, $-CHR^2-$,
 $-CF_2-$, $-CFR^2-$, $-C(O)-$, $-C(=NR^L)-$, and $-C(=CHR^L)-$;

wherein R^L is H or alkyl;

or wherein R^L and an occurrence of R^c taken together with the intervening
atoms form a substituted or unsubstituted heteroaryl ring;

R^2 is alkyl, hydroxyalkyl, or haloalkyl;

V is N or CH ; and

the stereochemical configuration at any chiral center is R , S , or a mixture of R and S .

In certain aspects, the invention provides a pharmaceutical composition, comprising a
compound of the invention, or a pharmaceutically acceptable salt or prodrug thereof; and a
pharmaceutically acceptable carrier.

In certain aspects, the invention provides methods of treating a disease or condition
characterized by aberrant complement system activity, comprising administering to a subject
in need thereof a therapeutically effective amount of a compound the invention, or a
pharmaceutically acceptable salt or prodrug thereof. In certain embodiments, the disease or
condition characterized by aberrant complement system activity is an immunological
disorder. In certain embodiments, the disease or condition characterized by aberrant
complement system activity is a disease of the central nervous system. In certain
embodiments, the disease or condition characterized by aberrant complement system activity

is a neurodegenerative disease or neurological disease. In certain embodiments, the disease or condition characterized by aberrant complement system activity is a renal disease. In certain embodiments, the disease or condition characterized by aberrant complement system activity is a cardiovascular disease. In certain embodiments, the disease or condition characterized by aberrant complement system activity is selected from the group consisting of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, organ transplant rejection, myasthenia gravis, neuromyelitis optica, membranoproliferative glomerulonephritis, dense-deposit disease, cold agglutinin disease, and catastrophic antiphospholipid syndrome.

DETAILED DESCRIPTION

Inhibitors of the complement system are useful in therapeutic methods and compositions suitable for use in treating disorders of the immune, renal, cardiovascular, and neurological systems. Provided herein are compounds of formulae (I) and (II) and pharmaceutically acceptable salts and prodrugs thereof that are useful in treating or preventing a disease or condition characterized by aberrant activity of the complement system.

Definitions

The articles “a” and “an” are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

The term “heteroatom” is art-recognized and refers to an atom of any element other than carbon or hydrogen. Illustrative heteroatoms include boron, nitrogen, oxygen, phosphorus, sulfur and selenium, and alternatively oxygen, nitrogen or sulfur.

The term “alkyl” as used herein is a term of art and refers to saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In certain embodiments, a straight-chain or branched-chain alkyl has about 30 or fewer carbon atoms in its backbone (e.g., C₁-C₃₀ for straight chain, C₃-C₃₀ for branched chain), and alternatively, about 20 or fewer, or 10 or fewer. In certain embodiments, the term “alkyl” refers to a C₁-C₁₀ alkyl group. In certain embodiments, the term “alkyl” refers to a C₁-C₆ alkyl group, for example a C₁-C₆ straight-chain alkyl group. In certain embodiments, the term “alkyl” refers to a C₃-C₁₂ branched-chain alkyl group. In certain embodiments, the

term “alkyl” refers to a C₃-C₈ branched-chain alkyl group. 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, and n-hexyl.

The term “cycloalkyl” means mono- or bicyclic or bridged saturated carbocyclic rings, each having from 3 to 12 carbon atoms. Certain cycloalkyls have from 5-12 carbon atoms in their ring structure, and may have 6-10 carbons in the ring structure. Preferably, cycloalkyl is (C₃-C₇)cycloalkyl, which represents a monocyclic saturated carbocyclic ring, having from 3 to 7 carbon atoms. Examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. Bicyclic cycloalkyl ring systems include bridged monocyclic rings and fused bicyclic rings. Bridged monocyclic rings contain a monocyclic cycloalkyl ring where two non-adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge of between one and three additional carbon atoms (*i.e.*, a bridging group of the form -(CH₂)_w-, where *w* is 1, 2, or 3). Representative examples of bicyclic ring systems include, but are not limited to, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, and bicyclo[4.2.1]nonane. Fused bicyclic cycloalkyl ring systems contain a monocyclic cycloalkyl ring fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocyclyl, or a monocyclic heteroaryl. The bridged or fused bicyclic cycloalkyl is attached to the parent molecular moiety through any carbon atom contained within the monocyclic cycloalkyl ring. Cycloalkyl groups are optionally substituted. In certain embodiments, the fused bicyclic cycloalkyl is a 5 or 6 membered monocyclic cycloalkyl ring fused to either a phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocyclyl, or a 5 or 6 membered monocyclic heteroaryl, wherein the fused bicyclic cycloalkyl is optionally substituted.

The term “(cycloalkyl)alkyl” as used herein refers to an alkyl group substituted with one or more cycloalkyl groups. An example of cycloalkylalkyl is cyclohexylmethyl group.

The term “heterocycloalkyl” as used herein refers to a radical of a non-aromatic ring system, including, but not limited to, monocyclic, bicyclic, and tricyclic rings, which can be completely saturated or which can contain one or more units of unsaturation, for the avoidance of doubt, the degree of unsaturation does not result in an aromatic ring system, and having 3 to 12 atoms including at least one heteroatom, such as nitrogen, oxygen, or sulfur. For purposes of exemplification, which should not be construed as limiting the scope of this invention, the following are examples of heterocyclic rings: aziridinyl, aziriny, oxiranyl,

thiiranyl, thiirenyl, dioxiranyl, diazirinyl, diazepanyl, 1,3-dioxanyl, 1,3-dioxolanyl, 1,3-dithiolanyl, 1,3-dithianyl, imidazolidinyl, isothiazolinyl, isothiazolidinyl, isoxazolinyl, isoxazolidinyl, azetyl, oxetanyl, oxetyl, thietanyl, thietyl, diazetidinyl, dioxetanyl, dioxetenyl, dithietanyl, dithietyl, dioxalanyl, oxazolyl, thiazolyl, triazinyl, isothiazolyl, isoxazolyl, azepines, azetidiny, morpholinyl, oxadiazolinyl, oxadiazolidinyl, oxazolinyl, oxazolidinyl, oxopiperidinyl, oxopyrrolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, quinuclidinyl, thiomorpholinyl, tetrahydropyranyl, tetrahydrofuranly, tetrahydrothienyl, thiadiazolinyl, thiadiazolidinyl, thiazolinyl, thiazolidinyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl (thiomorpholine sulfone), thiopyranly, trithianyl, and 2-azobicyclo[3.1.0]hexane. A heterocycloalkyl group is optionally substituted by one or more substituents as described below.

The term “(heterocycloalkyl)alkyl” as used herein refers to an alkyl group substituted with one or more heterocycloalkyl (i.e., heterocyclyl) groups.

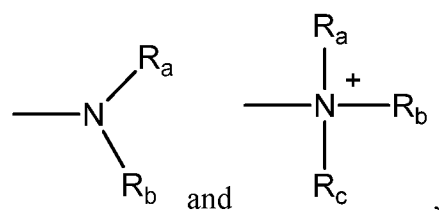
The term “alkenyl” as used herein means a straight or branched chain hydrocarbon radical containing from 2 to 10 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-decenyl. The unsaturated bond(s) of the alkenyl group can be located anywhere in the moiety and can have either the (Z) or the (E) configuration about the double bond(s).

The term “alkynyl” as used herein means a straight or branched chain hydrocarbon radical containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butenyl, 2-pentynyl, and 1-butynyl.

The term “alkylene” is art-recognized, and as used herein pertains to a diradical obtained by removing two hydrogen atoms of an alkyl group, as defined above. In one embodiment an alkylene refers to a disubstituted alkane, i.e., an alkane substituted at two positions with substituents such as halogen, azide, alkyl, arylalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, fluoroalkyl (such as trifluoromethyl), cyano, or the like. That is, in one embodiment, a “substituted alkyl” is an “alkylene”.

The term “amino” is a term of art and as used herein refers to both unsubstituted and

substituted amines, e.g., a moiety that may be represented by the general formulas:



wherein R_a , R_b , and R_c each independently represent a hydrogen, an alkyl, an alkenyl, $-(\text{CH}_2)_x\text{-R}_d$, or R_a and R_b , taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R_d represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocyclyl or a polycyclyl; and x is zero or an integer in the range of 1 to 8. In certain embodiments, only one of R_a or R_b may be a carbonyl, e.g., R_a , R_b , and the nitrogen together do not form an imide. In other embodiments, R_a and R_b (and optionally R_c) each independently represent a hydrogen, an alkyl, an alkenyl, or $-(\text{CH}_2)_x\text{-R}_d$. In certain embodiments, the term “amino” refers to $-\text{NH}_2$.

In certain embodiments, the term “alkylamino” refers to $-\text{NH}(\text{alkyl})$.

In certain embodiments, the term “dialkylamino” refers to $-\text{N}(\text{alkyl})_2$.

The term “amido”, as used herein, means $-\text{NHC}(=\text{O})-$, wherein the amido group is bound to the parent molecular moiety through the nitrogen. Examples of amido include alkylamido such as $\text{CH}_3\text{C}(=\text{O})\text{N}(\text{H})-$ and $\text{CH}_3\text{CH}_2\text{C}(=\text{O})\text{N}(\text{H})-$.

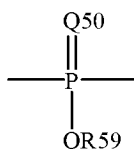
The term “acyl” is a term of art and as used herein refers to any group or radical of the form $\text{RCO}-$ where R is any organic group, e.g., alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl. Representative acyl groups include acetyl, benzoyl, and malonyl.

The term “aminoalkyl” as used herein refers to an alkyl group substituted with one or more amino groups. In one embodiment, the term “aminoalkyl” refers to an aminomethyl group, i.e., $-\text{CH}_2\text{NH}_2$.

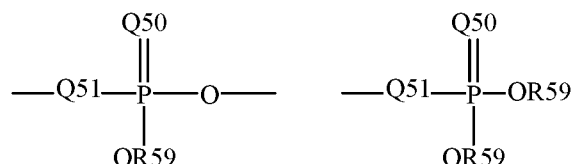
The term “aminoacyl” is a term of art and as used herein refers to an acyl group substituted with one or more amino groups.

The term “aminothionyl” as used herein refers to an analog of an aminoacyl in which the O of $\text{RC}(\text{O})-$ has been replaced by sulfur, hence is of the form $\text{RC}(\text{S})-$.

The term “phosphoryl” is a term of art and as used herein may in general be represented by the formula:



wherein Q50 represents S or O, and R59 represents hydrogen, a lower alkyl or an aryl; for example, -P(O)(OMe)- or -P(O)(OH)₂. When used to substitute, e.g., an alkyl, the phosphoryl group of the phosphorylalkyl may be represented by the general formulas:



wherein Q50 and R59, each independently, are defined above, and Q51 represents O, S or N; for example, -O-P(O)(OH)OMe or -NH-P(O)(OH)₂. When Q50 is S, the phosphoryl moiety is a “phosphorothioate.”

The term “aminophosphoryl” as used herein refers to a phosphoryl group substituted with at least one amino group, as defined herein; for example, -P(O)(OH)NMe₂.

The term “azide” or “azido”, as used herein, means an -N₃ group.

The term “carbonyl” as used herein refers to -C(=O)-.

The term “thiocarbonyl” as used herein refers to -C(=S)-.

The term “alkylphosphoryl” as used herein refers to a phosphoryl group substituted with at least one alkyl group, as defined herein; for example, -P(O)(OH)Me.

The term “alkylthio” as used herein refers to alkyl-S-. The term “(alkylthio)alkyl” refers to an alkyl group substituted by an alkylthio group.

The term “carboxy”, as used herein, means a -CO₂H group.

The term “aryl” is a term of art and as used herein refers to includes monocyclic, bicyclic and polycyclic aromatic hydrocarbon groups, for example, benzene, naphthalene, anthracene, and pyrene. Typically, an aryl group contains from 6-10 carbon ring atoms (i.e., (C₆-C₁₀)aryl). The aromatic ring may be substituted at one or more ring positions with one or more substituents, such as halogen, azide, alkyl, arylalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, fluoroalkyl (such as trifluoromethyl), cyano, or the like. The term “aryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are “fused rings”) wherein at least one of the rings is an aromatic hydrocarbon, e.g., the other cyclic rings may be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. In certain embodiments, the term “aryl” refers to a phenyl group.

The term “heteroaryl” is a term of art and as used herein refers to a monocyclic, bicyclic, and polycyclic aromatic group having 3 to 12 total atoms including one or more heteroatoms such as nitrogen, oxygen, or sulfur in the ring structure. Exemplary heteroaryl groups include azaindolyl, benzo(b)thienyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl, benzoxadiazolyl, furanyl, imidazolyl, imidazopyridinyl, indolyl, indoliny, indazolyl, isoindoliny, isoxazolyl, isothiazolyl, isoquinoliny, oxadiazolyl, oxazolyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrrolyl, pyrrolo[2,3-d]pyrimidinyl, pyrazolo[3,4-d]pyrimidinyl, quinoliny, quinazolinyl, triazolyl, thiazolyl, thiophenyl, tetrahydroindolyl, tetrazolyl, thiadiazolyl, thienyl, thiomorpholinyl, triazolyl or tropanyl, and the like. The “heteroaryl” may be substituted at one or more ring positions with one or more substituents such as halogen, azide, alkyl, arylalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, fluoroalkyl (such as trifluoromethyl), cyano, or the like. The term “heteroaryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are “fused rings”) wherein at least one of the rings is an aromatic group having one or more heteroatoms in the ring structure, e.g., the other cyclic rings may be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls.

The term “aralkyl” or “arylalkyl” is a term of art and as used herein refers to an alkyl group substituted with an aryl group, wherein the moiety is appended to the parent molecule through the alkyl group.

The term “heteroaralkyl” or “heteroarylalkyl” is a term of art and as used herein refers to an alkyl group substituted with a heteroaryl group, appended to the parent molecular moiety through the alkyl group.

The term “alkoxy” as used herein means an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, and hexyloxy.

The term “alkoxyalkyl” refers to an alkyl group substituted by an alkoxy group.

The term “alkoxycarbonyl” means an alkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, represented by -C(=O)-, as defined

herein. Representative examples of alkoxycarbonyl include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, and *tert*-butoxycarbonyl.

The term “alkylcarbonyl”, as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkylcarbonyl include, but are not limited to, acetyl, 1-oxopropyl, 2,2-dimethyl-1-oxopropyl, 1-oxobutyl, and 1-oxopentyl.

The term “arylcarbonyl”, as used herein, means an aryl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of arylcarbonyl include, but are not limited to, benzoyl and (2-pyridinyl)carbonyl.

The term “alkylcarbonyloxy” and “arylcarbonyloxy”, as used herein, means an alkylcarbonyl or arylcarbonyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkylcarbonyloxy include, but are not limited to, acetyloxy, ethylcarbonyloxy, and *tert*-butylcarbonyloxy. Representative examples of arylcarbonyloxy include, but are not limited to phenylcarbonyloxy.

The term “alkenoxy” or “alkenoxyl” means an alkenyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkenoxyl include, but are not limited to, 2-propen-1-oxyl (i.e., $\text{CH}_2=\text{CH}-\text{CH}_2-\text{O}-$) and vinyloxy (i.e., $\text{CH}_2=\text{CH}-\text{O}-$).

The term “aryloxy” as used herein means an aryl group, as defined herein, appended to the parent molecular moiety through an oxygen atom.

The term “heteroaryloxy” as used herein means a heteroaryl group, as defined herein, appended to the parent molecular moiety through an oxygen atom.

The term “carbocyclyl” as used herein means a monocyclic or multicyclic (e.g., bicyclic, tricyclic, etc.) hydrocarbon radical containing from 3 to 12 carbon atoms that is completely saturated or has one or more unsaturated bonds, and for the avoidance of doubt, the degree of unsaturation does not result in an aromatic ring system (e.g., phenyl). Examples of carbocyclyl groups include 1-cyclopropyl, 1-cyclobutyl, 2-cyclopentyl, 1-cyclopentenyl, 3-cyclohexyl, 1-cyclohexenyl and 2-cyclopentenylmethyl.

The term “cyano” is a term of art and as used herein refers to $-\text{CN}$.

The term “halo” is a term of art and as used herein refers to $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$.

The term “haloalkyl” as used herein refers to an alkyl group, as defined herein, wherein some or all of the hydrogens are replaced with halogen atoms.

The term “hydroxy” is a term of art and as used herein refers to $-\text{OH}$.

The term “hydroxyalkyl”, as used herein, means at least one hydroxy group, as defined herein, is appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of hydroxyalkyl include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2,3-dihydroxypentyl, and 2-ethyl-4-hydroxyheptyl.

The term “silyl”, as used herein, includes hydrocarbyl derivatives of the silyl ($\text{H}_3\text{Si}-$) group (i.e., $(\text{hydrocarbyl})_3\text{Si}-$), wherein a hydrocarbyl groups are univalent groups formed by removing a hydrogen atom from a hydrocarbon, e.g., ethyl, phenyl. The hydrocarbyl groups can be combinations of differing groups which can be varied in order to provide a number of silyl groups, such as trimethylsilyl (TMS), tert-butyldiphenylsilyl (TBDPS), tert-butyldimethylsilyl (TBS/TBDMS), triisopropylsilyl (TIPS), and [2-(trimethylsilyl)ethoxy]methyl (SEM).

The term “silyloxy”, as used herein, means a silyl group, as defined herein, is appended to the parent molecule through an oxygen atom.

Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, compounds of the present invention may also be optically active. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, (*R*)- and (*S*)-enantiomers, diastereoisomers, (*D*)-isomers, (*L*)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does

not spontaneously undergo transformation such as by rearrangement, fragmentation, decomposition, cyclization, elimination, or other reaction.

The term “substituted” is also contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above. The permissible substituents may be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

As used herein, the term “substituted or unsubstituted” when it precedes a list of chemical moieties means that the list of chemical moieties that follow are each substituted or unsubstituted. For example, “substituted or unsubstituted aryl, heteroaryl, and cycloalkyl” means substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted cycloalkyl.

The phrase “protecting group”, as used herein, means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991). Protected forms of the inventive compounds are included within the scope of this invention.

For purposes of the invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

Other chemistry terms herein are used according to conventional usage in the art, as exemplified by The McGraw-Hill Dictionary of Chemical Terms (ed. Parker, S., 1985), McGraw-Hill, San Francisco, incorporated herein by reference). Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains.

The term “pharmaceutically acceptable salt” as used herein includes salts derived from inorganic or organic acids including, for example, hydrochloric, hydrobromic, sulfuric,

nitric, perchloric, phosphoric, formic, acetic, lactic, maleic, fumaric, succinic, tartaric, glycolic, salicylic, citric, methanesulfonic, benzenesulfonic, benzoic, malonic, trifluoroacetic, trichloroacetic, naphthalene-2-sulfonic, and other acids. Pharmaceutically acceptable salt forms can include forms wherein the ratio of molecules comprising the salt is not 1:1. For example, the salt may comprise more than one inorganic or organic acid molecule per molecule of base, such as two hydrochloric acid molecules per molecule of compound of Formula I. As another example, the salt may comprise less than one inorganic or organic acid molecule per molecule of base, such as two molecules of compound of Formula I per molecule of tartaric acid.

The term “prodrug” as used herein refers to a compound that can be metabolized in vivo to provide a compound of formula I or II. Thus prodrugs include compounds that can be prepared by modifying one or more functional groups in a compound of formula I or II to provide a corresponding compound that can be metabolized in vivo to provide a compound of formula I or II. Such modifications are known in the art. For example, one or more hydroxyl groups or amine groups in a compound of formula I or II can be acylated with alkyl-C(=O)-groups or with residues from amino acids to provide a prodrug.

Prodrug forms of a compound bearing various nitrogen-containing functional groups (amino, hydroxyamino, amide, etc.) may include the following types of derivatives, where each R_p group individually may be hydrogen, substituted or unsubstituted alkyl, aryl, alkenyl, alkynyl, heterocycle, alkylaryl, arylalkyl, aralkenyl, aralkynyl, cycloalkyl or cycloalkenyl.

- (a) Carboxamides, represented as ---NHC(O)R_p
- (b) Carbamates, represented as ---NHC(O)OR_p
- (c) (Acyloxy)alkyl Carbamates, represented as NHC(O)OROC(O)R_p
- (d) Enamines, represented as $\text{---NHCR(=CHCO}_2\text{R}_p\text{)}$ or $\text{---NHCR(=CHCONR}_p\text{R}_p\text{)}$
- (e) Schiff Bases, represented as $\text{---N=CR}_p\text{R}_p$
- (f) Mannich Bases (from carboximide compounds), represented as $\text{RCONHCH}_2\text{NR}_p\text{R}_p$

Preparations of such prodrug derivatives are discussed in various literature sources (examples are: Alexander et al., J. Med. Chem. 1988, 31, 318; Aligas-Martin et al., PCT WO0041531, p. 30).

Prodrug forms of carboxyl-bearing compounds include esters ($\text{---CO}_2\text{R}_m$), where the R_m group corresponds to any alcohol whose release in the body through enzymatic or hydrolytic processes would be at pharmaceutically acceptable levels. Another prodrug

derived from a carboxylic acid form of the disclosure may be a quaternary salt type of structure described by Bodor et al., J. Med. Chem. 1980, 23, 469.

The terms “carrier” and “pharmaceutically acceptable carrier” as used herein refer to a diluent, adjuvant, excipient, or vehicle with which a compound is administered or formulated for administration. Non-limiting examples of such pharmaceutically acceptable carriers include liquids, such as water, saline, and oils; and solids, such as gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating, flavoring, and coloring agents may be used. Other examples of suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences* by E.W. Martin, herein incorporated by reference in its entirety.

The term “treat” as used herein means prevent, halt or slow the progression of, or eliminate a disease or condition in a subject. In one embodiment “treat” means halt or slow the progression of, or eliminate a disease or condition in a subject. In one embodiment, “treat” means reduce at least one objective manifestation of a disease or condition in a subject.

The term “effective amount” as used herein refers to an amount that is sufficient to bring about a desired biological effect.

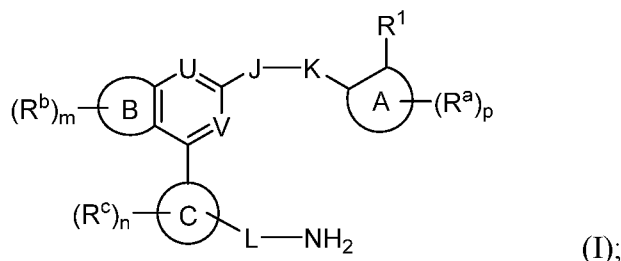
The term “therapeutically effective amount” as used herein refers to an amount that is sufficient to bring about a desired therapeutic effect.

The term “inhibit” as used herein means decrease by an objectively measurable amount or extent. In various embodiments “inhibit” means decrease by at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 95 percent compared to relevant control. In one embodiment “inhibit” means decrease 100 percent, i.e., halt or eliminate.

The term “subject” as used herein refers to a mammal. In various embodiments, a subject is a mouse, rat, rabbit, cat, dog, pig, sheep, horse, cow, or non-human primate. In one embodiment, a subject is a human.

Compounds

The present invention provides compounds having the structure of Formula (I), and pharmaceutically acceptable salts or prodrugs thereof:



(I);

wherein:

ring $\textcircled{A}$ is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

ring $\textcircled{B}$ is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

ring $\textcircled{C}$ is aryl or heteroaryl;

R^a , independently for each occurrence, is halogen, cyano, hydroxy, $-NH_2$, $-NH(Ac)$, $-NH(alkyl)$, $-NH(cycloalkyl)$, $-NH(heterocycloalkyl)$, $-NH(aryl)$, $-NH(heteroaryl)$, $-N(alkyl)_2$, $-NHC(O)(alkyl)$, $-CH(alkyl)NH_2$, $-CH(hydroxyalkyl)NH_2$, $-CH(haloalkyl)NH_2$, $-CH(cycloalkyl)NH_2$, $-CH(heterocycloalkyl)NH_2$, $-CH(aryl)NH_2$, $-CH(heteroaryl)NH_2$, $-CH_2NHC(O)(alkyl)$, $-C(O)NH_2$, $-C(O)(alkyl)$, $-SO_2NH_2$, $-SO_2(cycloalkyl)$, $-SO_2(heterocycloalkyl)$, $-SO_2(alkyl)$, $-SO_2(aryl)$, or $-SO_2(heteroaryl)$; or is selected from the group consisting of substituted or unsubstituted aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl;

R^b , independently for each occurrence, is halogen, cyano, $-CH_2(OCH_2CH_2)_qOCH_3$, $-alkylene-(branched\ or\ unbranched\ polyethylene\ glycol)$, $-alkylene-O-(branched\ or\ unbranched\ polyethylene\ glycol)$, or $-NR^jR^k$; or is selected from the group consisting of substituted or unsubstituted alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, (hydroxy)haloalkyl, hydroxy(cycloalkyl)alkyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, arylalkyl, heteroarylalkyl, (heteroarylalkoxy)alkyl, (arylalkoxy)alkyl, (aryloxy)alkyl, ((cycloalkyl)alkoxy)alkyl, ((heterocycloalkyl)alkoxy)alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-alkylene-NR^jR^k$, tosyl, $-SO_2(alkyl)$, $-SO_2(cycloalkyl)$, $-CO(alkyl)$, $-CO(aryl)$, $-CO(heteroaryl)$, $-CO(cycloalkyl)$, $-CO(heterocycloalkyl)$, $-CONH(alkyl)$, $-CONH(arylalkyl)$, $-$

CONH(heteroarylalkyl), -CON(alkyl)₂, -CONH(heterocycloalkyl), and -CONH(cycloalkyl);

R^c, independently for each occurrence, is selected from the group consisting of halogen, -OH, -NR^jR^k, alkoxy, alkyl, cycloalkyl, and heterocycloalkyl;

R¹ is selected from the group consisting of -NH₂, -COOH, -CH₂COOH, -CH(NH(CO)(alkyl))COOH, -CH(NH(CO)(arylalkyl))COOH, -CH(NH(CO)(cycloalkyl))COOH, -CH(NH(CO)(aryl substituted cycloalkyl))COOH, -CH(NH(CO)(heteroaryl substituted cycloalkyl))COOH, -CH(S(alkyl))COOH, -CO(NH)CH₂(substituted or unsubstituted aryl), -CO(NH)CH₂(substituted or unsubstituted heteroaryl), -CO(NH)(substituted or unsubstituted aryl), -CO(NH)(substituted or unsubstituted heteroaryl), and -CH₂(tetrazolyl);

n is 0, 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

p is 0, 1, 2, 3, or 4;

q is an integer from 1-20;

J is -C(O)-, -NH-, -CH₂-, -O-, -S-, -S(O)-, -SO₂-, -N(alkyl)-, -CH(alkyl)-, -CH(cycloalkyl)-, -N((C(O)O)arylalkyl)-, -N((C(O)O)heteroarylalkyl)-, or -N(C(O)arylalkyl)-;

K is -C(O)-, -NH-, -CH₂-, -O-, -S-, -S(O)-, -SO₂-, -N(alkyl)-, -CH(alkyl)-, -CH(cycloalkyl)-, -N((C(O)O)arylalkyl)-, -N((C(O)O)heteroarylalkyl)-, or -N(C(O)arylalkyl)-;

wherein at least one of J and K is -C(O)-, -CH₂-, or -CH(alkyl)-;

L is selected from the group consisting of a bond, -CH₂-, -CH₂CH₂-, -CHR²-, -CF₂-, -CFR²-, -C(O)-, -C(=NR^L)-, -C(=CHR^L)-, -S(O)₂-, and -S(O)-; wherein R^L is H or alkyl;

or wherein R^L and an occurrence of R^c taken together with the intervening atoms form a substituted or unsubstituted heteroaryl ring;

R² is alkyl, cycloalkyl, hydroxyalkyl, or haloalkyl;

R^j and R^k are each independently H or are selected from the group consisting of substituted or unsubstituted alkyl, aminoalkyl, (heterocycloalkyl)alkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, -CO(aryl), -CO(arylalkyl), -CO(heteroarylalkyl), and -CO((heterocycloalkyl)alkyl);

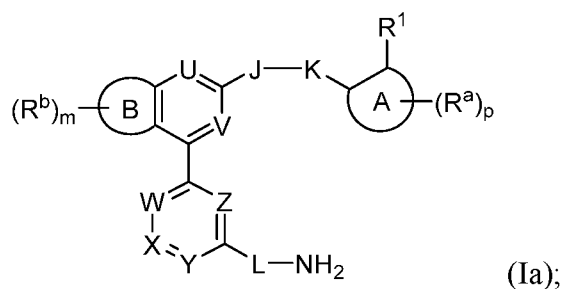
U is N or CR³;

R^3 is H, halogen, alkyl, cycloalkyl, aryl, heteroaryl, alkoxy, haloalkyl, -CN, -CONH₂, -CO₂H, -CH₂CO₂H, -NH₂, hydroxyalkyl, aminoalkyl, -OH, -NH(alkyl), -N(alkyl)₂, thioalkyl, or -S(alkyl);

V is N, CH, C(halogen), or C(alkyl); and

the stereochemical configuration at any chiral center is *R*, *S*, or a mixture of *R* and *S*.

In some embodiments, the compound of formula (I) has the structure of formula (Ia):



wherein:

W is N, CH, or CR^c;

X is N, CH, or CR^c;

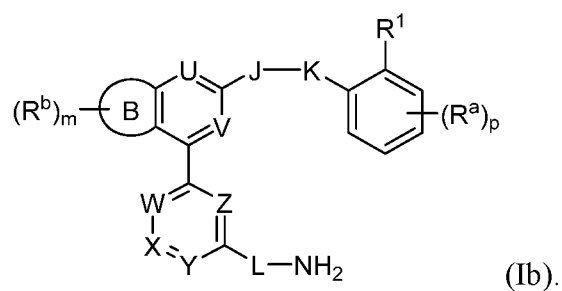
Y is N, CH, or CR^c; and

Z is N, CH, or CR^c.

In certain embodiments, ring $\textcircled{A}$ is naphthyl, indenyl, cyclopentyl, pyrrolidinyl, phenyl, benzofuranyl, thiophenyl, or pyridinyl.

In certain embodiments, ring $\textcircled{A}$ is phenyl, thiophenyl, or pyridinyl, preferably phenyl.

In certain embodiments, the compound of formula (I) has the structure of formula (Ib):



In certain embodiments, p is 1.

In certain such embodiments, R^a is halogen, cyano, hydroxy, $-NH_2$, $-NH(Ac)$, $-NH(alkyl)$, $-N(alkyl)_2$, $-NHC(O)(alkyl)$, $-CH_2NHC(O)(alkyl)$, $-C(O)NH_2$, or $-C(O)(alkyl)$; or is selected from the group consisting of substituted or unsubstituted aryl, heteroaryl, cycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl.

In other such embodiments, R^a is halogen, cyano, $-NH_2$, $-NH(Ac)$, $-C(O)CH_3$, $-C(O)NH_2$, hydroxymethyl, or substituted or unsubstituted aryl, heteroaryl, cycloalkyl, alkoxy, alkyl, or aminoalkyl.

In other such embodiments, R^a is halogen, $-NH(Ac)$, $-C(O)CH_3$, or substituted or unsubstituted aryl, heteroaryl, cycloalkyl, alkoxy, alkyl, or aminoalkyl. In further such embodiments, R^a is alkyl, cycloalkyl, or halogen.

Alternatively, in some embodiments, p is 0.

In certain embodiments, R^1 is $-CH_2COOH$.

Alternatively, in some embodiments, R^1 is $-CO(NH)CH_2$ (substituted or unsubstituted aryl).

In certain embodiments:

J is $-C(O)-$, $-NH-$, $-CH_2-$, $-O-$, $-S-$, $-S(O)-$, $-SO_2-$, $-N(alkyl)-$, $-CH(alkyl)-$, or $-N(C(O)arylalkyl)-$; and

K is $-C(O)-$, $-NH-$, $-O-$, $-CH_2-$, $-S-$, $-S(O)-$, $-SO_2-$, $-N(alkyl)-$, $-CH(alkyl)-$, or $-N(C(O)arylalkyl)-$.

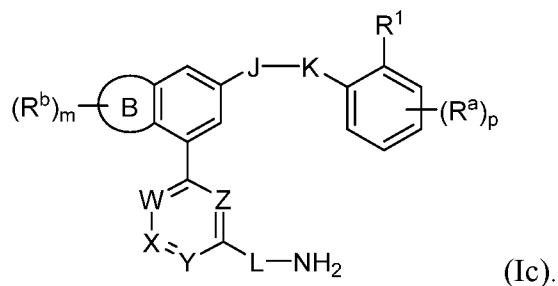
In some embodiments, $-J-K-$ is selected from the group consisting of $-C(O)-NH-$, $-NH-C(O)-$, and $-CH_2O-$, preferably $-CH_2O-$.

In certain embodiments, U is N or CR^3 , and R^3 is H , halogen, alkyl, cycloalkyl, aryl, heteroaryl, alkoxy, or haloalkyl.

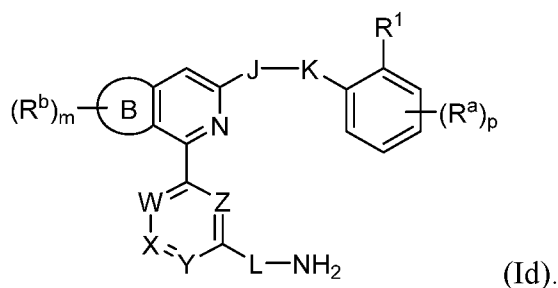
In certain embodiments, U is CH . In further embodiments, V is CH .

Alternatively, in some embodiments, U is CR^3 and R^3 is H , halogen, alkyl, alkoxy, or haloalkyl.

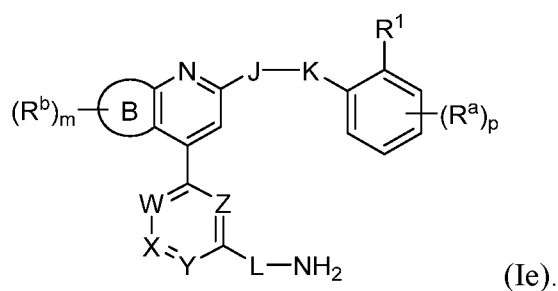
In some embodiments, the compound of formula (I) has the structure of formula (Ic):



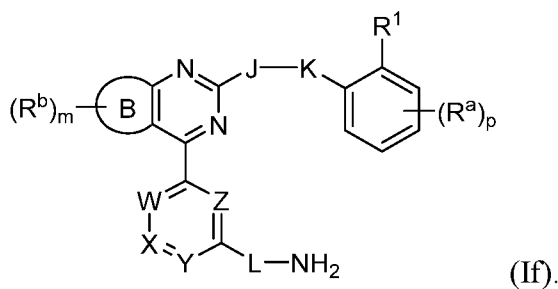
Alternatively, in some embodiments, the compound of formula (I) has the structure of formula (Id):



In still further embodiments, the compound of formula (I) has the structure of formula (Ie):



In yet further embodiments, the compound of formula (I) has the structure of formula (If):



In any of the foregoing embodiments, ring $\textcircled{\text{B}}$ may be heteroaryl. For example, in some embodiments, ring $\textcircled{\text{B}}$ is furyl, oxazolyl, isoxazolyl, thiophenyl, pyrrolyl, pyrazolyl,

or imidazolyl. In further embodiments, ring  is furyl, thiophenyl, or pyrrolyl, preferably furyl.

In some embodiments, m is 0.

In alternative embodiments, m is 1. In certain such embodiments, R^b , independently for each occurrence, is halogen, cyano, $-\text{CH}_2(\text{OCH}_2\text{CH}_2)_q\text{OCH}_3$, or $-\text{NR}^j\text{R}^k$; or is selected from the group consisting of substituted or unsubstituted alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, (hydroxy)haloalkyl, hydroxy(cycloalkyl)alkyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, arylalkyl, heteroarylalkyl, (heteroarylalkoxy)alkyl, (arylalkoxy)alkyl, (aryloxy)alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-\text{alkylene}-\text{NR}^j\text{R}^k$, tosyl, $-\text{SO}_2(\text{alkyl})$, $-\text{SO}_2(\text{cycloalkyl})$, $-\text{CO}(\text{alkyl})$, $-\text{CO}(\text{cycloalkyl})$, $-\text{CONH}(\text{alkyl})$, $-\text{CONH}(\text{arylalkyl})$, $-\text{CON}(\text{alkyl})_2$, and $-\text{CONH}(\text{cycloalkyl})$.

In certain embodiments, q is an integer from 1-5.

In other such embodiments, R^b is selected from the group consisting of substituted or unsubstituted alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, and (cycloalkyl)alkyl. In alternative embodiments, R^b is substituted or unsubstituted $-\text{alkylene}-\text{NR}^j\text{R}^k$.

In other alternative embodiments, m is 2. In certain such embodiments, each R^b is alkyl.

In certain embodiments, each of W, X, Y, and Z is CH.

In certain embodiments, at least one of W, X, Y, and Z is CR^c . For example, Z may be CR^c and/or Y may be CR^c . In certain such embodiments, R^c is selected from the group consisting of halogen, $-\text{OH}$, $-\text{NR}^j\text{R}^k$, alkoxy, and alkyl. In certain preferred embodiments, R^c is halogen, e.g., fluoride.

Alternatively, at least one of W, X, Y, and Z is N. For example, Z may be N. Alternatively, Y may be N.

In some embodiments, L is selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CHR}^2-$, $-\text{CF}_2-$, $-\text{CFR}^2-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{=NR}^L)-$, and $-\text{C}(\text{=CHR}^L)-$.

In some embodiments, L is $-\text{CH}_2-$.

In certain embodiments of the compounds of formula (I):

ring  is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

ring $\textcircled{\text{B}}$ is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

ring $\textcircled{\text{C}}$ is aryl or heteroaryl;

R^a , independently for each occurrence, is selected from the group consisting of halogen, cyano, hydroxy, $-\text{NH}_2$, $-\text{NH}(\text{Ac})$, $-\text{NH}(\text{alkyl})$, $-\text{N}(\text{alkyl})_2$, $-\text{NHC}(\text{O})(\text{alkyl})$, $-\text{CH}_2\text{NHC}(\text{O})(\text{alkyl})$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})(\text{alkyl})$, optionally substituted aryl, optionally substituted heteroaryl, cycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl;

R^b , independently for each occurrence, is selected from the group consisting of halogen, cyano, $-\text{NR}^j\text{R}^k$, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, (hydroxy)haloalkyl, hydroxy(cycloalkyl)alkyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-\text{alkylene}-\text{NR}^j\text{R}^k$, tosyl, $-\text{SO}_2(\text{alkyl})$, $-\text{SO}_2(\text{cycloalkyl})$, $-\text{CO}(\text{alkyl})$, $-\text{CO}(\text{cycloalkyl})$, $-\text{CONH}(\text{alkyl})$, $-\text{CON}(\text{alkyl})_2$, and $-\text{CONH}(\text{cycloalkyl})$;

R^c , independently for each occurrence, is selected from the group consisting of halogen, $-\text{OH}$, $-\text{NR}^j\text{R}^k$, alkoxy, and alkyl;

R^1 is selected from the group consisting of $-\text{NH}_2$, $-\text{CH}_2\text{COOH}$, $-\text{CH}(\text{NH}(\text{CO})(\text{alkyl}))\text{COOH}$, $-\text{CH}(\text{NH}(\text{CO})(\text{arylalkyl}))\text{COOH}$, $-\text{CH}(\text{NH}(\text{CO})(\text{cycloalkyl}))\text{COOH}$, $-\text{CH}(\text{NH}(\text{CO})(\text{aryl substituted cycloalkyl}))\text{COOH}$, $-\text{CO}(\text{NH})\text{CH}_2\text{aryl}$, $-\text{CO}(\text{NH})\text{CH}_2\text{heteroaryl}$, $-\text{CO}(\text{NH})\text{aryl}$, and $-\text{CO}(\text{NH})\text{heteroaryl}$;

n is 0, 1, or 2;

m is 0, 1, or 2;

p is 0, 1, or 2;

J is $-\text{C}(\text{O})-$, $-\text{NH}-$, $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{N}(\text{alkyl})-$, or $-\text{CH}(\text{alkyl})-$;

K is $-\text{C}(\text{O})-$, $-\text{NH}-$, $-\text{O}-$, $-\text{CH}_2-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{N}(\text{alkyl})-$, or $-\text{CH}(\text{alkyl})-$;

wherein at least one of J and K is $-\text{C}(\text{O})-$, $-\text{CH}_2-$, or $-\text{CH}(\text{alkyl})-$;

L is selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CHR}^2-$,

$-\text{CF}_2-$, $-\text{CFR}^2-$, $-\text{C}(\text{O})-$, $-\text{C}(=\text{NR}^L)-$, and $-\text{C}(=\text{CHR}^L)-$;

wherein R^L is H or alkyl;

or wherein R^L and an occurrence of R^c taken together with the intervening atoms form a substituted or unsubstituted heteroaryl ring;

R^2 is alkyl, hydroxyalkyl, or haloalkyl;

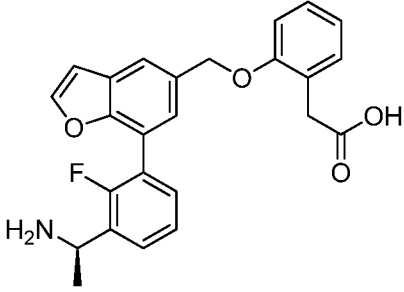
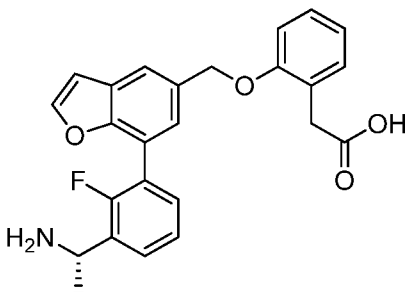
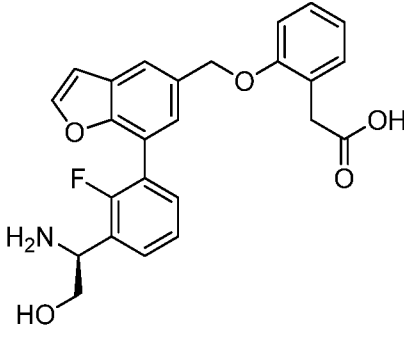
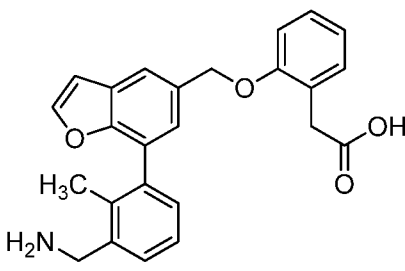
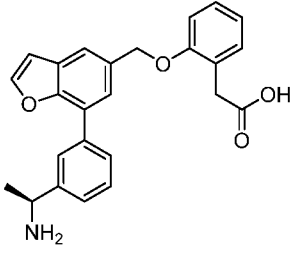
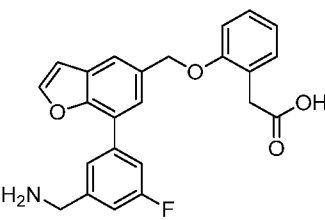
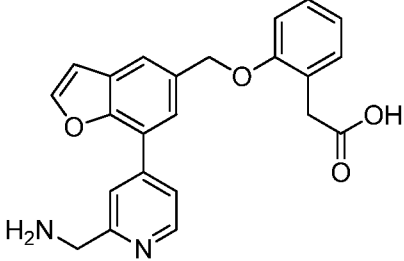
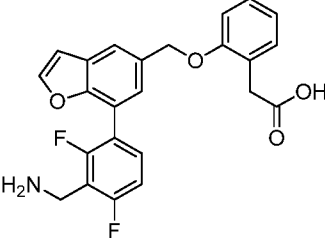
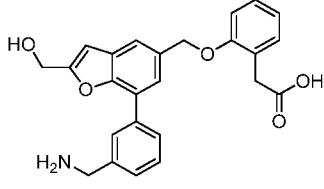
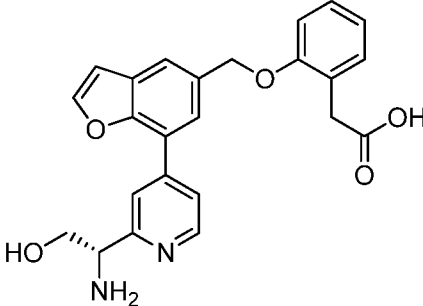
R^j and R^k are each independently selected from the group consisting of H, alkyl, aminoalkyl, (heterocycloalkyl)alkyl, and heterocycloalkyl;

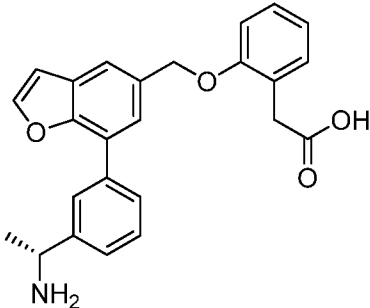
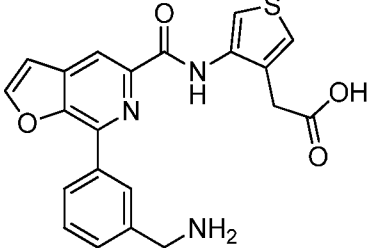
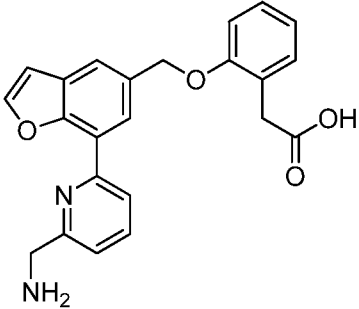
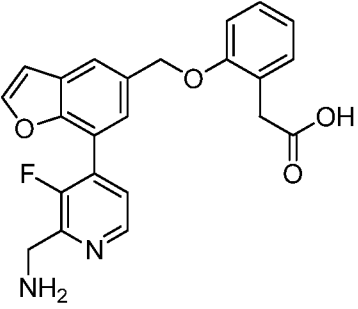
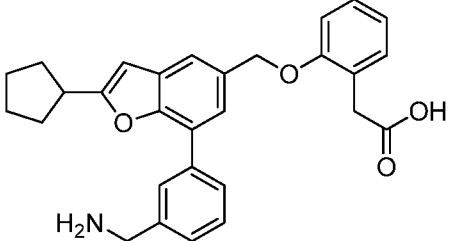
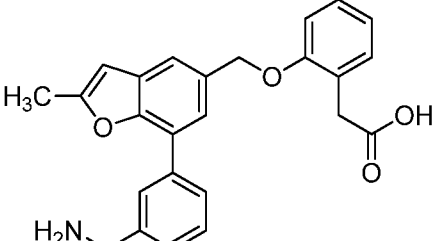
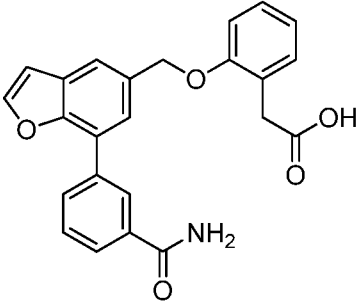
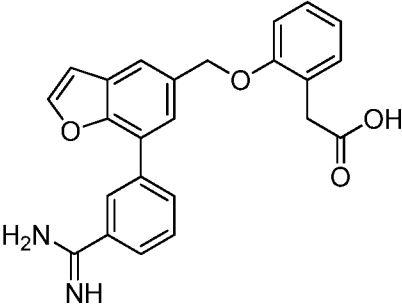
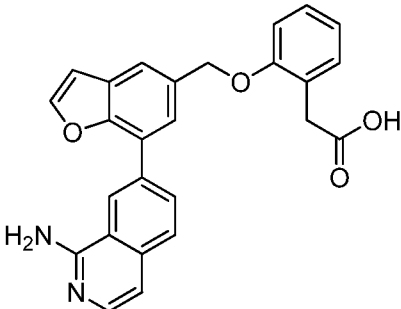
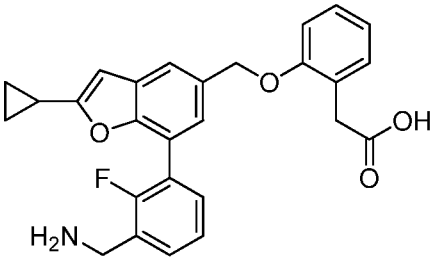
U is N or CR^3 ;

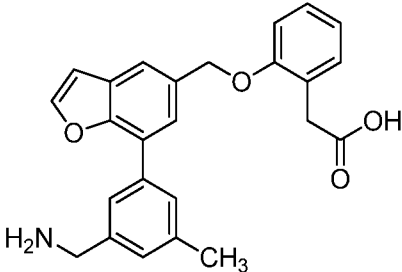
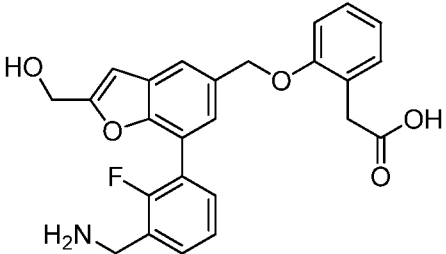
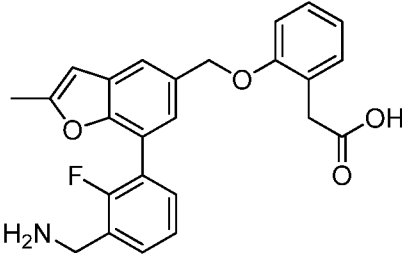
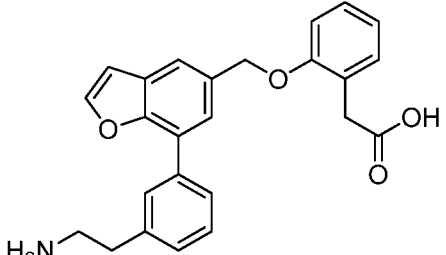
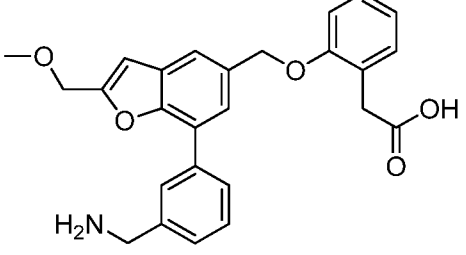
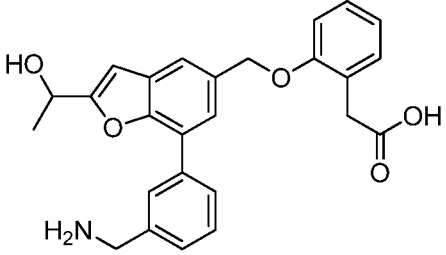
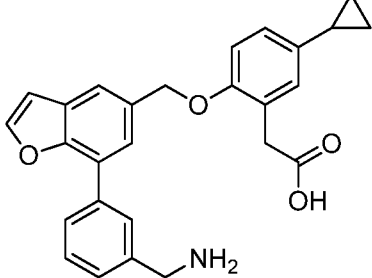
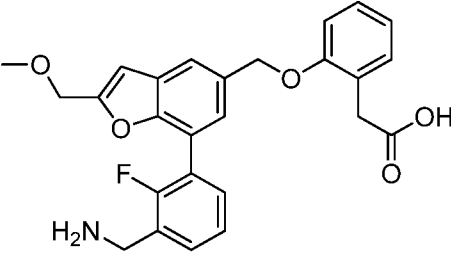
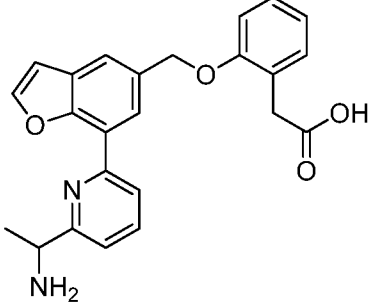
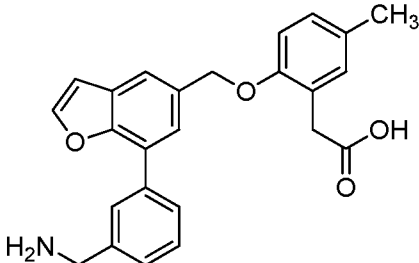
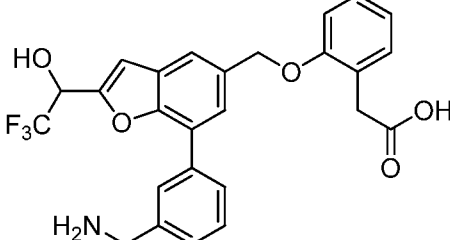
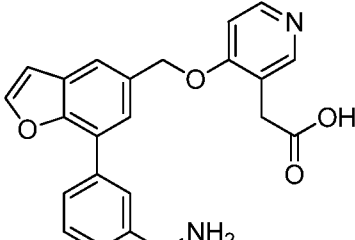
R^3 is H, halogen, alkyl, alkoxy, or haloalkyl; and

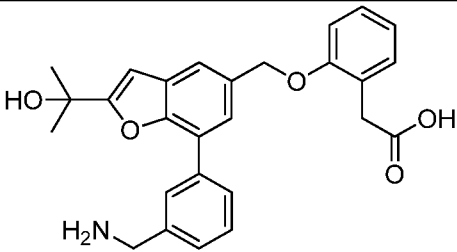
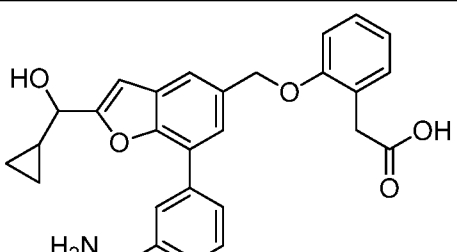
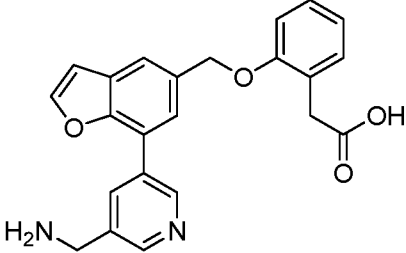
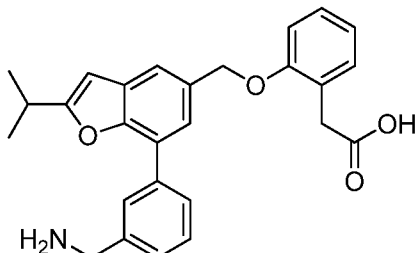
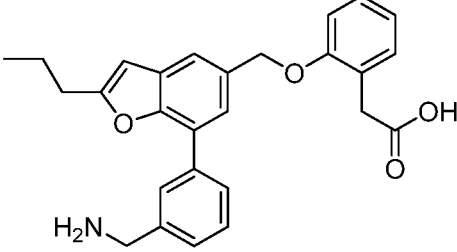
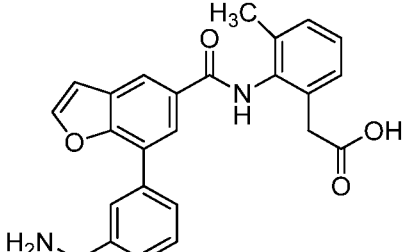
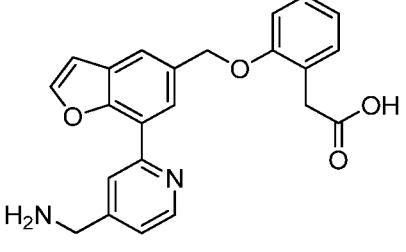
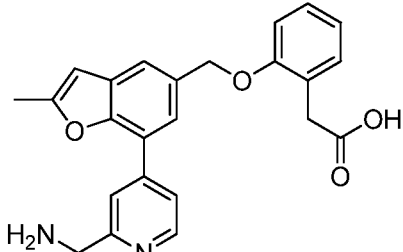
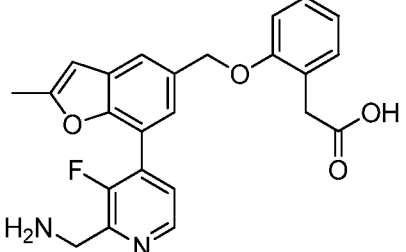
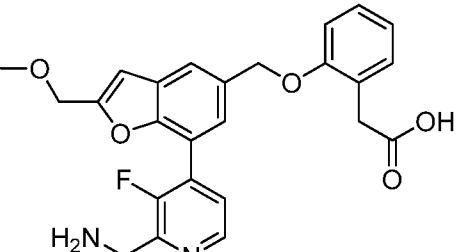
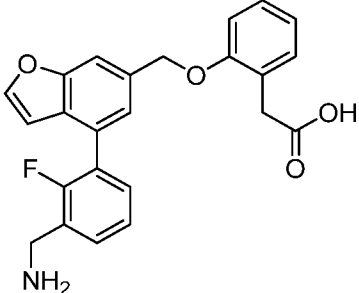
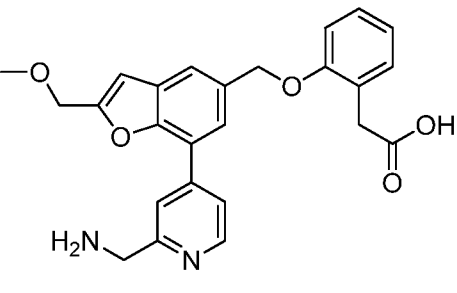
V is N or CH.

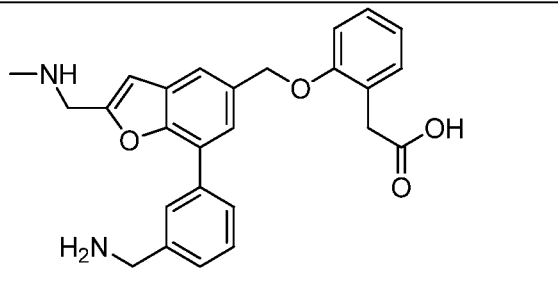
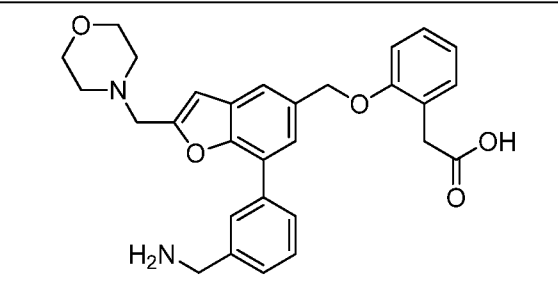
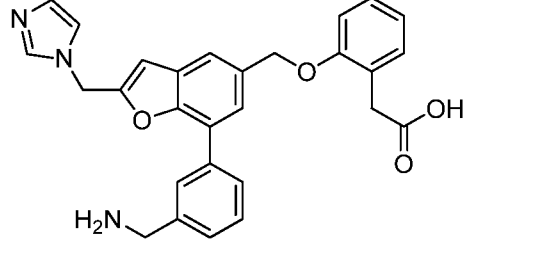
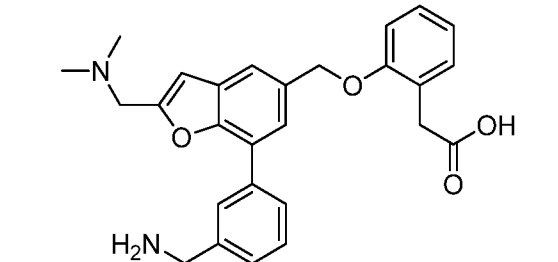
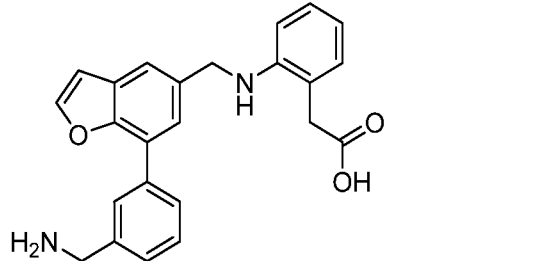
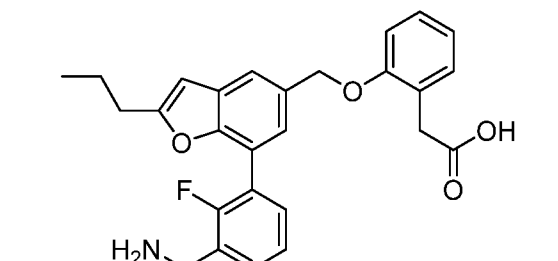
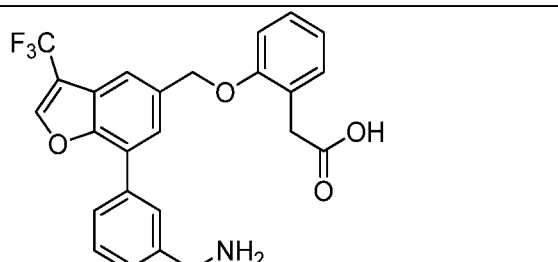
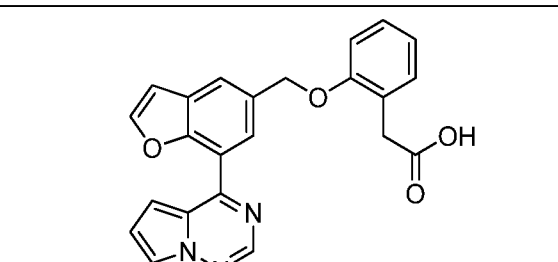
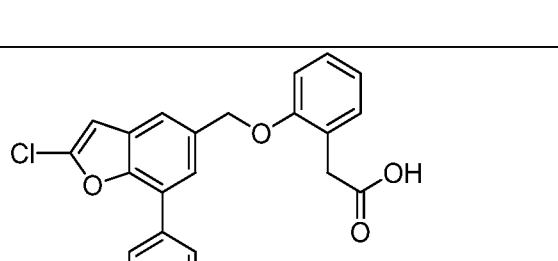
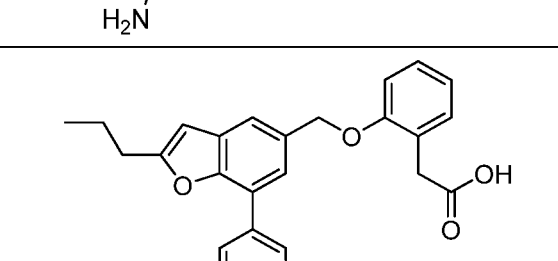
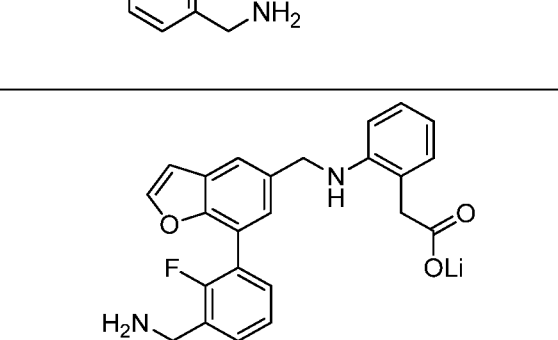
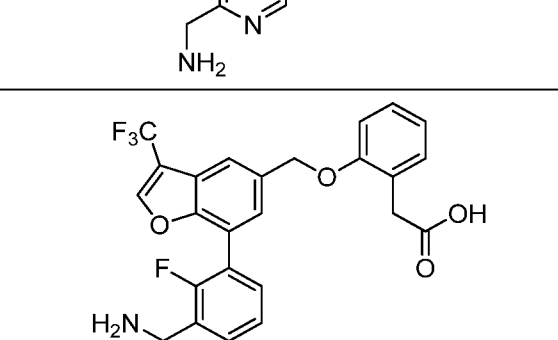
In certain embodiments, the compound of formula (I) is selected from the following table of compounds, and pharmaceutically acceptable salts and prodrugs thereof:

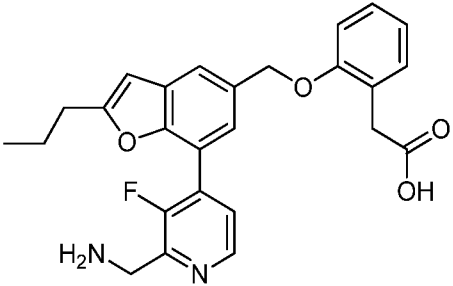
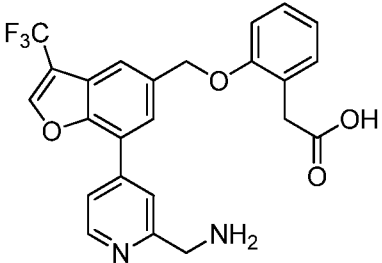
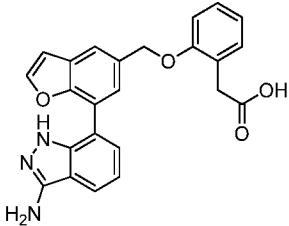
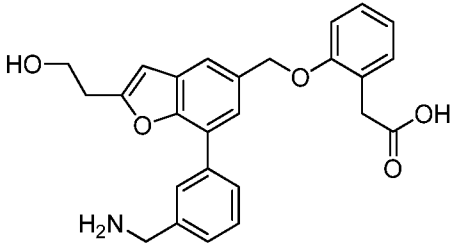
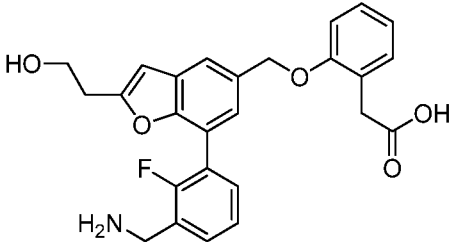
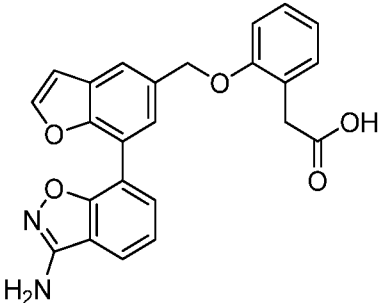
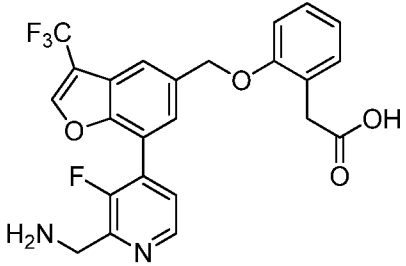
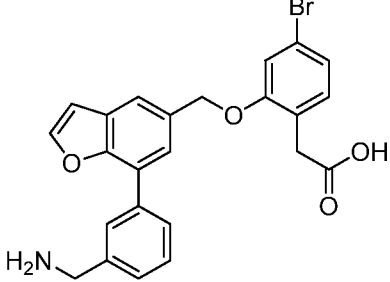
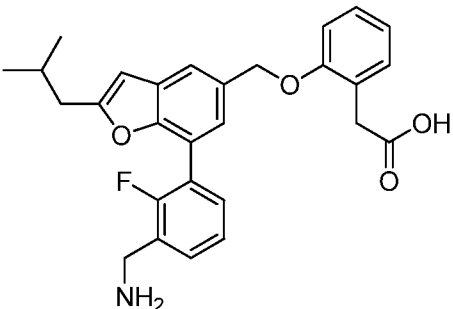
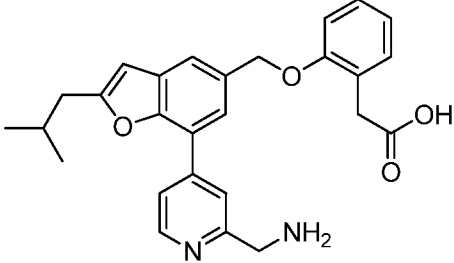
	
	
	
	
	

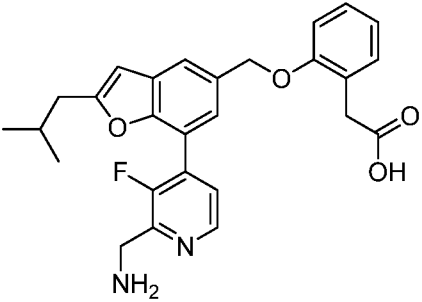
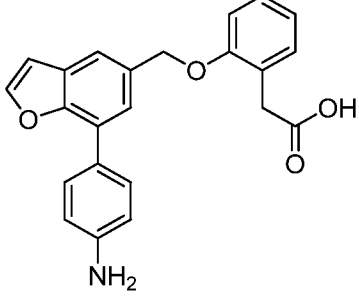
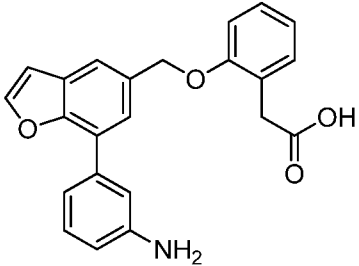
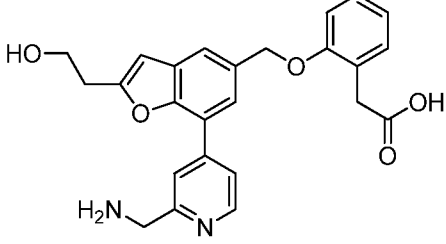
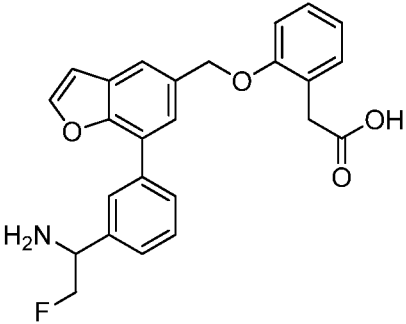
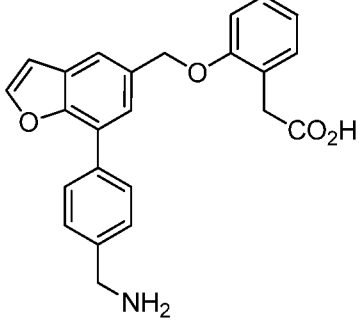
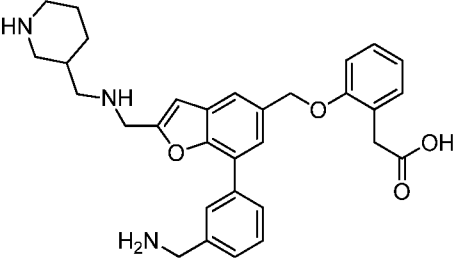
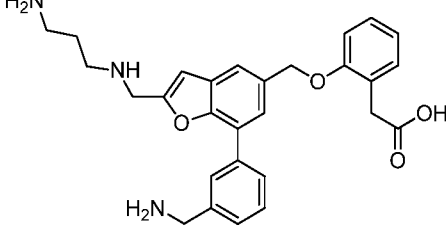
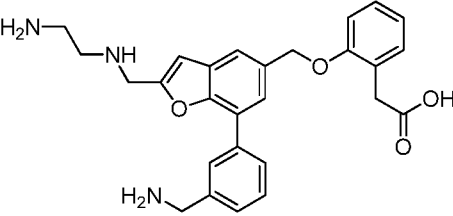
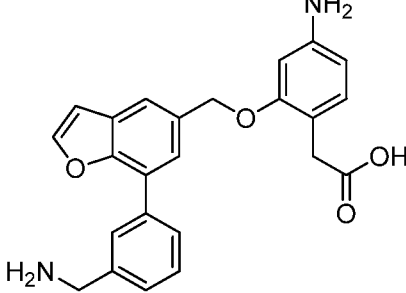
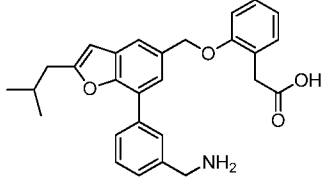
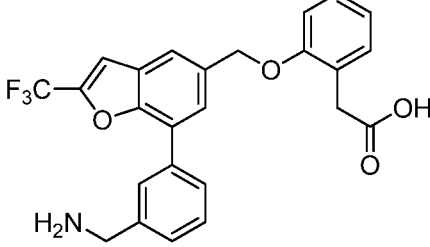
	
	
	
	
	

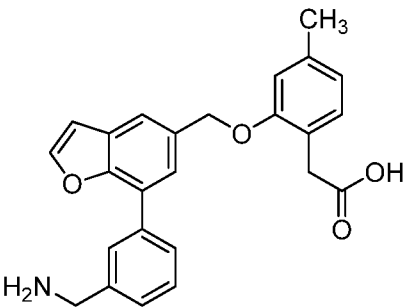
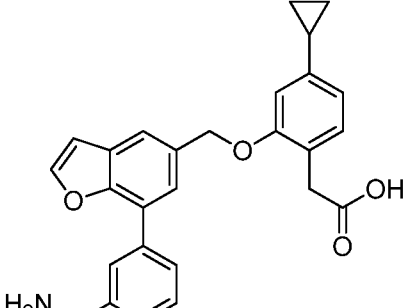
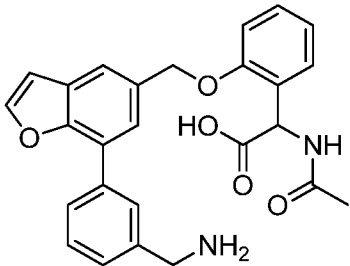
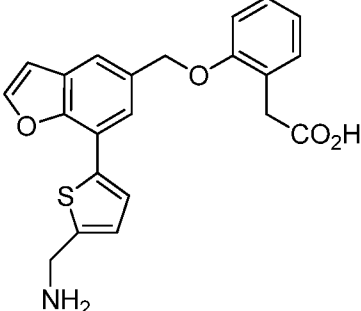
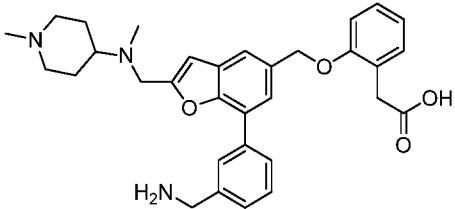
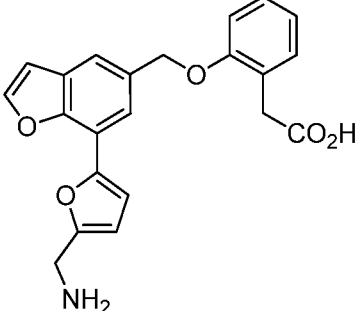
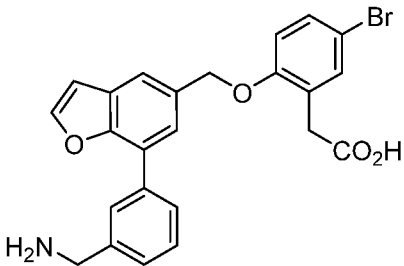
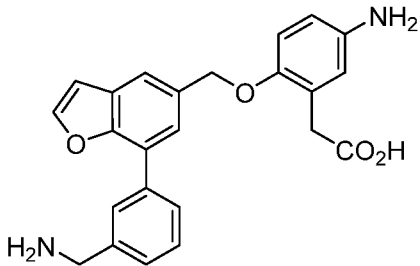
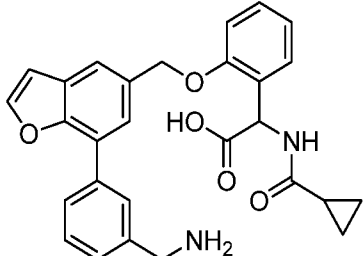
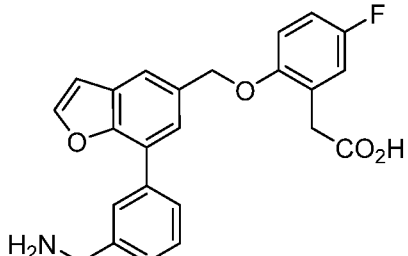
	
	
	
	
	
	

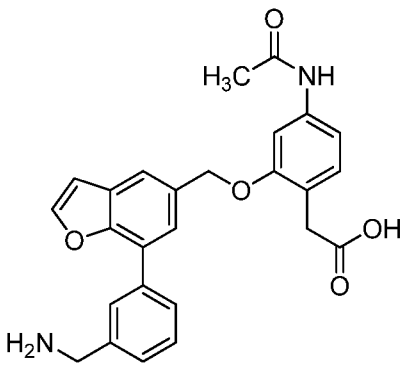
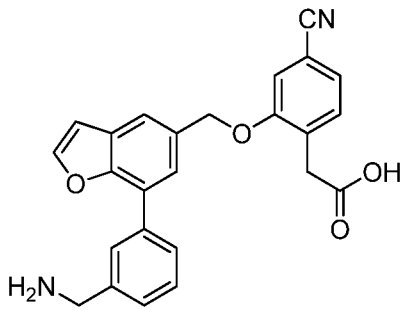
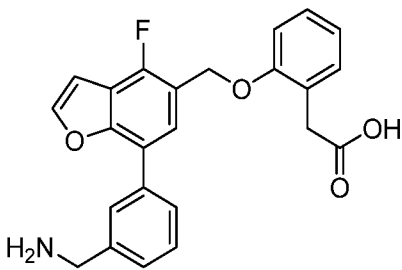
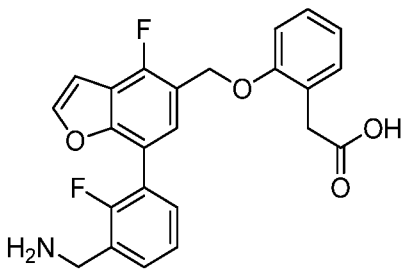
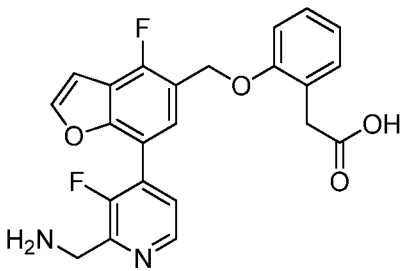
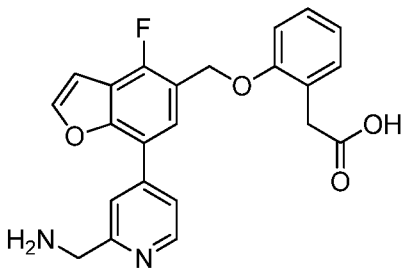
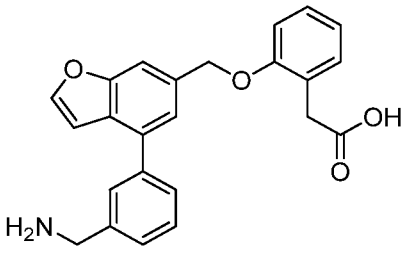
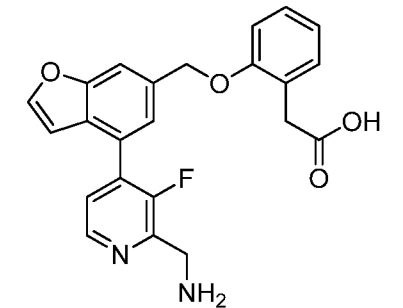
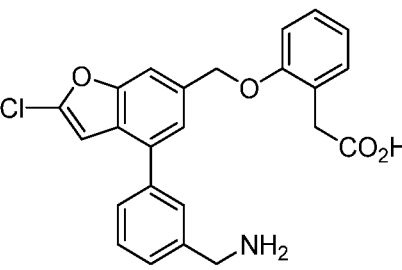
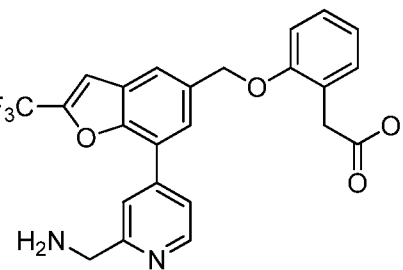
	
	
	
	
	
	

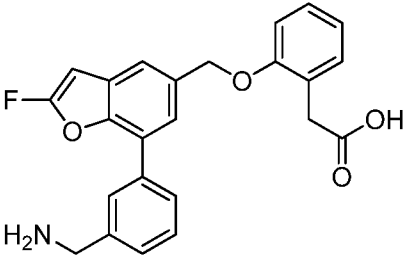
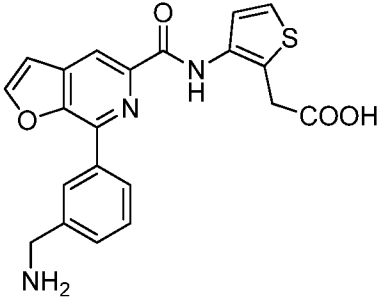
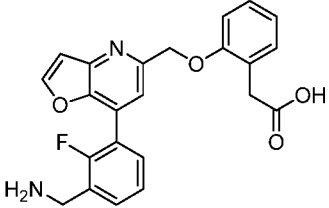
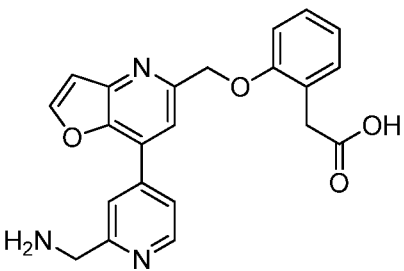
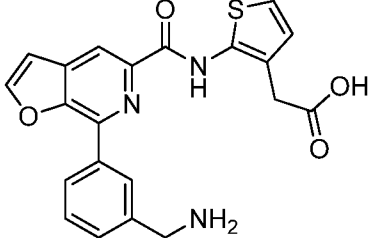
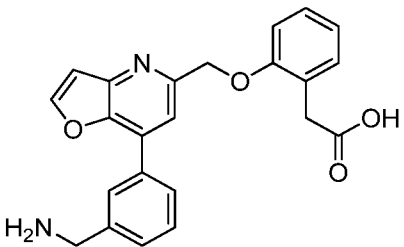
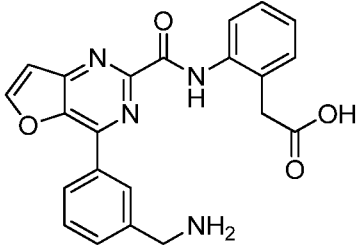
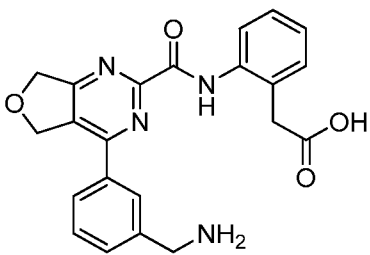
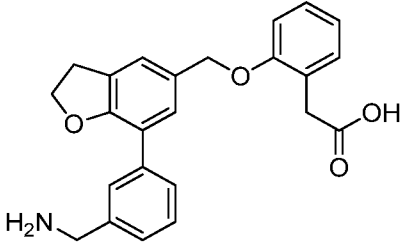
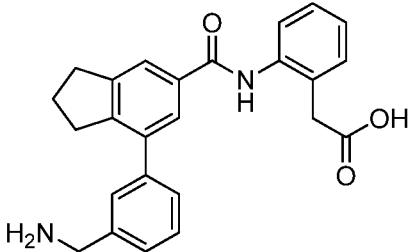
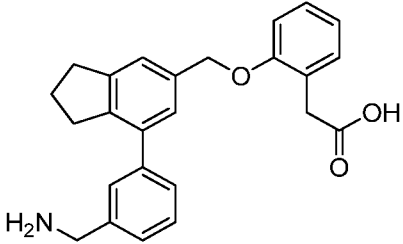
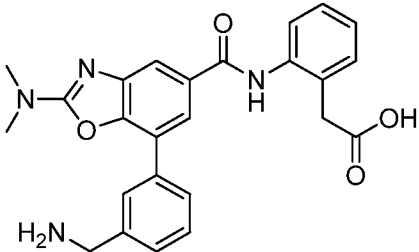
	
	
	
	
	
	

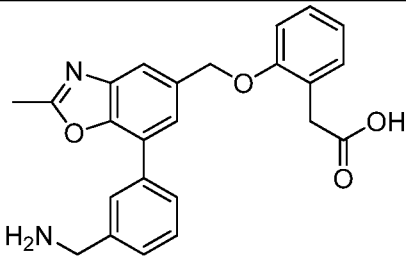
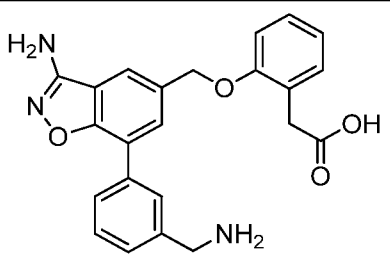
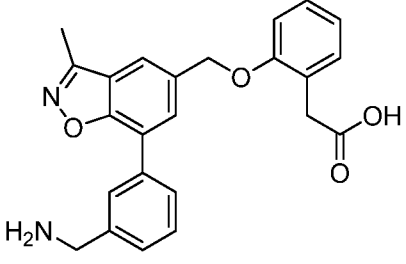
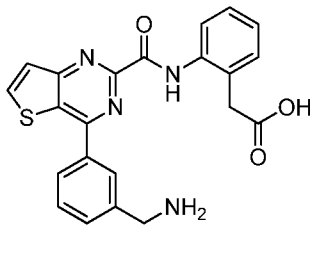
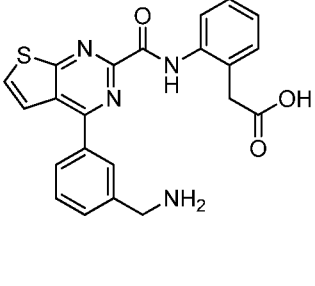
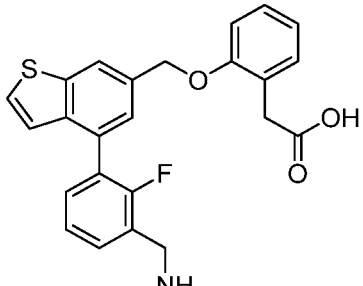
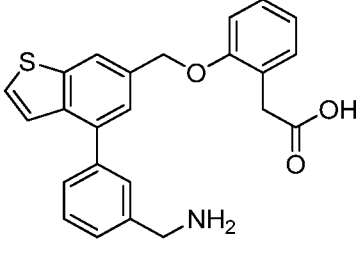
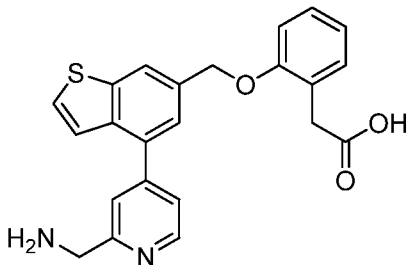
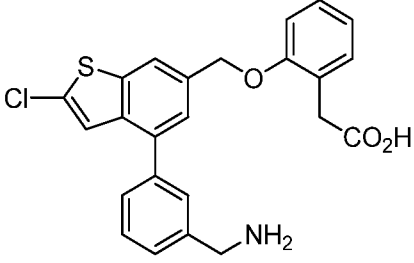
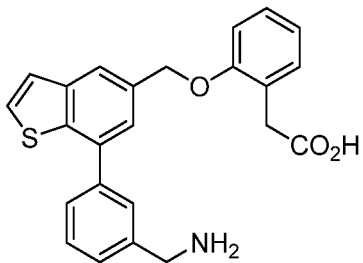
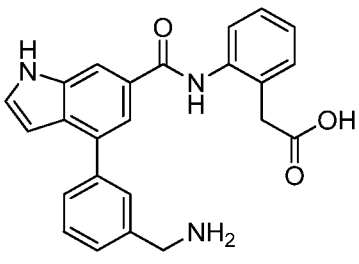
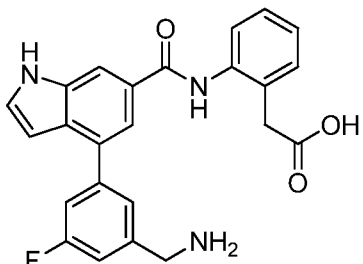
	
	
	
	
	

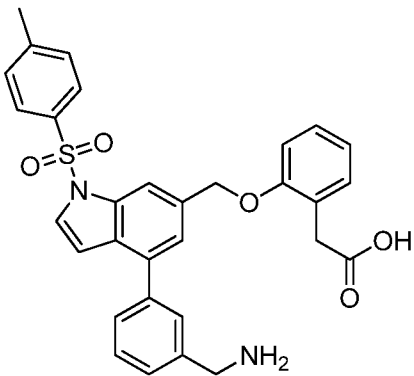
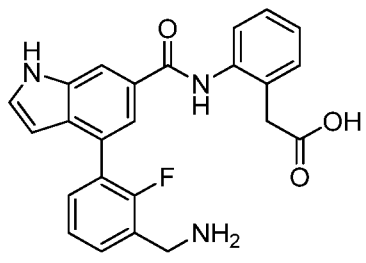
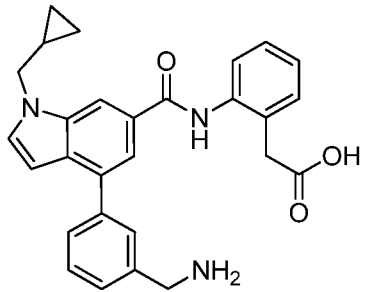
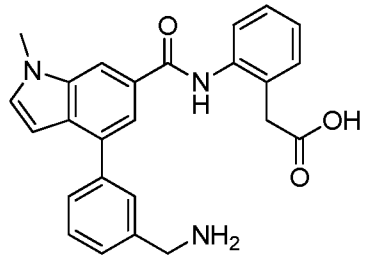
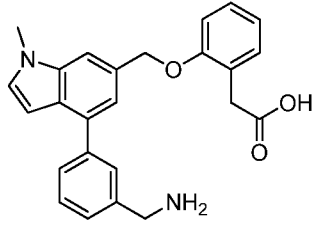
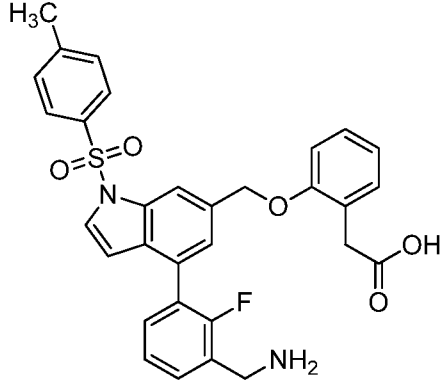
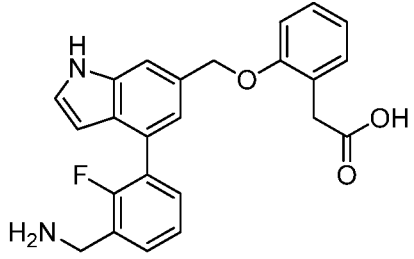
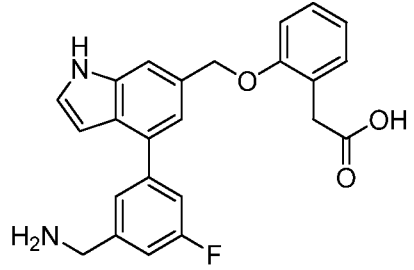
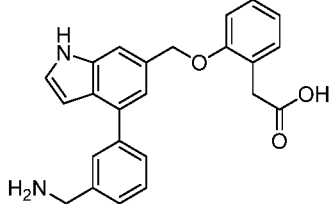
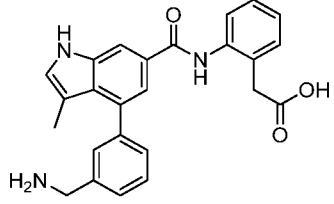
	
	
	
	
	
	

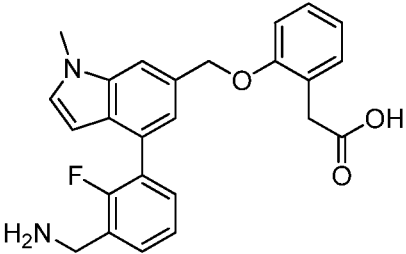
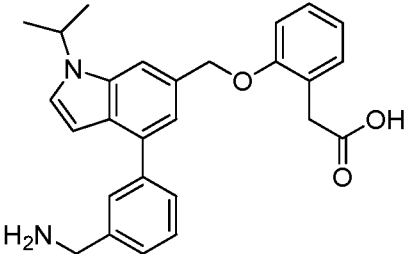
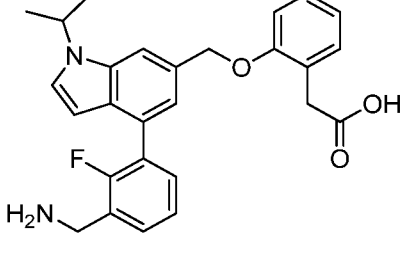
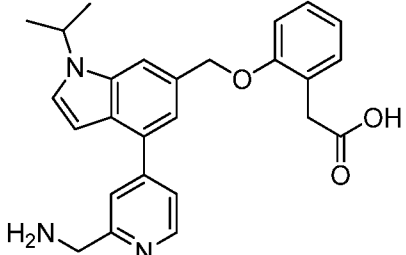
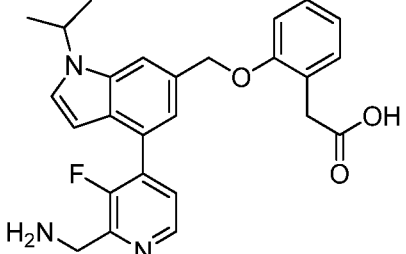
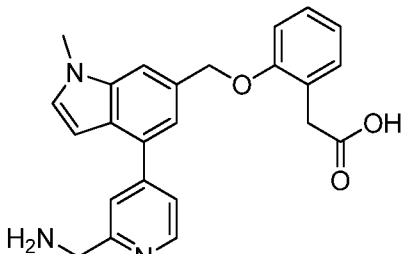
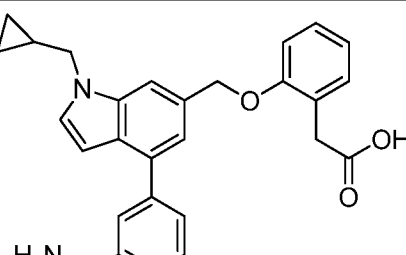
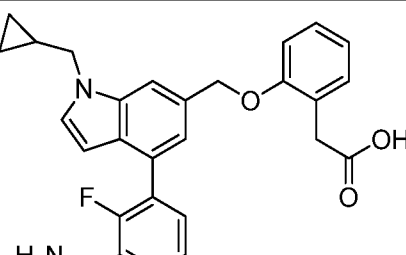
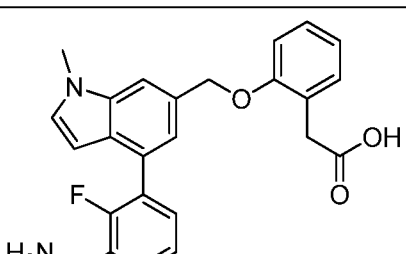
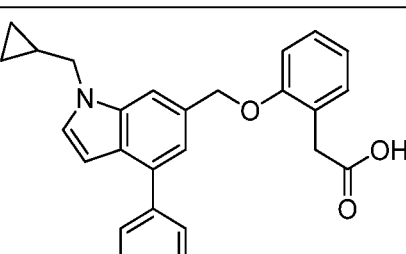
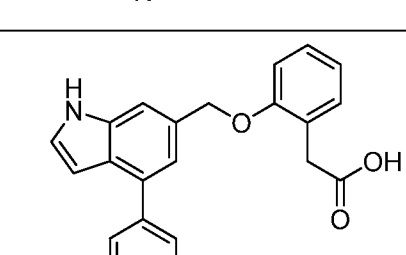
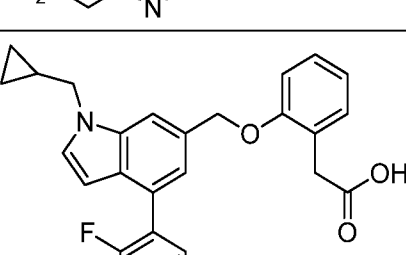
	
	
	
	
	

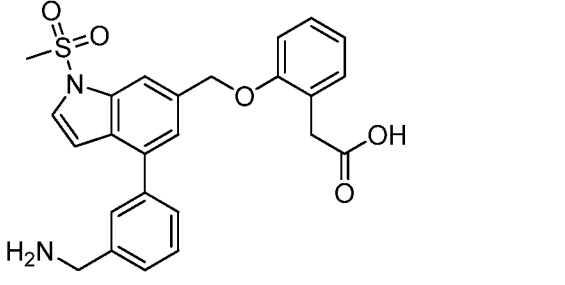
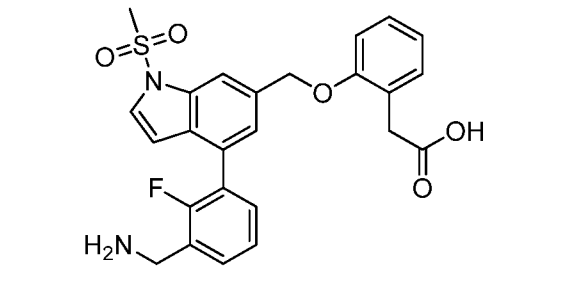
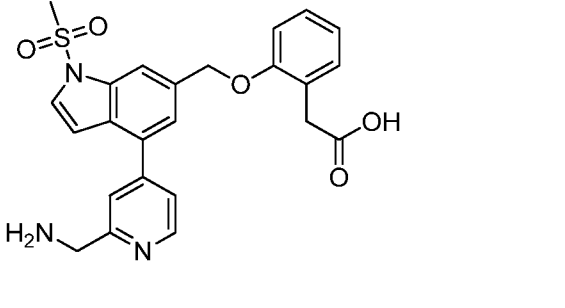
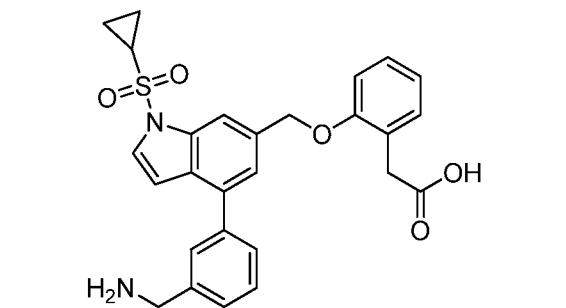
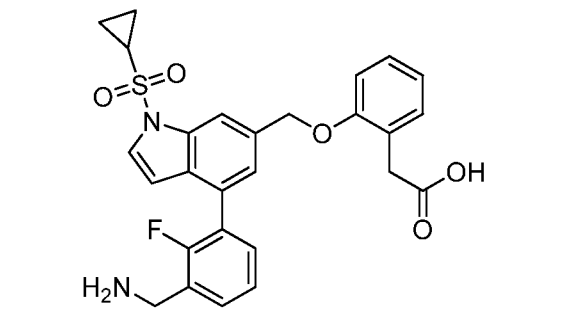
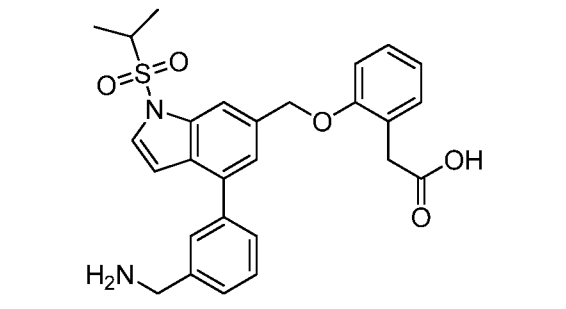
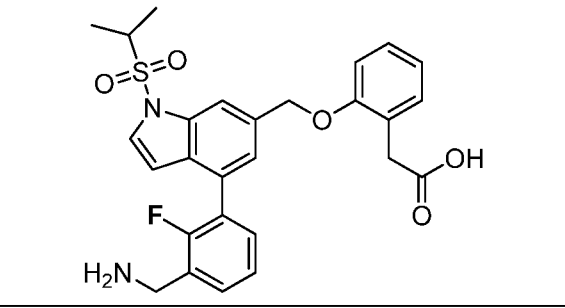
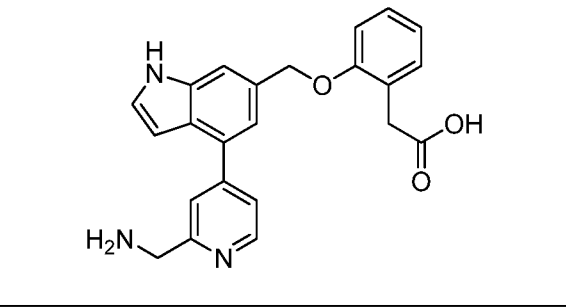
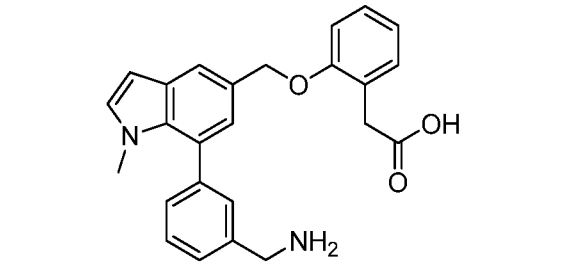
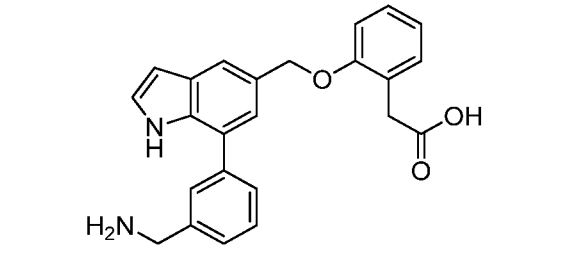
	
	
	
	
	

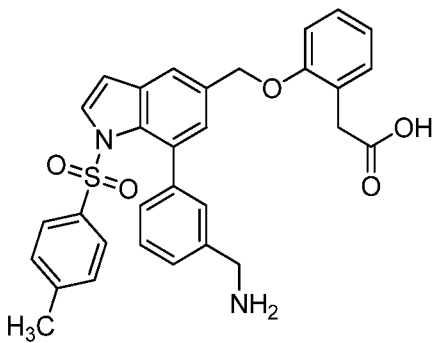
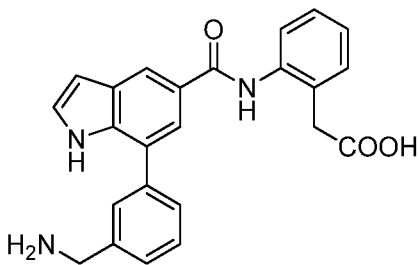
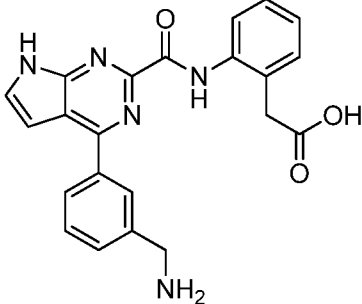
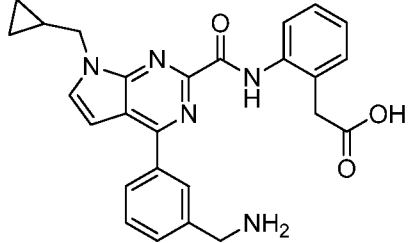
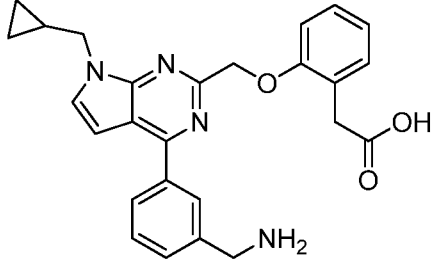
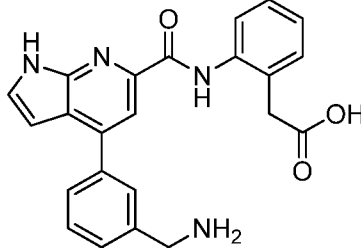
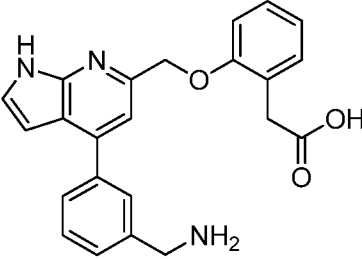
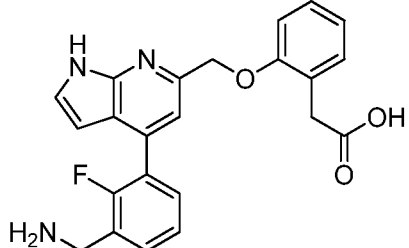
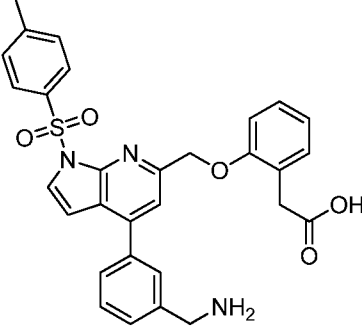
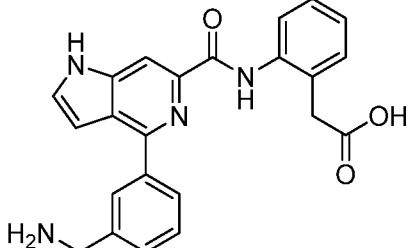
	
	
	
	
	
	

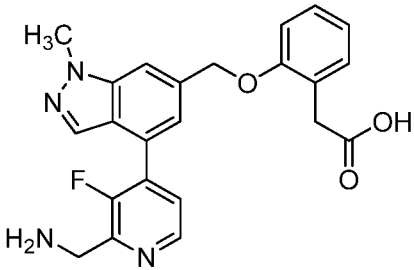
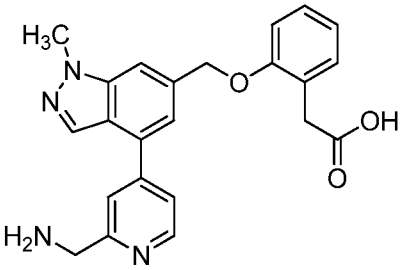
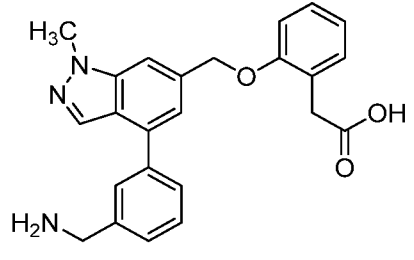
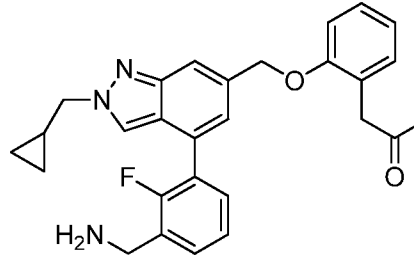
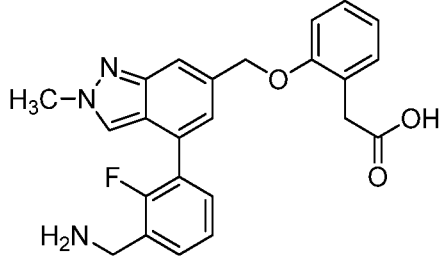
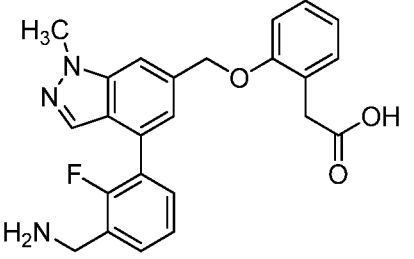
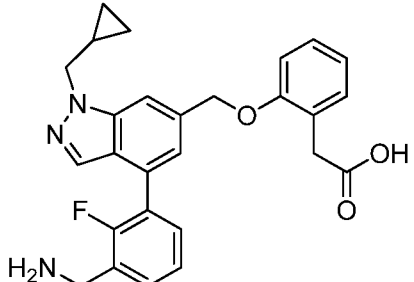
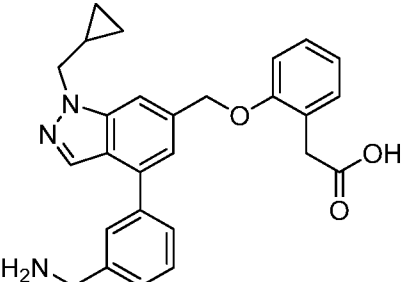
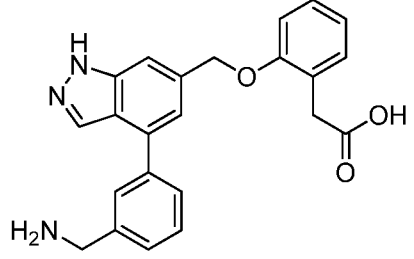
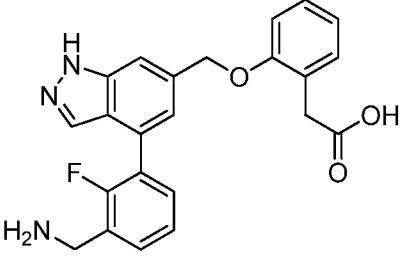
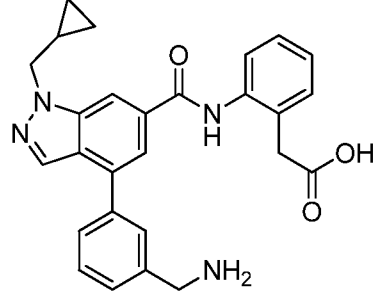
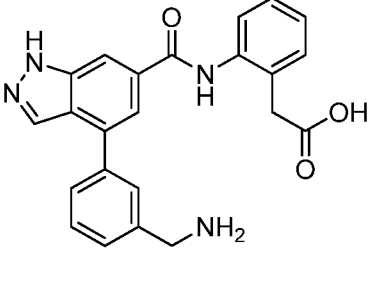
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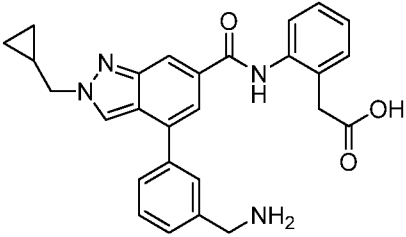
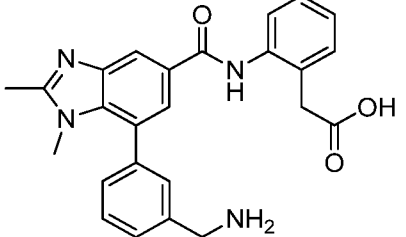
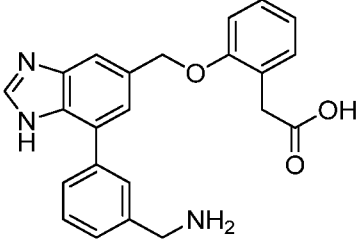
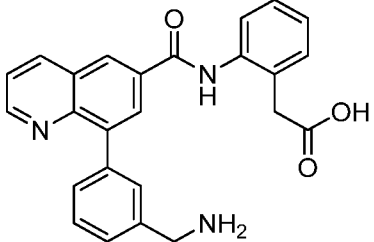
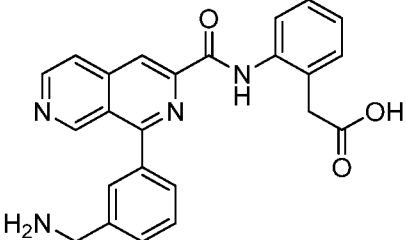
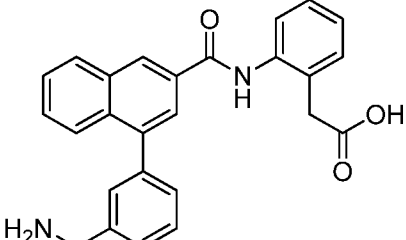
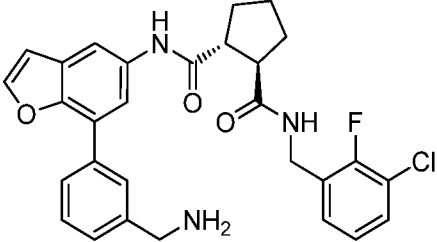
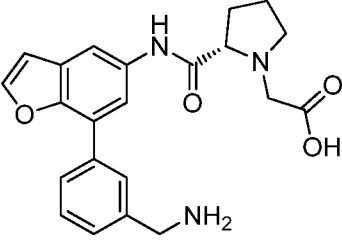
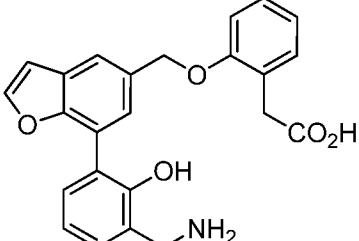
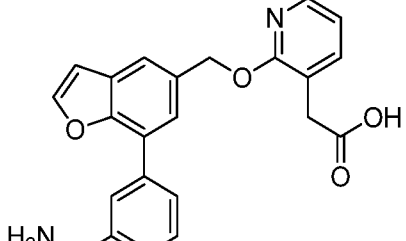
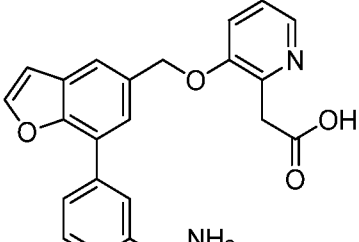
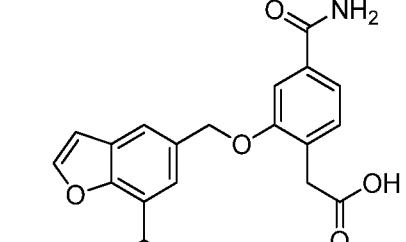
	
	
	
	
	

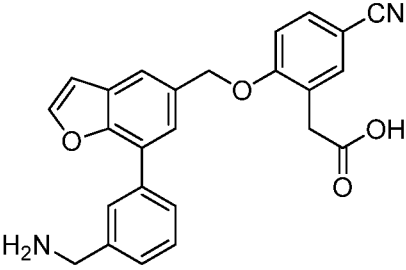
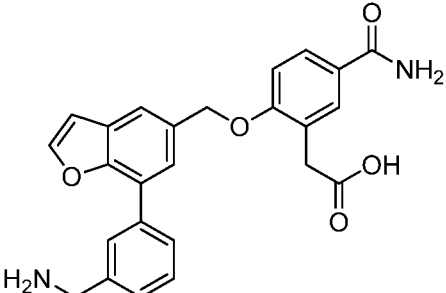
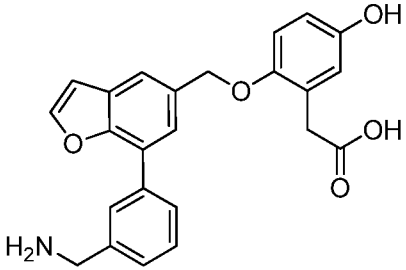
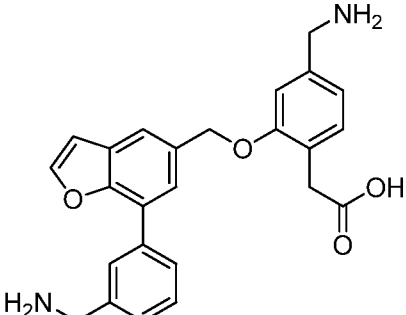
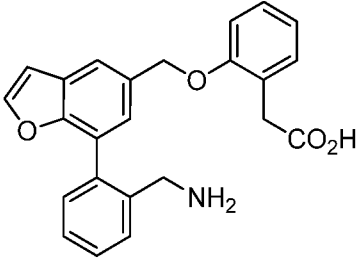
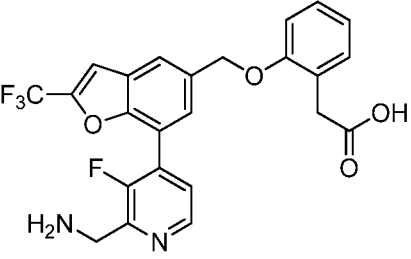
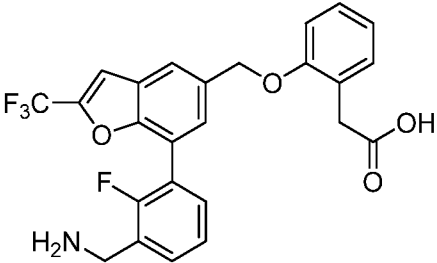
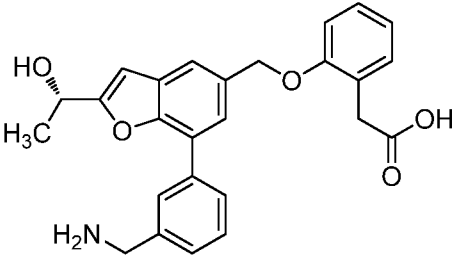
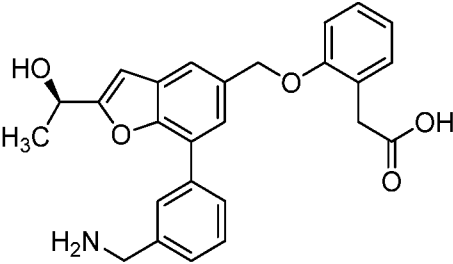
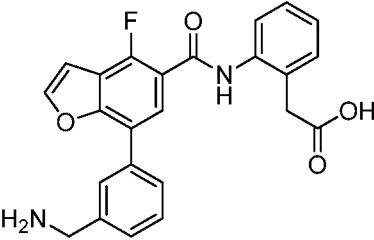
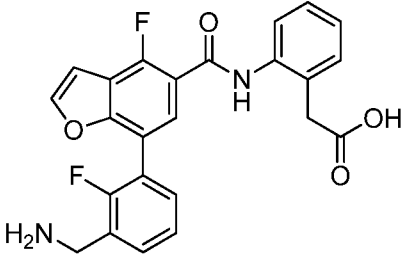
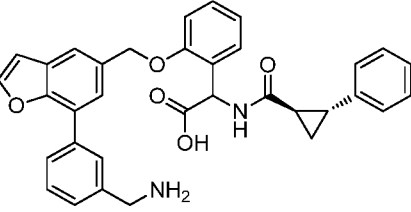
	
	
	
	
	
	

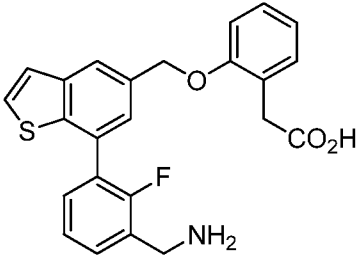
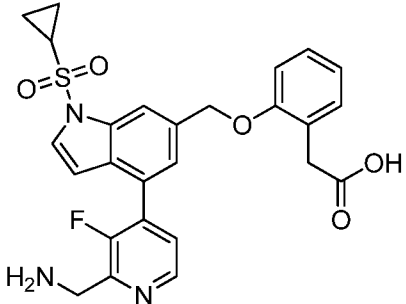
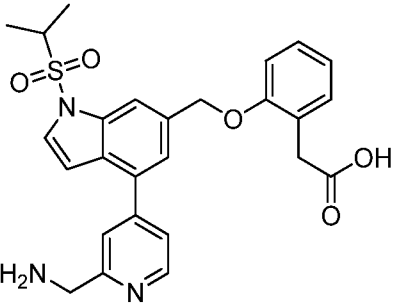
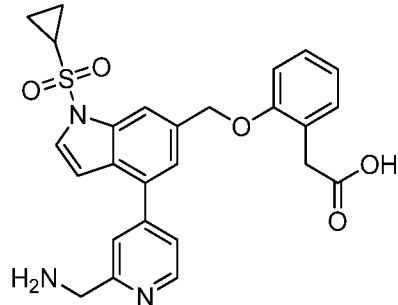
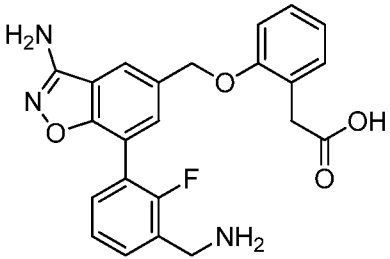
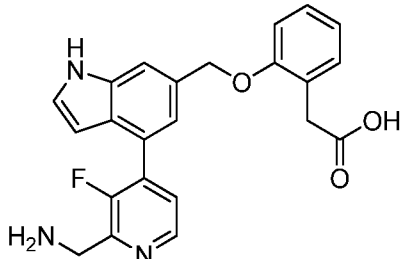
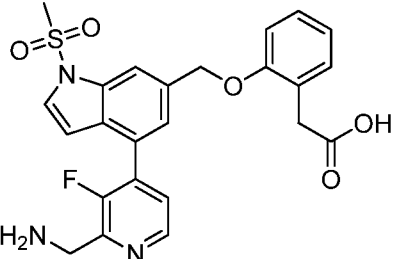
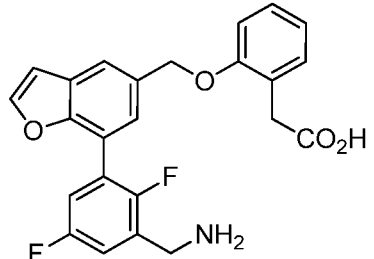
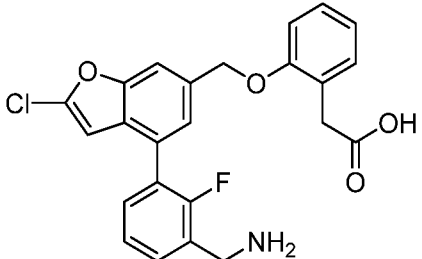
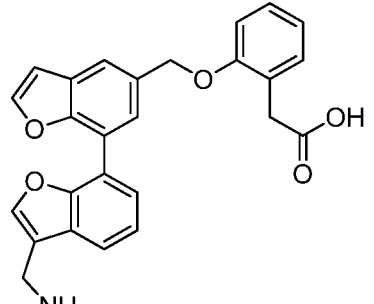
	
	
	
	
	

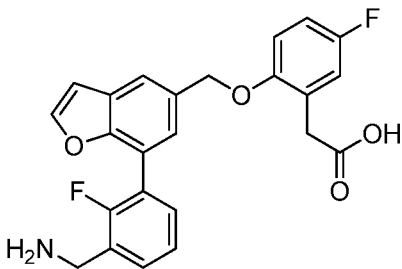
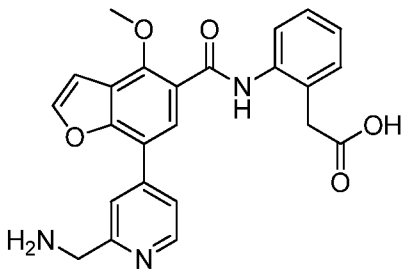
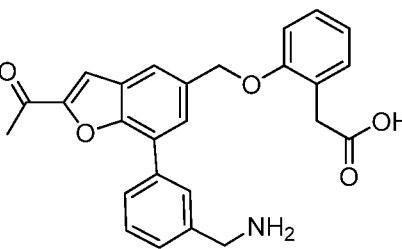
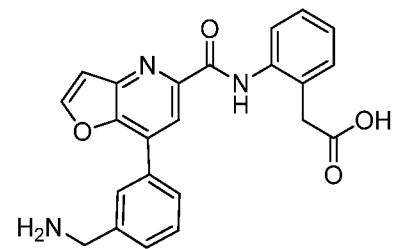
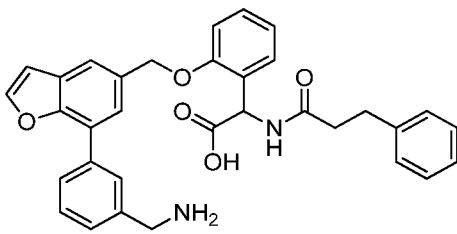
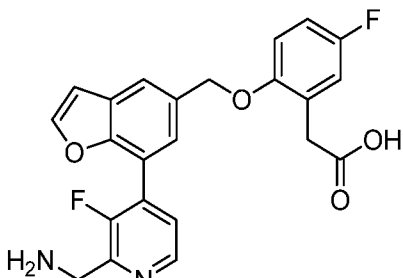
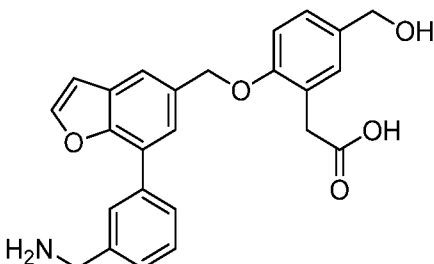
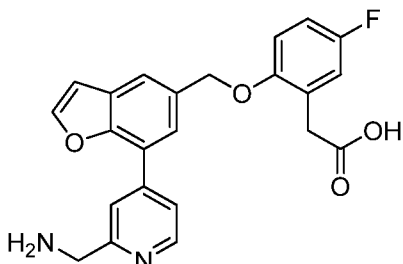
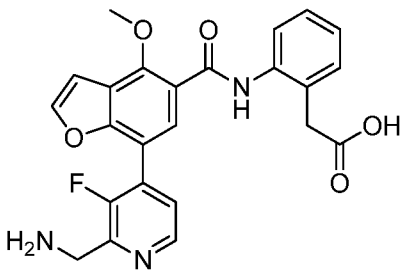
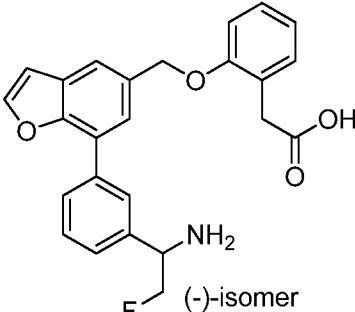
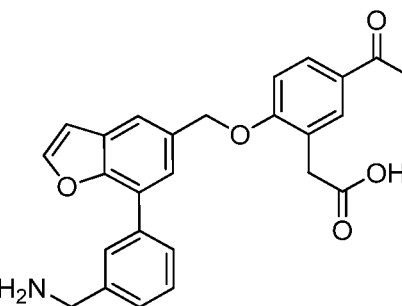
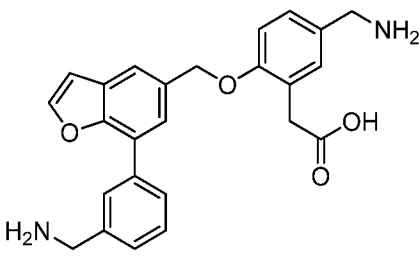
	
	
	
	
	

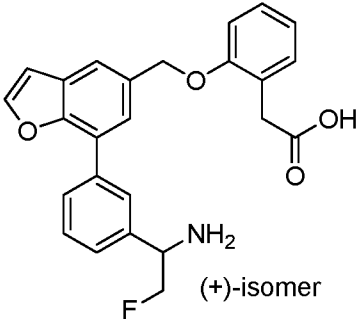
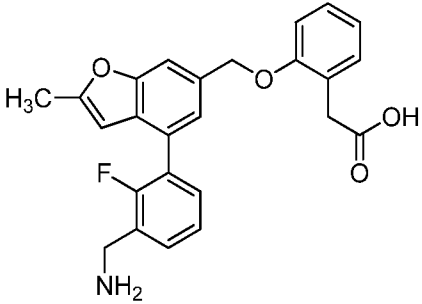
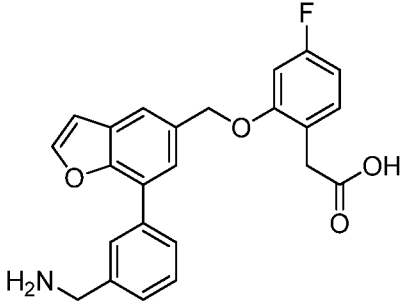
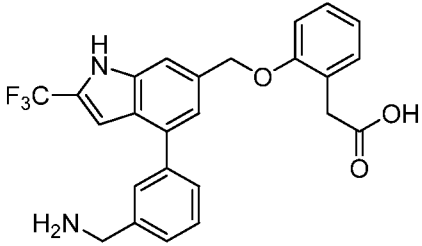
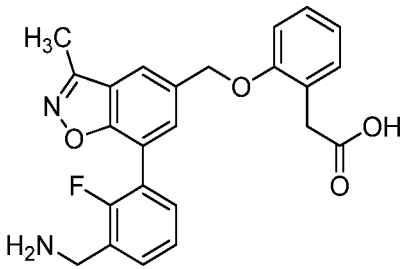
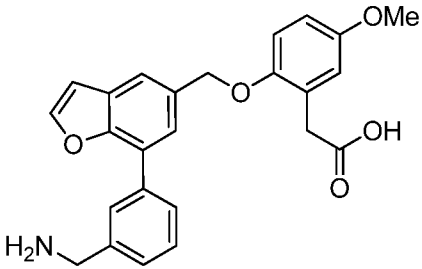
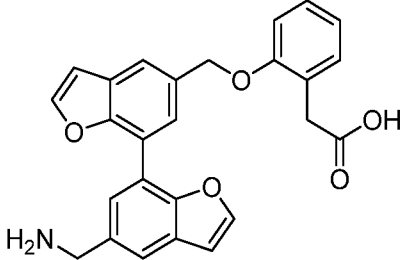
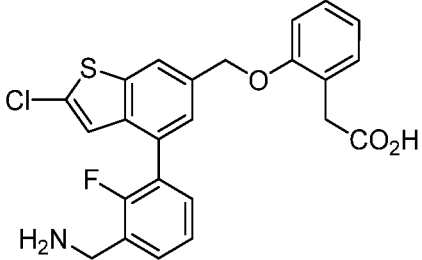
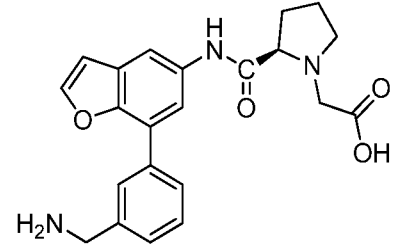
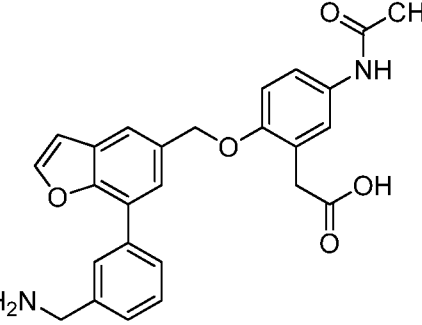
	
	
	
	
	
	

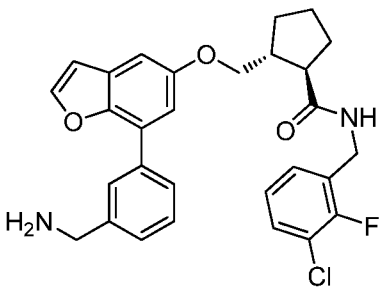
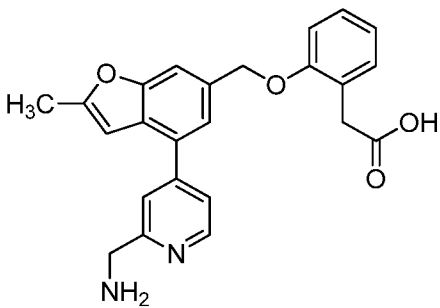
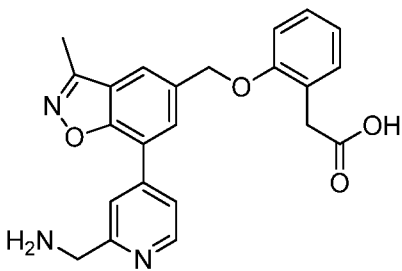
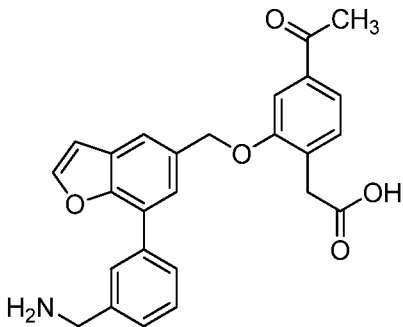
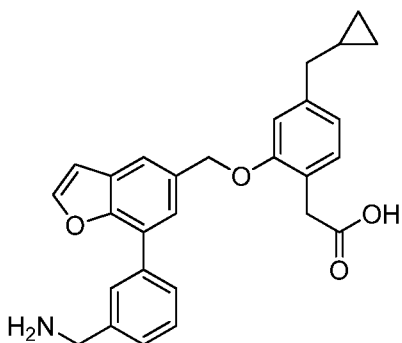
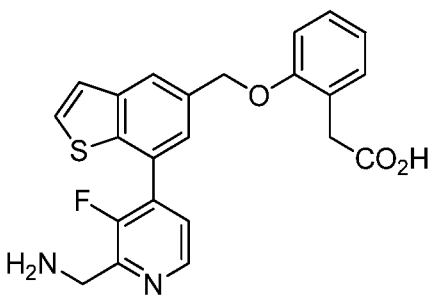
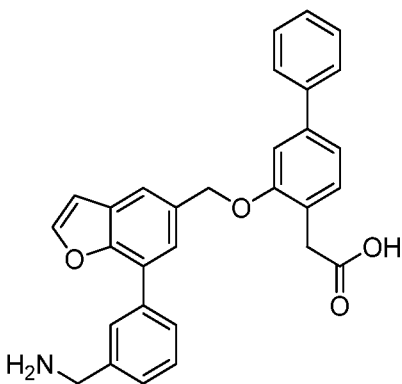
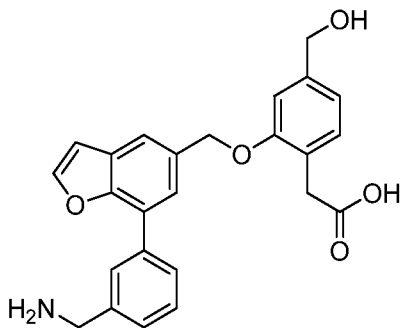
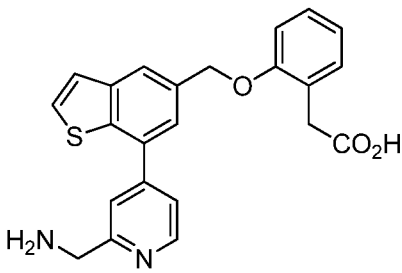
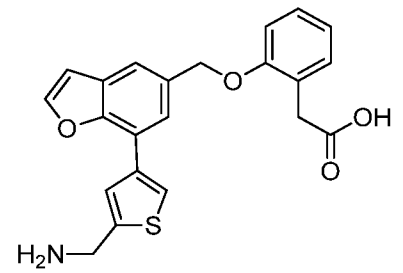
	
	
	
	
	
	

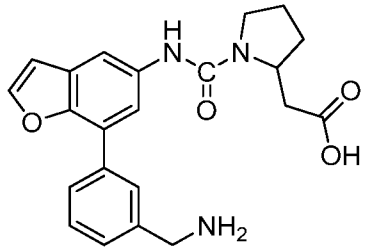
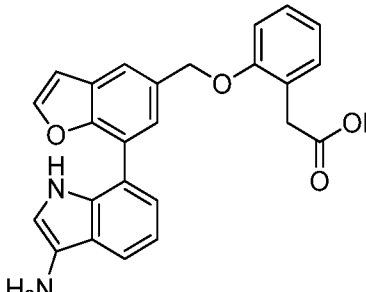
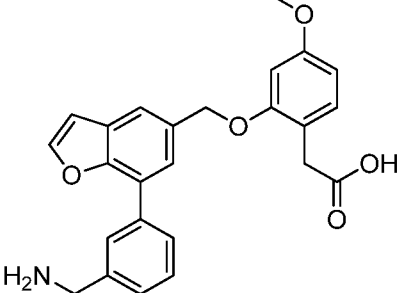
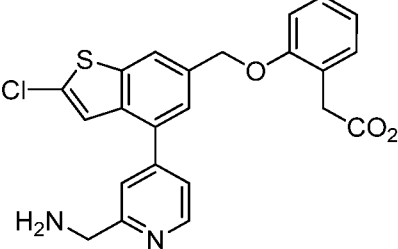
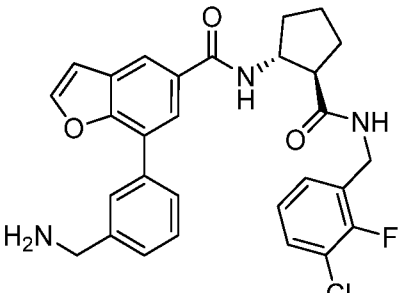
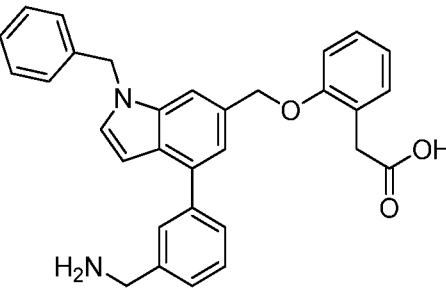
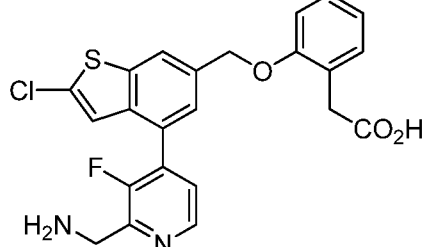
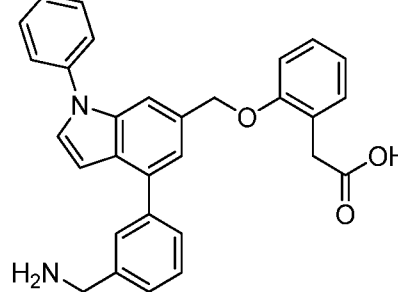
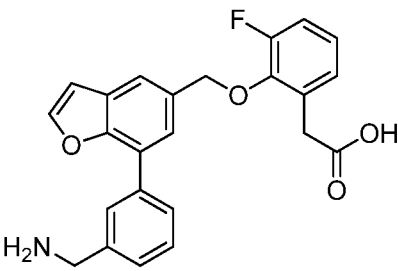
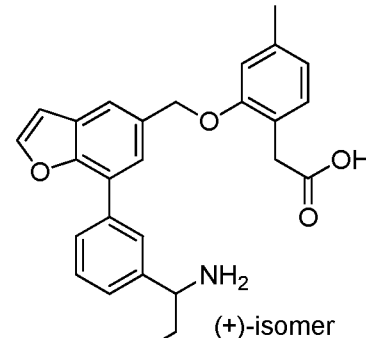
	
	
	
	
	
	

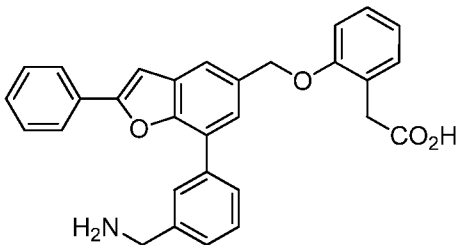
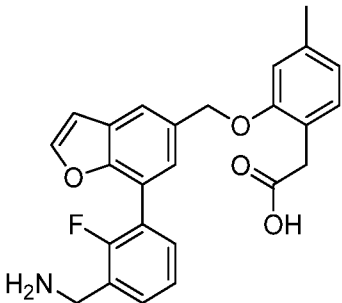
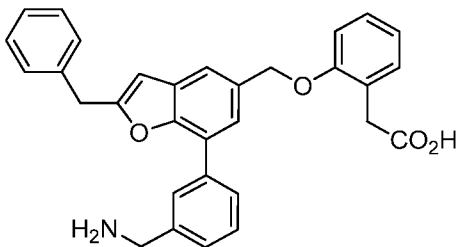
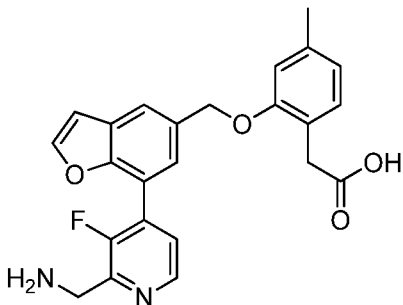
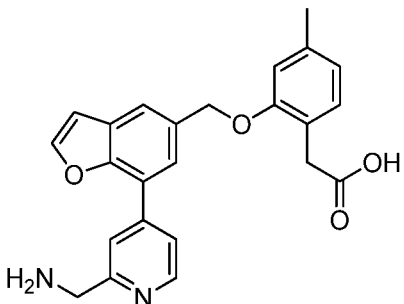
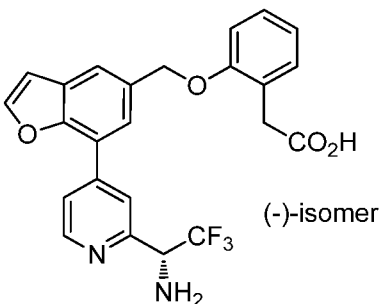
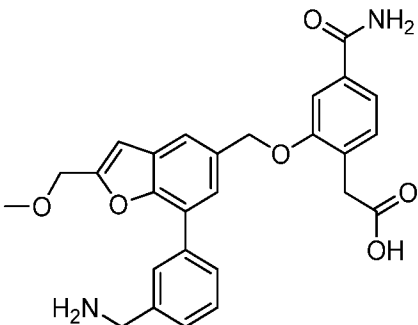
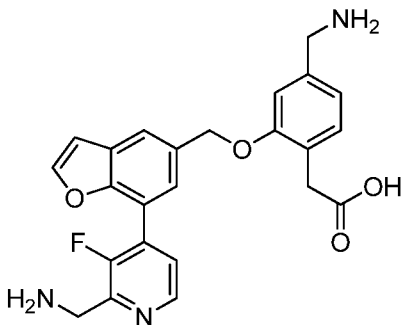
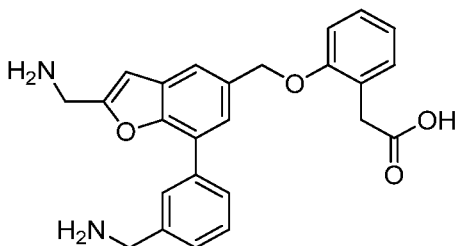
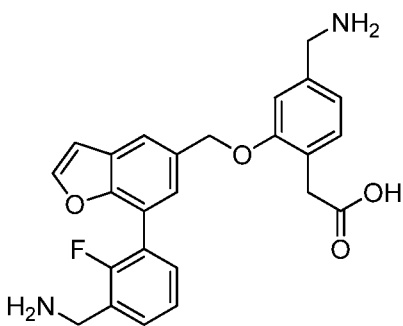
	
	
	
	
	

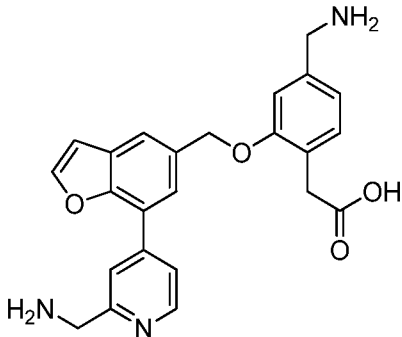
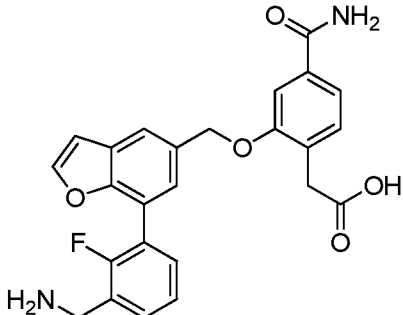
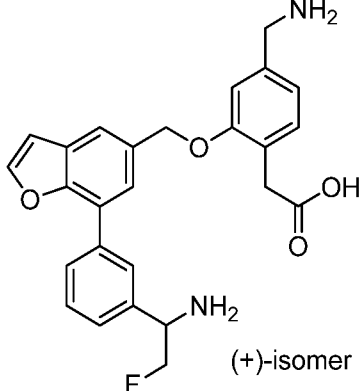
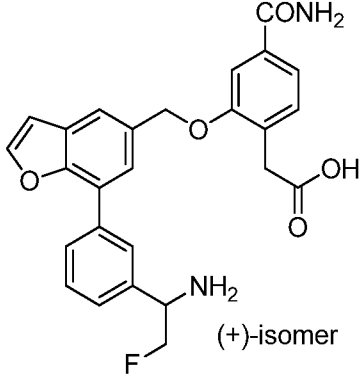
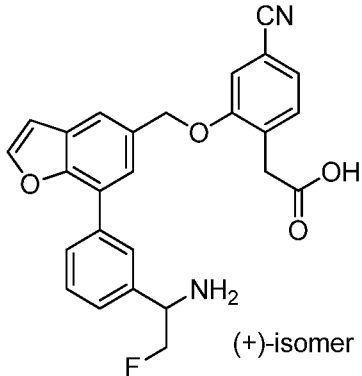
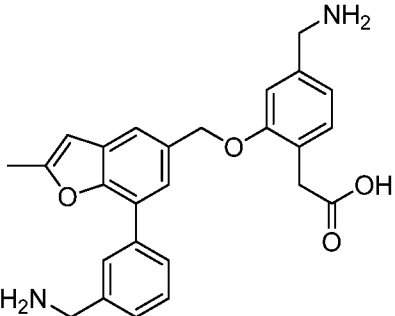
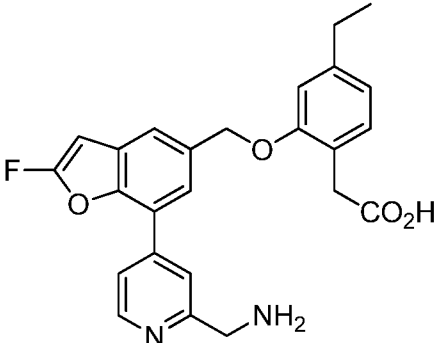
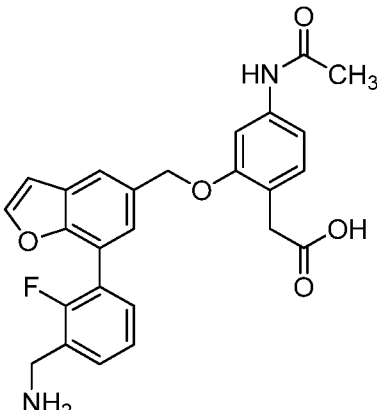
	
	
	
	
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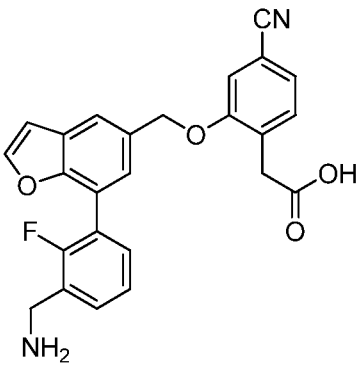
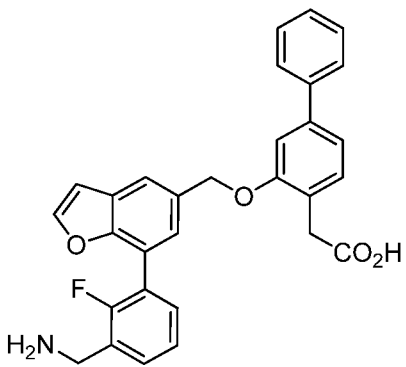
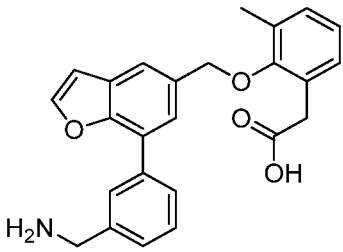
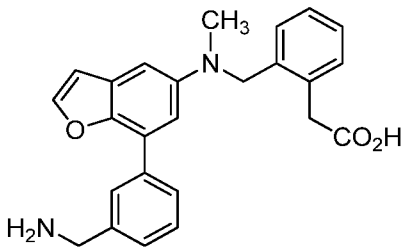
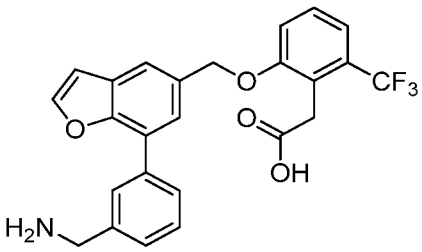
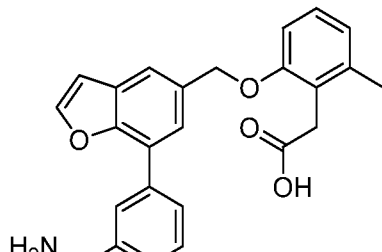
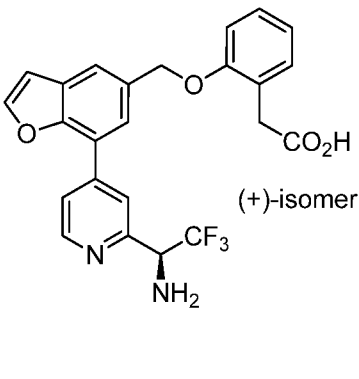
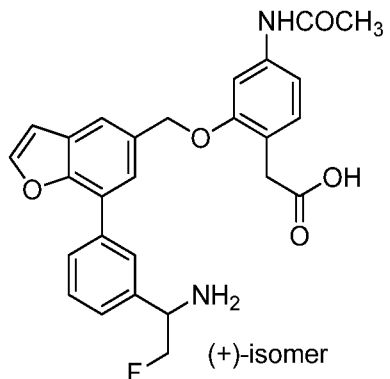
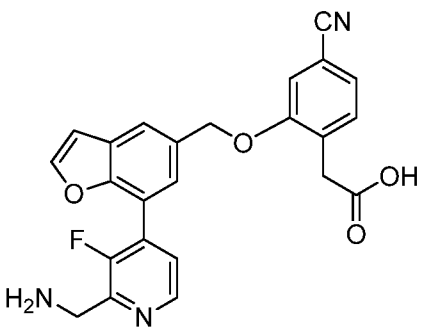
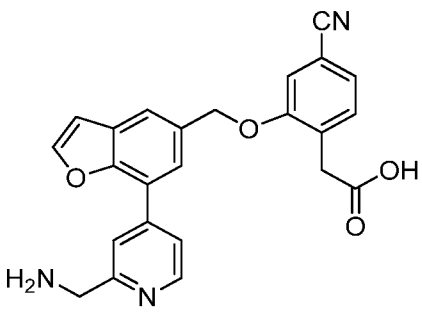
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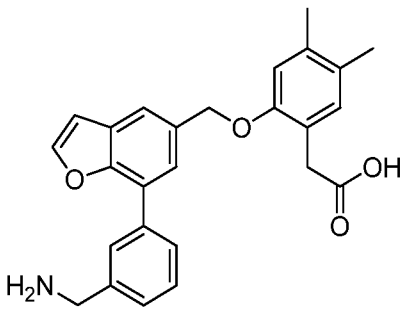
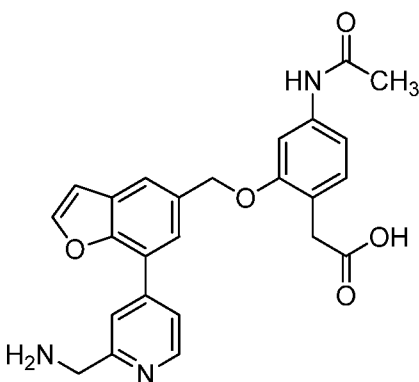
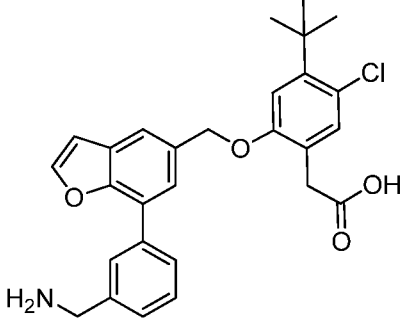
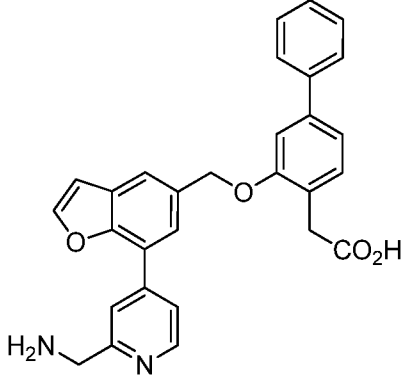
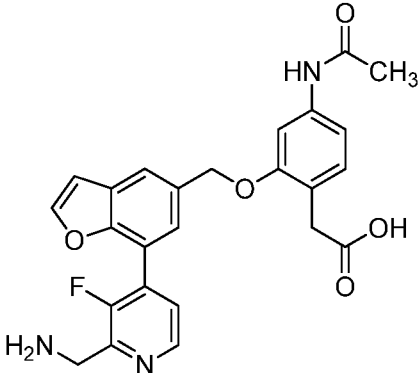
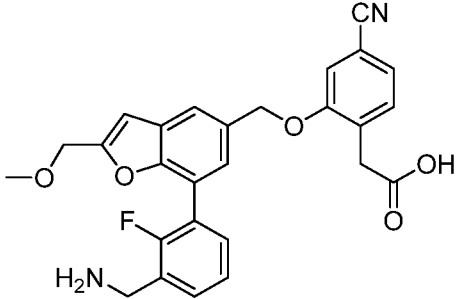
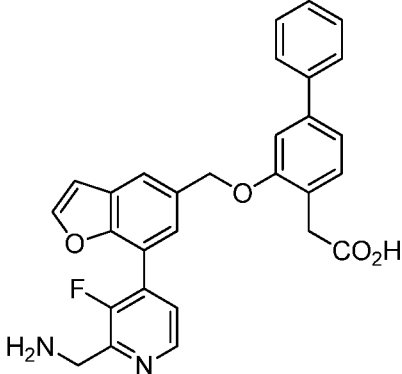
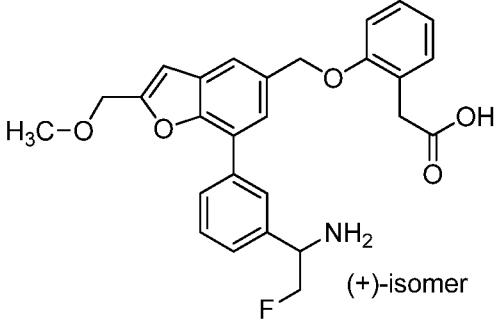
	
	
	
	
	

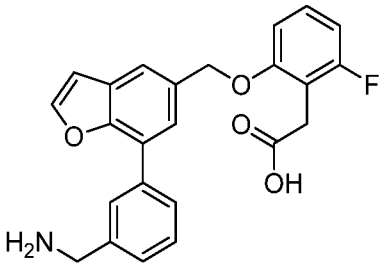
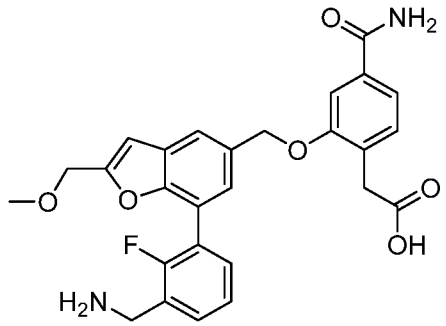
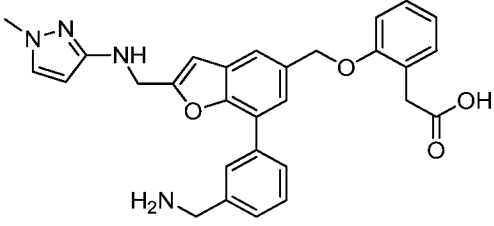
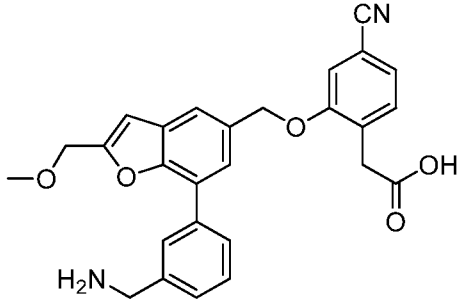
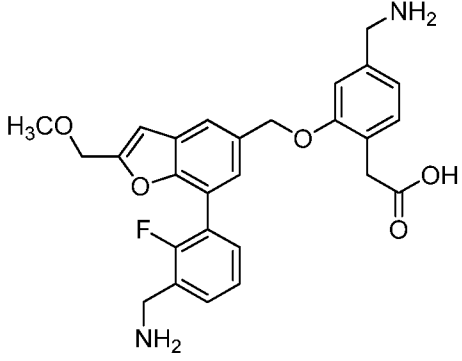
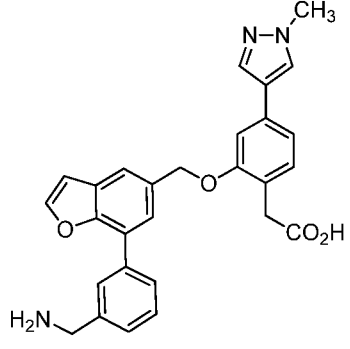
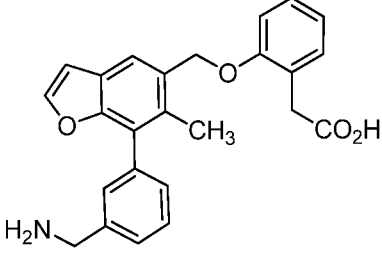
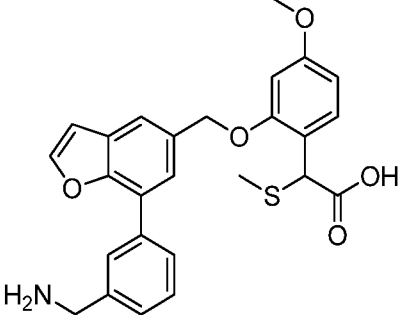
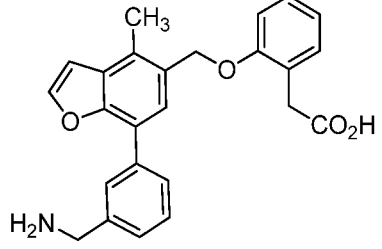
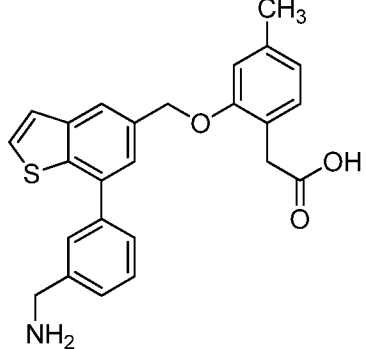
	
	
	
	
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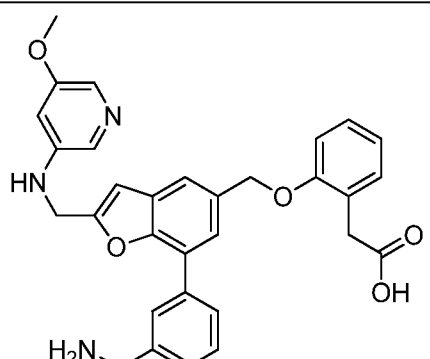
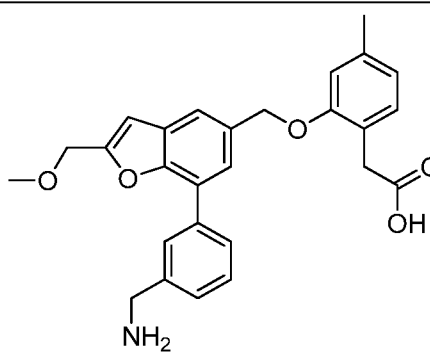
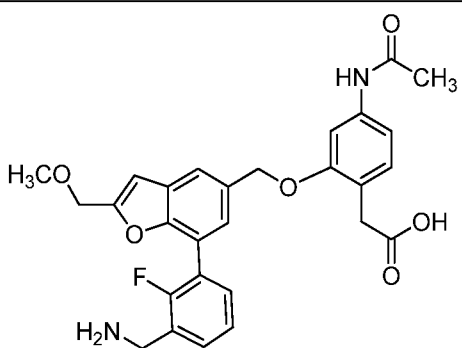
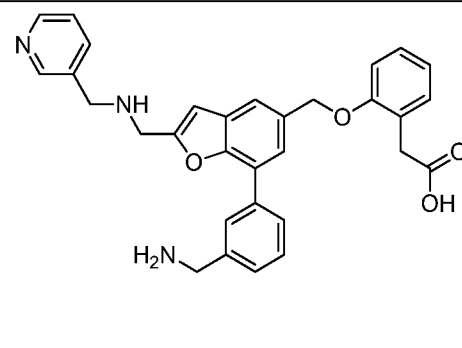
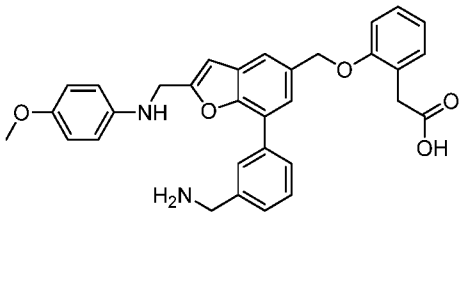
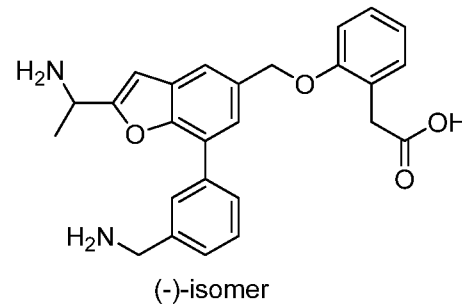
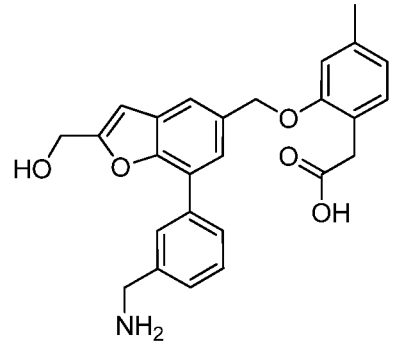
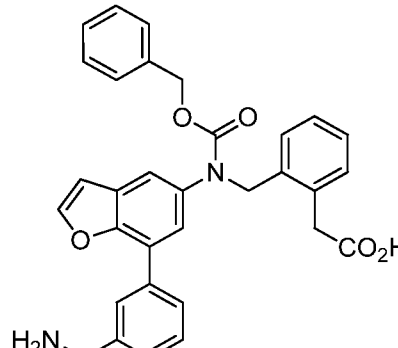
	
	
	
	
	

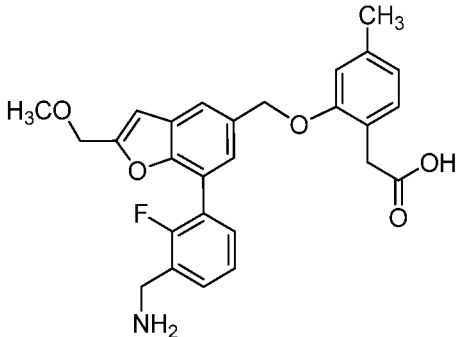
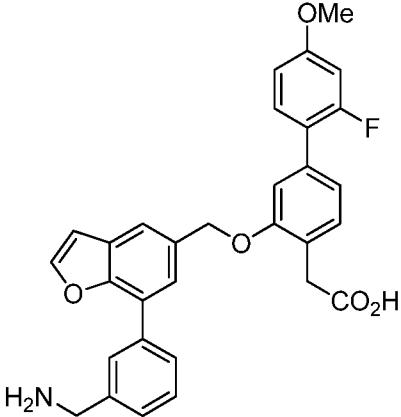
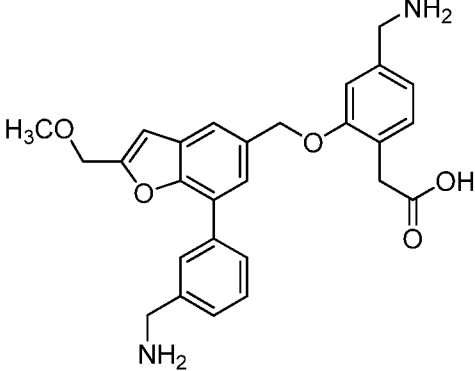
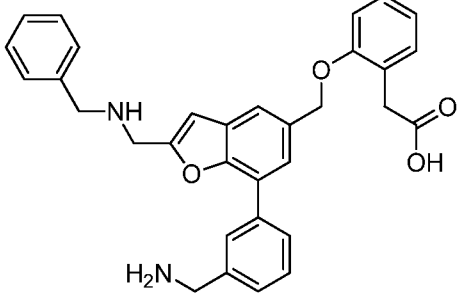
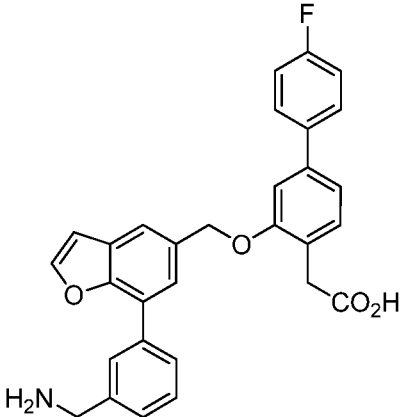
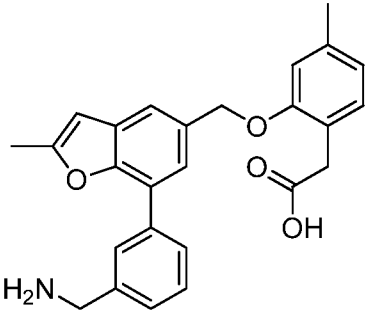
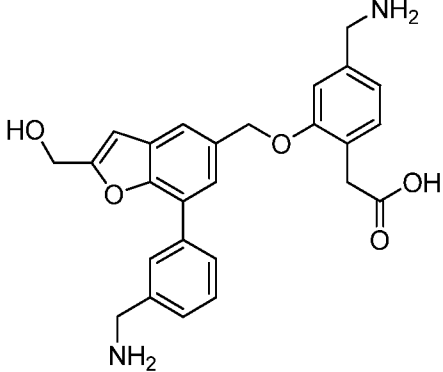
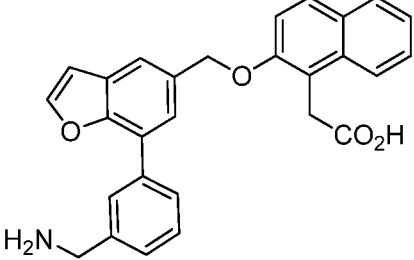
	
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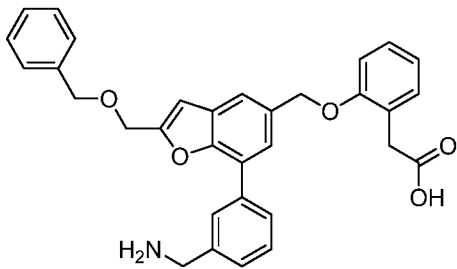
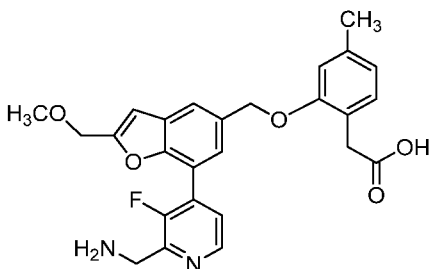
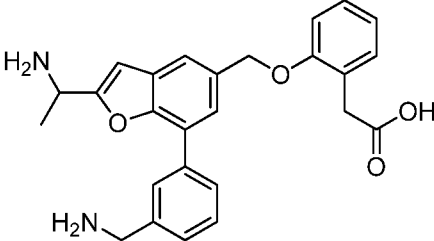
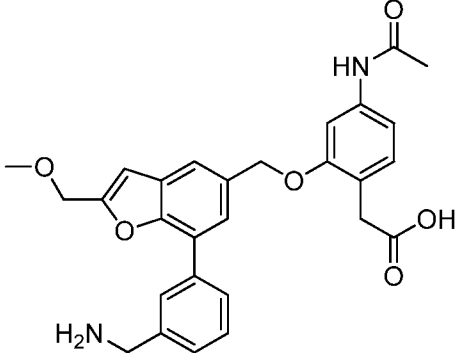
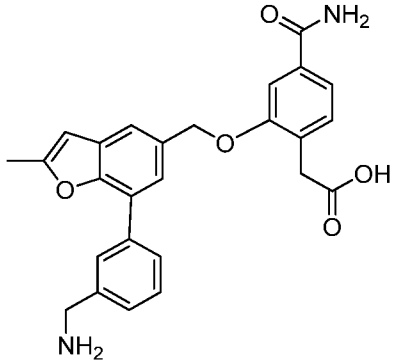
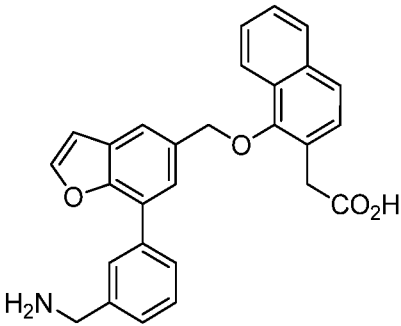
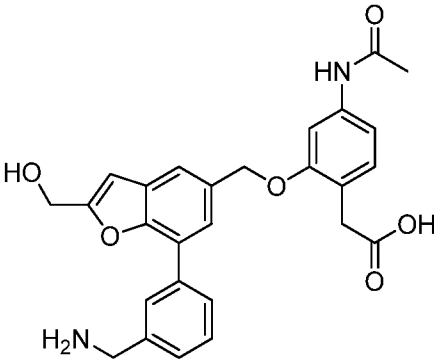
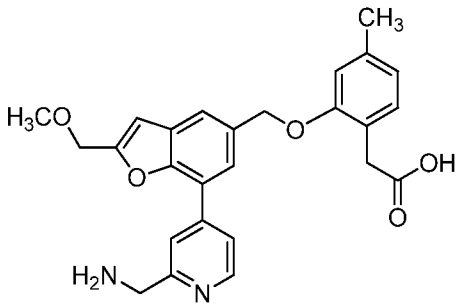
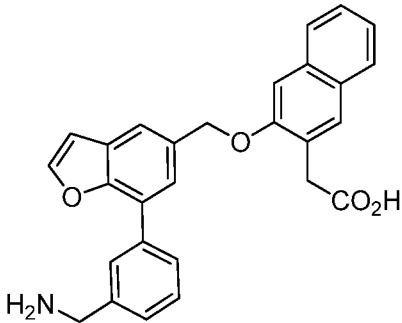
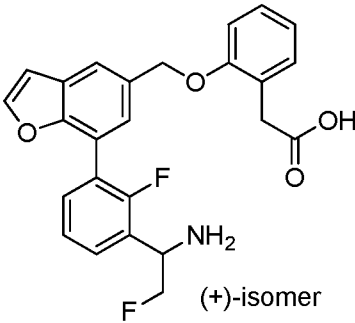
	
	
	
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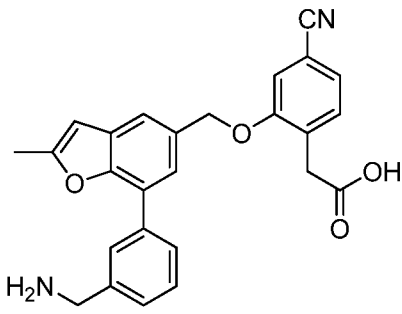
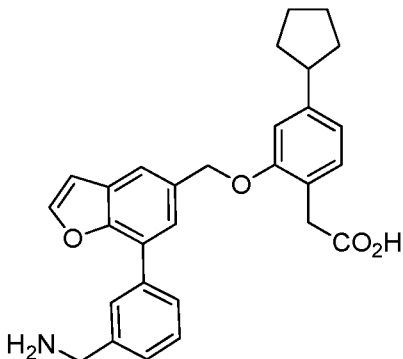
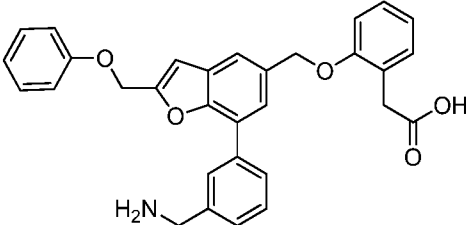
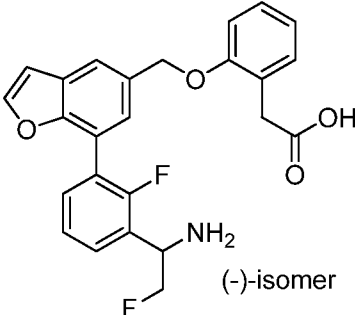
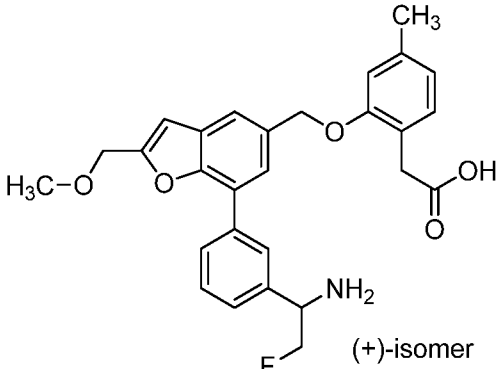
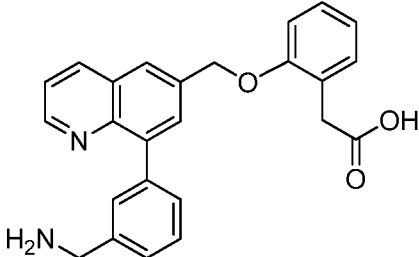
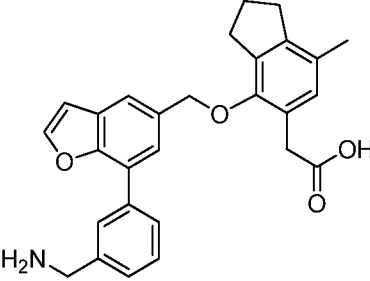
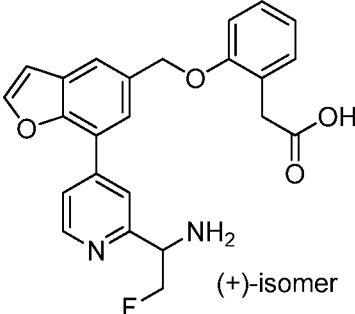
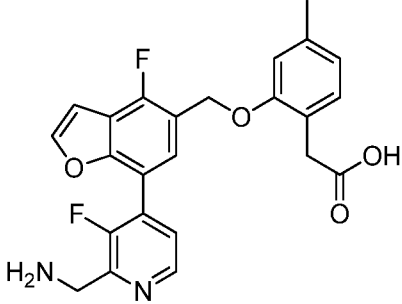
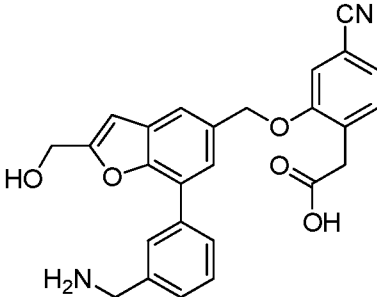
	
	
	
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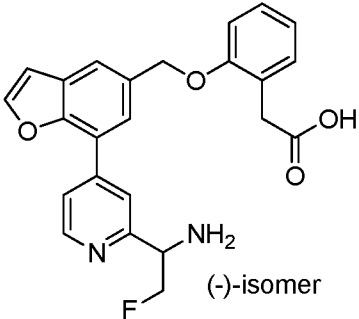
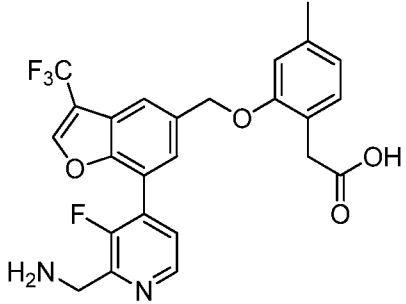
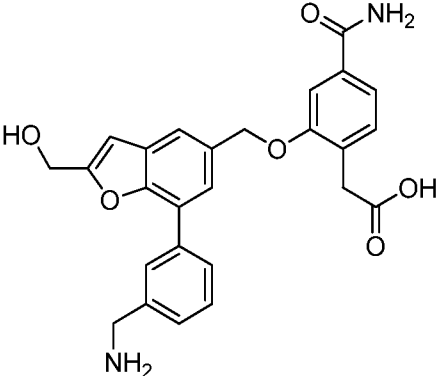
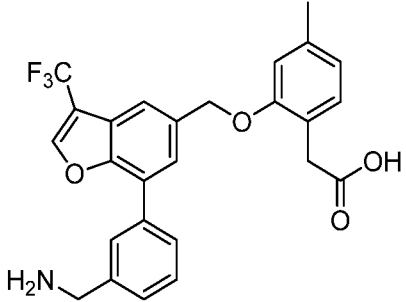
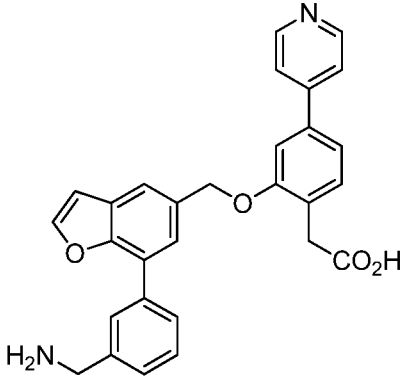
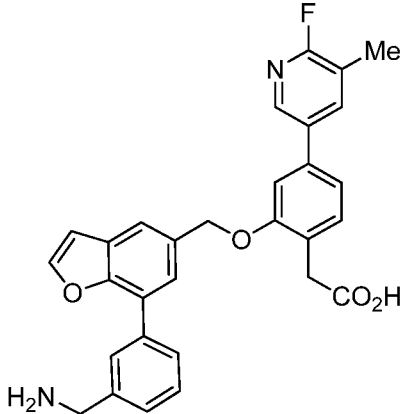
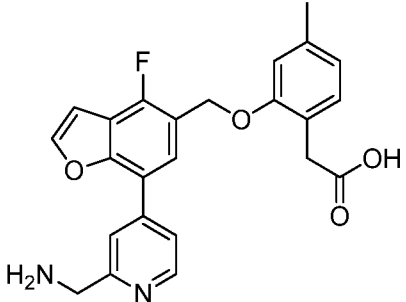
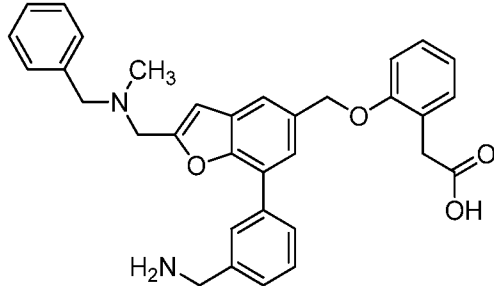
	
	
	
	
	

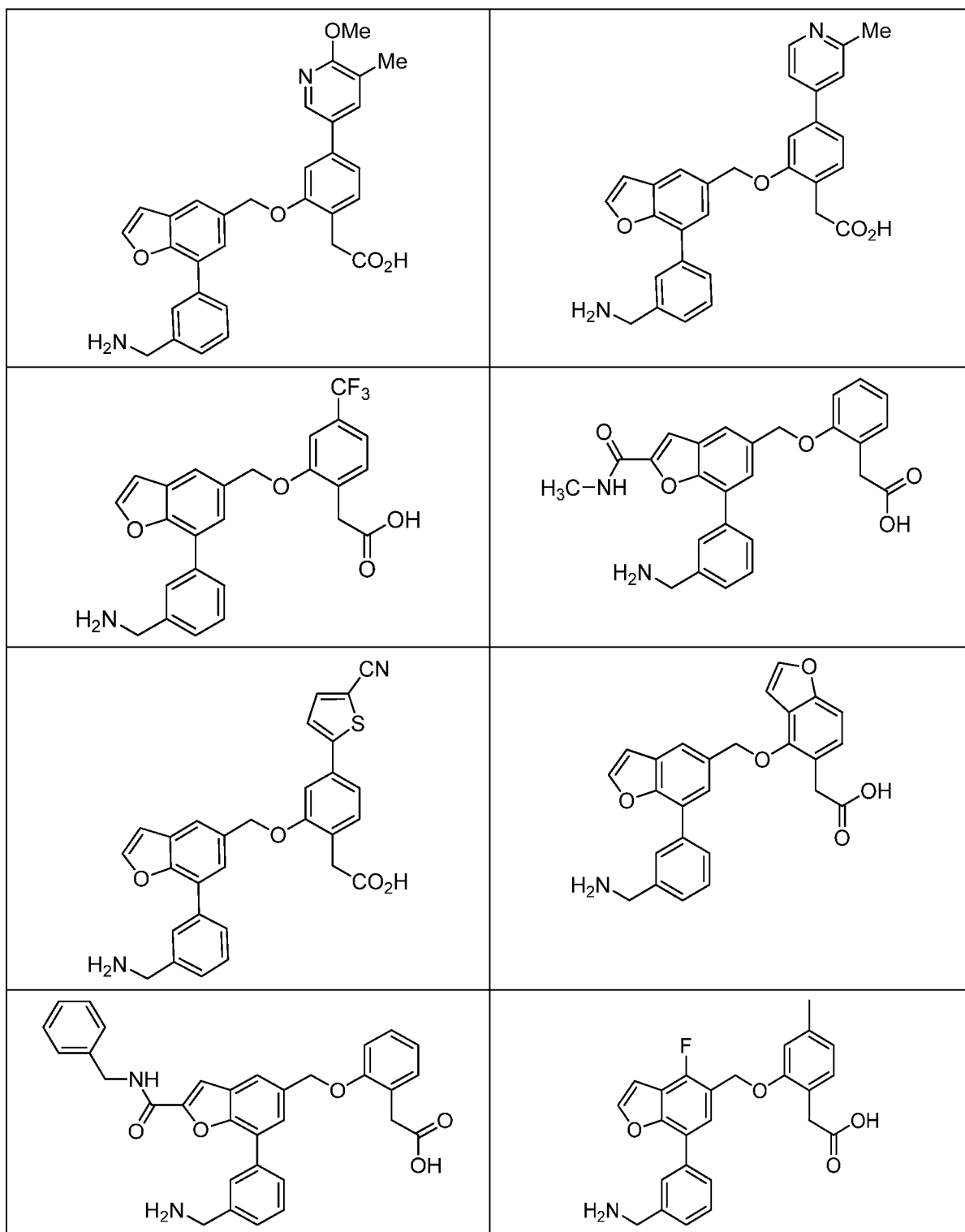
	
	
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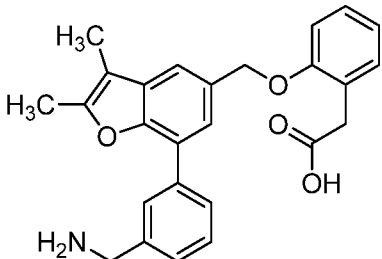
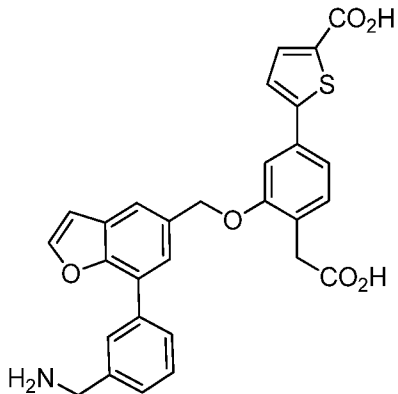
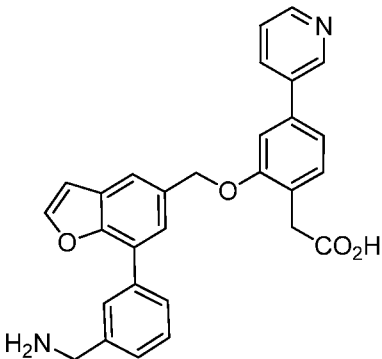
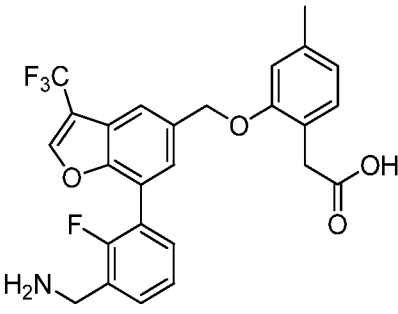
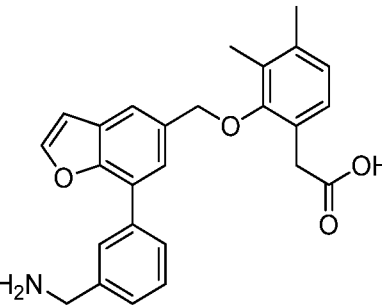
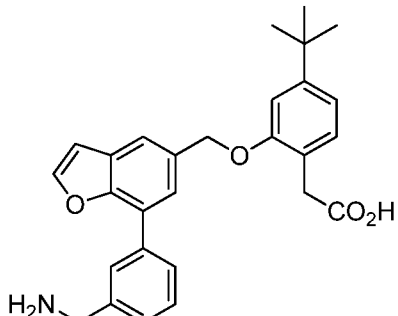
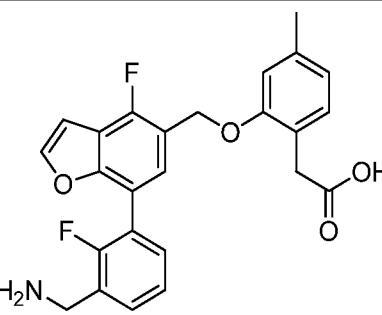
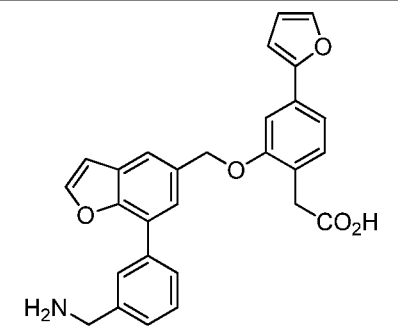
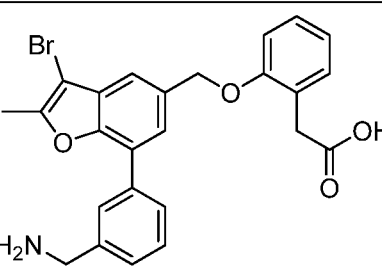
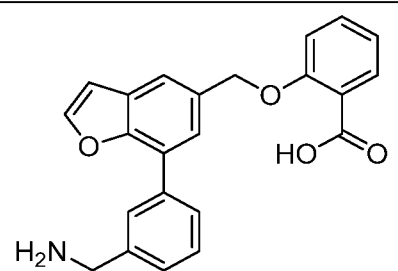
	
	
	
	

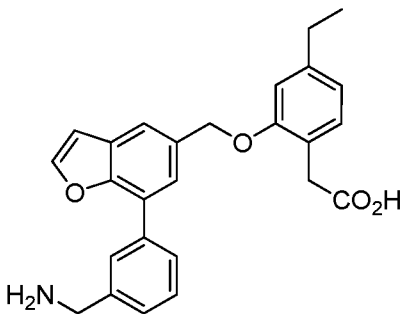
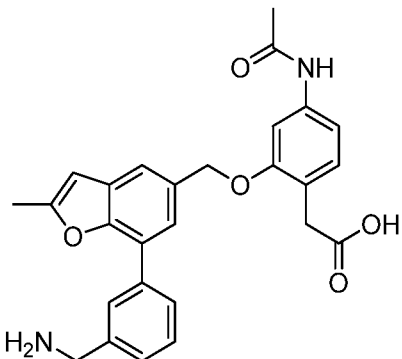
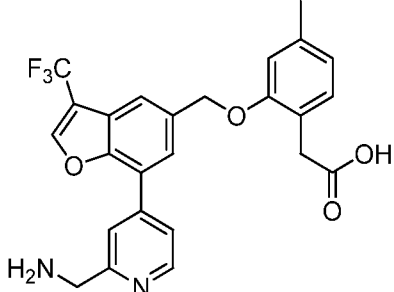
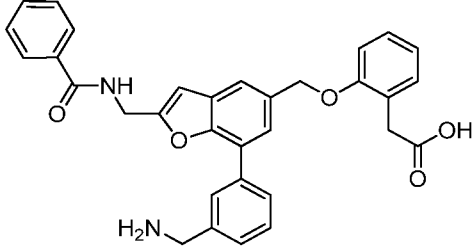
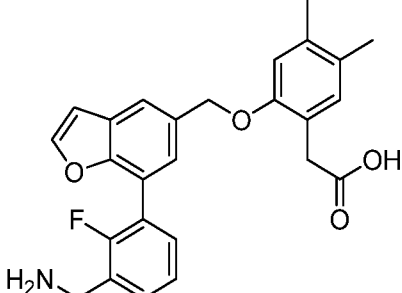
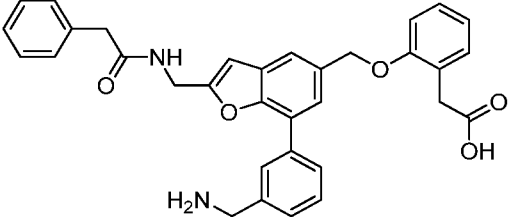
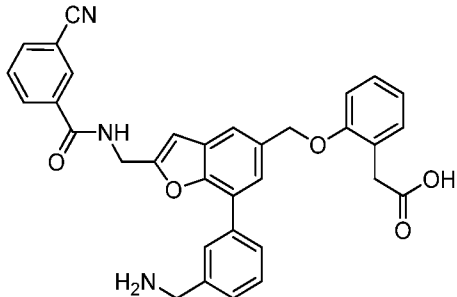
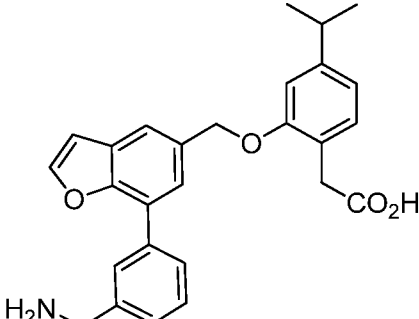
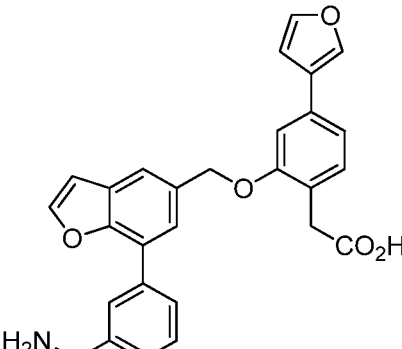
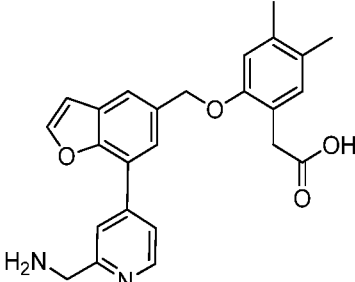
	
	
	
	
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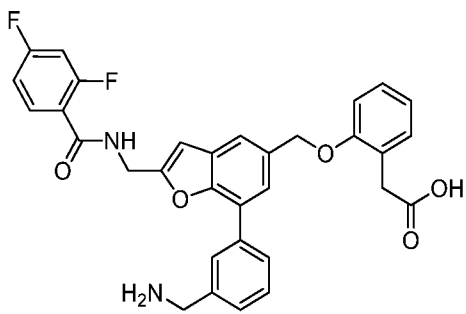
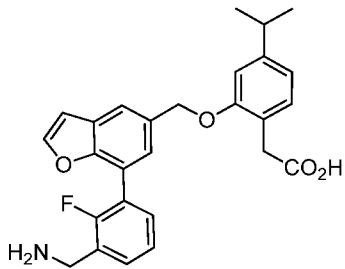
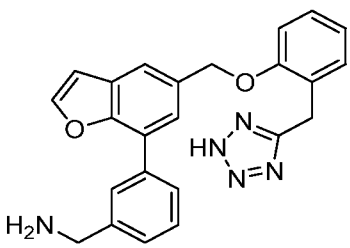
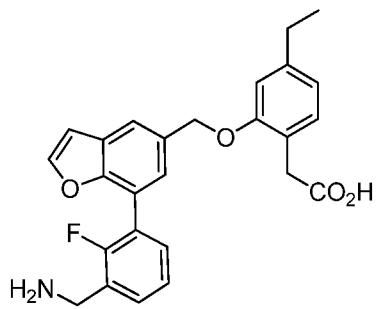
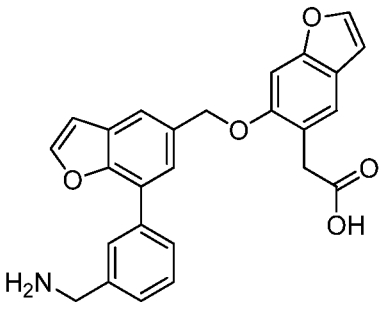
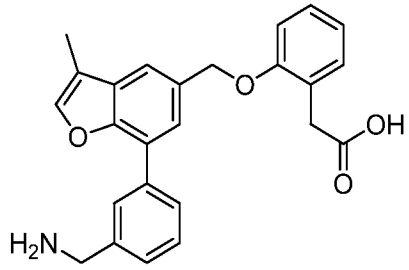
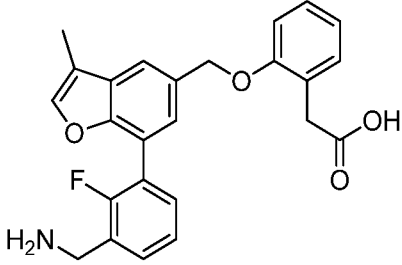
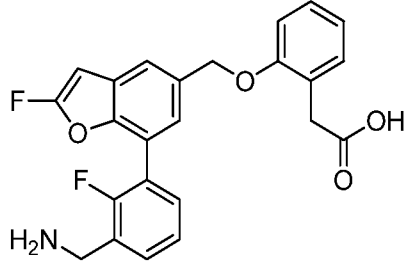
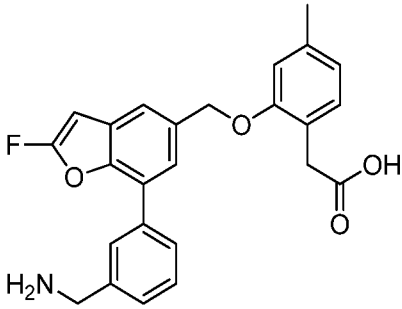
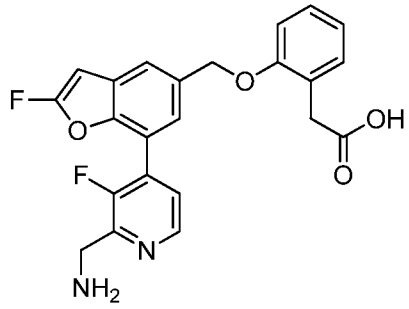
	
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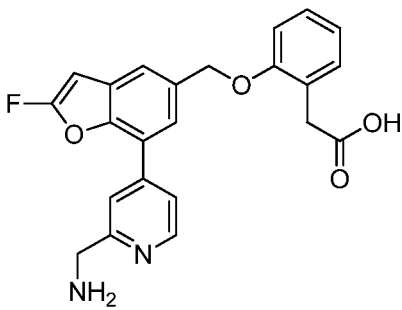
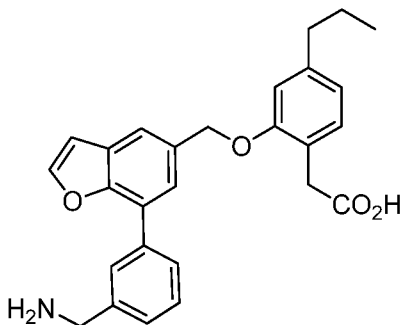
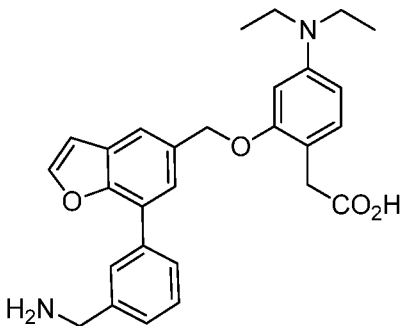
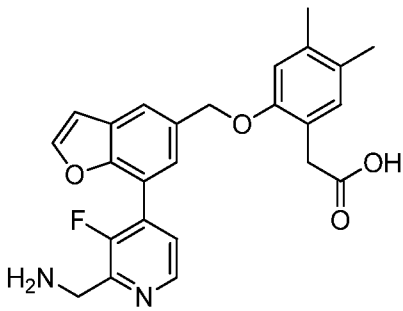
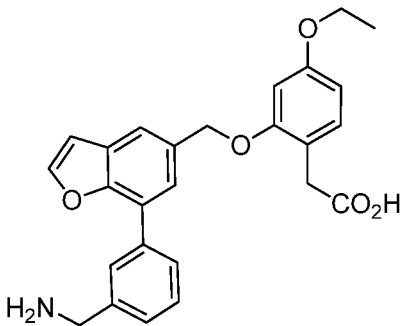
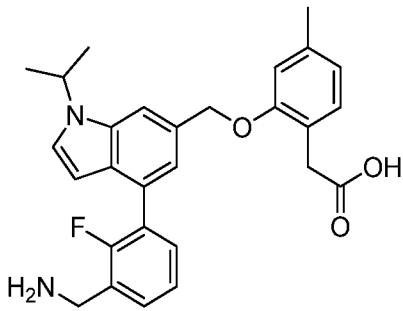
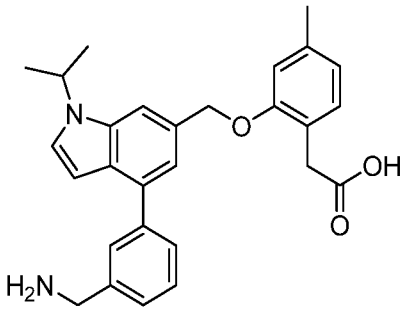
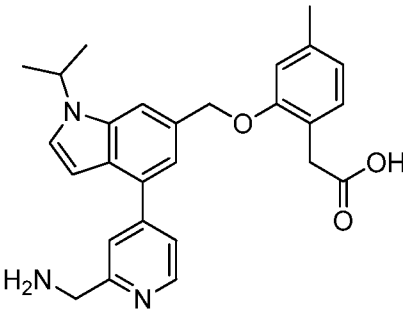
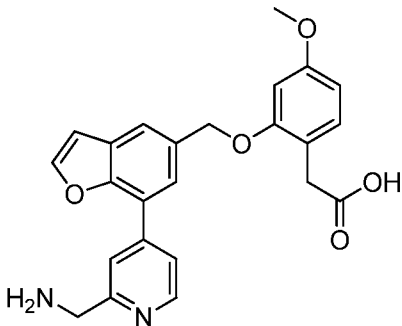
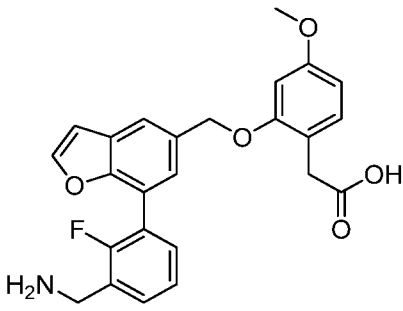
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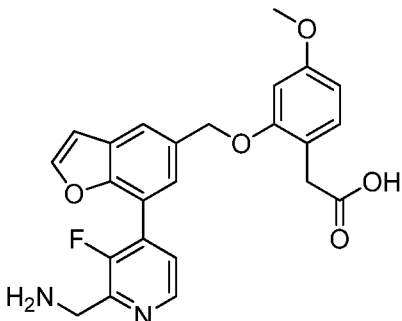
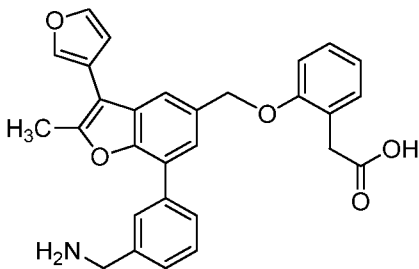
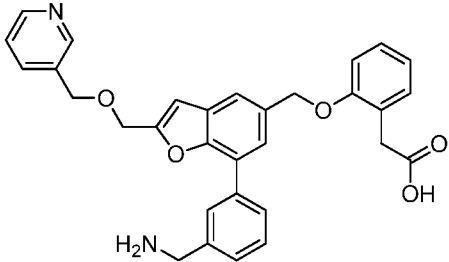
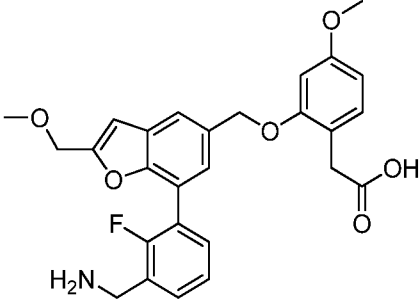
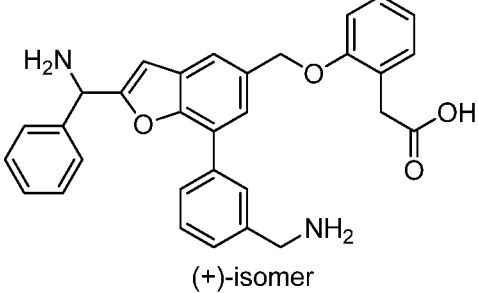
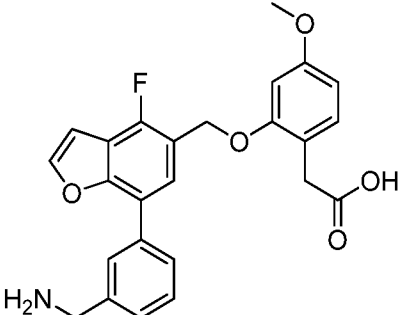
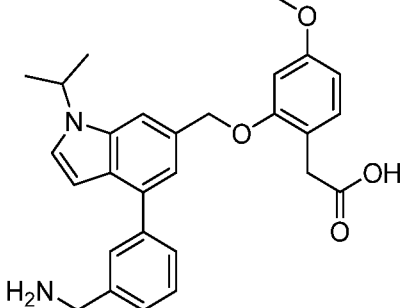
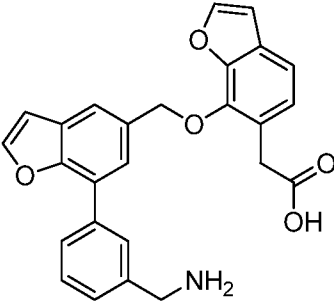
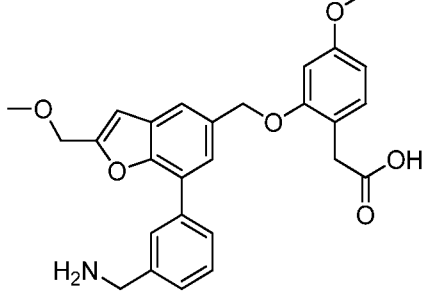
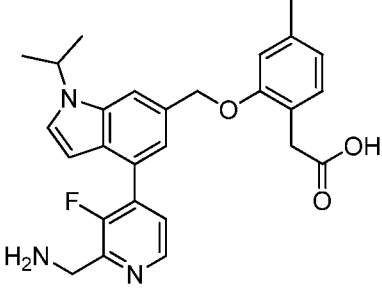


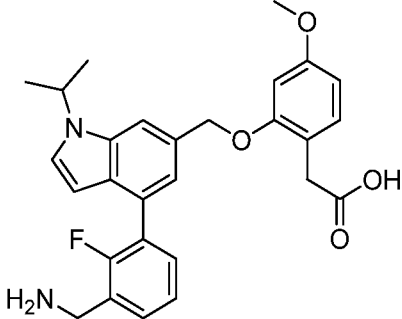
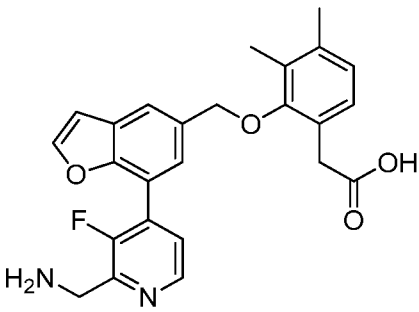
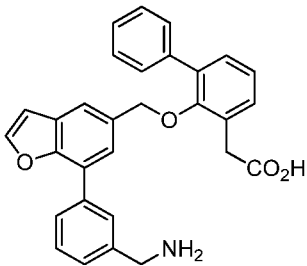
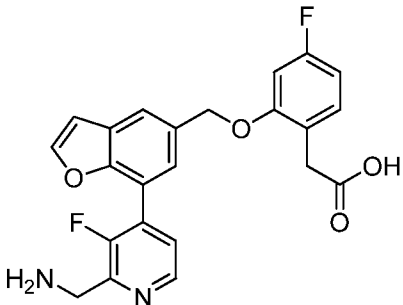
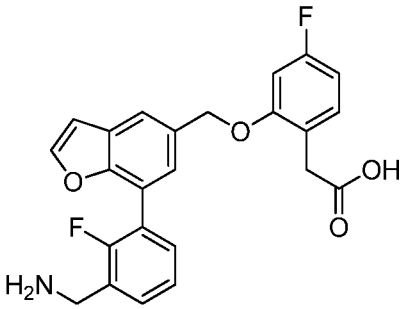
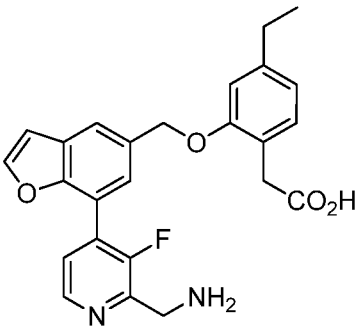
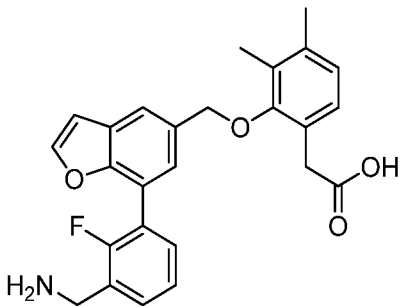
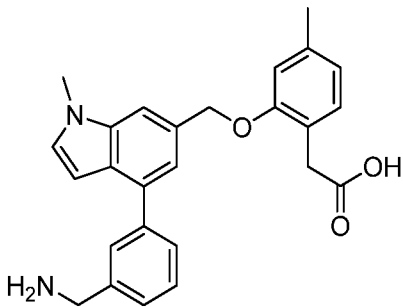
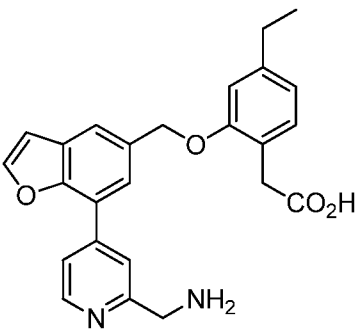
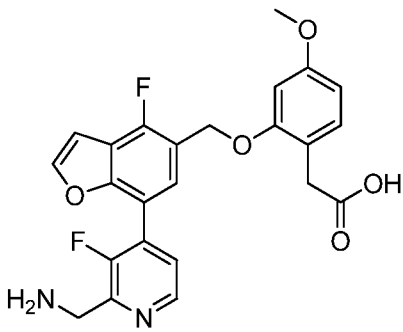
	
	
	
	
	

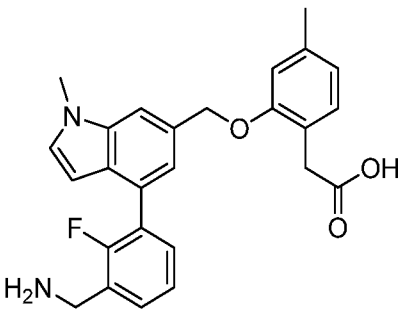
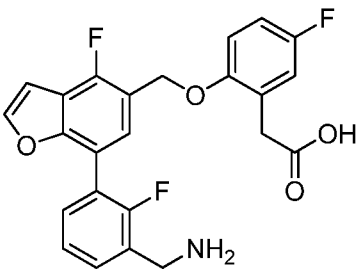
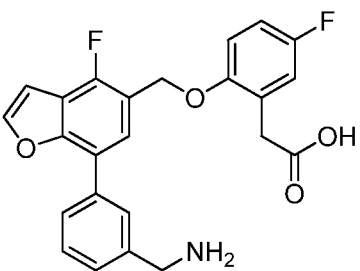
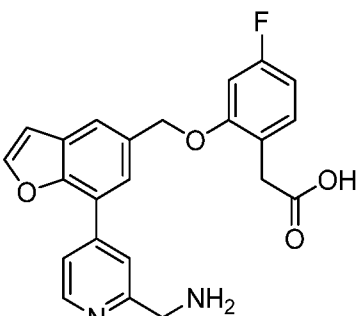
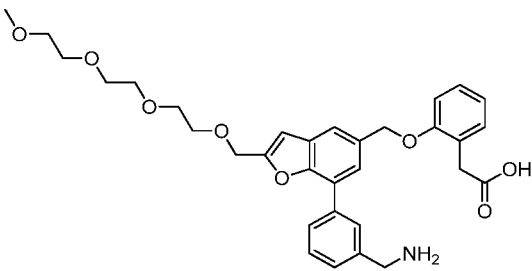
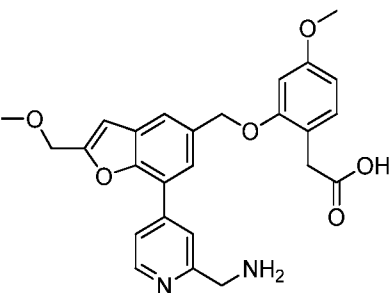
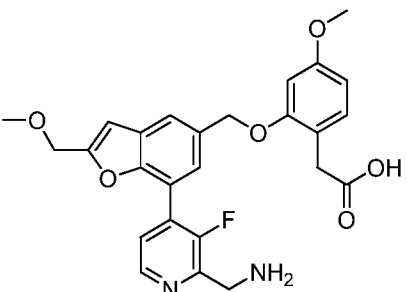
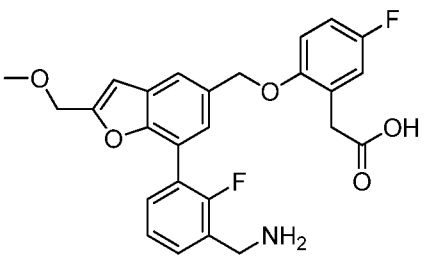
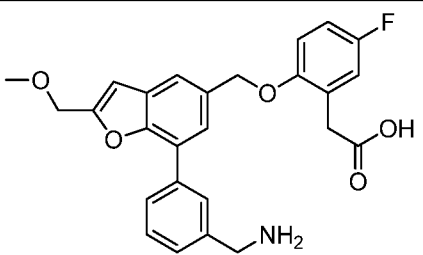
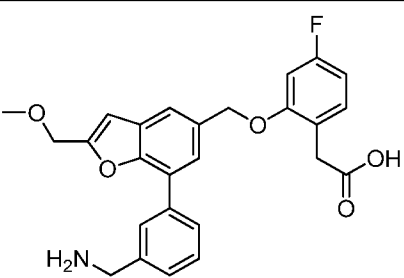
	
	
	
	
	

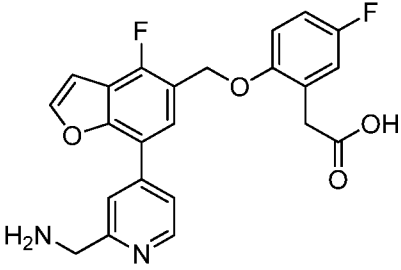
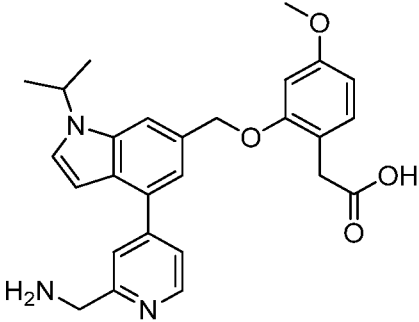
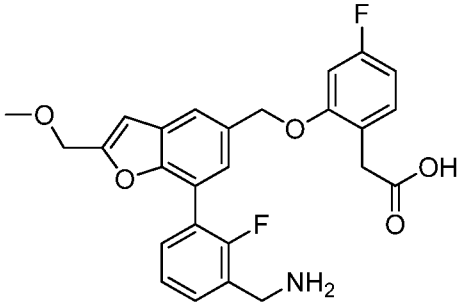
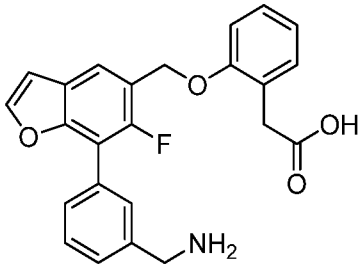
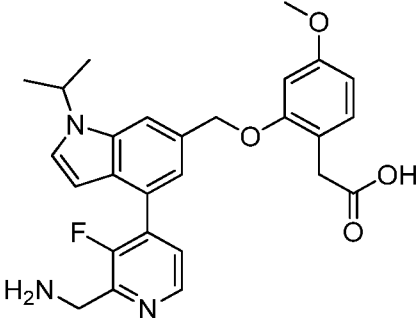
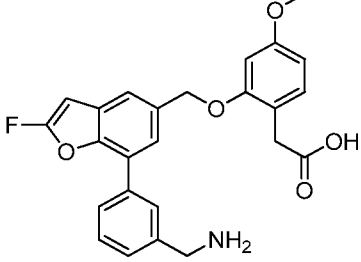
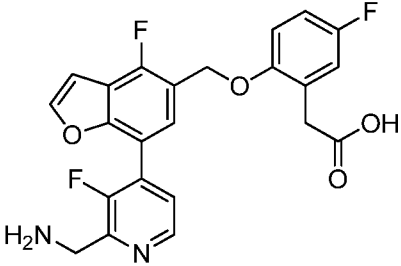
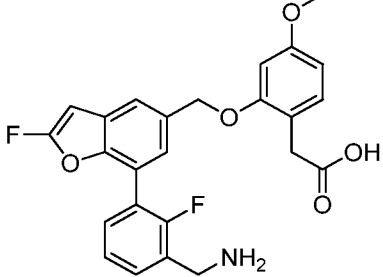
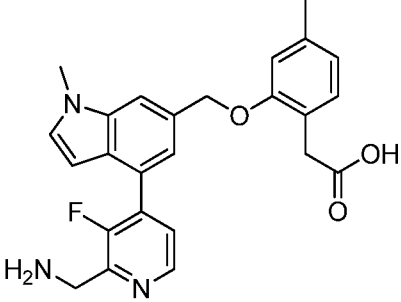
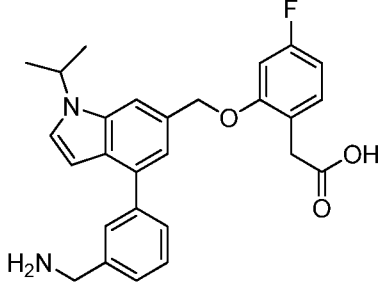
	
	
	
	
	

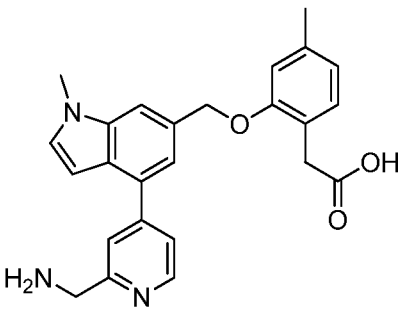
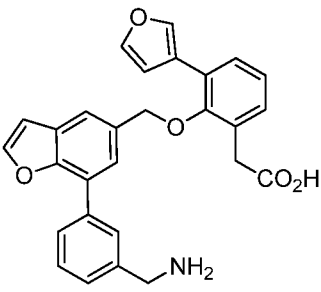
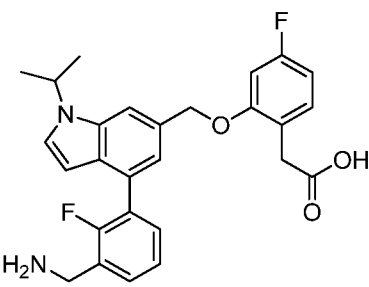
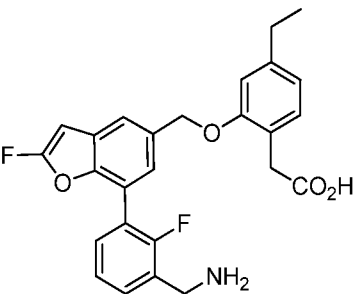
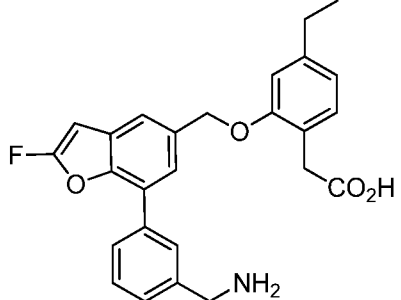
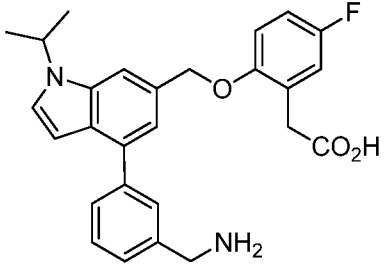
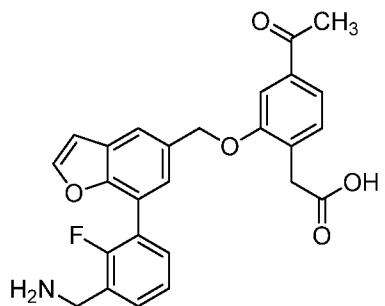
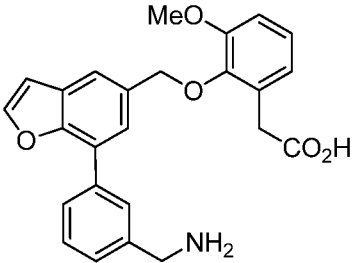
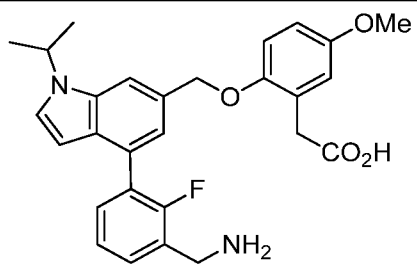
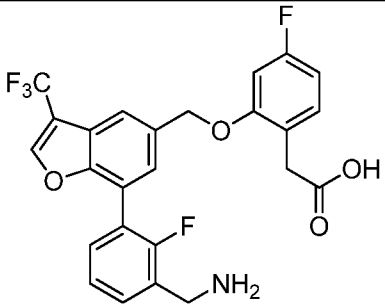
	
	
	
	
	

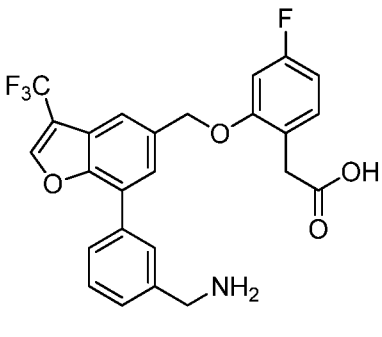
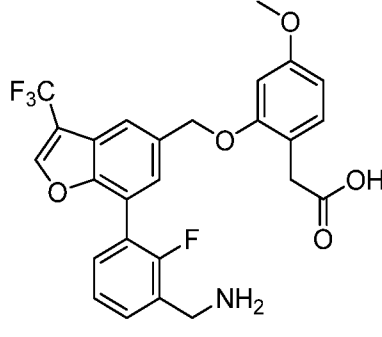
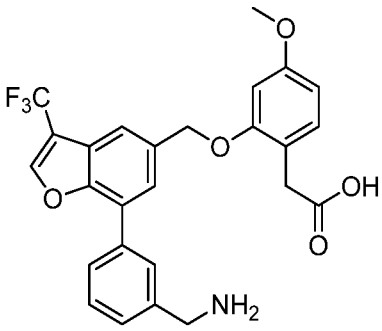
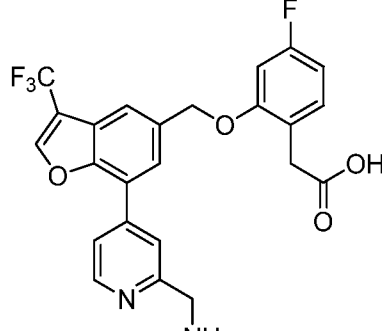
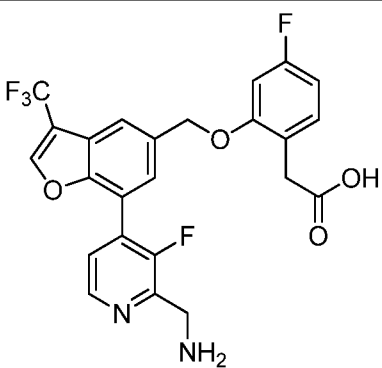
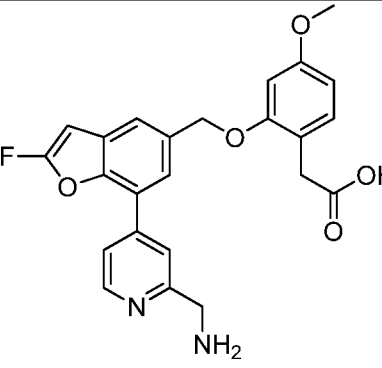
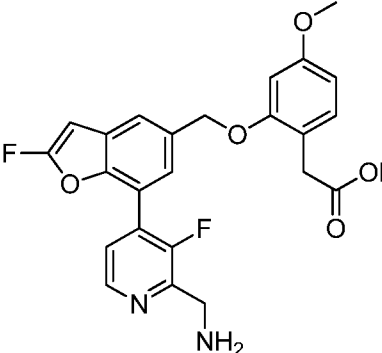
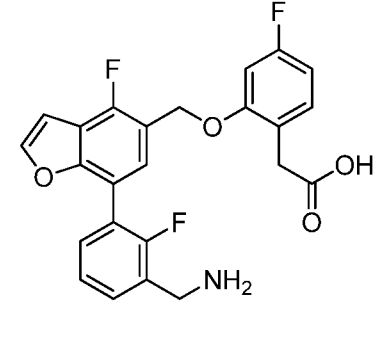
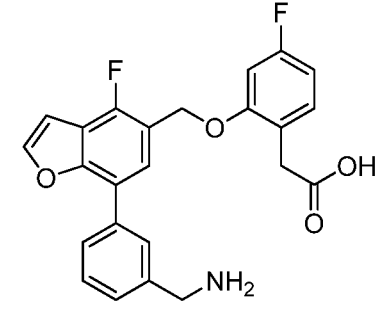
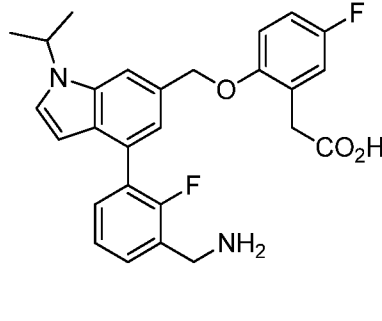
	
	
 (+)-isomer	
	
	

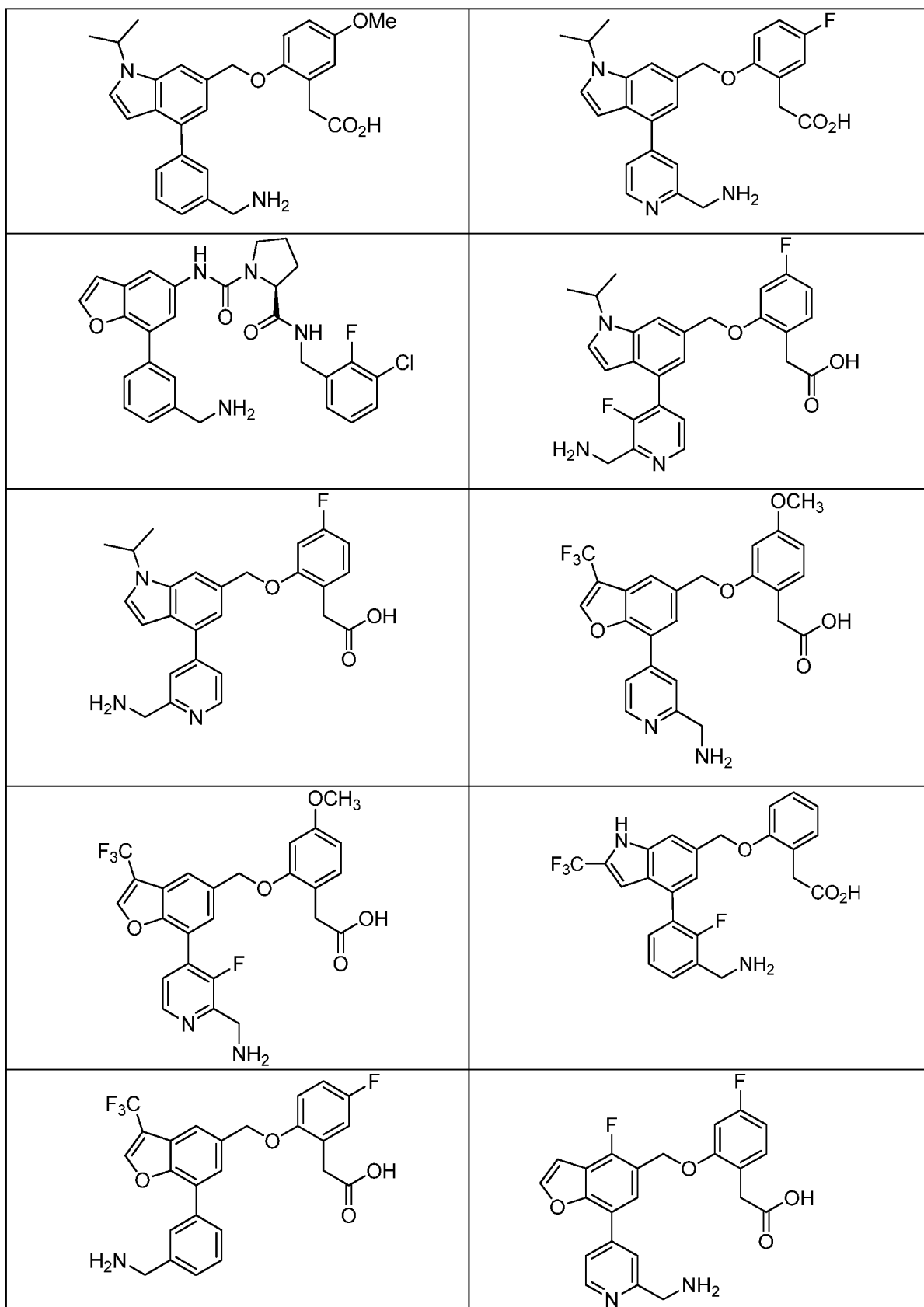
	
	
	
	
	

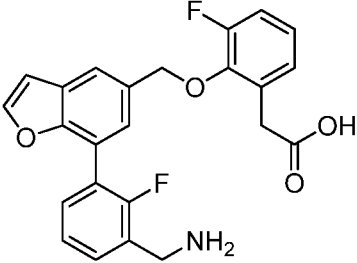
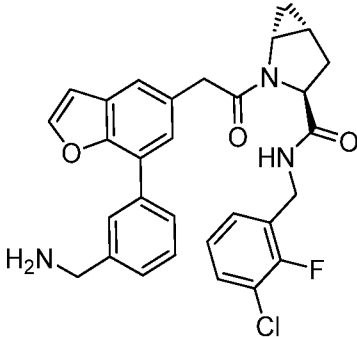
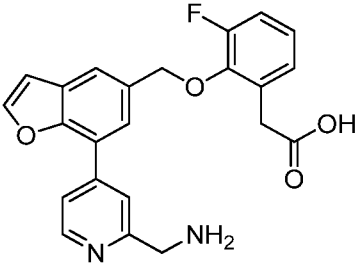
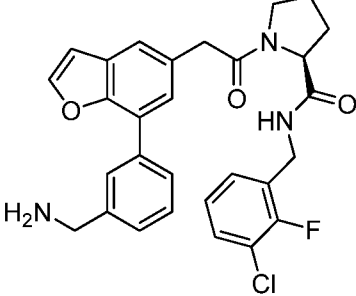
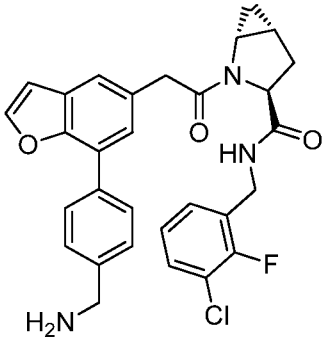
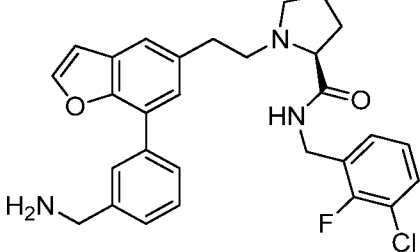
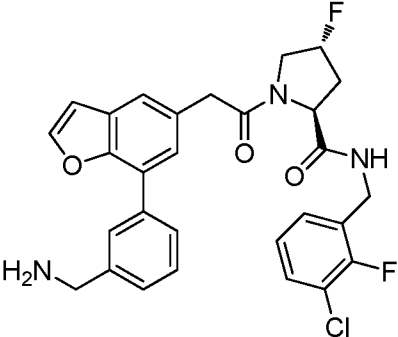
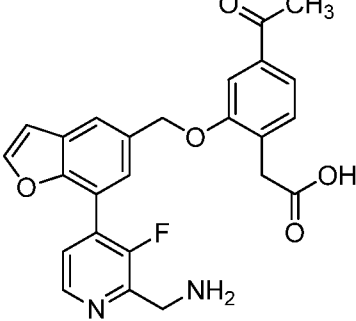
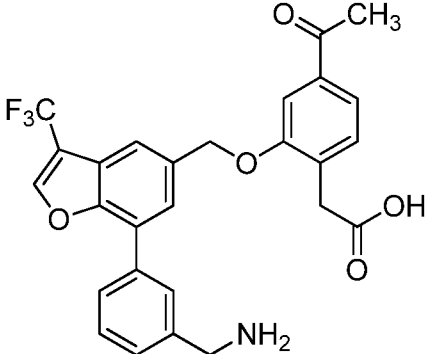
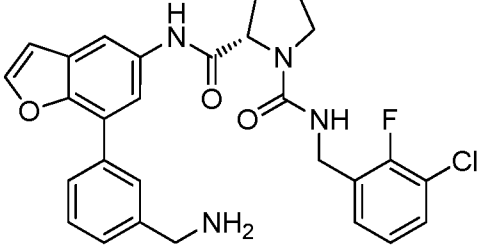
	
	
	
	
	

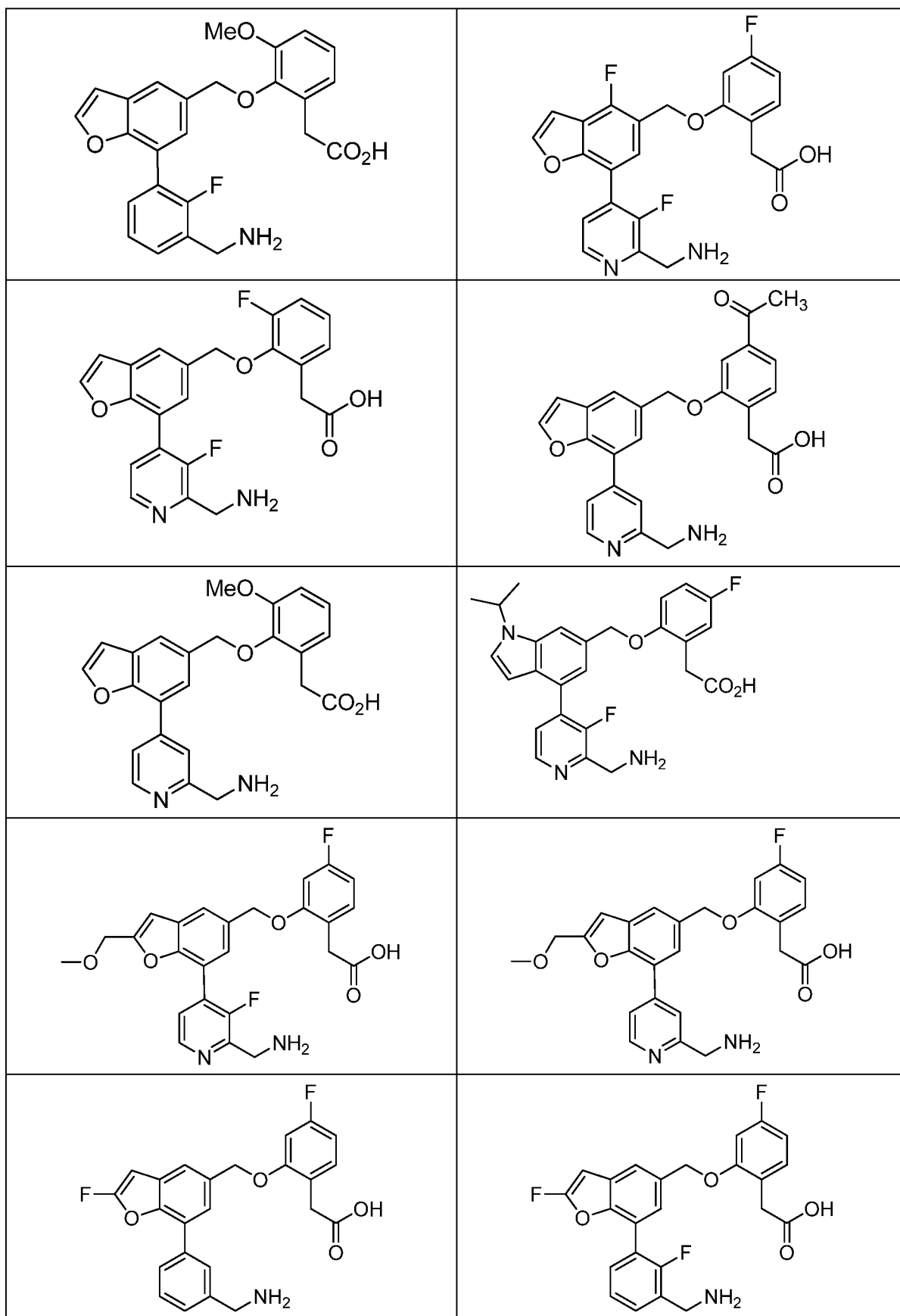
	
	
	
	
	

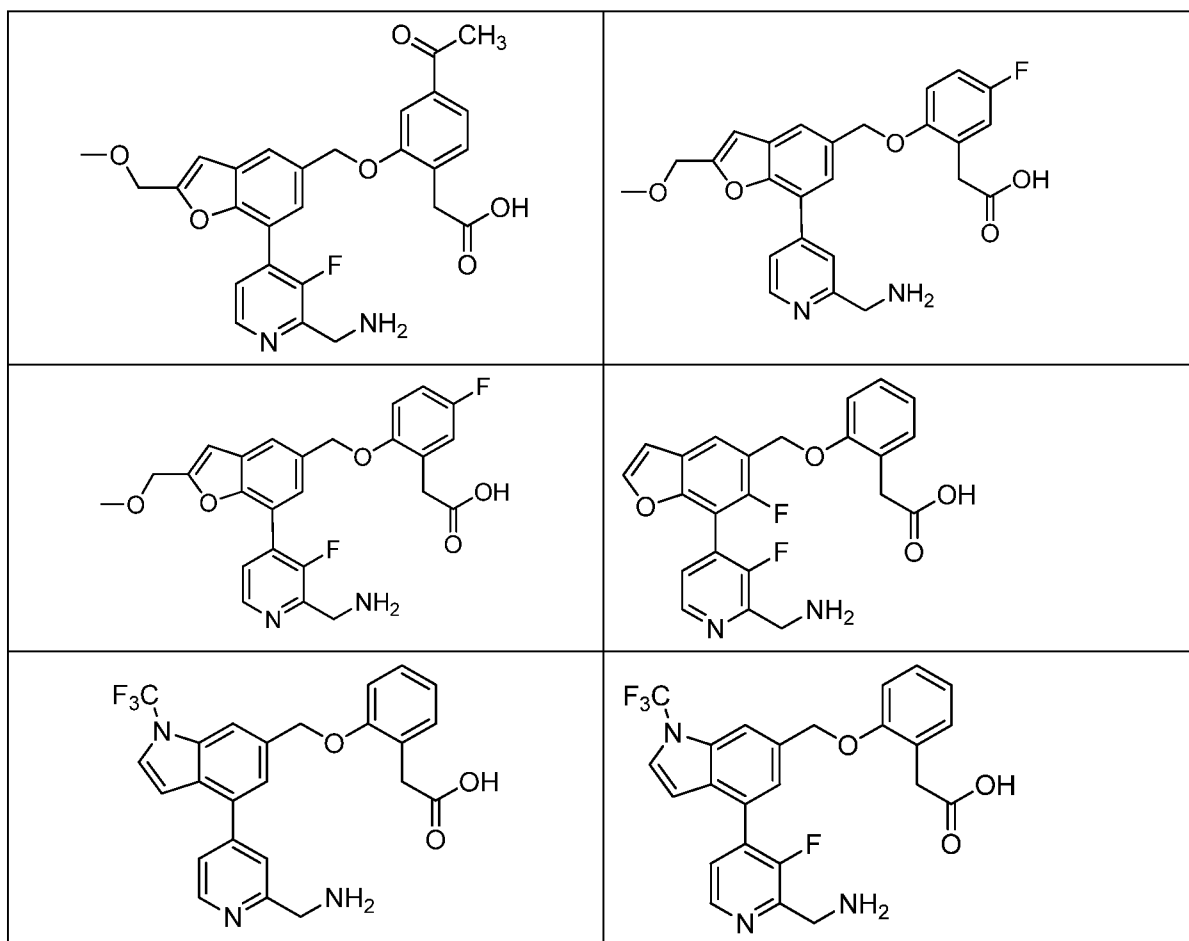
	
	
	
	
	

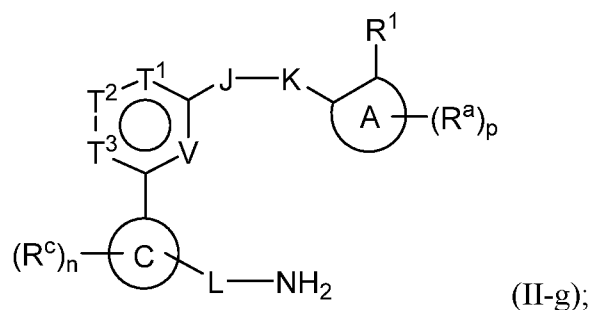






In other aspects, the invention provides compounds having the structure of Formula (II-g), or a pharmaceutically acceptable salt or prodrug thereof:



wherein:

ring $\textcircled{A}$ is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

ring $\textcircled{C}$ is aryl or heteroaryl;

R^a , independently for each occurrence, is halogen, cyano, hydroxy, $-\text{NH}_2$, $-\text{NH}(\text{Ac})$, $-\text{NH}(\text{alkyl})$, $-\text{NH}(\text{cycloalkyl})$, $-\text{NH}(\text{heterocycloalkyl})$, $-\text{NH}(\text{aryl})$, $-\text{NH}(\text{heteroaryl})$, $-\text{N}(\text{alkyl})_2$, $-\text{NHC}(\text{O})(\text{alkyl})$, $-\text{CH}(\text{alkyl})\text{NH}_2$, -

CH(hydroxyalkyl)NH₂, -CH(haloalkyl)NH₂, -CH(cycloalkyl)NH₂, -CH(heterocycloalkyl)NH₂, -CH(aryl)NH₂, -CH(heteroaryl)NH₂, -CH₂NHC(O)(alkyl), -C(O)NH₂, -C(O)(alkyl), -SO₂NH₂, -SO₂(cycloalkyl), -SO₂(heterocycloalkyl), -SO₂(alkyl), -SO₂(aryl), or -SO₂(heteroaryl); or is selected from the group consisting of substituted or unsubstituted aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl;

T¹ is N, CH, NR^{T1}, or CR^{T1};

T² is NR^{T2} or CR^{T2};

T³ is N, CH, NR^{T3}, or CR^{T3};

wherein:

(a) T¹ is CR^{T1} or NR^{T1}, wherein R^{T1} and R^{T2}, taken together with the intervening atoms, form an optionally substituted cycloalkyl, aryl, or heteroaryl ring; and

T³ is N or CH; or

(b) T³ is CR^{T3} or NR^{T3}; wherein R^{T3} and R^{T2}, taken together with the intervening atoms, form an optionally substituted heteroaryl ring; and

T¹ is N or CH; and

at least one of (a) T² is NR^{T2}, (b) T³ is N, or (c) T¹ is NR^{T1};

R¹ is selected from the group consisting of -NH₂, -COOH, -CH₂COOH, -CH(NH(CO)(alkyl))COOH, -CH(NH(CO)(arylalkyl))COOH, -CH(NH(CO)(cycloalkyl))COOH, -CH(NH(CO)(aryl substituted cycloalkyl))COOH, -CH(NH(CO)(heteroaryl substituted cycloalkyl))COOH, -CH(S(alkyl))COOH, -CO(NH)CH₂(substituted or unsubstituted aryl), -CO(NH)CH₂(substituted or unsubstituted heteroaryl), -CO(NH)(substituted or unsubstituted aryl), -CO(NH)(substituted or unsubstituted heteroaryl), and -CH₂(tetrazolyl);

n is 0, 1, 2, 3, or 4;

p is 0, 1, 2, 3, or 4;

J is -C(O)-, -NH-, -CH₂-, -O-, -S-, -S(O)-, -SO₂-, -N(alkyl)-, -CH(alkyl)-, -CH(cycloalkyl)-, -N((C(O)O)arylalkyl)-, -N((C(O)O)heteroarylalkyl)-, or -N(C(O)arylalkyl)-;

K is $-\text{C}(\text{O})-$, $-\text{NH}-$, $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{N}(\text{alkyl})-$, $-\text{CH}(\text{alkyl})-$, $-\text{CH}(\text{cycloalkyl})-$, $-\text{N}((\text{C}(\text{O})\text{O})\text{arylalkyl})-$, $-\text{N}((\text{C}(\text{O})\text{O})\text{heteroarylalkyl})-$, or $-\text{N}(\text{C}(\text{O})\text{arylalkyl})-$;

R^c , independently for each occurrence, is selected from the group consisting of halogen, $-\text{OH}$, $-\text{NR}^j\text{R}^k$, alkoxy, alkyl, cycloalkyl, and heterocycloalkyl;

L is selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CHR}^2-$, $-\text{CF}_2-$, $-\text{CFR}^2-$, $-\text{C}(\text{O})-$, $-\text{C}(=\text{NR}^L)-$, $-\text{C}(=\text{CHR}^L)-$, $-\text{S}(\text{O})_2-$, and $-\text{S}(\text{O})-$; wherein R^L is H or alkyl;

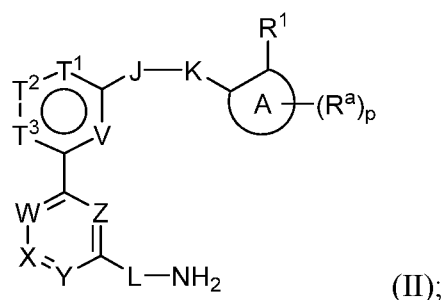
or wherein R^L and an occurrence of R^c taken together with the intervening atoms form a substituted or unsubstituted heteroaryl ring;

R^2 is alkyl, cycloalkyl, hydroxyalkyl, or haloalkyl;

V is N or CH; and

the stereochemical configuration at any chiral center is *R*, *S*, or a mixture of *R* and *S*.

In other aspects, the invention provides compounds having the structure of Formula (II), or a pharmaceutically acceptable salt or prodrug thereof:



wherein:

ring A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^a , independently for each occurrence, is selected from the group consisting of halogen, cyano, hydroxy, $-\text{NH}_2$, $-\text{NH}(\text{Ac})$, $-\text{NH}(\text{alkyl})$, $-\text{N}(\text{alkyl})_2$, $-\text{NHC}(\text{O})(\text{alkyl})$, $-\text{CH}_2\text{NHC}(\text{O})(\text{alkyl})$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})(\text{alkyl})$, optionally substituted aryl, optionally substituted heteroaryl, cycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl;

T^1 is N, CH, $\text{NR}^{\text{T}1}$, or $\text{CR}^{\text{T}1}$;

T^2 is $\text{NR}^{\text{T}2}$ or $\text{CR}^{\text{T}2}$;

T^3 is N, CH, $\text{NR}^{\text{T}3}$, or $\text{CR}^{\text{T}3}$;

wherein:

(a) T^1 is CR^{T1} or NR^{T1} , wherein R^{T1} and R^{T2} , taken together with the intervening atoms, form an optionally substituted cycloalkyl, aryl, or heteroaryl ring; and

T^3 is N or CH; or

(b) T^3 is CR^{T3} or NR^{T3} ; wherein R^{T3} and R^{T2} , taken together with the intervening atoms, form an optionally substituted heteroaryl ring; and

T^1 is N or CH; and

at least one of (a) T^2 is NR^{T2} , (b) T^3 is N, or (c) T^1 is NR^{T1} ;

R^1 is selected from the group consisting of $-NH_2$, $-CH_2COOH$,

$-CH(NH(CO)(alkyl))COOH$, $-CH(NH(CO)(cycloalkyl))COOH$,

$-CO(NH)CH_2aryl$, $-CO(NH)CH_2heteroaryl$, $-CO(NH)aryl$, and

$-CO(NH)heteroaryl$;

p is 0, 1, or 2;

J is $-C(O)-$, $-NH-$, $-CH_2-$, $-O-$, $-S-$, $-S(O)-$, $-SO_2-$, $-N(alkyl)-$, or $-CH(alkyl)-$;

K is $-C(O)-$, $-NH-$, $-O-$, $-CH_2-$, $-S-$, $-S(O)-$, $-SO_2-$, $-N(alkyl)-$, or $-CH(alkyl)-$;

wherein at least one of J and K is $-C(O)-$, $-CH_2-$, or $-CH(alkyl)-$;

W is N, CH, or CR^c ;

X is N, CH, or CR^c ;

Y is N, CH, or CR^c ;

Z is N, CH, or CR^c ;

R^c , independently for each occurrence, is selected from the group consisting of halogen, $-OH$, $-NR^jR^k$, alkoxy, and alkyl;

L is selected from the group consisting of a bond, $-CH_2-$, $-CH_2CH_2-$, $-CHR^2-$,

$-CF_2-$, $-CFR^2-$, $-C(O)-$, $-C(=NR^L)-$, and $-C(=CHR^L)-$;

wherein R^L is H or alkyl;

or wherein R^L and an occurrence of R^c taken together with the intervening atoms form a substituted or unsubstituted heteroaryl ring;

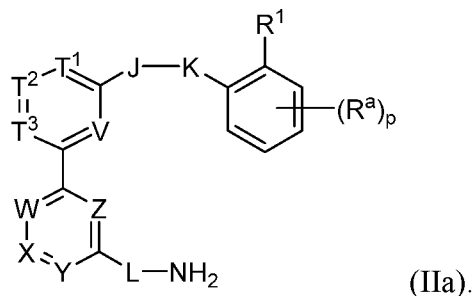
R^2 is alkyl, hydroxyalkyl, or haloalkyl;

V is N or CH; and

the stereochemical configuration at any chiral center is *R*, *S*, or a mixture of *R* and *S*.

In certain embodiments, ring  is phenyl, thiophenyl, furyl, pyrazole, or pyridinyl, preferably phenyl.

In certain embodiments, the compound of formula (II) has the structure of formula (IIa):



In certain embodiments of formula (II) or (IIa), p is 1. In certain such embodiments, R^a is alkyl or alkoxy.

In certain embodiments, p is 0.

In certain embodiments, R^1 is $-\text{CH}_2\text{COOH}$.

In some embodiments, $-\text{J}-\text{K}-$ is selected from the group consisting of $-\text{C}(\text{O})-\text{NH}-$, $-\text{NH}-\text{C}(\text{O})-$, and $-\text{CH}_2\text{O}-$, preferably $-\text{CH}_2\text{O}-$.

In certain embodiments, U is CH. In further embodiments, V is CH.

In certain embodiments, each of W, X, Y, and Z is CH.

In certain embodiments, at least one of W, X, Y, and Z is CR^c . For example, Z may be CR^c and/or Y may be CR^c . In certain such embodiments, R^c is halogen, e.g., fluoride.

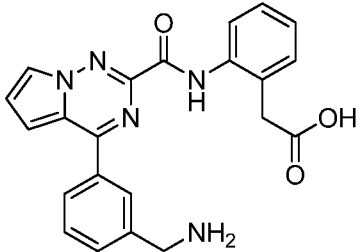
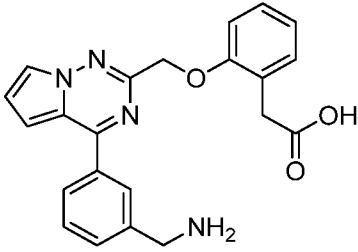
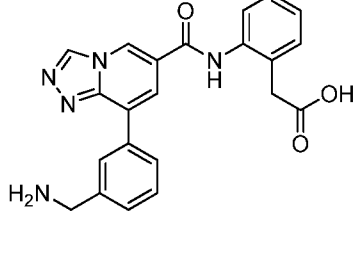
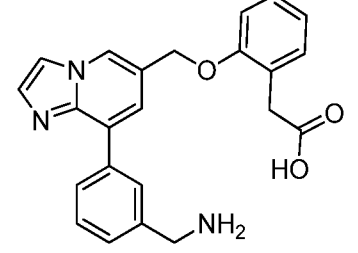
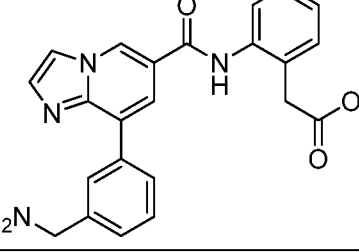
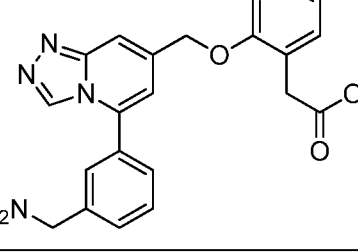
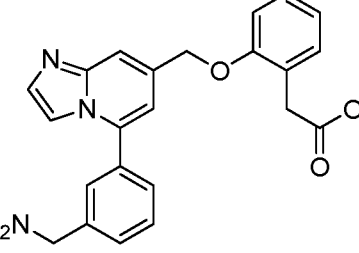
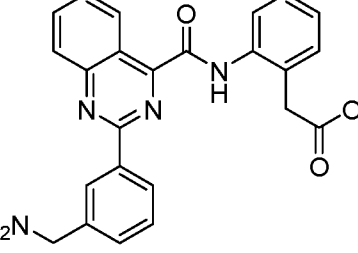
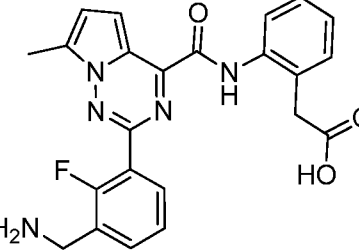
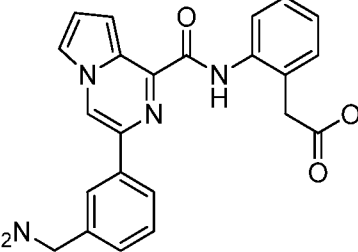
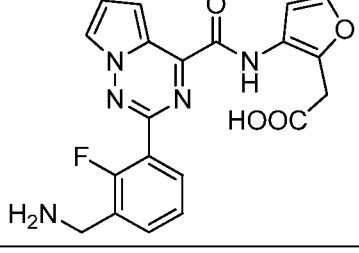
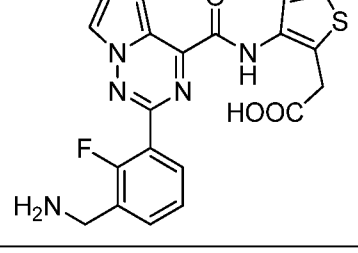
Alternatively, at least one of W, X, Y, and Z is N. For example, Z may be N. Alternatively, Y may be N.

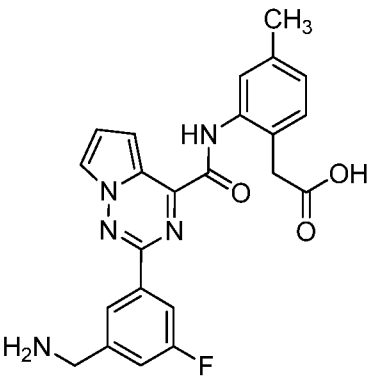
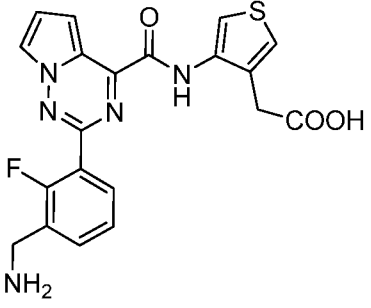
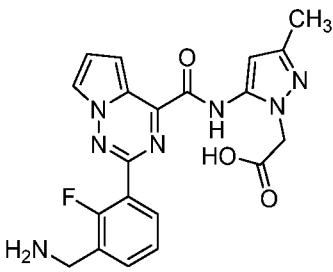
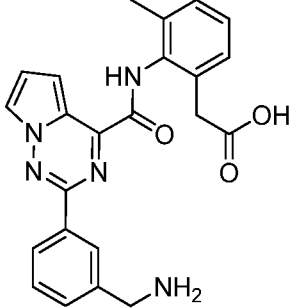
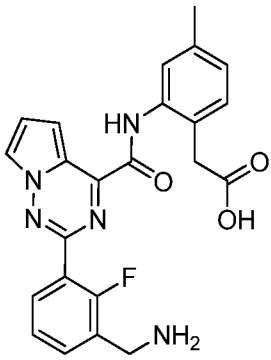
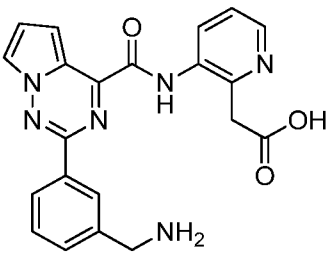
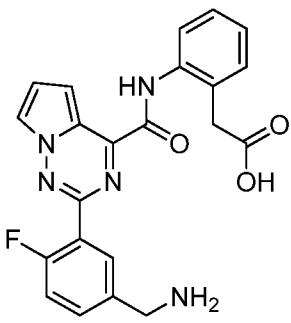
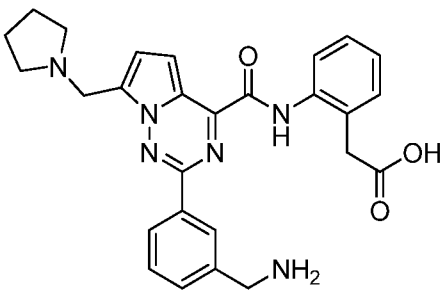
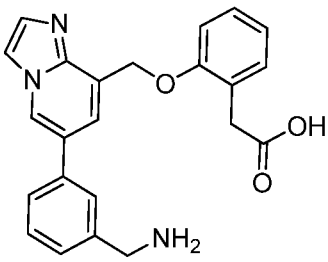
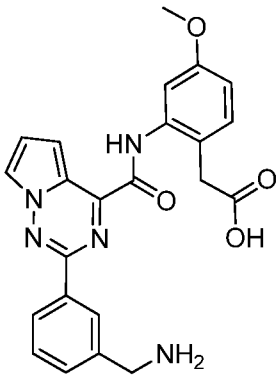
In some embodiments, L is $-\text{CH}_2-$.

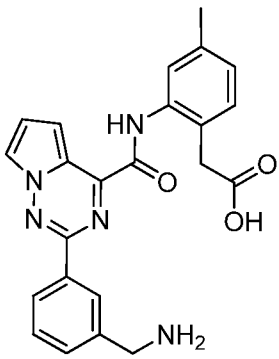
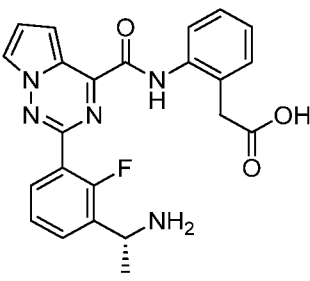
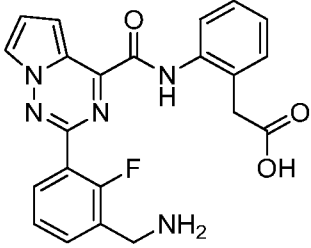
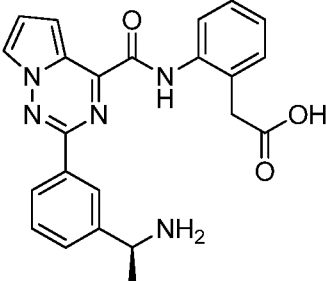
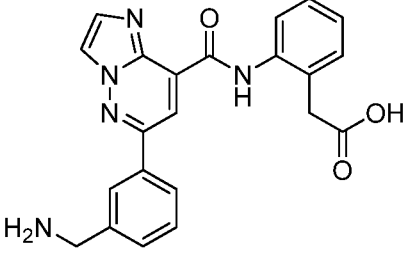
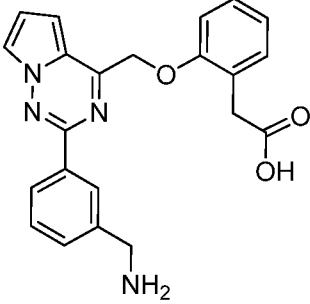
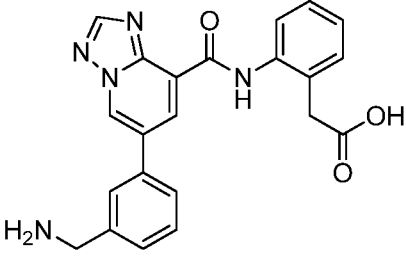
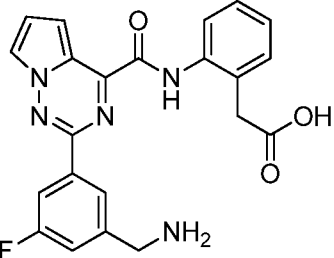
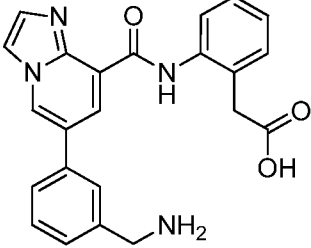
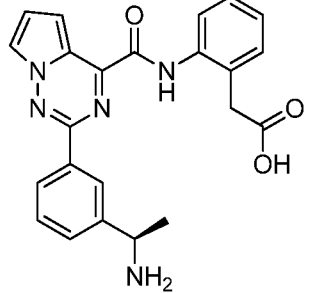
In certain embodiments of the compound of formula (II) or (IIa), T^1 is CR^{T1} ; and R^{T1} and R^{T2} , taken together with the intervening atoms, form an optionally substituted heteroaryl ring, such as pyrrole, imidazole, or 1,2,4-triazole.

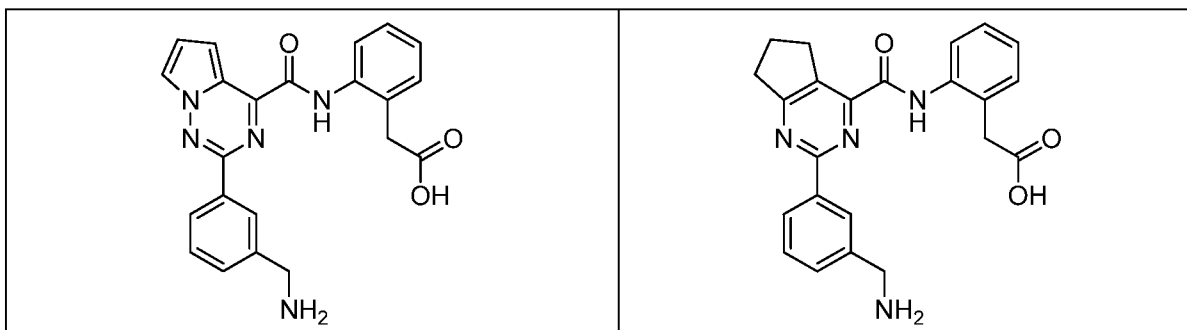
In alternative embodiments of the compound of formula (II) or (IIa), T^3 is CR^{T3} ; and R^{T3} and R^{T2} , taken together with the intervening atoms, form an optionally substituted heteroaryl ring, such as pyrrole, imidazole, 1,2,4-triazole, or pyridine.

In certain embodiments, the compound of formula (II) is selected from the following table of compounds, and pharmaceutically acceptable salts and prodrugs thereof:



Pharmaceutical Compositions

The invention provides pharmaceutical compositions, each comprising one or more compounds of the invention, or pharmaceutically acceptable salts or prodrugs thereof, and a pharmaceutically acceptable carrier. In certain embodiments, the pharmaceutical composition comprises a compound of the invention, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier. In certain embodiments, the pharmaceutical composition comprises a plurality of compounds of the invention, which may include pharmaceutically acceptable salts and/or prodrugs thereof, and a pharmaceutically acceptable carrier.

In certain embodiments, a pharmaceutical composition of the invention further comprises at least one additional pharmaceutically active agent other than a compound of the invention. The at least one additional pharmaceutically active agent can be an agent useful in the treatment of a disease or condition characterized by aberrant complement system activity.

Pharmaceutical compositions of the invention can be prepared by combining one or more compounds of the invention with a pharmaceutically acceptable carrier and, optionally, one or more additional pharmaceutically active agents.

Methods of Use

The present invention provides compounds, and pharmaceutically acceptable salts and prodrugs thereof, that are useful for treating or preventing a disease or condition characterized by aberrant complement system activity.

In certain aspects, the invention provides a compound of the invention, or a pharmaceutically acceptable salt or prodrug thereof, for use as a medicament.

In certain aspects, the invention provides methods of treating or preventing a disease or condition characterized by aberrant complement system activity. The method includes the step of administering to a subject in need thereof a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt or prodrug thereof, thereby

treating or preventing the disease or condition characterized by aberrant complement system activity. By reducing complement system activity in the subject, the disease or condition characterized by aberrant complement system activity is treated.

Alternatively, in certain aspects, the invention provides a compound of the invention, or a pharmaceutically acceptable salt or prodrug thereof, for treatment of a disease or condition characterized by aberrant complement system activity.

Alternatively, in certain aspects, the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for use in treatment of a disease or condition characterized by aberrant complement system activity.

As used herein, a “disease or condition characterized by aberrant complement system activity” refers to any disease or condition in which it is desirable to reduce complement system activity. For example, it may be desirable to reduce complement system activity in the setting of inappropriate activation or hyperactivation of the complement system.

In certain embodiments, the disease or condition characterized by aberrant complement system activity is an immunological disorder.

In certain embodiments, the disease or condition characterized by aberrant complement system activity is a disease of the central nervous system.

In certain embodiments, the disease or condition characterized by aberrant complement system activity is a renal disease.

In certain embodiments, the disease or condition characterized by aberrant complement system activity is a cardiovascular disease.

In certain embodiments, the disease or condition characterized by aberrant complement system activity is a neurodegenerative disease or neurological disease.

In certain embodiments, the disease or condition characterized by aberrant complement system activity is selected from the group consisting of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, organ transplant rejection, myasthenia gravis, neuromyelitis optica, membranoproliferative glomerulonephritis, dense-deposit disease, cold agglutinin disease, and catastrophic antiphospholipid syndrome.

In certain embodiments, the disease or condition is paroxysmal nocturnal hemoglobinuria.

In certain embodiments, the disease or condition is atypical hemolytic uremic syndrome.

In certain embodiments, the disease or condition is organ transplant rejection.

In certain embodiments, the disease or condition is myasthenia gravis.

In certain embodiments, the disease or condition is neuromyelitis optica.

In certain embodiments, the disease or condition is membranoproliferative glomerulonephritis.

In certain embodiments, the disease or condition is dense-deposit disease.

In certain embodiments, the disease or condition is cold agglutinin disease.

In certain embodiments, the disease or condition is catastrophic antiphospholipid syndrome.

In other embodiments, the disease or condition characterized by aberrant complement system activity is adult respiratory distress syndrome, myocardial infarct, lung inflammation, hyperacute rejection (transplantation rejection), sepsis, cardiopulmonary bypass, burns, asthma, restenosis, multiple organ dysfunction syndrome, Guillain-Barré syndrome, hemorrhagic shock, paroxysmal nocturnal hemoglobinuria, glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis, infertility, Alzheimer's disease, organ rejection (transplantation), myasthenia gravis, multiple sclerosis, platelet storage, or hemodialysis.

In other embodiments, the disease or condition characterized by aberrant complement system activity is selected from the group consisting of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), warm autoimmune hemolytic anemia, IgA nephropathy, C3 glomerulonephritis, and focal segmental glomerulosclerosis.

In certain embodiments, the disease or condition characterized by aberrant complement system activity is a hematological disorder.

In other embodiments, the disease or condition characterized by aberrant complement system activity is an ocular disorder or an eye disorder.

In certain embodiments, the disease or condition characterized by aberrant complement system activity is macular degeneration, age-related macular degeneration (AMD), macular edema, diabetic macular edema, choroidal neovascularization (CNV), uveitis, Behcet's uveitis, proliferative diabetic retinopathy, non-proliferative diabetic retinopathy, glaucoma, hypertensive retinopathy, a corneal neovascularization disease, post-corneal transplant rejection, a corneal dystrophic disease, an autoimmune dry eye disease, Stevens-Johnson syndrome, Sjogren's syndrome, an environmental dry eye disease, Fuchs' endothelial dystrophy, retinal vein occlusion, or post-operative inflammation.

Formulations, Routes of Administration, and Dosing

The compounds of the invention, and pharmaceutically acceptable salts or prodrugs thereof, can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient, in a variety of forms adapted to the chosen route of administration, e.g., orally or parenterally, by intravenous, intraperitoneal, intramuscular, topical, or subcutaneous routes. Additional routes of administration are also contemplated by the invention.

Thus, the present compounds may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2% to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following diluents and carriers: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water or physiologically acceptable aqueous solution, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation can include vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or

glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the compounds of the invention to the skin are known in the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392; incorporated herein by reference), Geria (U.S. Pat. No. 4,992,478; incorporated herein by reference), Smith et al. (U.S. Pat. No. 4,559,157; incorporated herein by reference), and Wortzman (U.S. Pat. No. 4,820,508; incorporated herein by reference).

Useful dosages of the compounds of the invention can be determined, at least initially, by comparing their *in vitro* activity and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known in the art; for example, see U.S. Pat. No. 4,938,949 (incorporated herein by reference).

The amount of the compound, or pharmaceutically acceptable salt or prodrug thereof, required for use in treatment will vary not only with the particular compound, salt, or prodrug selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

In general, however, a suitable dose will be in the range of from about 0.5 to about 100 mg/kg body weight of the recipient per day, e.g., from about 3 to about 90 mg/kg of body weight per day, from about 6 to about 75 mg per kilogram of body weight per day, from about 10 to about 60 mg/kg of body weight per day, or from about 15 to about 50 mg/kg of body weight per day.

Compounds of the invention, or pharmaceutically acceptable salts or prodrugs thereof, can be conveniently formulated in unit dosage form; for example, containing 5 to 1000 mg, 10 to 750 mg, or 50 to 500 mg of active ingredient per unit dosage form. In one embodiment, the invention provides a composition comprising a compound of the invention, or pharmaceutically acceptable salts or prodrugs thereof, formulated in such a unit dosage form.

The desired dose may conveniently be presented in a single dose or as divided doses to be administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations.

Compounds of the invention, or pharmaceutically acceptable salts or prodrugs thereof, can also be administered in combination with other therapeutic agents, for example, other agents that are useful for treating or preventing ischemia, blood loss, or reperfusion injury. In certain embodiments, compounds of the invention, and pharmaceutically acceptable salts or prodrugs thereof, can also be administered in combination with one or more other therapeutic agents that are useful for treating or preventing an ocular disorder or eye disorder.

Other delivery systems can include time-release, delayed release, or sustained release delivery systems such as are well-known in the art. Such systems can avoid repeated administrations of the active compound, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. Use of a long-term sustained release implant may be desirable. Long-term release, as used herein, means that the delivery system or is implant constructed and arranged to deliver therapeutic levels of the active ingredient for at least 30 days, and preferably 60 days.

In certain embodiments, a compound of the invention is formulated for intraocular administration, for example direct injection or insertion within or in association with an intraocular medical device. In certain embodiments, a compound of the invention is formulated as an ophthalmic solution. In certain embodiments, a compound of the invention can be administered via ocular delivery, for example, by local ocular administration, including topical, intravitreal, periocular, transscleral, retrobulbar, juxtасcleral, suprachoroidal, or sub-tenon administration. A compound of the invention can be administered via ocular delivery either alone or in combination with one or more additional therapeutic agents.

The compounds of the invention may be formulated for depositing into a medical device, which may include any of a variety of conventional grafts, stents, including stent grafts, catheters, balloons, baskets, or other device that can be deployed or permanently implanted within a body lumen. As a particular example, it would be desirable to have devices and methods which can deliver compounds of the invention to the region of a body which has been treated by interventional technique.

In exemplary embodiment, a compound of the invention may be deposited within a medical device, such as a stent, and delivered to the treatment site for treatment of a portion of the body.

Stents have been used as delivery vehicles for therapeutic agents (i.e., drugs). Intravascular stents are generally permanently implanted in coronary or peripheral vessels. Stent designs include those of U.S. Pat. No. 4,733,655 (Palmaz), U.S. Pat. No. 4,800,882 (Gianturco), or U.S. Pat. No. 4,886,062 (Wiktor). Such designs include both metal and polymeric stents, as well as self-expanding and balloon-expandable stents. Stents may also be used to deliver a drug at the site of contact with the vasculature, as disclosed in U.S. Pat. No. 5,102,417 (Palmaz), U.S. Pat. No. 5,419,760 (Narciso, Jr.), U.S. Pat. No. 5,429,634 (Narciso, Jr.), and in International Patent Application Nos. WO 91/12779 (Medtronic, Inc.) and WO 90/13332 (Cedars-Sinai Medical Center), for example.

The term “deposited” means that the compound is coated, adsorbed, placed, or otherwise incorporated into the device by methods known in the art. For example, the compound may be embedded and released from within (“matrix type”) or surrounded by and released through (“reservoir type”) polymer materials that coat or span the medical device. In the latter example, the compound may be entrapped within the polymer materials or coupled to the polymer materials using one or more the techniques for generating such materials known in the art. In other formulations, the compound may be linked to the surface of the medical device without the need for a coating, for example by means of detachable bonds, and release with time or can be removed by active mechanical or chemical processes. In other formulations, the compound may be in a permanently immobilized form that presents the compound at the implantation site.

In certain embodiments, the compound may be incorporated with polymer compositions during the formation of biocompatible coatings for medical devices, such as stents. The coatings produced from these components are typically homogeneous and are useful for coating a number of devices designed for implantation.

The polymer may be either a biostable or a bioabsorbable polymer depending on the desired rate of release or the desired degree of polymer stability, but frequently a bioabsorbable polymer is preferred for this embodiment since, unlike a biostable polymer, it will not be present long after implantation to cause any adverse, chronic local response. Bioabsorbable polymers that could be used include, but are not limited to, poly(L-lactic acid), polycaprolactone, polyglycolide (PGA), poly(lactide-co-glycolide) (PLLA/PGA), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester,

polyanhydride, poly(glycolic acid), poly(D-lactic acid), poly(L-lactic acid), poly(D, L-lactic acid), poly(D, L-lactide) (PLA), poly(L-lactide) (PLLA), poly(glycolic acid-co-trimethylene carbonate) (PGA/PTMC), polyethylene oxide (PEO), polydioxanone (PDS), polyphosphoester, polyphosphoester urethane, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), copoly(ether-esters) (e.g., PEO/PLA), polyalkylene oxalates, polyphosphazenes and biomolecules such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, cross linked or amphipathic block copolymers of hydrogels, and other suitable bioabsorbable polymers known in the art. Also, biostable polymers with a relatively low chronic tissue response such as polyurethanes, silicones, and polyesters could be used, and other polymers could also be used if they can be dissolved and cured or polymerized on the medical device such as polyolefins, polyisobutylene and ethylene-alphaolefin copolymers; acrylic polymers and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinylpyrrolidone; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile, polyvinyl ketones; polyvinyl aromatics, such as polystyrene, polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers; pyran copolymer; polyhydroxy-propyl-methacrylamide-phenol; polyhydroxyethyl-aspartamide-phenol; polyethyleneoxide-polylysine substituted with palmitoyl residues; polyamides, such as Nylon 66 and polycaprolactam; alkyd resins, polycarbonates; polyoxymethylenes; polyimides; polyethers; epoxy resins, polyurethanes; rayon; rayon-triacetate; cellulose, cellulose acetate, cellulose butyrate; cellulose acetate butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers; and carboxymethyl cellulose.

Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

In certain embodiments of the invention, the compound of the invention is coupled to a polymer or semipermeable polymer matrix that is formed as a stent or stent-graft device.

Typically, polymers are applied to the surface of an implantable device by spin coating, dipping, or spraying. Additional methods known in the art can also be utilized for this purpose. Methods of spraying include traditional methods as well as microdeposition techniques with an inkjet type of dispenser. Additionally, a polymer can be deposited on an

implantable device using photo-patterning to place the polymer on only specific portions of the device. This coating of the device provides a uniform layer around the device which allows for improved diffusion of various analytes through the device coating.

In certain embodiments of the invention, the compound is formulated for release from the polymer coating into the environment in which the medical device is placed. Preferably, the compound is released in a controlled manner over an extended time frame (e.g., months) using at least one of several well-known techniques involving polymer carriers or layers to control elution. Some of these techniques are described in U.S. Patent Application 2004/0243225A1, the entire disclosure of which is incorporated herein in its entirety.

Moreover, as described for example in U.S. Pat. No. 6,770,729, which is incorporated herein in its entirety, the reagents and reaction conditions of the polymer compositions can be manipulated so that the release of the compound from the polymer coating can be controlled. For example, the diffusion coefficient of the one or more polymer coatings can be modulated to control the release of the compound from the polymer coating. In a variation on this theme, the diffusion coefficient of the one or more polymer coatings can be controlled to modulate the ability of an analyte that is present in the environment in which the medical device is placed (e.g., an analyte that facilitates the breakdown or hydrolysis of some portion of the polymer) to access one or more components within the polymer composition (and for example, thereby modulate the release of the compound from the polymer coating). Yet another embodiment of the invention includes a device having a plurality of polymer coatings, each having a plurality of diffusion coefficients. In such embodiments of the invention, the release of the compound from the polymer coating can be modulated by the plurality of polymer coatings.

In yet another embodiment of the invention, the release of the compound from the polymer coating is controlled by modulating one or more of the properties of the polymer composition, such as the presence of one or more endogenous or exogenous compounds, or alternatively, the pH of the polymer composition. For example, certain polymer compositions can be designed to release a compound in response to a decrease in the pH of the polymer composition.

Kits

The invention also provides a kit, comprising a compound of the invention, or a pharmaceutically acceptable salt or prodrug thereof, at least one other therapeutic agent, packaging material, and instructions for administering the compound of the invention or the

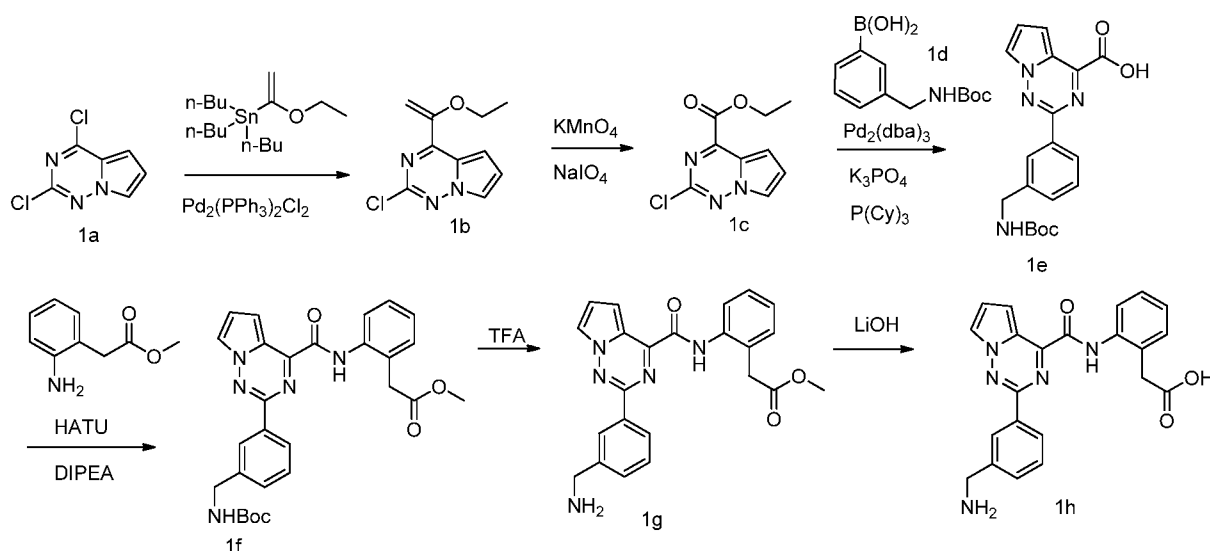
pharmaceutically acceptable salt or prodrug thereof and the other therapeutic agent or agents to a mammal to treat or prevent a disease or condition characterized by aberrant complement activity. In one embodiment, the mammal is a human.

It will be understood by one of ordinary skill in the relevant arts that other suitable modifications and adaptations to the compositions and methods described herein are readily apparent from the description of the invention contained herein in view of information known to the ordinarily skilled artisan, and may be made without departing from the scope of the invention or any embodiment thereof.

EXAMPLES

Having now described the present invention in detail, the same will be more clearly understood by reference to the following examples, which are included herewith for purposes of illustration only and are not intended to be limiting of the invention.

Scheme-1



Preparation of 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**1h**)

Step-1: Preparation of 2-chloro-4-(1-ethoxyvinyl)pyrrolo[2,1-f][1,2,4]triazine (**1b**)

To a solution of 2,4-dichloropyrrolo[2,1-f][1,2,4]triazine (**1a**) (3 g, 15.96 mmol, CAS# 918538-05-3) in DMF (50 mL) under Ar atmosphere was added 1-ethoxyvinyltri-*n*-butyltin (7.07 mL, 20.74 mmol, CAS# 97674-02-7) and bis(triphenylphosphine)Palladium(II)chloride (0.56 g, 0.8 mmol). The mixture was heated with stirring at 100 °C for 30 min, cooled to room temp and diluted with EtOAc (150 mL). The reaction mixture was washed with water

(50 mL), brine (30 mL), dried, filtered and concentrated in vacuum to dryness. The residue obtained was purified by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-50%] to afford 2-chloro-4-(1-ethoxyvinyl)pyrrolo[2,1-f][1,2,4]triazine (**1b**) (2.2 g, 62 % yield) as an orange oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.23 (dd, *J* = 2.6, 1.4 Hz, 1H), 7.34 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.11 (dd, *J* = 4.7, 2.6 Hz, 1H), 5.64 (d, *J* = 2.4 Hz, 1H), 4.88 (d, *J* = 2.4 Hz, 1H), 4.03 (q, *J* = 7.0 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H).

Step-2: Preparation of ethyl 2-chloropyrrolo[2,1-f][1,2,4]triazine-4-carboxylate (**1c**)

Sodium periodate (1.17 g, 5.47 mmol) was suspended in water (9 mL) and sonicated until a clear solution (pH ~4) was obtained. This solution was added to a solution of 2-chloro-4-(1-ethoxyvinyl)pyrrolo[2,1-f][1,2,4]triazine (**1b**) (612 mg, 2.74 mmol) in 1,4-dioxane (40 mL). KMnO₄ (43 mg, 0.27 mmol) was added and the reaction mixture was stirred at room temp for 2 h. The pH of reaction mixture was adjusted between 7-8 using saturated aqueous K₂CO₃ solution. The precipitate was filtered off, rinsed thoroughly with DCM (4 x 20 mL). The combined filtrates were washed with water, brine, dried, filtered and concentrated in vacuum to dryness. The residue obtained was purified by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] to afford ethyl 2-chloropyrrolo[2,1-f][1,2,4]triazine-4-carboxylate (**1c**) (212 mg, 34 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.43 (dd, *J* = 2.5, 1.3 Hz, 1H), 7.45 (dd, *J* = 4.8, 1.3 Hz, 1H), 7.30 (dd, *J* = 4.8, 2.5 Hz, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).

Step-3: Preparation of 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**1e**)

To a solution of ethyl 2-chloropyrrolo[2,1-f][1,2,4]triazine-4-carboxylate (**1c**) (150 mg, 0.67 mmol) in dioxane (6 mL) was added 3-(((*tert*-butoxycarbonyl)amino)methyl)phenylboronic acid (**1d**) (192 mg, 0.77 mmol; CAS# 199609-62-6), potassium triphosphate (282 mg, 1.33 mmol) in water (1 mL), tricyclohexylphosphine (56 mg, 0.2 mmol) and Pd₂(dba)₃ (61 mg, 0.07 mmol). The mixture was degassed and filled with Ar, then heated at 125 °C for 30 min. The mixture was cooled to room temperature, diluted with EtOAc, washed with water, brine, filtered and concentrated in vacuum to dryness. The residue obtained was purified by flash column chromatography [silica (12 g), eluting with MeOH in DCM from 0-30%] to afford 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**1e**) (150 mg, 61 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.21 – 8.08 (m, 3H), 7.53 (dd, *J* = 11.2, 5.0 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.14 – 7.08 (m, 1H), 7.06 – 7.00 (m, 1H), 4.22 (d, *J* = 6.2 Hz, 2H), 1.41 (s, 9H).

Step-4: Preparation of methyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**1f**)

To a solution of 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylic acid (**1e**) (95 mg, 0.26 mmol) in DMF (8 mL) was added methyl 2-(2-aminophenyl)acetate (51 mg, 0.31 mmol, CAS# 35613-44-6), DIPEA (0.14 mL, 0.77 mmol) and HATU (118 mg, 0.31 mmol). The resulting mixture was stirred at RT overnight, diluted with EtOAc (60 mL), washed with water (3 xs), brine, filtered and concentrated in vacuum to dryness. The residue obtained was purified by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc/MeOH (9:1) in hexane from 0-100%] to afford methyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**1f**) (98 mg, 74 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.78 (s, 1H), 8.44 (d, *J* = 7.8 Hz, 1H), 8.41 – 8.31 (m, 2H), 7.82 – 7.75 (m, 1H), 7.58 – 7.48 (m, 3H), 7.46 – 7.37 (m, 3H), 7.31 – 7.23 (m, 2H), 4.27 (d, *J* = 6.1 Hz, 2H), 3.89 (s, 2H), 3.56 (s, 3H), 1.41 (s, 9H).

Step-5: Preparation of methyl 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**1g**)

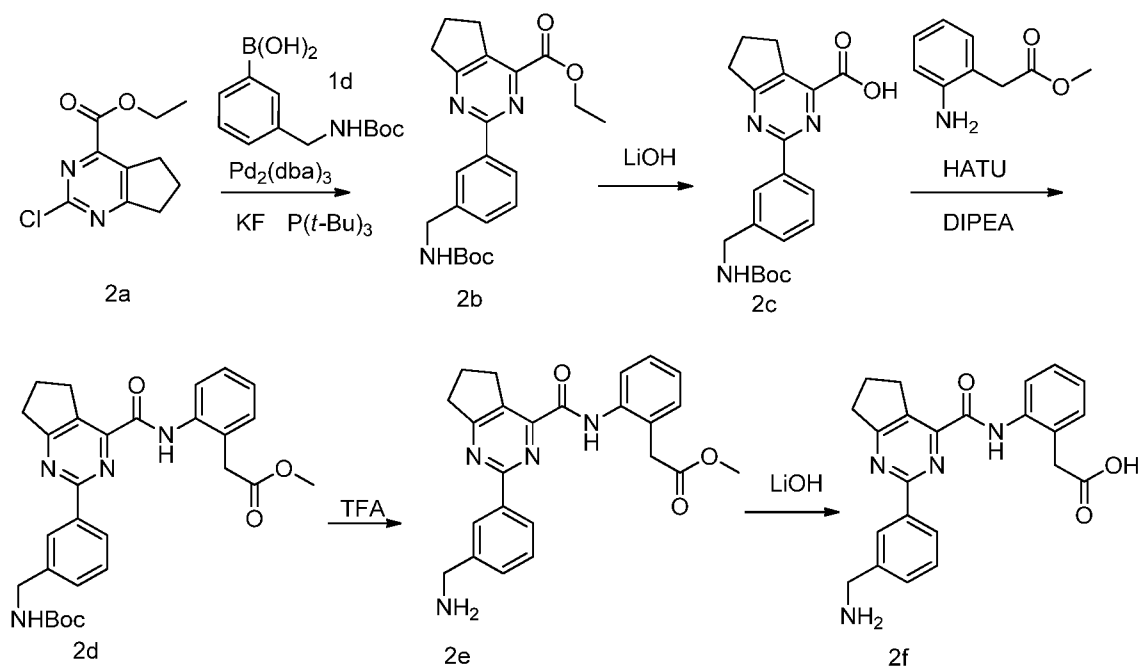
To a solution of methyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**1f**) (92 mg, 0.18 mmol) in DCM (8 mL) was added TFA (0.28 mL, 3.57 mmol). The resulting mixture was stirred at RT for 2h and concentrated in vacuum to dryness. The residue obtained was purified by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-60%] to afford compound (**1g**) (73 mg, 98 % yield) as a yellow solid, 23 mg was converted into HCl salt and lyophilized to give methyl 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**1g**) (25 mg) HCl salt as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.80 (s, 1H, D₂O exchangeable), 8.69 – 8.62 (m, 1H), 8.58 (d, *J* = 7.5, 1.6 Hz, 1H), 8.50 – 8.39 (m, 3H, D₂O exchangeable), 8.39 – 8.33 (m, 1H), 7.77 – 7.56 (m, 4H), 7.47 – 7.36 (m, 2H), 7.34 – 7.24 (m, 2H), 4.23 – 4.11 (m, 2H), 3.90 (s, 2H), 3.55 (s, 3H); MS (ES⁺): 416.3 (M+1); (ES⁻): 414.4 (M-1), 450.3 (M+Cl); HPLC, purity 92.70%.

Step-6: Preparation of 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**1h**)

To a solution of methyl 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**1g**) (62 mg, 0.15 mmol) in THF (10 mL) was added lithium hydroxide hydrate (63 mg, 1.49 mmol) in water (2 mL). The resulting mixture was stirred at

RT overnight. THF was removed under vacuum, the residue obtained was acidified to pH 4 with HCl (2N), the solid obtained was collected by filtration, washed with water (3 x 2mL) and dried in vacuum to afford 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**1h**) (36 mg, 61 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.51 (s, 1H, D₂O exchangeable), 9.36 (s, 1H), 9.19 (s, 3H, D₂O exchangeable), 8.43 – 8.33 (m, 1H), 8.33 – 8.21 (m, 1H), 8.00 – 7.84 (m, 1H), 7.72 – 7.61 (m, 1H), 7.60 – 7.48 (m, 2H), 7.34 – 7.22 (m, 3H), 7.19 – 7.05 (m, 1H), 4.13 (s, 2H), 3.50 (s, 2H); MS (ES⁺): 402.4 (M+1); (ES⁻): 400.4 (M-1); HPLC purity, 90.46%.

Scheme-2



Preparation of 2-(2-(2-(3-(aminomethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-4-carboxamido)phenyl)acetic acid (**2f**)

Step-1: Preparation of ethyl 2-(3-(((tert-butoxycarbonyl)amino)methyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-4-carboxylate (**2b**)

Compound **2b** was prepared according to the procedure reported in step-3 of Scheme-1, from ethyl 2-chloro-6,7-dihydro-5H-cyclopenta[d]pyrimidine-4-carboxylate (**2a**) (200 mg, 0.88 mmol; CAS # 1660116-32-4; prepared according to the procedure reported by Blaquiére, Nicole et al in PCT Int. Appl., 2015025026, 26 Feb 2015) in DMF (20 mL) using 3-(((tert-butoxycarbonyl)amino)methyl)phenylboronic acid (**1d**) (251 mg, 0.97 mmol), potassium fluoride (169 mg, 2.91 mmol), tri-*tert*-butylphosphine (1.59 mL, 1.59 mmol) and Pd₂(dba)₃ (162 mg, 0.18 mmol) under a nitrogen atmosphere by heating at 120 °C for 14 h. This gave after workup and purification by flash column chromatography [silica (12 g),

eluting with hexanes/ethyl acetate (1:0 to 4:1)] ethyl 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-4-carboxylate (**2b**) (128 mg, 37% yield) as a colorless gum; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.32 – 8.22 (m, 2H), 7.57 – 7.33 (m, 3H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.22 (d, *J* = 6.2 Hz, 2H), 3.22 (t, *J* = 7.5 Hz, 2H), 3.07 (t, *J* = 7.8 Hz, 2H), 2.12 (p, *J* = 7.7 Hz, 2H), 1.46 – 1.30 (m, 12H); MS (ES⁺): 420.3 (M+Na).

Step-2: Preparation of 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-4-carboxylic acid (**2c**)

Compound **2c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-4-carboxylate (**2b**) (125 mg, 0.31 mmol) in THF (10 mL) and MeOH (10 mL) using a solution of lithium hydroxide hydrate (81 mg, 1.89 mmol) in water (10 mL) This gave after workup 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-4-carboxylic acid (**2c**), which was used as such for next step; MS (ES⁻) 368.4 (M-1).

Step-3: Preparation of methyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-4-carboxamido)phenyl)acetate (**2d**)

Compound **2d** was prepared according to the procedure reported in step-4 of Scheme-1, from 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-4-carboxylic acid (**2c**) using methyl 2-(2-aminophenyl)acetate (104 mg, 0.63 mmol), DIPEA (0.22 mL, 1.26 mmol) and HATU (239 mg, 0.63 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with hexanes/ethyl acetate (1:0 to 2:1)] methyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-4-carboxamido)phenyl)acetate (**2d**) (127 mg) as a yellow solid, which was used as such for next step; MS (ES⁺): 517.4 (M+1), 539.4 (M+Na); (ES⁻): 515.4 (M-1).

Step-4: Preparation of methyl 2-(2-(2-(3-(aminomethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-4-carboxamido)phenyl)acetate (**2e**)

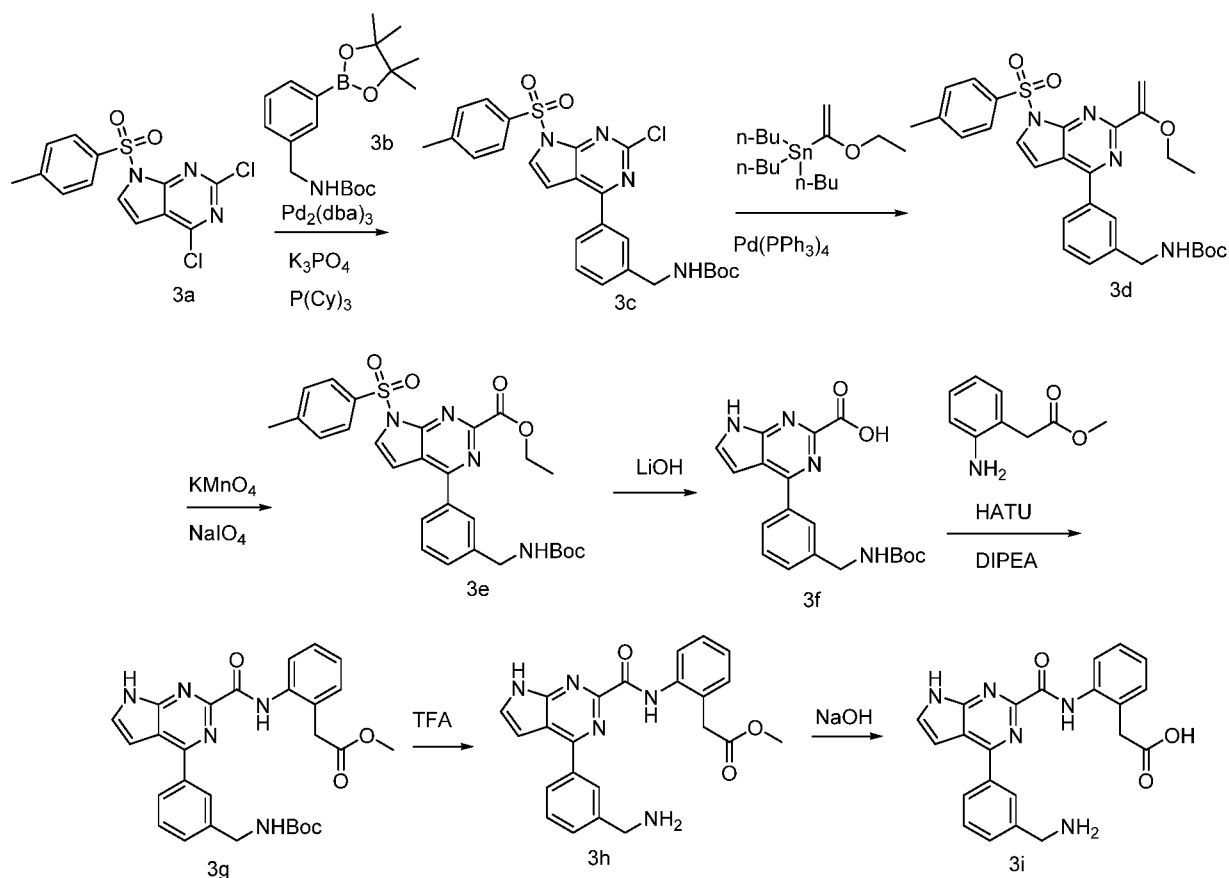
Compound **2e** was prepared according to the procedure reported in step-5 of Scheme-1, from methyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-4-carboxamido)phenyl)acetate (**2d**) (127 mg, 0.25 mmol) using TFA (0.57 mL, 7.38 mmol) in DCM (20 mL). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DCM/DMA-80 (1:0 to 4:1)] methyl 2-(2-(2-(3-(aminomethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-4-

carboxamido)phenyl)acetate (**2e**) (68 mg, 66% yield for three steps) as a white solid; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 10.67 (s, 1H), 8.58 – 8.54 (m, 1H), 8.47 – 8.42 (m, 1H), 7.91 – 7.67 (m, 1H), 7.56 – 7.43 (m, 2H), 7.42 – 7.34 (m, 2H), 7.29 – 7.17 (m, 1H), 3.87 (s, 2H), 3.84 (s, 2H), 3.55 (s, 3H), 3.09 (t, $J = 7.8$ Hz, 2H), 2.21 – 2.07 (m, 2H); MS (ES⁺): 417.3 (M+1); (ES⁻) 415.3 (M-1).

Step-5: Preparation of 2-(2-(2-(3-(aminomethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-4-carboxamido)phenyl)acetic acid (**2f**)

Compound **2f** was prepared according to the procedure reported in step-6 of Scheme-1, from methyl 2-(2-(2-(3-(aminomethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-4-carboxamido)phenyl)acetate (**2e**) (34 mg, 0.082 mmol) in THF (5 mL) and MeOH (5 mL) using a solution of lithium hydroxide hydrate (21 mg, 0.49 mmol) in water (5 mL) This gave after workup 2-(2-(2-(3-(aminomethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-4-carboxamido)phenyl)acetic acid (**2f**) (24 mgs, 73% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 12.35 (s, 1H), 9.46 (s, 1H), 9.27 (s, 3H), 8.46 – 8.23 (m, 1H), 7.87 – 7.77 (m, 1H), 7.55 – 7.47 (m, 2H), 7.30 – 7.19 (m, 2H), 7.13 – 7.05 (m, 1H), 4.11 (s, 2H), 3.42 (s, 2H), 3.08 (t, $J = 7.8$ Hz, 2H), 2.22 – 2.05 (m, 2H); MS (ES⁺): 403.3 (M+1); (ES⁻): 401.4 (M-1).

Scheme-3



Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxamido)phenyl)acetic acid (**3i**)

Step-1: Preparation of *tert*-butyl 3-(2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzylcarbamate (**3c**)

Compound **3c** was prepared according to the procedure reported in step-3 of Scheme-1 from 2,4-dichloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine (**3a**) (5 g, 14.61 mmol; CAS # 934524-10-4; prepared according to the procedure reported by Su, Qibin et al; in Journal of Medicinal Chemistry, 57(1), 144-158; 2014) in dioxane (100 mL) using *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylcarbamate (**3b**) (3.25 g, 9.74 mmol; CAS#: 832114-05-3), tripotassium phosphate (4.55 g, 21.43 mmol) in water (1 mL), tricyclohexylphosphine (0.82 g, 2.92 mmol) and Pd₂(dba)₃ (0.89 g, 0.97 mmol) in argon atmosphere and heating at 120 °C for 1h. This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-70%] *tert*-butyl 3-(2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzylcarbamate (**3c**) (2.9 g, 58.0 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.14 (d, *J* = 4.1 Hz, 1H), 8.10 – 8.07 (m, 1H), 8.06 – 8.04 (m, 1H), 7.96 – 7.90 (m, 2H), 7.58 – 7.44 (m, 5H), 7.24 (d, *J* = 4.1

Hz, 1H), 4.23 (d, $J = 6.2$ Hz, 2H), 2.39 (s, 3H), 1.40 (s, 9H); MS (ES⁺): 535.3, 537.3 (M+Na); (ES⁻): 511.3, 513.3 (M-1).

Step-2: Preparation of *tert*-butyl 3-(2-(1-ethoxyvinyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzylcarbamate (**3d**)

Compound **3d** was prepared according to the procedure reported in step-1 of Scheme-1 from *tert*-butyl 3-(2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzylcarbamate (**3c**) (2.5 g, 4.87 mmol) in DMF (100 mL) using 1-ethoxyvinyltri-*n*-butyltin (2.16 mL, 6.34 mmol) and Pd(Ph₃P)₄ (0.28 g, 0.24 mmol) in argon atmosphere and heating at 110 °C for 4h. This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-70%] *tert*-butyl 3-(2-(1-ethoxyvinyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzylcarbamate (**3d**) (1.7 g, 64% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.24 (d, $J = 8.4$ Hz, 2H), 8.07 (d, $J = 4.0$ Hz, 1H), 8.01 – 7.94 (m, 2H), 7.59 – 7.50 (m, 2H), 7.50 – 7.40 (m, 3H), 7.18 (d, $J = 4.1$ Hz, 1H), 5.72 (d, $J = 1.7$ Hz, 1H), 4.73 (d, $J = 1.7$ Hz, 1H), 4.24 (d, $J = 6.2$ Hz, 2H), 4.02 (q, $J = 6.9$ Hz, 2H), 2.38 (s, 3H), 1.52 (t, $J = 6.9$ Hz, 3H), 1.40 (s, 9H); MS (ES⁺): 571.4 (M+Na); (ES⁻): 547.4 (M-1).

Step-3: Preparation of ethyl 4-(3-((*tert*-butoxycarbonylamino)methyl)phenyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine-2-carboxylate (**3e**)

Compound **3e** was prepared according to the procedure reported in step-2 of Scheme-1 from *tert*-butyl 3-(2-(1-ethoxyvinyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzylcarbamate (**3d**) (1.5 g, 2.73 mmol) in 1,4-dioxane (50 mL) using sodium periodate solution (1.17 g, 5.47 mmol) in water (10 mL) and KMnO₄ (2 x 86 mg, 2 x 0.55 mmol, second dosing after 12 h). This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-60%] ethyl 4-(3-((*tert*-butoxycarbonylamino)methyl)phenyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine-2-carboxylate (**3e**) (500 mg, 33 % yield) as a yellow solid; MS (ES⁺): 551.3 (M+1), 573.3 (M+Na); (ES⁻): 549.4 (M-1).

Step-4: Preparation of 4-(3-((*tert*-butoxycarbonylamino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxylic acid (**3f**)

Compound **3f** was prepared according to the procedure reported in step-6 of Scheme-1 from ethyl 4-(3-((*tert*-butoxycarbonylamino)methyl)phenyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine-2-carboxylate (**3e**) (500 mg, 0.91 mmol) in THF (10 mL) using lithium hydroxide hydrate (76 mg, 1.82 mmol) in water (4 mL). This gave after workup 4-(3-((*tert*-butoxycarbonylamino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxylic acid (**3f**) (145 mg, 43 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.18 (s, 1H, D₂O

exchangeable), 12.69 (d, $J = 21.6$ Hz, 1H, D₂O exchangeable), 8.18 – 8.05 (m, 2H), 7.97 – 7.88 (m, 1H), 7.62 – 7.53 (m, 2H), 7.48 – 7.40 (m, 1H), 7.05 – 6.97 (m, 1H), 4.27 (d, $J = 6.3$ Hz, 2H), 1.41 (s, 9H); MS (ES⁻): 367.3 (M-1).

Step-5: Preparation of methyl 2-(2-(4-(3-((*tert*-butoxycarbonylamino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxamido)phenyl)acetate (**3g**)

Compound **3g** was prepared according to the procedure reported in step-4 of Scheme-1 from 4-(3-((*tert*-butoxycarbonylamino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxylic acid (**3f**) (120 mg, 0.33 mmol) in DMF (5 mL) using methyl 2-(2-aminophenyl)acetate (161 mg, 0.98 mmol), DIPEA (0.11 mL, 0.65 mmol) and HATU (186 mg, 0.49 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc/MeOH (9:1) in hexane from 0-100%] methyl 2-(2-(4-(3-((*tert*-butoxycarbonylamino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxamido)phenyl)acetate (**3g**) (42 mg, 25 % yield) as a white solid; MS (ES⁺) 538.3 (M+1).

Step-6: Preparation of methyl 2-(2-(4-(3-(aminomethyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxamido)phenyl)acetate (**3h**)

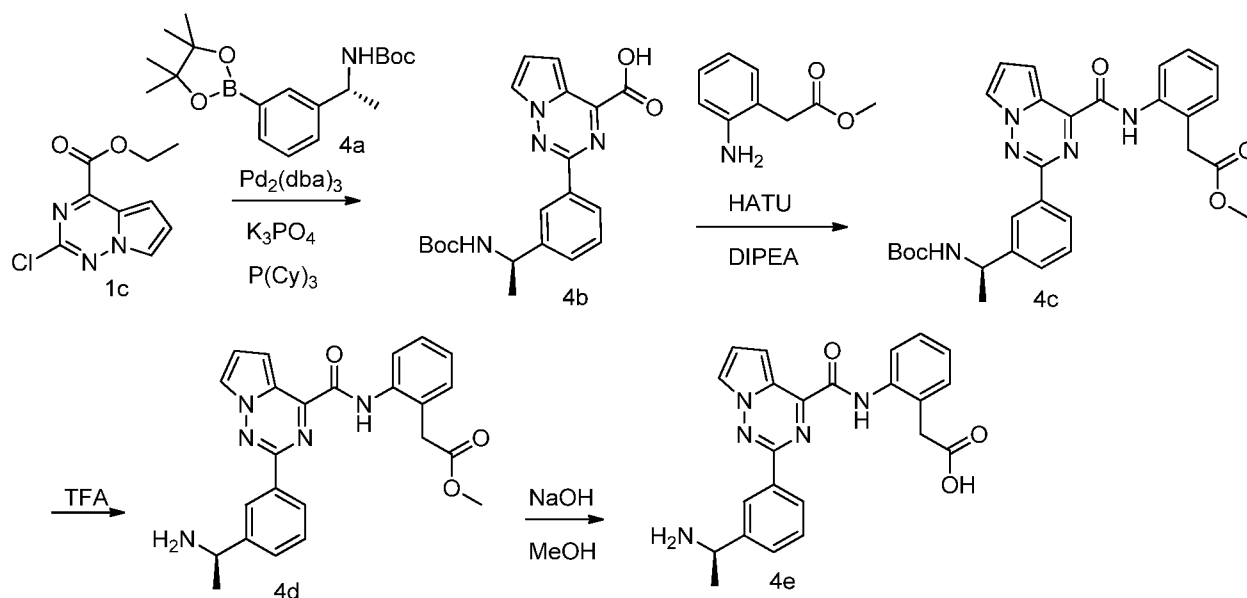
Compound **3h** was prepared according to the procedure reported in step-5 of Scheme-1 from methyl 2-(2-(4-(3-((*tert*-butoxycarbonylamino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxamido)phenyl)acetate (**3g**) (40 mg, 0.078 mmol) in DCM (8 mL) using TFA (0.06 mL, 0.78 mmol). This gave methyl 2-(2-(4-(3-(aminomethyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxamido)phenyl)acetate (**3h**) (13 mg, 40 % yield) which was used as such for next step.

Step-7: Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxamido)phenyl)acetic acid (**3i**)

To a solution of methyl 2-(2-(4-(3-(aminomethyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxamido)phenyl)acetate (**3h**) (13 mg from above step) in MeOH (5 mL) was added NaOH (12 mg, 0.31 mmol) in water (1 mL) and stirred at RT for 2h. MeOH was removed under vacuum, the residue was acidified to pH 3 and purified by reverse phase chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] to give 2-(2-(4-(3-(aminomethyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxamido)phenyl)acetic acid (**3i**) (2 mg, 6% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.78 (s, 1H, D₂O exchangeable), 10.83 (s, 1H, D₂O exchangeable), 8.49 – 8.23 (m, 5H, partially D₂O exchangeable), 8.01 – 7.92 (m, 2H), 7.69 (d, $J = 4.8$ Hz, 2H), 7.43 –

7.32 (m, 2H), 7.27 – 7.12 (m, 2H), 4.28 – 4.14 (m, 2H), 3.77 (s, 2H); MS (ES⁺): 402.3 (M+1); (ES⁻): 436.3 (M+Cl); HPLC purity 98.03%.

Scheme-4



Preparation of (R)-2-(2-(2-(3-(1-aminoethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**4e**)

Step-1: Preparation of (R)-2-(3-(1-(*tert*-butoxycarbonylamino)ethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**4b**)

Compound **4b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-chloropyrrolo[2,1-f][1,2,4]triazine-4-carboxylate (**1c**) (300 mg, 1.33 mmol) in dioxane (6 mL) using (R)-*tert*-butyl 1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethylcarbamate (**4a**) (600 mg, 1.73 mmol; CAS# 887254-66-2, prepared according to procedure reported in PCT Int. Appl., 2015009977, 22 Jan 2015), solution of tripotassium phosphate (564 mg, 2.66 mmol) in water (1 mL), tricyclohexylphosphine (112 mg, 0.4 mmol) and Pd₂(dba)₃ (122 mg, 0.13 mmol) in argon atmosphere and heating at 125 °C for 30 min. This gave after workup and purification by flash column chromatography [silica (12 g), eluting with MeOH in DCM from 0-30%] (R)-2-(3-(1-(*tert*-butoxycarbonylamino)ethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**4b**) (150 mg, 30 % yield) as a yellow solid; MS (ES⁻): 381.3 (M-1).

Step-2: Preparation of (R)-methyl 2-(2-(2-(3-(1-(*tert*-butoxycarbonylamino)ethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetate (**4c**)

Compound **4c** was prepared according to the procedure reported in step-4 of Scheme-1 from (R)-2-(3-(1-(*tert*-butoxycarbonylamino)ethyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylic acid (**4b**) (150 mg, 0.39 mmol) in DMF (8 mL) using methyl 2-(2-aminophenyl)acetate (78 mg, 0.47 mmol), DIPEA (0.21 mL, 1.18 mmol) and HATU (179 mg, 0.47 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc/MeOH (9:1) in hexane from 0-100%] (R)-methyl 2-(2-(2-(3-(1-(*tert*-butoxycarbonylamino)ethyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**4c**) (60 mg, 29 % yield) as a yellow solid; MS (ES⁺): 552.4 (M+1).

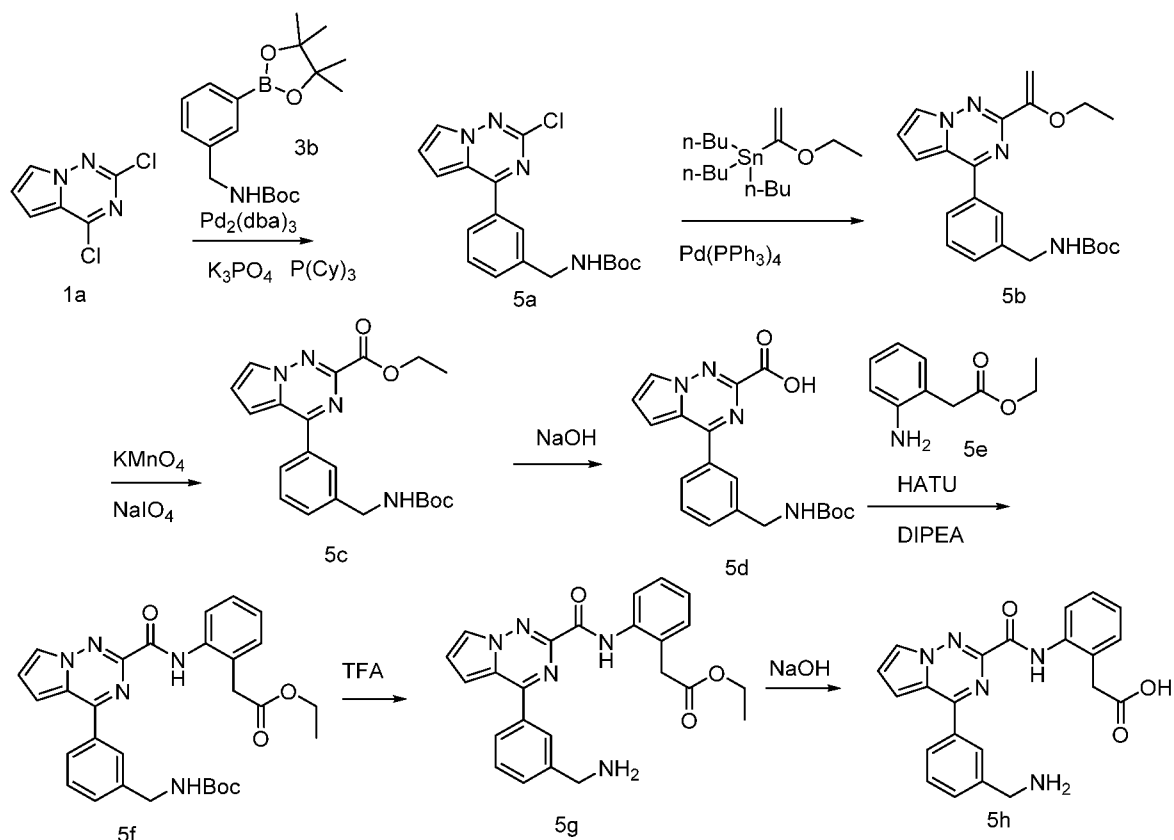
Step-3: Preparation of (R)-methyl 2-(2-(2-(3-(1-aminoethyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**4d**)

Compound **4d** was prepared according to the procedure reported in step-5 of Scheme-1 from (R)-methyl 2-(2-(2-(3-(1-(*tert*-butoxycarbonylamino)ethyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**4c**) (60 mg, 0.11 mmol) in DCM (8 mL) using TFA (0.087 mL, 1.13 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-100%] (R)-methyl 2-(2-(2-(3-(1-aminoethyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**4d**) (12 mg, 25 % yield), MS (ES⁺): 452.3 (M+Na); (ES⁻): 428.3 (M-1).

Step-4: Preparation of (R)-2-(2-(2-(3-(1-aminoethyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**4e**)

To a solution of (R)-methyl 2-(2-(2-(3-(1-aminoethyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**4d**) (12 mg, 0.028 mmol) in MeOH (5 mL) was added a solution of NaOH (18 mg, 0.45 mmol) in water (1 mL). The resulting mixture was stirred for 2h at RT and concentrated in vacuum to remove MeOH. The residue was acidified to PH~3 and purified by reverse phase chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] to afford (R)-2-(2-(2-(3-(1-aminoethyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**4e**) (7 mg, 15 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.74 (s, 1H, D₂O exchangeable), 10.89 (s, 1H, D₂O exchangeable), 8.70 – 8.46 (m, 5H, partially D₂O exchangeable), 8.42 – 8.35 (m, 1H), 7.89 – 7.81 (m, 1H), 7.78 – 7.69 (m, 1H, D₂O exchangeable), 7.69 – 7.58 (m, 2H), 7.46 – 7.35 (m, 2H), 7.33 – 7.21 (m, 2H), 4.65 – 4.47 (m, 1H), 3.81 (s, 2H), 1.60 (d, *J* = 6.7 Hz, 3H); MS (ES⁺): 438.3 (M+Na); (ES⁻): 414.4 (M-1); HPLC purity, 98.78%.

Scheme-5



Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-2-carboxamido)phenyl)acetic acid (**5h**)

Step-1: Preparation of *tert*-butyl 3-(2-chloropyrrolo[2,1-f][1,2,4]triazin-4-yl)benzylcarbamate (**5a**)

Compound **5a** was prepared according to the procedure reported in step-3 of Scheme-1 from 2,4-dichloropyrrolo[2,1-f][1,2,4]triazine (**1a**) (1 g, 5.32 mmol) in dioxane (50 mL) using *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylcarbamate (**3b**) (1.48 g, 4.43 mmol), tripotassium phosphate (1.88 g, 8.86 mmol) in water (5 mL), tricyclohexylphosphine (373 mg, 1.33 mmol) and Pd₂(dba)₃ (0.406 g, 0.44 mmol) in Ar atmosphere and heating at 75 °C for 60 min. This gave after workup and purification by flash column chromatography [silica (12 g), eluting with MeOH in DCM from 0-30%] *tert*-butyl 3-(2-chloropyrrolo[2,1-f][1,2,4]triazin-4-yl)benzylcarbamate (**5a**) (1 g, 63 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.34 – 8.27 (m, 1H), 8.08 – 7.98 (m, 2H), 7.65 – 7.50 (m, 3H), 7.40 – 7.30 (m, 1H), 7.24 – 7.14 (m, 1H), 4.27 (d, *J* = 6.2 Hz, 2H), 1.41 (s, 9H).

Step-2: Preparation of *tert*-butyl 3-(2-(1-ethoxyvinyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)benzylcarbamate (**5b**)

Compound **5b** was prepared according to the procedure reported in step-1 of Scheme-1 from *tert*-butyl 3-(2-chloropyrrolo[2,1-*f*][1,2,4]triazin-4-yl)benzylcarbamate (**5a**) (3.2 g, 8.92 mmol) in DMF (60 mL) using 1-ethoxyvinyltri-*n*-butyltin (3.65 mL, 10.70 mmol) and Pd(PPh₃)₄ (0.515 g, 0.45 mmol) in argon atmosphere and heating at 110 °C for 10h. This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-70%] *tert*-butyl 3-(2-(1-ethoxyvinyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)benzylcarbamate (**5b**) (3.1 g, 88 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.28 – 8.21 (m, 1H), 8.11 – 8.00 (m, 2H), 7.64 – 7.47 (m, 3H), 7.22 (dd, *J* = 4.6, 1.4 Hz, 1H), 7.12 – 7.04 (m, 1H), 5.74 (d, *J* = 1.8 Hz, 1H), 4.79 (d, *J* = 1.8 Hz, 1H), 4.28 (d, *J* = 6.2 Hz, 2H), 3.99 (q, *J* = 6.9 Hz, 2H), 1.46 – 1.31 (m, 12H).

Step-3: Preparation of ethyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-2-carboxylate (**5c**)

Compound **5c** was prepared according to the procedure reported in step-2 of Scheme-1 from *tert*-butyl 3-(2-(1-ethoxyvinyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)benzylcarbamate (**5b**) (500 mg, 1.27 mmol) in 1,4-dioxane (50 mL) using sodium periodate solution (542 mg, 2.54 mmol) in water (20 mL) and KMnO₄ (120 mg, 0.76 mmol, first dosing and second dosing 40 mg, 0.25 mmol after 12 h). This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-60%] ethyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-2-carboxylate (**5c**) (255 mg, 51 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.45 – 8.39 (m, 1H), 8.10 – 8.01 (m, 2H), 7.64 – 7.49 (m, 3H), 7.38 – 7.33 (m, 1H), 7.33 – 7.26 (m, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.27 (d, *J* = 6.2 Hz, 2H), 1.47 – 1.31 (m, 12H); MS (ES⁺): 397.3 (M+1); (ES⁻): 395.4 (M-1)

Step-4: Preparation of 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-2-carboxylic acid (**5d**)

Compound **5d** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-2-carboxylate (**5c**) (1.6 g, 4.04 mmol) in MeOH/THF (20 mL, 1:1) using sodium hydroxide (258 mg, 6.46 mmol) in water (3 mL). This gave after workup and purification by flash column chromatography [silica (24 g), eluting with MeOH in DCM from 0-10%] 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-*f*][1,2,4]triazine-2-carboxylic acid (**5d**) (960 mg, 65 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.71 (s, 1H), 8.43 – 8.33 (m, 1H), 8.11 – 8.02 (m, 2H), 7.64 – 7.47 (m, 3H), 7.34 (dd, *J* = 4.6, 1.4 Hz, 1H), 7.32

– 7.25 (m, 1H), 4.27 (d, $J = 6.2$ Hz, 2H), 1.41 (s, 9H); MS (ES+): 369.3 (M+1); (ES-): 367.3 (M-1).

Step-5: Preparation of ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-2-carboxamido)phenyl)acetate (**5f**)

Compound **5f** was prepared according to the procedure reported in step-4 of Scheme-1 from 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-2-carboxylic acid (**5d**) (200 mg, 0.54 mmol) in DMF (10 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (117 mg, 0.65 mmol), DIPEA (0.142 mL, 0.81 mmol) and HATU (248 mg, 0.65 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-100%] followed by reverse column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-2-carboxamido)phenyl)acetate (**5f**) (212 mg, 74 % yield) as a yellow solid; ^1H NMR (300 MHz, DMSO- d_6) δ 10.64 (s, 1H), 8.44 (dd, $J = 2.7, 1.3$ Hz, 1H), 8.29 – 8.18 (m, 2H), 7.85 – 7.75 (m, 1H), 7.66 – 7.53 (m, 3H), 7.47 – 7.41 (m, 1H), 7.38 (d, $J = 7.5$ Hz, 2H), 7.34 – 7.29 (m, 1H), 7.28 – 7.19 (m, 1H), 4.30 (d, $J = 6.2$ Hz, 2H), 3.98 (q, $J = 7.1$ Hz, 2H), 3.84 (s, 2H), 1.40 (s, 9H), 0.99 (t, $J = 7.1$ Hz, 3H); MS (ES+): 530.4 (M+1); (ES-): 528.5 (M-1).

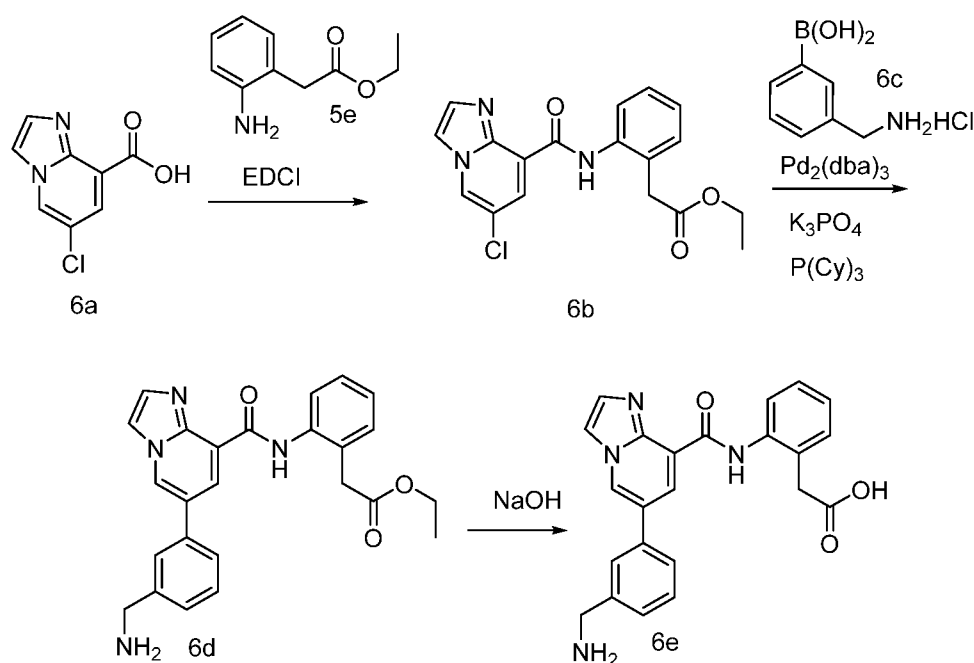
Step-6: Preparation of ethyl 2-(2-(4-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-2-carboxamido)phenyl)acetate (**5g**)

Compound **5g** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-2-carboxamido)phenyl)acetate (**5f**) (210 mg, 0.4 mmol) in DCM (10 mL) using TFA (0.31 mL, 3.97 mmol). This gave after work up and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-100%] followed by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(4-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-2-carboxamido)phenyl)acetate (**5g**) (152 mg, 89 % yield) as a yellow solid; ^1H NMR (300 MHz, DMSO- d_6) δ 10.64 (s, 1H, D $_2$ O exchangeable), 8.62 (s, 3H, D $_2$ O exchangeable), 8.51 – 8.44 (m, 2H), 8.42 – 8.35 (m, 1H), 7.86 – 7.80 (m, 1H), 7.80 – 7.64 (m, 3H), 7.43 – 7.31 (m, 3H), 7.28 – 7.20 (m, 1H), 4.23 – 4.17 (m, 2H), 3.98 (q, $J = 7.1$ Hz, 2H), 3.84 (s, 2H), 1.00 (t, $J = 7.1$ Hz, 3H); MS (ES+): 430.3 (M+1), 452.3 (M+Na); HPLC purity, 99.46%.

Step-7: Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-2-carboxamido)phenyl)acetic acid (**5h**)

Compound **5h** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(4-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-2-carboxamido)phenyl)acetate (**5g**) (70 mg, 0.16 mmol) in MeOH (10 mL) using sodium hydroxide (33 mg, 0.82 mmol) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(4-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-2-carboxamido)phenyl)acetic acid (**5h**) (39 mg, 60% yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.75 (s, 1H, D₂O exchangeable), 10.78 (s, 1H, D₂O exchangeable), 8.59 – 8.32 (m, 6H), 7.90 – 7.83 (m, 1H), 7.84 – 7.77 (m, 1H), 7.72 (t, *J* = 7.7 Hz, 1H), 7.64 (dd, *J* = 4.7, 1.3 Hz, 1H), 7.42 – 7.31 (m, 3H), 7.27 – 7.18 (m, 1H), 4.22 (s, 2H), 3.75 (s, 2H); MS (ES⁺): 402.3 (M+1); (ES⁻): 400.4 (M-1), 436.3 (M+Cl); HPLC purity, 99.40%.

Scheme-6



Preparation of 2-(2-(6-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridine-8-carboxamido)phenyl)acetic acid (**6e**)

Step-1: Preparation of ethyl 2-(2-(6-chloroimidazo[1,2-a]pyridine-8-carboxamido)phenyl)acetate (**6b**)

To a solution of 6-chloroimidazo[1,2-a]pyridine-8-carboxylic acid (**6a**) (650 mg, 3.31 mmol; CAS# 155735-02-7) in MeOH (10 mL) was added ethyl 2-(2-aminophenyl)acetate (**5e**) (593 mg, 3.31 mmol; CAS # 87-25-2) and N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (EDCI, 697 mg, 3.64 mmol), the resulting mixture was stirred at RT overnight and diluted with EtOAc (60 mL). The organic layer was separated washed with

water (3 xs), brine, dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-100%], followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] to afford ethyl 2-(2-(6-chloroimidazo[1,2-a]pyridine-8-carboxamido)phenyl)acetate (**6b**) (770 mg, 65 % yield) as an off white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (s, 1H), 9.15 (d, *J* = 2.1 Hz, 1H), 8.22 - 8.08 (m, 2H), 8.03 (d, *J* = 2.0 Hz, 1H), 7.74 (d, *J* = 1.3 Hz, 1H), 7.40 - 7.32 (m, 2H), 7.17 (td, *J* = 7.5, 1.3 Hz, 1H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 2H), 1.07 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 358.2 (M+1), 380.2 (M+Na).

Step-2: Preparation of ethyl 2-(2-(6-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridine-8-carboxamido)phenyl)acetate (**6d**)

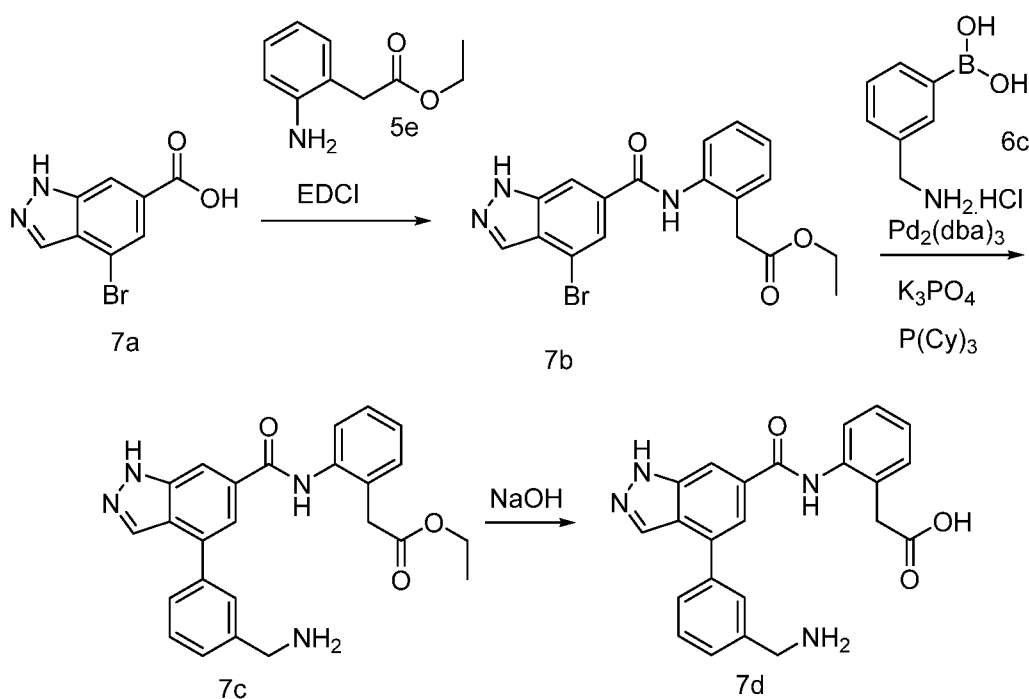
Compound **6d** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(6-chloroimidazo[1,2-a]pyridine-8-carboxamido)phenyl)acetate (**6b**) (250 mg, 0.70 mmol) in dioxane (3 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (196 mg, 1.05 mmol; CAS # 146285-80-5), tripotassium phosphate (1.3 M solution) (1.61 mL, 2.10 mmol), tricyclohexylphosphine (58.8 mg, 0.210 mmol) and Pd₂(dba)₃ (64.0 mg, 0.07 mmol) under an Ar atmosphere and heating at 125 °C for 30min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-60%], followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(6-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridine-8-carboxamido)phenyl)acetate (**6d**) (195 mg, 65 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆ with D₂O) δ 9.29 (s, 1H), 8.73 (s, 1H), 8.33 – 8.26 (m, 1H), 7.99 – 7.89 (m, 2H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.67 – 7.60 (m, 1H), 7.60 – 7.52 (m, 1H), 7.43 – 7.33 (m, 2H), 7.33 – 7.22 (m, 1H), 4.16 – 4.09 (m, 2H), 3.93 – 3.92 (m, 2H), 3.83 (s, 2H), 0.99 – 0.89 (m, 3H); MS (ES⁺): 429.3 (M+1); 451.3 (M+Na); (ES⁻): 463.4 (M+Cl); HPLC purity 99.56%.

Step-3: Preparation of 2-(2-(6-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridine-8-carboxamido)phenyl)acetic acid (**6e**)

Compound **6e** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(6-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridine-8-carboxamido)phenyl)acetate (**6d**) (108 mg, 0.25 mmol) in MeOH (10 mL) using sodium hydroxide (50.4 mg, 1.26 mmol) in water (2.0 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(6-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridine-8-carboxamido)phenyl)acetic

acid (**6e**) (90 mg, 89 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6 with D $_2$ O) δ 9.29 (d, $J = 1.7$ Hz, 1H), 8.73 (d, $J = 1.7$ Hz, 1H), 8.28 (d, $J = 1.9$ Hz, 1H), 7.95 (d, $J = 1.8$ Hz, 1H), 7.91 (s, 1H), 7.86 (d, $J = 7.7$ Hz, 1H), 7.73 (d, $J = 7.9$ Hz, 1H), 7.63 (t, $J = 7.6$ Hz, 1H), 7.59 – 7.52 (m, 1H), 7.42 – 7.31 (m, 2H), 7.31 – 7.21 (m, 1H), 4.12 (s, 2H), 3.77 (s, 2H); MS (ES $^+$): 401.3 (M+1); (ES $^-$): 399.4 (M-1), 435.4 (M+Cl); HPLC purity, 100%.

Scheme-7



Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-1H-indazole-6-carboxamido)phenyl)acetic acid (**7d**)

Step-1: Preparation of ethyl 2-(2-(4-bromo-1H-indazole-6-carboxamido)phenyl)acetate (**7b**)

To a solution of 4-bromo-1H-indazole-6-carboxylic acid (**7a**) (500 mg, 2.07 mmol; CAS# 885523-43-3) in MeOH (10 mL) was added ethyl 2-(2-aminophenyl)acetate (**5e**) (372 mg, 2.07 mmol) and N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (EDCI, 437 mg, 2.28 mmol), stirred at RT overnight and concentrated in vacuum to remove MeOH. The residue obtained was taken up in water (5 mL) and TBME (3 mL), stirred at RT for 30min at RT and the solid was collected via filtration to afford ethyl 2-(2-(4-bromo-1H-indazole-6-carboxamido)phenyl)acetate (**7b**) (650 mg, 78 % yield) as a tan solid; ^1H NMR (300 MHz, DMSO- d_6) δ 13.87 (s, 1H), 10.22 (s, 1H), 8.17 (s, 2H), 7.86 (s, 1H), 7.44 – 7.20 (m, 4H), 3.96 (q, $J = 7.1$ Hz, 2H), 3.75 (s, 2H), 1.01 (t, $J = 7.1$ Hz, 3H).

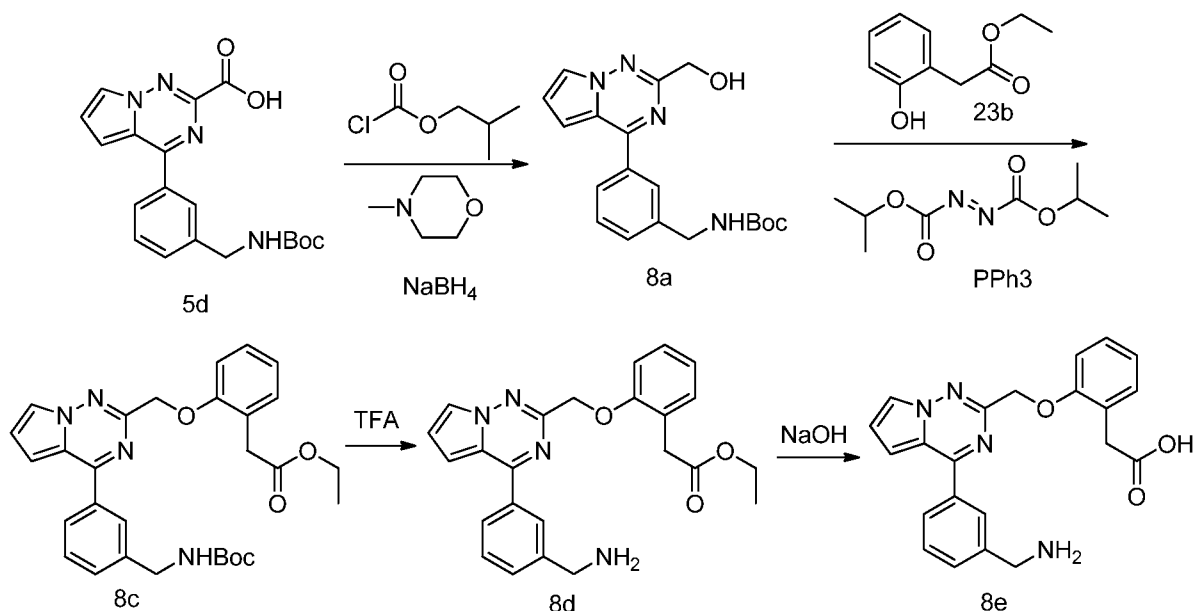
Step-2: Preparation of ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-1H-indazole-6-carboxamido)phenyl)acetate (**7c**)

Compound **7c** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(4-bromo-1H-indazole-6-carboxamido)phenyl)acetate (**7b**) (300 mg, 0.75 mmol) in dioxane (3 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (210 mg, 1.12 mmol), tripotassium phosphate (1.3 M solution) (1.72 mL, 2.24 mmol), tricyclohexylphosphine (63 mg, 0.22 mmol) and Pd₂(dba)₃ (68 mg, 0.075 mmol) under an Ar atmosphere and heating at 125 °C for 30 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-60 %] ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-1H-indazole-6-carboxamido)phenyl)acetate (**7c**) (210 mg, 66 % yield) as a white solid; 110mg product was taken and further purified by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] to give ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-1H-indazole-6-carboxamido)phenyl)acetate (**7c**) (57 mg) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆ with D₂O) δ 10.28 (s, 1H, D₂O exchangeable), 8.56 (s, 3H, D₂O exchangeable), 8.47 (d, *J* = 1.0 Hz, 1H), 8.18 (s, 1H), 8.01 (d, *J* = 2.0 Hz, 1H), 7.91 – 7.81 (m, 2H), 7.68 – 7.54 (m, 2H), 7.46 – 7.39 (m, 1H), 7.39 – 7.31 (m, 2H), 7.31 – 7.22 (m, 1H), 4.15 (t, *J* = 5.9 Hz, 3H), 3.95 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 2H), 0.97 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 429.3 (M+1); 451.3 (M+Na); (ES⁻): 463.4 (M+Cl); HPLC, purity 99.41%.

Step-3: Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-1H-indazole-6-carboxamido)phenyl)acetic acid (**7d**)

Compound **7d** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-1H-indazole-6-carboxamido)phenyl)acetate (**7c**) (95 mg, 0.22 mmol) in MeOH (10 mL) using sodium hydroxide (44 mg, 1.11 mmol) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(4-(3-(aminomethyl)phenyl)-1H-indazole-6-carboxamido)phenyl)acetic acid (**7d**) (40 mg, 45% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.75 (brs, 1H, D₂O exchangeable), 10.28 (s, 1H, D₂O exchangeable), 8.59 – 8.43 (m, 4H, partially D₂O exchangeable), 8.19 (s, 1H), 8.00 (s, 1H), 7.91 – 7.82 (m, 2H), 7.67 – 7.54 (m, 2H), 7.51 – 7.44 (m, 1H), 7.40 – 7.30 (m, 2H), 7.30 – 7.19 (m, 1H), 4.20 – 4.15 (m, 2H), 3.72 (s, 2H); MS (ES⁺): 401.3 (M+1); 423.3 (M+Na); (ES⁻): 399.3 (M-1), 435.3 (M+Cl); HPLC, purity, 100%.

Scheme-8



Preparation of 2-(2-((4-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl)methoxy)phenyl)acetic acid (**8e**)

Step-1: Preparation of *tert*-butyl 3-(2-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)benzylcarbamate (**8a**)

To the stirred solution of 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-2-carboxylic acid (**5d**) (390 mg, 1.06 mmol) and N-methylmorpholine (0.13 mL, 1.17 mmol) in THF (5 mL) was added isobutyl chloroformate (0.15 mL, 1.17 mmol) at -5°C . After 10 min, the mixture was filtered over Celite and the precipitate was washed with THF (3×5 mL). The filtrate was cooled to 0°C and added carefully dropwise a solution of NaBH₄ (60 mg, 1.59 mmol) in water (0.5 mL). The reaction mixture was diluted with water (10 mL) and extracted with EtOAc ($3 \times$). The organic layers were combined, dried, filtered and concentrated in vacuum to afford *tert*-butyl 3-(2-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)benzylcarbamate (**8a**) (300 mg, 80 % yield) as a yellow oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.19 – 8.11 (m, 1H), 8.07 – 7.95 (m, 2H), 7.63 – 7.45 (m, 3H), 7.21 – 7.13 (m, 1H), 7.11 – 7.03 (m, 1H), 5.51 (t, *J* = 6.3 Hz, 1H), 4.60 (d, *J* = 5.7 Hz, 2H), 4.26 (d, *J* = 6.2 Hz, 2H), 1.41 (s, 9H); MS (ES⁺): 355.3 (M+1); (ES⁻): 353.3 (M-1).

Step-2: Preparation of ethyl 2-(2-((4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl)methoxy)phenyl)acetic acid (**8c**)

To a solution of *tert*-butyl 3-(2-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)benzylcarbamate (**8a**) (250 mg, 0.71 mmol) in THF (5 mL) at 0°C was added DIAD (0.18 mL, 0.92 mmol), ethyl 2-(2-hydroxyphenyl)acetate (**23b**) (165 mg, 0.917 mmol; CAS#

41873-65-8) and triphenylphosphine (241 mg, 0.92 mmol). The resulting mixture was stirred at RT overnight. The reaction mixture was quenched with water and extracted with EtOAc (3x). The organic layers were combined, washed with saturated aqueous NH₄Cl, water, brine, dried and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] to afford ethyl 2-(2-((4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl)methoxy)phenyl)acetate (**8c**) (300 mg, 82 % yield) as a yellow oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.23 – 8.17 (m, 1H), 8.08 – 7.94 (m, 2H), 7.63 – 7.48 (m, 3H), 7.31 – 7.16 (m, 4H), 7.15 – 7.09 (m, 1H), 6.93 (td, *J* = 7.3, 1.3 Hz, 1H), 5.22 (s, 2H), 4.26 (d, *J* = 6.2 Hz, 2H), 3.92 (q, *J* = 7.1 Hz, 2H), 3.34 (s, 2H), 1.39 (s, 9H), 0.96 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 517.4 (M+1); (ES⁻): 515.4 (M-1).

Step-3: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl)methoxy)phenyl)acetate (**8d**)

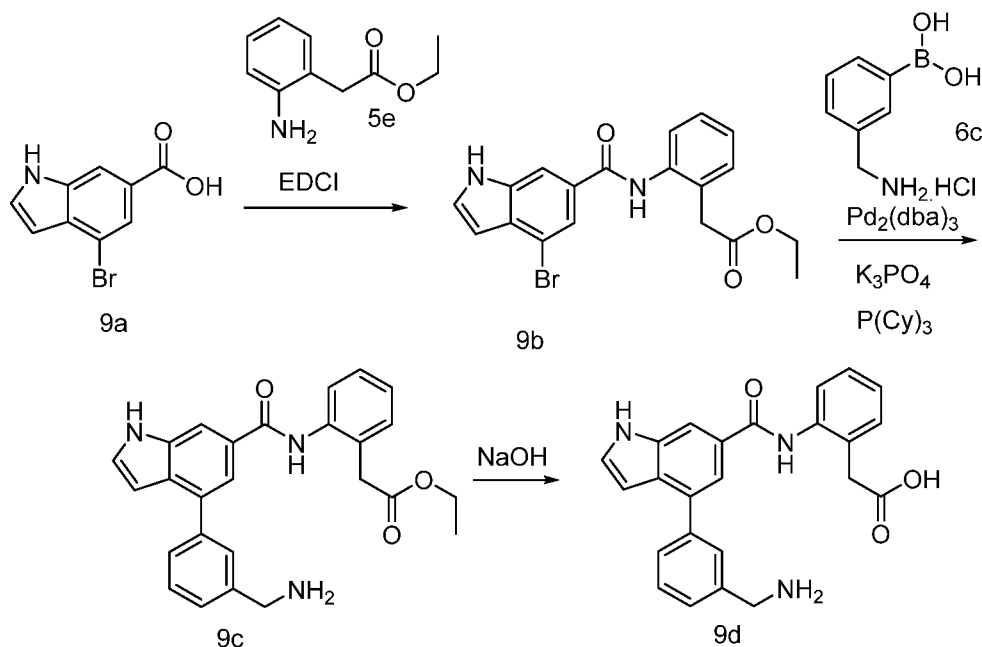
Compound **8d** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-((4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl)methoxy)phenyl)acetate (**8c**) (300 mg, 0.58 mmol) in DCM (10 mL) using TFA (0.45 mL, 5.81 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-100%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((4-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl)methoxy)phenyl)acetate (**8d**) (200 mg, 83 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.75 (brs, 1H, D₂O exchangeable), 10.28 (s, 1H, D₂O exchangeable), 8.59 – 8.43 (m, 4H, partially D₂O exchangeable), 8.19 (s, 1H), 8.00 (s, 1H), 7.91 – 7.82 (m, 2H), 7.67 – 7.54 (m, 2H), 7.51 – 7.44 (m, 1H), 7.40 – 7.30 (m, 2H), 7.30 – 7.19 (m, 1H), 4.20 – 4.15 (m, 2H), 3.72 (s, 2H); MS (ES⁺): 417.3 (M+1); 439.3 (M+Na); HPLC purity, 99.88%.

Step-4: Preparation of 2-(2-((4-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl)methoxy)phenyl)acetic acid (**8e**)

Compound **8e** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-((4-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl)methoxy)phenyl)acetate (**8d**) (100 mg, 0.24 mmol) in MeOH/THF (10 mL, 1:1) using sodium hydroxide (48 mg, 1.2 mmol) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((4-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl)methoxy)phenyl)acetic acid (**8e**) (71 mg, 76 % yield) as a yellow solid;

^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 8.57 (s, 3H, D_2O exchangeable), 8.30 – 8.20 (m, 2H), 8.19 – 8.11 (m, 1H), 7.84 – 7.74 (m, 1H), 7.67 (t, $J = 7.7$ Hz, 1H), 7.43 (dd, $J = 4.7, 1.3$ Hz, 1H), 7.28 – 7.11 (m, 4H), 6.92 (t, $J = 7.2, 1.4$ Hz, 1H), 5.26 (s, 2H), 4.22 – 4.14 (m, 2H), 3.61 (s, 2H); MS (ES⁺): 389.4 (M+1); (ES⁻): 387.4 (M-1); 423.4 (M+Cl); HPLC purity, 100%.

Scheme-9



Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-1H-indole-6-carboxamido)phenyl)acetic acid (**9d**)

Step-1: Preparation of ethyl 2-(2-(4-bromo-1H-indole-6-carboxamido)phenyl)acetate (**9b**)

Compound **9b** was prepared according to the procedure reported in step-1 of Scheme-7 from 4-bromo-1H-indole-6-carboxylic acid (**9a**) (500 mg, 2.08 mmol; CAS# 374633-27-9) in MeOH (10 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (411 mg, 2.29 mmol) and EDCI (479 mg, 2.5 mmol). This gave after workup, purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] ethyl 2-(2-(4-bromo-1H-indole-6-carboxamido)phenyl)acetate (**9b**) (320 mg, 38 % yield) as an off white solid; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 11.89 (s, 1H), 10.02 (s, 1H), 8.10 – 8.02 (m, 1H), 7.83 (d, $J = 1.3$ Hz, 1H), 7.68 (t, $J = 2.8$ Hz, 1H), 7.42 – 7.28 (m, 3H), 7.28 – 7.19 (m, 1H), 6.54 – 6.44 (m, 1H), 3.96 (q, $J = 7.1$ Hz, 2H), 3.74 (s, 2H), 1.01 (t, $J = 7.1$ Hz, 3H).

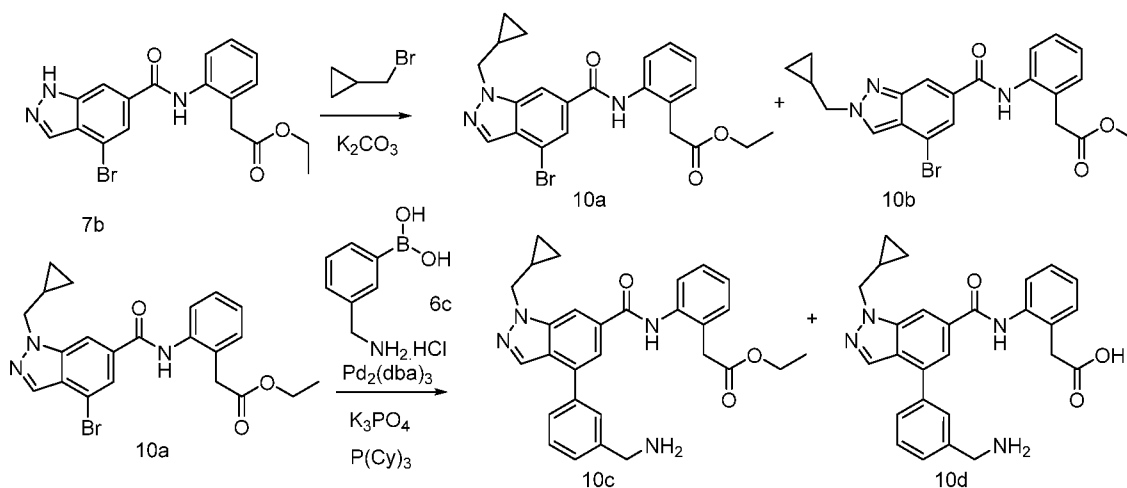
Step-2: Preparation of ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-1H-indole-6-carboxamido)phenyl)acetate (**9c**)

Compound **9c** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(4-bromo-1H-indole-6-carboxamido)phenyl)acetate (**9b**) (300 mg, 0.75 mmol) in

dioxane (3 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (210 mg, 1.12 mmol), tripotassium phosphate (1.3 M solution) (1.72 mL, 2.24 mmol), tricyclohexylphosphine (63 mg, 0.22 mmol) and Pd₂(dba)₃ (69 mg, 0.075 mmol) under an Ar atmosphere and heating at 125 °C for 30 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-60%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-1H-indole-6-carboxamido)phenyl)acetate (**9c**) (133 mg, 42 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.74 (s, 1H), 10.03 (s, 1H), 8.38 (s, 3H, D₂O exchangeable), 8.08 (s, 1H), 7.90 (s, 1H), 7.82 – 7.72 (m, 2H), 7.65 (t, *J* = 2.8 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.46 – 7.39 (m, 1H), 7.37 – 7.29 (m, 2H), 7.27 – 7.20 (m, 1H), 6.76 (t, *J* = 2.4 Hz, 1H), 4.23 – 4.08 (m, 2H), 3.96 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 2H), 0.99 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 428.3 (M+1); 450.3 (M+Na); (ES⁻): 426.4 (M-1); HPLC purity, 97.82%. Step-3: Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-1H-indole-6-carboxamido)phenyl)acetic acid (**9d**)

Compound **9d** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-1H-indole-6-carboxamido)phenyl)acetate (**9c**) (70 mg, 0.16 mmol) in MeOH (10 mL) using sodium hydroxide (66 mg, 1.61 mmol) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(4-(3-(aminomethyl)phenyl)-1H-indole-6-carboxamido)phenyl)acetic acid (**9d**) (23 mg, 35% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.28 (s, 1H, D₂O exchangeable), 11.76 (t, 1H), 10.08 (s, 1H, D₂O exchangeable), 8.48 (s, 3H, D₂O exchangeable), 8.10 (s, 1H), 7.91 (s, 1H), 7.83 – 7.74 (m, 2H), 7.65 (t, *J* = 2.8 Hz, 1H), 7.61 – 7.46 (m, 3H), 7.37 – 7.27 (m, 2H), 7.25 – 7.17 (m, 1H), 6.79 – 6.72 (m, 1H), 4.20 – 4.08 (m, 2H), 3.70 (s, 2H); MS (ES⁺) 400.3 (M+1); 422.3 (M+Na); (ES⁻) 398.4 (M-1); 434.4 (M+Cl); HPLC purity, 99.02%.

Scheme-10



Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-1-(cyclopropylmethyl)-1H-indazole-6-carboxamido)phenyl)acetic acid (**10d**)

Step-1: Preparation of ethyl 2-(2-(4-bromo-1-(cyclopropylmethyl)-1H-indazole-6-carboxamido)phenyl)acetate (**10a**) and ethyl 2-(2-(4-bromo-2-(cyclopropylmethyl)-2H-indazole-6-carboxamido)phenyl)acetate (**10b**)

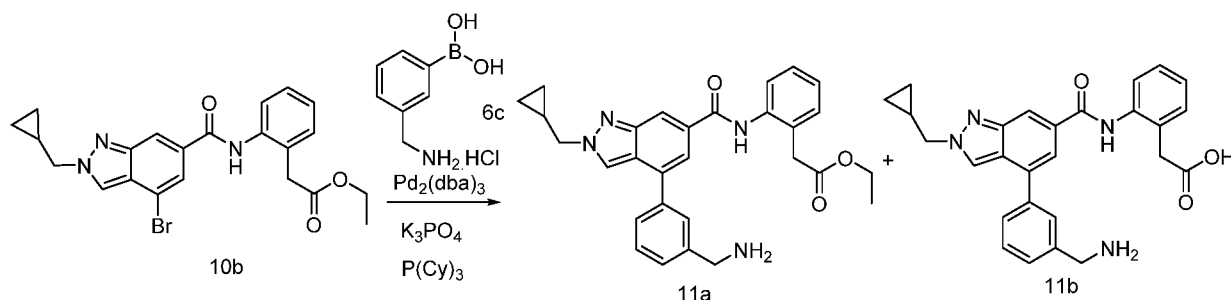
To a solution of ethyl 2-(2-(4-bromo-1H-indazole-6-carboxamido)phenyl)acetate (**7b**) (300 mg, 0.75 mmol) in DMF was added (bromomethyl)cyclopropane (151 mg, 1.12 mmol) and potassium carbonate (206 mg, 1.49 mmol). The resulting mixture was stirred at 60 °C overnight, cooled to RT, diluted with EtOAc (100 mL), washed with water (3x), brine, dried and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] afforded ethyl 2-(2-(4-bromo-1-(cyclopropylmethyl)-1H-indazole-6-carboxamido)phenyl)acetate (**10a**) (106 mg, 31 % yield); ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.28 (s, 1H), 8.14 (s, 1H), 7.83 (s, 1H), 7.44 – 7.15 (m, 4H), 4.34 (d, *J* = 7.0 Hz, 2H), 3.96 – 3.89 (m, 2H), 3.71 (s, 2H), 1.37 – 1.23 (m, 1H), 0.94 (t, *J* = 7.1 Hz, 3H), 0.53 – 0.32 (m, 4H); further elution gave ethyl 2-(2-(4-bromo-2-(cyclopropylmethyl)-2H-indazole-6-carboxamido)phenyl)acetate (**10b**) (86 mg, 25 % yield); ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.10 (s, 1H), 8.58 (s, 1H), 8.32 (s, 1H), 7.79 – 7.73 (m, 1H), 7.41 (d, *J* = 6.9 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.28 – 7.21 (m, 1H), 4.37 (d, *J* = 7.3 Hz, 2H), 3.96 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 2H), 1.53 – 1.31 (m, 1H), 1.02 (t, *J* = 7.1, 2.1 Hz, 3H), 0.68 – 0.41 (m, 4H).

Step-2: Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-1-(cyclopropylmethyl)-1H-indazole-6-carboxamido)phenyl)acetic acid (**10d**)

Compound **10d** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(4-bromo-1-(cyclopropylmethyl)-1H-indazole-6-carboxamido)phenyl)acetate

(**10a**) (95 mg, 0.21 mmol) in dioxane (3 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (59 mg, 0.31 mmol), tripotassium phosphate (1.3 M solution) (0.48 mL, 0.63 mmol), tricyclohexylphosphine (18 mg, 0.06 mmol) and $\text{Pd}_2(\text{dba})_3$ (19 mg, 0.021 mmol) under an Ar atmosphere and heating at 125 °C for 30 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-60 %] followed by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-1-(cyclopropylmethyl)-1H-indazole-6-carboxamido)phenyl)acetate (**10c**) (26 mg, 0.054 mmol, 25.9 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.27 (s, 1H, D_2O exchangeable), 8.52 (s, 3H, D_2O exchangeable), 8.46 – 8.36 (m, 2H), 8.00 (s, 1H), 7.93 – 7.78 (m, 2H), 7.67 – 7.53 (m, 2H), 7.50 – 7.41 (m, 1H), 7.41 – 7.32 (m, 2H), 7.32 – 7.22 (m, 1H), 4.44 (d, $J = 7.0$ Hz, 2H), 4.21 – 4.11 (m, 2H), 3.94 (q, $J = 7.1$ Hz, 2H), 3.80 (s, 2H), 1.45 – 1.32 (m, 1H), 0.96 (t, $J = 7.1$ Hz, 3H), 0.59 – 0.38 (m, 4H); MS (ES⁺): 483.4 (M+1); (ES⁻): 517.5 (M+Cl); HPLC purity, 97.36%, and 2-(2-(4-(3-(aminomethyl)phenyl)-1-(cyclopropylmethyl)-1H-indazole-6-carboxamido)phenyl)acetic acid (**10d**) (7 mg, 0.015 mmol, 7.40 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.25 (s, 1H, D_2O exchangeable), 8.55 – 8.33 (m, 5H), 7.98 (d, $J = 1.7$ Hz, 1H, partially D_2O exchangeable), 7.91 – 7.80 (m, 2H), 7.67 – 7.54 (m, 2H), 7.54 – 7.45 (m, 1H), 7.41 – 7.30 (m, 2H), 7.30 – 7.18 (m, 1H), 4.44 (d, $J = 7.0$ Hz, 2H), 4.22 – 4.09 (m, 2H), 3.72 (s, 2H), 1.50 – 1.33 (m, 1H), 0.64 – 0.38 (m, 4H); MS (ES⁺): 455.4 (M+1); (ES⁻): 453.4 (M-1), 489.4 (M+Cl); HPLC purity, 99.31%.

Scheme-11

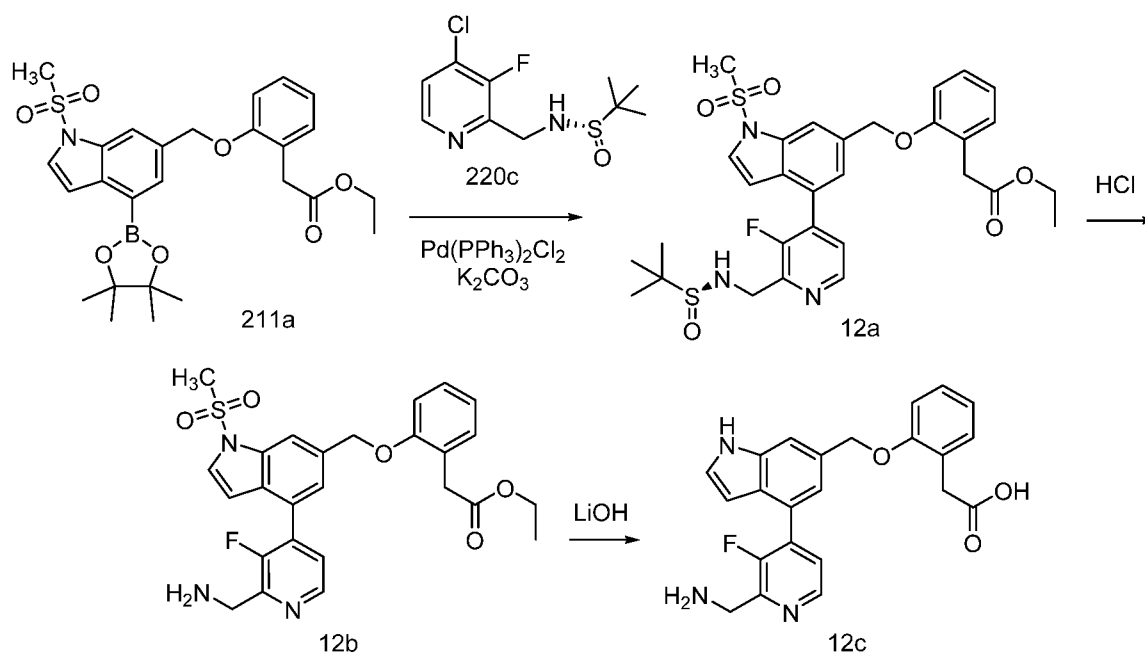


Preparation of ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-2-(cyclopropylmethyl)-2H-indazole-6-carboxamido)phenyl)acetate (**11a**) and 2-(2-(4-(3-(aminomethyl)phenyl)-2-(cyclopropylmethyl)-2H-indazole-6-carboxamido)phenyl)acetic acid (**11b**)

Compounds **11a** and **11b** were prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(4-bromo-2-(cyclopropylmethyl)-2H-indazole-6-carboxamido)phenyl)acetate (**10b**) (86 mg, 0.19 mmol) in dioxane (3 mL) using 3-

(aminomethyl)phenylboronic acid hydrochloride (**6c**) (53 mg, 0.28 mmol), tripotassium phosphate (1.3 M solution) (0.44 mL, 0.57 mmol), tricyclohexylphosphine (16 mg, 0.06 mmol) and $\text{Pd}_2(\text{dba})_3$ (17 mg, 0.02 mmol) under an Ar atmosphere and heating at 125 °C for 30 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-60 %] followed by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-2-(cyclopropylmethyl)-2H-indazole-6-carboxamido)phenyl)acetate (**11a**) (10 mg, 11% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.13 (s, 1H, D_2O exchangeable), 8.94 (s, 1H), 8.55 (s, 3H, D_2O exchangeable), 8.33 (s, 1H), 7.96 (s, 1H), 7.87 – 7.72 (m, 2H), 7.68 – 7.52 (m, 2H), 7.48 – 7.41 (m, 1H), 7.39 – 7.30 (m, 2H), 7.30 – 7.21 (m, 1H), 4.39 (d, $J = 7.2$ Hz, 2H), 4.16 (q, $J = 6.0$ Hz, 2H), 3.96 (q, $J = 7.1$ Hz, 2H), 3.80 (s, 2H), 1.53 – 1.39 (m, 1H), 1.01 (t, $J = 7.1$ Hz, 3H), 0.62 – 0.44 (m, 4H); MS (ES⁺): 483.4 (M+1); 505.4 (M+Na); (ES⁻): 481.4 (M-1); HPLC purity, 95.20% and 2-(2-(4-(3-(aminomethyl)phenyl)-2-(cyclopropylmethyl)-2H-indazole-6-carboxamido)phenyl)acetic acid (**11b**) (13 mg, 15% yield) as an off white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.17 (s, 1H, D_2O exchangeable), 8.96 (s, 1H), 8.59 (s, 3H, D_2O exchangeable), 8.33 (s, 1H), 7.97 (s, 1H), 7.86 – 7.80 (m, 1H), 7.80 – 7.74 (m, 1H), 7.66 – 7.48 (m, 3H), 7.39 – 7.29 (m, 2H), 7.28 – 7.19 (m, 1H), 4.38 (d, $J = 7.3$ Hz, 2H), 4.21 – 4.09 (m, 2H), 3.73 (s, 2H), 1.57 – 1.38 (m, 1H), 0.61 – 0.45 (m, 4H); MS (ES⁺): 455.4 (M+1); 477.4 (M+Na); (ES⁻): 453.4 (M-1); HPLC purity, 98.50%.

Scheme-12



Preparation of 2-(2-((4-(2-(aminomethyl)-3-fluoropyridin-4-yl)-1H-indol-6-yl)methoxy)phenyl)acetic acid (**12c**)

Step-1: Preparation of (S)-ethyl 2-(2-((4-(2-((1,1-dimethylethylsulfonamido)methyl)-3-fluoropyridin-4-yl)-1-(methylsulfonyl)-1H-indol-6-yl)methoxy)phenyl)acetate (**12a**)

Compound **12a** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((1-(methylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-6-yl)methoxy)phenyl)acetate (**211a**) (0.6 g, 1.17 mmol) in dioxane (5 mL) using (S)-N-((4-chloro-3-fluoropyridin-2-yl)methyl)-2-methylpropane-2-sulfonamide (**220c**) (0.46 g, 1.75 mmol), bis(triphenylphosphine)palladium(II) chloride (0.12 g, 0.18 mmol) and a solution of K₂CO₃ (0.40 g, 2.92 mmol) in water (0.5 mL) under an Ar atmosphere and heating at 90 °C for 4 h on oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH=9:1 in DCM from 0-70%] (S)-ethyl 2-(2-((4-(2-((1,1-dimethylethylsulfonamido)methyl)-3-fluoropyridin-4-yl)-1-(methylsulfonyl)-1H-indol-6-yl)methoxy)phenyl)acetate (**12a**) (0.33 g, 46 % yield) as a yellow solid; MS (ES⁺): 616.0 (M+1).

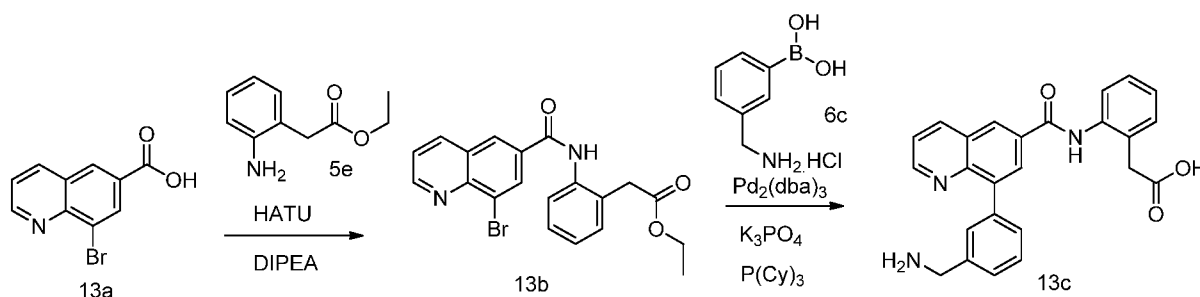
Step-2: Preparation of ethyl 2-(2-((4-(2-(aminomethyl)-3-fluoropyridin-4-yl)-1-(methylsulfonyl)-1H-indol-6-yl)methoxy)phenyl)acetate (**12b**)

Compound **12b** was prepared according to the procedure reported in step-5 of Scheme-220 from (S)-ethyl 2-(2-((4-(2-((1,1-dimethylethylsulfonamido)methyl)-3-fluoropyridin-4-yl)-1-(methylsulfonyl)-1H-indol-6-yl)methoxy)phenyl)acetate (**12a**) (0.33 g, 0.54 mmol) in methanol (10 mL) using hydrochloric acid (4 M in 1,4-dioxane, 0.40 mL, 1.61 mmol). This gave after workup compound **12b** (0.26 g, 95 % yield) as a yellow solid. This was subjected to purification using reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] to afford ethyl 2-(2-((4-(2-(aminomethyl)-3-fluoropyridin-4-yl)-1-(methylsulfonyl)-1H-indol-6-yl)methoxy)phenyl)acetate (**12b**) HCl salt as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.68 (s, 3H), 8.61 (d, J = 4.9 Hz, 1H), 8.10 (t, J = 1.0 Hz, 1H), 7.75 (d, J = 3.8 Hz, 1H), 7.67 (t, J = 5.3 Hz, 1H), 7.54 – 7.52 (m, 1H), 7.31 – 7.19 (m, 2H), 7.14 (dd, J = 8.3, 1.1 Hz, 1H), 6.91 (td, J = 7.4, 1.1 Hz, 1H), 6.81 – 6.76 (m, 1H), 5.32 (s, 2H), 4.34 (d, J = 6.0 Hz, 2H), 3.91 (q, J = 7.1 Hz, 2H), 3.63 (s, 2H), 3.55 (s, 3H), 0.97 (t, J = 7.1 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -128.70; MS (ES⁺): 512.9 (M+1).

Step-3: Preparation of 2-(2-((4-(2-(aminomethyl)-3-fluoropyridin-4-yl)-1H-indol-6-yl)methoxy)phenyl)acetic acid (**12c**)

Compound **12c** was prepared according to the procedure reported in step-6 of Scheme-1 from ethyl 2-(2-((4-(2-(aminomethyl)-3-fluoropyridin-4-yl)-1-(methylsulfonyl)-1H-indol-6-yl)methoxy)phenyl)acetate (**12b**) (0.15 g, 0.29 mmol) in MeOH/THF (4 mL, each) using lithium hydroxide hydrate (123 mg, 2.93 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((4-(2-(aminomethyl)-3-fluoropyridin-4-yl)-1H-indol-6-yl)methoxy)phenyl)acetic acid (**12c**) (0.06 g, 52 % yield) HCl salt as a yellow solid; ^1H NMR (300 MHz, DMSO- d_6) δ 11.51 (s, 1H), 8.57 (s, 3H), 8.56 – 8.54 (m, 1H), 7.69 (t, J = 5.4 Hz, 1H), 7.65 (d, J = 1.1 Hz, 1H), 7.49 (t, J = 2.8 Hz, 1H), 7.27 (d, J = 1.2 Hz, 1H), 7.26 – 7.18 (m, 2H), 7.14 – 7.08 (m, 1H), 6.89 (td, J = 7.4, 1.1 Hz, 1H), 6.39 (t, J = 2.7 Hz, 1H), 5.26 (s, 2H), 4.44 – 4.30 (m, 2H), 3.57 (s, 2H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -128.77; MS (ES+): 406.0 (M+1). HPLC purity: 98.02 %.

Scheme-13



Preparation of 2-(2-(8-(3-(aminomethyl)phenyl)quinoline-6-carboxamido)phenyl)acetic acid (**13c**)

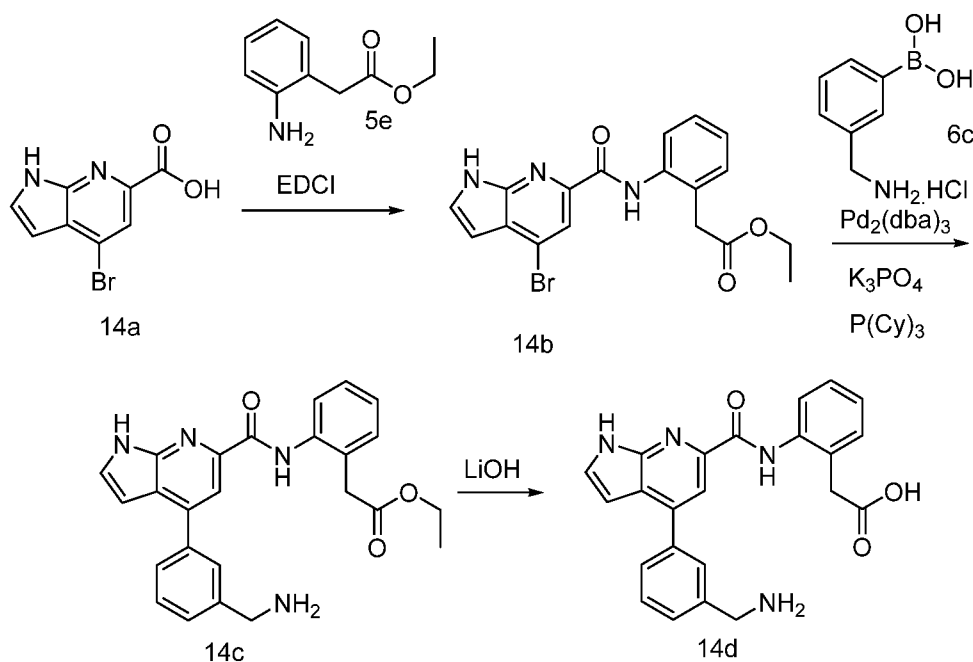
Step-1: Preparation of ethyl 2-(2-(8-bromoquinoline-6-carboxamido)phenyl)acetate (**13b**)

Compound **13b** was prepared according to the procedure reported in step-4 of Scheme-1, from 8-bromoquinoline-6-carboxylic acid (**13a**) (250 mg, 0.992 mmol, CAS # 791632-21-8) using ethyl 2-(2-aminophenyl)acetate (**5e**) (213 mg, 1.19 mmol), DIPEA (0.52 mL, 2.98 mmol) and HATU (453 mg, 1.19 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with MeOH:EtOAc (9:1) in hexanes 0 to 60%] ethyl 2-(2-(8-bromoquinoline-6-carboxamido)phenyl)acetate (**13b**) (315 mg, 77 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 10.35 (s, 1H), 9.13 (dd, J = 4.2, 1.6 Hz, 1H), 8.66 (d, J = 1.9 Hz, 1H), 8.62 (td, J = 4.1, 1.7 Hz, 2H), 7.75 (dd, J = 8.3, 4.2 Hz, 1H), 7.45 – 7.23 (m, 4H), 3.96 (q, J = 7.1 Hz, 2H), 3.78 (s, 2H), 1.00 (t, J = 7.1 Hz, 3H).

Step-2: Preparation of 2-(2-(8-(3-(aminomethyl)phenyl)quinoline-6-carboxamido)phenyl)acetic acid (**13c**)

Compound **13c** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(8-bromoquinoline-6-carboxamido)phenyl)acetate (**13b**) (150 mg, 0.36 mmol) in dioxane (2 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (68 mg, 0.363 mmol), tripotassium phosphate (1.3 M solution) (0.84 mL, 1.09 mmol), tricyclohexylphosphine (31 mg, 0.11 mmol) and $\text{Pd}_2(\text{dba})_3$ (33 mg, 0.036 mmol) under an Ar atmosphere and heating at 125 °C for 1 h in a microwave. This gave after workup, purification by flash column chromatography [silica (40 g), eluting with ethyl acetate in hexanes (0 to 40%)] followed by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(8-(3-(aminomethyl)phenyl)quinoline-6-carboxamido)phenyl)acetic acid (**13c**) (18 mg, 12 % yield) as a white powder; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.43 (s, 1H, D_2O exchangeable), 9.04 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.70 (s, 1H), 8.65 (dt, $J = 8.5, 1.8$ Hz, 1H), 8.50 (s, 3H, D_2O exchangeable), 8.35 (t, $J = 1.6$ Hz, 1H), 7.87 (s, 1H), 7.82 – 7.76 (m, 1H), 7.76 – 7.69 (m, 1H), 7.60 – 7.55 (m, 2H), 7.48 (d, $J = 7.6$ Hz, 1H), 7.40 – 7.30 (m, 2H), 7.30 – 7.21 (m, 1H), 4.14 (q, $J = 5.9$ Hz, 2H), 3.73 (s, 2H); MS (ES⁺): 412.3 (M+1); MS (ES⁻): 410.4 (M-1); HPLC purity: 93.59 %.

Scheme-14



Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine-6-carboxamido)phenyl)acetic acid (**14d**)

Step-1: Preparation of ethyl 2-(2-(4-bromo-1H-pyrrolo[2,3-b]pyridine-6-carboxamido)phenyl)acetate (**14b**)

Compound **14b** was prepared according to the procedure reported in step-1 of Scheme-7 from 4-bromo-1H-pyrrolo[2,3-b]pyridine-6-carboxylic acid (**14a**) (300 mg, 1.25 mmol; CAS # 1190321-81-3) in MeOH (10 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (268 mg, 1.49 mmol) and EDCI (286 mg, 1.49 mmol). This gave after workup, purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] ethyl 2-(2-(4-bromo-1H-pyrrolo[2,3-b]pyridine-6-carboxamido)phenyl)acetate (**14b**) (356 mg, 71 % yield) as an off white solid; MS (ES⁺): 424.2, 426.2 (M+Na), (ES⁻): 400.2, 402.3 (M-1).

Step-2: Preparation of ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine-6-carboxamido)phenyl)acetate (**14c**)

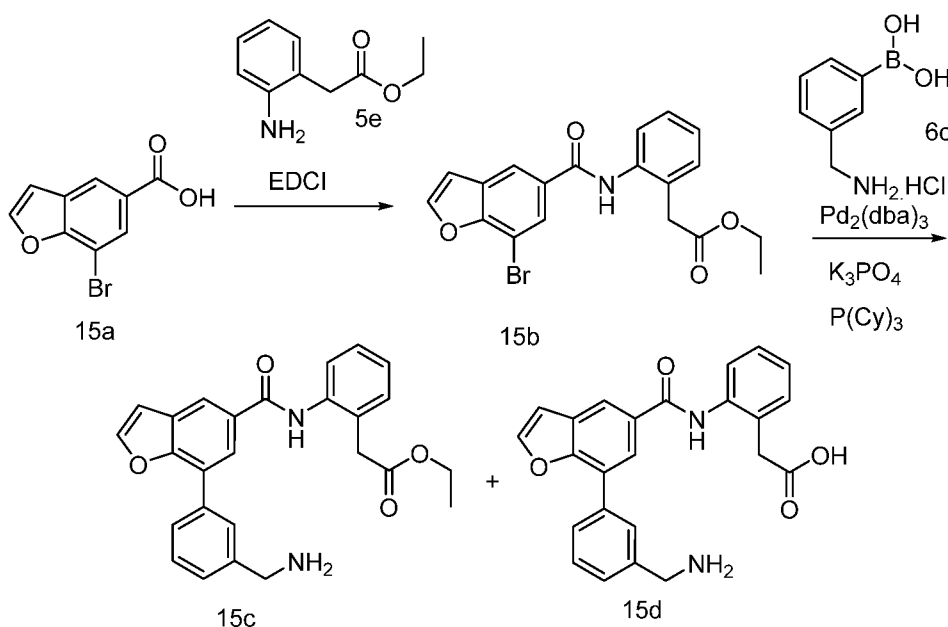
Compound **14c** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(4-bromo-1H-pyrrolo[2,3-b]pyridine-6-carboxamido)phenyl)acetate (**14b**) (200 mg, 0.55 mmol) in dioxane (3 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (154 mg, 0.82 mmol), tripotassium phosphate (1.3 M solution) (0.72 mL, 0.93 mmol), tricyclohexylphosphine (46 mg, 0.16 mmol) and Pd₂(dba)₃ (50 mg, 0.055 mmol) under an Ar atmosphere and heating at 125 °C for 1 h in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-70%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine-6-carboxamido)phenyl)acetate (**14c**) (108 mg, 46 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.14 (s, 1H, D₂O exchangeable), 10.31 (s, 1H, D₂O exchangeable), 8.55 (s, 3H, D₂O exchangeable), 8.06 (s, 1H), 7.98 (s, 1H), 7.89 – 7.76 (m, 3H), 7.64 (d, *J* = 4.5 Hz, 2H), 7.42 – 7.29 (m, 2H), 7.27 – 7.14 (m, 1H), 6.93 – 6.82 (m, 1H), 4.23 – 4.12 (m, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 2H), 1.06 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 429.4 (M+1); (ES⁻): 427.4 (M-1), 463.4 (M+Cl); HPLC purity, 99.45%.

Step-3: Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine-6-carboxamido)phenyl)acetic acid (**14d**)

Compound **14d** was prepared according to the procedure reported in step-6 of Scheme-1 from ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine-6-carboxamido)phenyl)acetate (**14c**) (16 mg, 0.038 mmol) in MeOH/THF (3 mL) using lithium hydroxide hydrate (7.98 mg, 0.19 mmol) in water (1 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(4-(3-(aminomethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine-6-carboxamido)phenyl)acetic acid (**14d**) (12 mg, 79 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.15 (s, 1H, D₂O exchangeable), 10.35 (s,

1H, D₂O exchangeable), 8.39 (s, 3H, D₂O exchangeable), 8.07 (s, 1H), 7.98 (s, 1H), 7.90 – 7.78 (m, 3H), 7.70 – 7.57 (m, 2H), 7.43 – 7.30 (m, 2H), 7.26 – 7.13 (m, 1H), 6.90 – 6.80 (m, 1H), 4.18 (q, *J* = 5.9 Hz, 2H), 3.73 (s, 2H); MS (ES⁺): 401.3 (M+1); (ES⁻): 399.3 (M-1), 435.4 (M+Cl); HPLC purity, 96.09%.

Scheme-15



Preparation of 2-(2-(7-(3-(aminomethyl)phenyl)benzofuran-5-carboxamido)phenyl)acetic acid (**15d**)

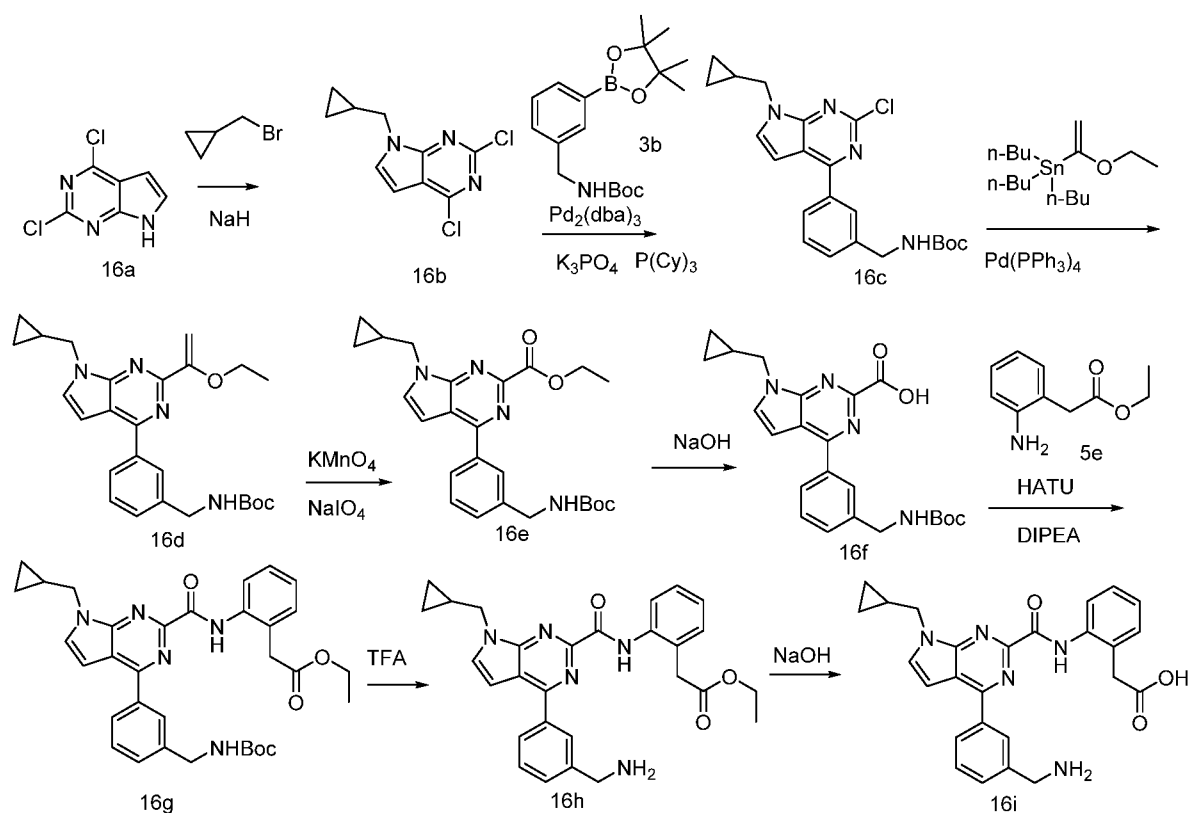
Step-1: Preparation of ethyl 2-(2-(7-bromobenzofuran-5-carboxamido)phenyl)acetate (**15b**)
Compound **15b** was prepared according to the procedure reported in step-1 of Scheme-7 from 7-bromobenzofuran-5-carboxylic acid (**15a**) (100 mg, 0.42 mmol; CAS# 286836-25-7) in MeOH (10 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (89 mg, 0.5 mmol) and EDCI (95 mg, 0.5 mmol). This gave after workup, purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] ethyl 2-(2-(7-bromobenzofuran-5-carboxamido)phenyl)acetate (**15b**) (80 mg, 48 % yield) as an pink semi-solid; MS (ES⁺): 424.2, 426.2 (M+Na), (ES⁻): 400.2, 402.2 (M-1)

Step-2: Preparation of 2-(2-(7-(3-(aminomethyl)phenyl)benzofuran-5-carboxamido)phenyl)acetic acid (**15d**)

Compound **15d** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(7-bromobenzofuran-5-carboxamido)phenyl)acetate (**15b**) (80 mg, 0.2 mmol) in dioxane (3 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (56 mg, 0.3 mmol), tripotassium phosphate (1.3 M solution) (0.26 mL, 0.34 mmol), tricyclohexylphosphine (17 mg, 0.06 mmol) and Pd₂(dba)₃ (18 mg, 0.02 mmol) under an Ar

atmosphere and heating at 125 °C for 1 h in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-70%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(7-(3-(aminomethyl)phenyl)benzofuran-5-carboxamido)phenyl)acetate (**15c**) (21 mg, 25% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.17 (s, 1H, D₂O exchangeable), 8.43 (s, 3H, D₂O exchangeable), 8.33 – 8.27 (m, 1H), 8.22 (d, *J* = 2.2 Hz, 1H), 8.21 – 8.18 (m, 1H), 8.08 (s, 1H), 8.03 – 7.94 (m, 1H), 7.67 – 7.54 (m, 2H), 7.45 – 7.39 (m, 1H), 7.38 – 7.30 (m, 2H), 7.30 – 7.18 (m, 2H), 4.16 (s, 2H), 3.95 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 2H), 0.98 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 429.3 (M+1); 451.3 (M+Na); (ES⁻): 463.3 (M+Cl); HPLC purity, 99.50% and 2-(2-(7-(3-(aminomethyl)phenyl)benzofuran-5-carboxamido)phenyl)acetic acid (**15d**) (25 mg, 31 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.31 (s, 1H, D₂O exchangeable), 10.20 (s, 1H, D₂O exchangeable), 8.41 (s, 3H, D₂O exchangeable), 8.34 – 8.29 (m, 1H), 8.24 – 8.20 (m, 1H), 8.20 – 8.16 (m, 1H), 8.09 – 8.04 (m, 1H), 8.02 – 7.96 (m, 1H), 7.66 – 7.55 (m, 2H), 7.51 – 7.44 (m, 1H), 7.38 – 7.28 (m, 2H), 7.27 – 7.19 (m, 2H), 4.21 – 4.09 (m, 2H), 3.71 (s, 2H); MS (ES⁺): 401.3 (M+1); 423.3 (M+Na); (ES⁻): 399.3 (M-1), 435.3 (M+Cl); HPLC purity, 92.60%.

Scheme-16



Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxamido)phenyl)acetic acid (**16i**)

Step-1: Preparation of 2,4-dichloro-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine (**16b**)

To a solution of 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (**16a**) (1 g, 5.32 mmol; CAS # 90213-66-4) in acetonitrile (35 mL) at 0 °C was added sodium hydride (319 mg, 7.98 mmol) portion-wise. The reaction mixture was stirred at room temperature for 30 minutes until gas evolution ceased. Then (bromomethyl)cyclopropane (1.62 g, 11.97 mmol) was added and the resulting mixture was stirred at RT overnight. The reaction mixture was poured into water and extracted with EtOAc (3 x). The organic layers were combined, dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-60%] to afford 2,4-dichloro-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine (**16b**) (998 mg, 78 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.88 (d, *J* = 3.6 Hz, 1H), 6.71 (d, *J* = 3.6 Hz, 1H), 4.09 (d, *J* = 7.2 Hz, 2H), 1.34 – 1.17 (m, 1H), 0.58 – 0.48 (m, 2H), 0.48 – 0.37 (m, 2H); MS (ES⁺): 265.3 (M+Na).

Step-2: Preparation of *tert*-butyl 3-(2-chloro-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzylcarbamate (**16c**)

Compound **16c** was prepared according to the procedure reported in step-3 of Scheme-1 from 2,4-dichloro-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine (**16b**) (4.5 g, 18.59 mmol) in dioxane (100 mL) using *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylcarbamate (**3b**) (4.42 g, 13.28 mmol), tripotassium phosphate (22.47 mL, 29.2 mmol, 1.3 M solution in water), tricyclohexylphosphine (1.12 g, 3.98 mmol) and Pd₂(dba)₃ (1.22 g, 1.33 mmol) in Ar atmosphere and heating at 120 °C for 60 min on oil bath. This gave after workup and purification by flash column chromatography [silica (80 g), eluting with EtOAc in hexane from 0-70%] *tert*-butyl 3-(2-chloro-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzylcarbamate (**16c**) (3.2 g, 58 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.10 – 7.97 (m, 2H), 7.87 (d, *J* = 3.7 Hz, 1H), 7.61 – 7.50 (m, 2H), 7.49 – 7.41 (m, 1H), 6.99 (d, *J* = 3.7 Hz, 1H), 4.25 (d, *J* = 6.2 Hz, 2H), 4.11 (d, *J* = 7.2 Hz, 2H), 1.41 (s, 9H), 1.35 – 1.31 (m, 1H), 0.58 – 0.49 (m, 2H), 0.49 – 0.40 (m, 2H); MS (ES⁺): 413.4 (M+1); 435.3 (M+Na); (ES⁻): 411.4 (M-1)

Step-3: Preparation of *tert*-butyl 3-(7-(cyclopropylmethyl)-2-(1-ethoxyvinyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzylcarbamate (**16d**)

Compound **16d** was prepared according to the procedure reported in step-1 of Scheme-1 from *tert*-butyl 3-(2-chloro-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzylcarbamate (**16c**) (3.2 g, 7.75 mmol) in DMF (35 mL) using 1-ethoxyvinyltri-*n*-butyltin (3.17 mL, 9.30 mmol) and Pd(PPh₃)₄ (0.448 g, 0.39 mmol) in argon atmosphere and heating at 110 °C for 12 h. This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-60%] *tert*-butyl 3-(7-(cyclopropylmethyl)-2-(1-ethoxyvinyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzylcarbamate (**16d**) (2.5 g, 72 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.14 - 8.02 (m, 2H), 7.83 (d, *J* = 3.6 Hz, 1H), 7.55 (q, *J* = 7.8, 7.0 Hz, 2H), 7.45 - 7.36 (m, 1H), 6.92 (d, *J* = 3.6 Hz, 1H), 5.63 (d, *J* = 1.4 Hz, 1H), 4.61 (d, *J* = 1.5 Hz, 1H), 4.26 (d, *J* = 6.2 Hz, 2H), 4.16 (d, *J* = 7.2 Hz, 2H), 3.98 (q, *J* = 7.0 Hz, 2H), 1.45 - 1.25 (m, 13H), 0.57 - 0.46 (m, 4H); MS (ES+) 449.4 (M+1); (ES-) 447.4 (M-1).

Step-4: Preparation of ethyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxylate (**16e**)

Compound **16e** was prepared according to the procedure reported in step-2 of Scheme-1 from *tert*-butyl 3-(7-(cyclopropylmethyl)-2-(1-ethoxyvinyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzylcarbamate (**16d**) (2.5 g, 5.57 mmol) in 1,4-dioxane (50 mL) using sodium periodate solution (2.384 g, 11.15 mmol) in water (20 mL) and KMnO₄ (0.881 g, 5.57 mmol in 4 mL water as first dose and second dose of 528 mg, 3.34 mmol after 12 h). This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-60%] ethyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxylate (**16e**) (1.06 g, 42 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.12 - 8.03 (m, 3H), 7.62 - 7.52 (m, 2H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 3.5 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.27 (d, *J* = 6.2 Hz, 2H), 4.22 (d, *J* = 7.2 Hz, 2H), 1.45 - 1.30 (m, 13H), 0.57 - 0.45 (m, 4H).

Step-5: Preparation of 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxylic acid (**16f**)

Compound **16f** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxylate (**16e**) (1.06 g, 2.353 mmol) in MeOH/THF (15 mL, 1:1) using sodium hydroxide (235 mg, 5.88 mmol) in water (3 mL). This gave after workup and purification by flash column chromatography [silica (24 g), eluting with MeOH in DCM from 0-20%] 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(cyclopropylmethyl)-7H-

pyrrolo[2,3-d]pyrimidine-2-carboxylic acid (**16f**) (650 mg, 65 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.11 - 8.00 (m, 2H), 7.89 (d, *J* = 3.6 Hz, 1H), 7.60 - 7.48 (m, 2H), 7.46 - 7.38 (m, 1H), 6.94 (d, *J* = 3.5 Hz, 1H), 4.26 (d, *J* = 6.2 Hz, 2H), 4.18 (d, *J* = 7.2 Hz, 2H), 1.41 (s, 9H), 1.34 - 1.30 (m, 1H), 0.56 - 0.43 (m, 4H); MS (ES⁺) 423.3 (M+1); 445.3 (M+Na); (ES⁻), 421.4 (M-1), 457.4 (M+Cl).

Step-6: Preparation of ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxamido)phenyl)acetate (**16g**)

Compound **16g** was prepared according to the procedure reported in step-4 of Scheme-1 from 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxylic acid (**16f**) (150 mg, 0.536 mmol) in DMF (5 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (95 mg, 0.533 mmol), DIPEA (0.12 mL, 0.71 mmol) and HATU (203 mg, 0.533 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane from 0-100%] ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxamido)phenyl)acetate (**16g**) (152 mg, 73 % yield) as a white solid; MS (ES⁺) 584.5 (M+1).

Step-7: Preparation of ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxamido)phenyl)acetate (**16h**)

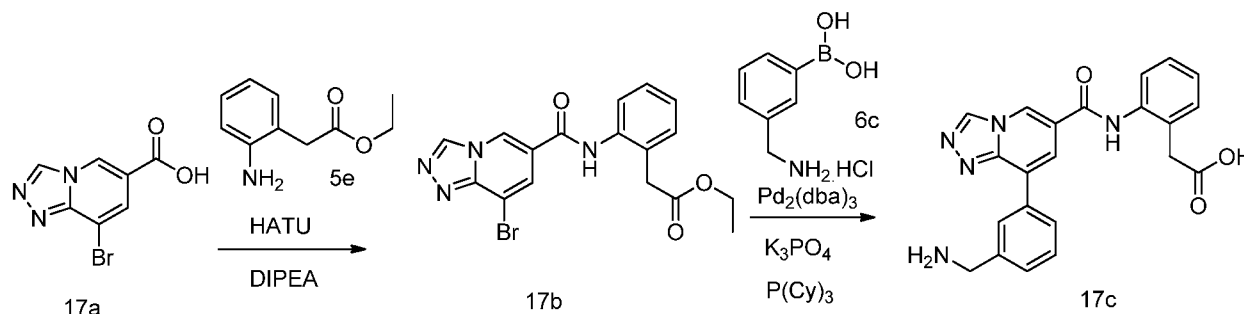
Compound **16h** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxamido)phenyl)acetate (**16g**) (150 mg, 0.26 mmol) in DCM (10 mL) using TFA (0.4 mL, 5.14 mmol). This gave after work up and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-100%] followed by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxamido)phenyl)acetate (**16h**) (88 mg, 71 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.79 (s, 1H, D₂O exchangeable), 8.68 (s, 3H, D₂O exchangeable), 8.46 (d, *J* = 1.7 Hz, 1H), 8.43 - 8.35 (m, 1H), 8.11 (d, *J* = 3.6 Hz, 1H), 7.93 - 7.87 (m, 1H), 7.79 - 7.73 (m, 1H), 7.73 - 7.61 (m, 1H), 7.44 - 7.36 (m, 2H), 7.34 (d, *J* = 3.6 Hz, 1H), 7.27 - 7.15 (m, 1H), 4.37 - 4.25 (m, 2H), 4.17 (s, 2H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 2H), 1.46 - 1.32 (m, 1H), 1.00 (t, *J* = 7.1 Hz, 3H), 0.60 - 0.45 (m, 4H); MS (ES⁺): 484.5 (M+1); (ES⁻): 482.5 (M-1); 518.5 (M+Cl); HPLC purity, 99.46%.

Step-8: Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxamido)phenyl)acetic acid (**16i**)

Compound **16i** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxamido)phenyl)acetate (**16h**) (50 mg, 0.10 mmol) in MeOH (10 mL) using sodium hydroxide (21 mg, 0.52 mmol) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%]

2-(2-(4-(3-(aminomethyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxamido)phenyl)acetic acid (**16i**) (24 mg, 51% yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.85 (s, 1H, D₂O exchangeable), 8.56 (s, 3H, D₂O exchangeable), 8.46 – 8.40 (m, 1H), 8.40 – 8.32 (m, 1H), 8.11 (d, *J* = 3.6 Hz, 1H), 7.98 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.78 – 7.63 (m, 2H), 7.44 – 7.33 (m, 2H), 7.31 (d, *J* = 3.6 Hz, 1H), 7.27 – 7.13 (m, 1H), 4.29 (d, *J* = 7.2 Hz, 2H), 4.23 – 4.18 (m, 2H), 3.78 (s, 2H), 1.44 – 1.31 (m, 1H), 0.59 – 0.47 (m, 4H); MS (ES⁺): 456.3 (M+1); 478.3 (M+Na); (ES⁻): 454.3 (M-1); 490.3 (M+Cl); HPLC, purity, 99.60%.

Scheme-17



Preparation of 2-(2-(8-(3-(aminomethyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxamido)phenyl)acetic acid (**17c**)

Step-1: Preparation of ethyl 2-(2-(8-bromo-[1,2,4]triazolo[4,3-a]pyridine-6-carboxamido)phenyl)acetate (**17b**)

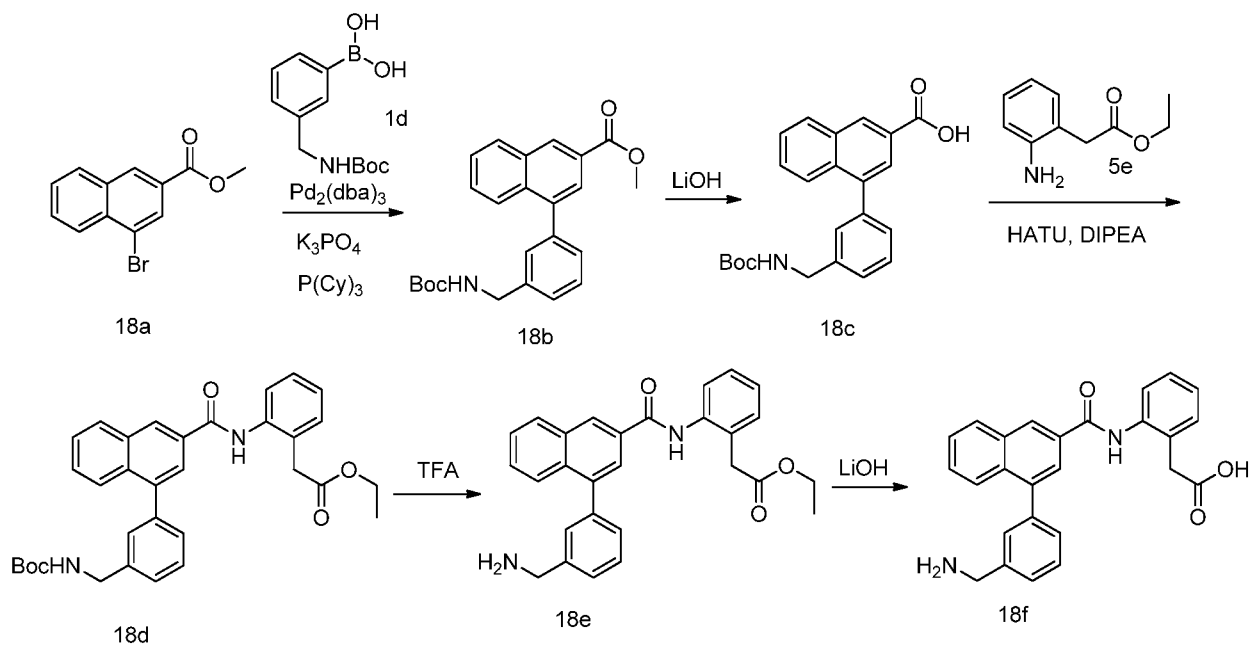
Compound **17b** was prepared according to the procedure reported in step-4 of Scheme-1, from 8-bromo-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (**17a**) (500 mg, 2.07 mmol, CAS # 1216475-30-7) using ethyl 2-(2-aminophenyl)acetate (**5e**) (648 mg, 3.62 mmol), DIPEA (1.08 mL, 6.2 mmol) and HATU (1375 mg, 3.62 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with MeOH:EtOAc (9:1) in hexanes 0 to 100%] ethyl 2-(2-(8-bromo-[1,2,4]triazolo[4,3-a]pyridine-6-

carboxamido)phenyl)acetate (**17b**) (200 mgs, 24% yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 10.27 (s, 1H), 9.56 (s, 1H), 9.25 (s, 1H), 8.20 (s, 1H), 7.41 – 7.23 (m, 4H), 3.98 (q, J = 7.1 Hz, 2H), 3.74 (s, 2H), 1.05 (t, J = 7.1 Hz, 3H).

Step-2: Preparation of 2-(2-(8-(3-(aminomethyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxamido)phenyl)acetic acid (**17c**)

Compound **17c** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(8-bromo-[1,2,4]triazolo[4,3-a]pyridine-6-carboxamido)phenyl)acetate (**17b**) (200 mg, 0.5 mmol) in dioxane (3 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (139 mg, 0.74 mmol), tripotassium phosphate (1.3 M solution) (1.145 mL, 1.49 mmol), tricyclohexylphosphine (42 mg, 0.15 mmol) and $\text{Pd}_2(\text{dba})_3$ (45 mg, 0.05 mmol) under an Ar atmosphere and heating at 120 °C for 1 h in a microwave. This gave after workup, purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(8-(3-(aminomethyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridine-6-carboxamido)phenyl)acetic acid (**17c**) (41 mg, 21 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 10.52 (s, 1H, D $_2$ O exchangeable), 9.66 – 9.54 (m, 1H), 9.39 – 9.28 (m, 1H), 8.56 (s, 3H, D $_2$ O exchangeable), 8.41 (s, 1H), 8.39 – 8.30 (m, 2H), 7.64 (d, J = 4.4 Hz, 2H), 7.48 – 7.38 (m, 1H), 7.42 – 7.31 (m, 2H), 7.33 – 7.23 (m, 1H), 4.32 – 4.02 (m, 2H), 3.72 (d, J = 2.3 Hz, 2H); MS (ES $^+$): 402.3 (M+1); MS (ES $^-$): 400.4 (M-1); HPLC purity: 93.65 %.

Scheme-18



Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-2-naphthamido)phenyl)acetic acid (**18f**)

Step-1: Preparation of methyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-naphthoate (**18b**)

Compound **18b** was prepared according to the procedure reported in step-3 of Scheme-1, from methyl 4-bromo-2-naphthoate (**18a**) (250 mg, 0.94 mmol; CAS # 1013-80-5) in DMF (3 mL) using 3-(((*tert*-butoxycarbonylamino)methyl)phenyl)boronic acid (**1d**) (355 mg, 1.42 mmol), tripotassium phosphate (1.3 M solution, 1.45 mL, 1.89 mmol), tricyclohexylphosphine (79 mg, 0.28 mmol) and Pd(dba)₃ (86 mg, 0.09 mmol) under a nitrogen atmosphere by heating at 120 °C for 14 h. This gave after workup and purification by flash column chromatography [silica (40 g), eluting with hexanes/ethyl acetate 0% to 100%] methyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-naphthoate (**18b**) (257 mg, 70 % yield) as an oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.69 (s, 1H), 8.32 – 8.19 (m, 1H), 7.95 – 7.81 (m, 2H), 7.72 – 7.61 (m, 2H), 7.57 – 7.47 (m, 2H), 7.44 – 7.27 (m, 3H), 4.27 – 4.16 (m, 2H), 3.93 (s, 3H), 1.38 (s, 9H).

Step-2: Preparation of 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-naphthoic acid (**18c**)

Compound **18c** was prepared according to the procedure reported in step-6 of Scheme-1, from methyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-naphthoate (**18b**) (240 mg, 0.613 mmol) in THF (10 mL) using a solution of lithium hydroxide hydrate (29 mg, 1.23 mmol) in water (2 mL) This gave after workup 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-naphthoic acid (**18c**) (150 mgs, 65%), which was used as such for next step; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.61 (s, 1H), 8.24 – 8.11 (m, 1H), 7.89 – 7.77 (m, 2H), 7.67 – 7.56 (m, 2H), 7.48 (m, 2H), 7.35 (m, 3H), 4.22 (d, *J* = 6.1 Hz, 2H), 1.35 (s, 9H).

Step-3: Preparation of ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-naphthamido)phenyl)acetate (**18d**)

Compound **18d** was prepared according to the procedure reported in step-4 of Scheme-1, from 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-naphthoic acid (**18c**) (150 mg, 0.397 mmol) in DMF (8 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (125 mg, 0.695 mmol), DIPEA (0.21 mL, 1.2 mmol) and HATU (264 mg, 0.695 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc/MeOH (9:1) in hexane from 0-100%] ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-naphthamido)phenyl)acetate (**18d**) (169 mg, 79 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.24 (s, 1H), 8.59 (s, 1H), 8.13 (dd, *J* = 20.3, 7.9 Hz, 1H), 7.97 – 7.83 (m, 2H), 7.64 (p, *J* = 7.0 Hz, 2H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.46 – 7.29 (m, 7H), 7.30 – 7.08 (m, 1H), 4.25 (d, *J* = 6.2 Hz, 2H), 3.94 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 2H), 1.38 (s, 9H), 0.96 (t, *J* = 7.1 Hz, 3H).

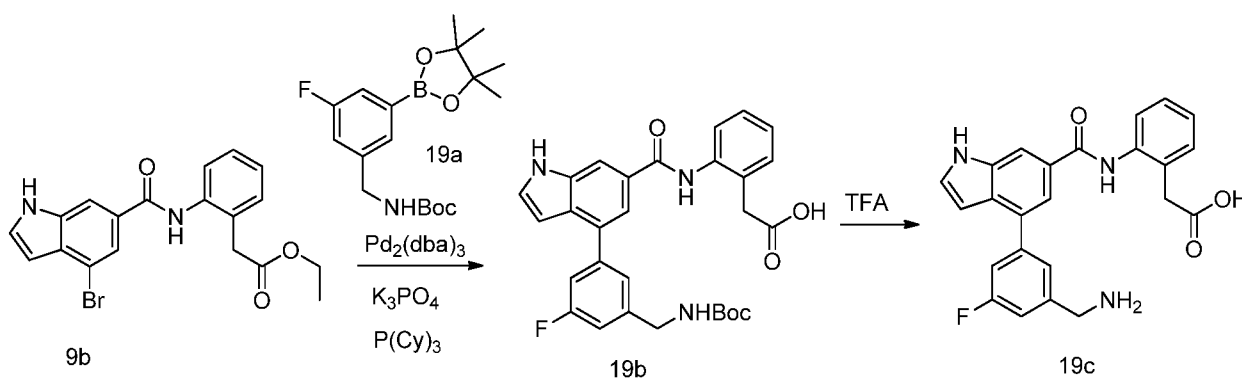
Step-4: Preparation of ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-2-naphthamido)phenyl)acetate (**18e**)

Compound **18e** was prepared according to the procedure reported in step-5 of Scheme-1, from ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-naphthamido)phenyl)acetate (**18d**) (150 mg, 0.28 mmol) using TFA (0.22 mL, 2.78 mmol) in DCM (10 mL). This gave after workup ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-2-naphthamido)phenyl)acetate (**18e**) (84 mg, 69%) which was used as such for next step; MS (ES⁺): 439.4 (M+1).

Step-5: Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-2-naphthamido)phenyl)acetic acid (**18f**)

Compound **18f** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-2-naphthamido)phenyl)acetate (**18e**) (70 mg, 0.16 mmol) in THF (5 mL) using a solution of lithium hydroxide hydrate (19 mg, 0.8 mmol) in water (2 mL) This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(4-(3-(aminomethyl)phenyl)-2-naphthamido)phenyl)acetic acid (**18f**) (43 mg, 66 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.39 (s, 1H, D₂O exchangeable), 10.41 (s, 1H, D₂O exchangeable), 8.64 (s, 1H), 8.34 (s, 3H, D₂O exchangeable), 8.17 (d, *J* = 7.7 Hz, 1H), 7.99 (d, *J* = 1.9 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.74 – 7.56 (m, 6H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.39 – 7.28 (m, 2H), 7.28 – 7.20 (m, 1H), 4.16 (s, 2H), 3.70 (s, 2H); MS (ES⁺): 411.3 (M+1), 433.3 (M+Na), (ES⁻): 409.4 (M-1, 445.4 (M+Cl); HPLC purity: 93.35 %.

Scheme-19



Preparation of 2-(2-(4-(3-(aminomethyl)-5-fluorophenyl)-1H-indole-6-carboxamido)phenyl)acetic acid (**19c**)

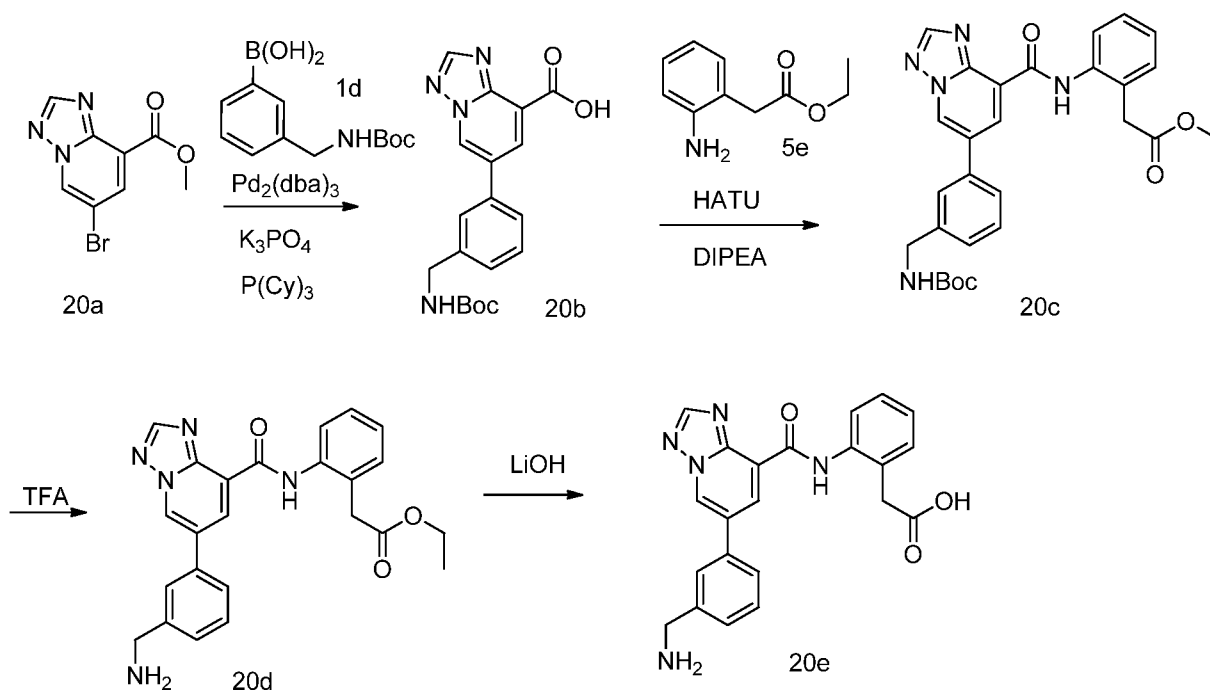
Step-1: Preparation of 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorophenyl)-1H-indole-6-carboxamido)phenyl)acetic acid (**19b**)

Compound **19b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(4-bromo-1H-indole-6-carboxamido)phenyl)acetate (**9b**) (320 mg, 0.80 mmol) in dioxane (3 mL) using *tert*-butyl 3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylcarbamate (**19a**) (420 mg, 1.2 mmol; CAS# 1421773-36-5), tripotassium phosphate (1.3 M solution) (1.23 mL, 1.60 mmol), tricyclohexylphosphine (67 mg, 0.24 mmol) and Pd₂(dba)₃ (73 mg, 0.08 mmol) under an Ar atmosphere and heating at 120 °C for 60 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-90%] 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorophenyl)-1H-indole-6-carboxamido)phenyl)acetic acid (**19b**) (175 mg, 42 % yield) as a yellow solid; MS (ES⁺): 518.4 (M+1); (ES⁻): 516.4 (M-1).

Step-2: Preparation of 2-(2-(4-(3-(aminomethyl)-5-fluorophenyl)-1H-indole-6-carboxamido)phenyl)acetic acid (**19c**)

Compound **19c** was prepared according to the procedure reported in step-5 of Scheme-1 from 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorophenyl)-1H-indole-6-carboxamido)phenyl)acetic acid (**19b**) (170 mg, 0.33 mmol) in DCM (10 mL) using TFA (0.25 mL, 3.28 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-100%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(4-(3-(aminomethyl)-5-fluorophenyl)-1H-indole-6-carboxamido)phenyl)acetic acid (**19c**) (69 mg, 50% yield) as an off white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.37 (s, 1H, D₂O exchangeable), 11.80 (t, *J* = 2.2 Hz, 1H), 10.08 (s, 1H, D₂O exchangeable), 8.52 (s, 3H, D₂O exchangeable), 8.12 (s, 1H), 7.86 – 7.81 (m, 1H), 7.80 – 7.75 (m, 1H), 7.68 (t, *J* = 2.8 Hz, 1H), 7.64 – 7.56 (m, 1H), 7.53 – 7.39 (m, 2H), 7.38 – 7.28 (m, 2H), 7.27 – 7.18 (m, 1H), 6.84 – 6.76 (m, 1H), 4.17 (s, 2H), 3.70 (s, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -112.22; MS (ES⁺): 418.4 (M+1); (ES⁻): 416.4 (M-1); 452.4 (M+Cl); HPLC purity; 98.96%.

Scheme-20



Preparation of 2-(2-(6-(3-(aminomethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridine-8-carboxamido)phenyl)acetic acid (**20e**)

Step-1: Preparation of 6-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridine-8-carboxylic acid (**20b**)

Compound **20b** was prepared according to the procedure reported in step-3 of Scheme-1, from methyl 6-bromo-[1,2,4]triazolo[1,5-a]pyridine-8-carboxylate (**20a**) (500 mg, 1.953 mmol; CAS # 1801262-20-3) in dioxane (3 mL) using 3-(((*tert*-butoxycarbonylamino)methyl)phenyl)boronic acid (**1d**) (735 mg, 2.93 mmol), tripotassium phosphate (1.3 M solution, 3.0 mL, 3.91 mmol), tricyclohexylphosphine (164 mg, 0.59 mmol) and $\text{Pd}_2(\text{dba})_3$ (179 mg, 0.2 mmol) under a nitrogen atmosphere by heating at 120 °C for 1 h in microwave. This gave after workup and purification by flash column chromatography [silica (40 g), eluting with ethyl acetate in hexanes 0% to 100%] 6-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridine-8-carboxylic acid (**20b**) (200 mg, 28%) as an oil; MS (ES-) 367.3 (M-1)

Step-2: Preparation of ethyl 2-(2-(6-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridine-8-carboxamido)phenyl)acetate (**20c**)

Compound **20c** was prepared according to the procedure reported in step-4 of Scheme-1, from 6-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridine-8-carboxylic acid (**20b**) (200 mg, 0.54 mmol) in DMF (8 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (170 mg, 0.95 mmol), DIPEA (0.28 mL, 1.63 mmol) and HATU (361 mg, 0.95 mmol). This gave after workup and purification by flash column

chromatography [silica (12 g), eluting with 0-60% EtOAc/MeOH (9:1) in hexane from 0-100%] ethyl 2-(2-(6-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridine-8-carboxamido)phenyl)acetate (**20c**) (153 mg, 53 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.27 (s, 1H), 9.63 (d, *J* = 1.8 Hz, 1H), 8.78 (s, 1H), 8.70 (d, *J* = 1.8 Hz, 1H), 8.19 – 8.09 (m, 1H), 7.77 (m, 2H), 7.51 (m, 2H), 7.38 (m, 3H), 7.23 (m, 1H), 4.26 (d, *J* = 6.1 Hz, 2H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.96 (s, 2H), 1.40 (s, 9H), 1.09 (t, *J* = 7.1 Hz, 3H).

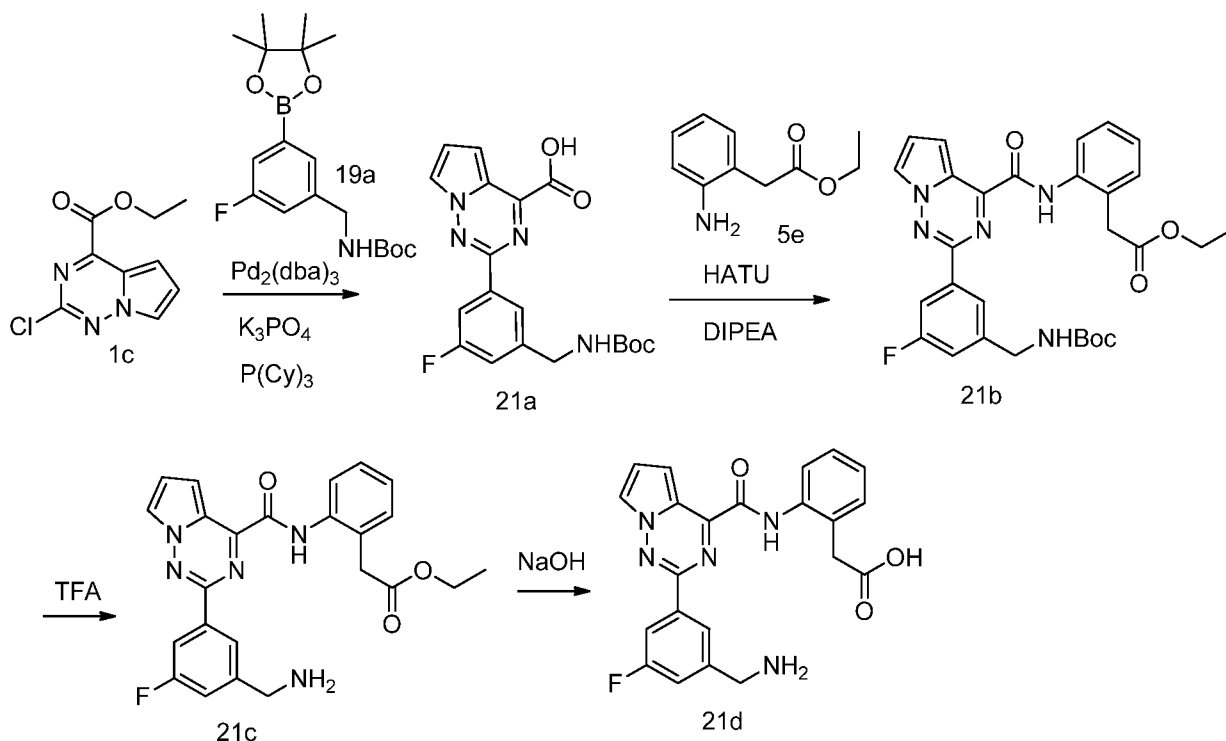
Step-3: Preparation of ethyl 2-(2-(6-(3-(aminomethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridine-8-carboxamido)phenyl)acetate (**20d**)

Compound **20d** was prepared according to the procedure reported in step-5 of Scheme-1, from ethyl 2-(2-(6-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridine-8-carboxamido)phenyl)acetate (**20c**) (140 mg, 0.264 mmol) using TFA (0.41 mL, 5.29 mmol) in DCM (2 mL). This gave after workup ethyl 2-(2-(6-(3-(aminomethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridine-8-carboxamido)phenyl)acetate (**20d**) (65 mg, 57%) which was used as such for next step; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.27 (s, 1H), 9.64 (d, *J* = 1.8 Hz, 1H), 8.77 (s, 1H), 8.71 (d, *J* = 1.8 Hz, 1H), 8.13 (dd, *J* = 7.3, 2.0 Hz, 1H), 7.87 (s, 1H), 7.76 – 7.68 (m, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.40 – 7.35 (m, 2H), 7.26 – 7.16 (m, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 2H), 3.82 (s, 2H), 2.11 (s, 2H), 1.09 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 430.4 (M+1).

Step-4: Preparation of 2-(2-(6-(3-(aminomethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridine-8-carboxamido)phenyl)acetic acid (**20e**)

Compound **20e** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-(6-(3-(aminomethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridine-8-carboxamido)phenyl)acetate (**20d**) (60 mg, 0.14 mmol) in THF (5 mL) using a solution of lithium hydroxide hydrate (17 mg, 0.7 mmol) in water (1 mL) This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(6-(3-(aminomethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyridine-8-carboxamido)phenyl)acetic acid (**20e**) (53 mg, 95 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.39 (s, 1H), 9.69 (d, *J* = 1.8 Hz, 1H), 8.79 (d, *J* = 1.8 Hz, 1H), 8.76 (s, 1H), 8.48 (s, 3H, D₂O exchangeable), 8.21 – 8.13 (m, 1H), 8.09 (s, 1H), 7.95 (dt, *J* = 6.5, 2.3 Hz, 1H), 7.66 – 7.55 (m, 2H), 7.43 – 7.31 (m, 2H), 7.25 – 7.16 (m, 1H), 4.16 (d, *J* = 5.8 Hz, 2H), 3.89 (s, 2H); MS (ES⁺) 402.3 (M+1), (ES⁻) 400.4 (M-1), 436.4 (M+Cl); HPLC purity: 98.75 %.

Scheme-21



Preparation of 2-(2-(2-(3-(aminomethyl)-5-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**21d**)

Step-1: Preparation of 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**21a**)

Compound **21a** was prepared according to the procedure reported in step-3 of Scheme-1, from ethyl 2-chloropyrrolo[2,1-f][1,2,4]triazine-4-carboxylate (**1c**) (200 mg, 0.89 mmol); in dioxane (3 mL) using *tert*-butyl 3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylcarbamate (**19a**) (467 mg, 1.33 mmol), tripotassium phosphate (1.3 M solution, 1.36 mL, 0.089 mmol), tricyclohexylphosphine (75 mg, 0.27 mmol) and $\text{Pd}_2(\text{dba})_3$ (81 mg, 0.089 mmol) under a nitrogen atmosphere by heating at 120 °C for 1 h in microwave. This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-90%] 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**21a**) (118 mg, 35 % yield) as a yellow solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.04 (s, 1H), 8.01 (t, $J = 2.0$ Hz, 1H), 7.90 – 7.83 (m, 1H), 7.58 (t, $J = 6.2$ Hz, 1H), 7.17 (dt, $J = 9.8, 2.0$ Hz, 1H), 6.99 – 6.93 (m, 2H), 4.23 (d, $J = 6.2$ Hz, 2H), 1.41 (s, 9H).

Step-2: Preparation of ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetate (**21b**)

Compound **21b** was prepared according to the procedure reported in step-4 of Scheme-1 from 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylic acid (**21a**) (110 mg, 0.29 mmol) in DMF (5 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (77 mg, 0.43 mmol), DIPEA (0.1 mL, 0.57 mmol) and HATU (162 mg, 0.43 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc/MeOH (9:1) in hexane from 0-100%] ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**21b**) (125 mg, 80 % yield) as a yellow solid; MS (ES⁻): 546.5 (M-1).

Step-3: Preparation of ethyl 2-(2-(2-(3-(aminomethyl)-5-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**21c**)

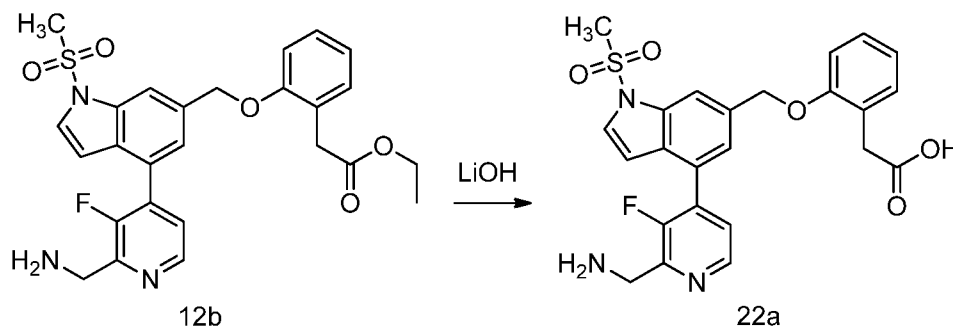
Compound **21c** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**21b**) (42 mg, 0.08 mmol) using TFA (0.06 mL, 0.77 mmol) in DCM (10 mL). This gave after workup followed by purification by flash chromatography [silica (12 g), eluting with DMA80 in DCM from 0-100%] then reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(2-(3-(aminomethyl)-5-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**21c**) (33 mg, 96 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.92 (s, 1H), 8.58 – 8.49 (m, 1H), 8.45 – 8.36 (m, 2H), 8.26 (s, 3H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.60 – 7.53 (m, 1H), 7.46 – 7.38 (m, 2H), 7.35 – 7.25 (m, 2H), 4.20 (s, 2H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 2H), 1.00 (t, *J* = 7.1 Hz, 3H).

Step-4: Preparation of 2-(2-(2-(3-(aminomethyl)-5-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**21d**)

Compound **21d** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(2-(3-(aminomethyl)-5-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**21c**) (19 mg, 0.042 mmol) in MeOH (10 mL) using sodium hydroxide (17 mg, 0.43 mmol) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(2-(3-(aminomethyl)-5-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**21d**) (15 mg, 84 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.68 (s, 1H, D₂O exchangeable), 10.94 (s, 1H, D₂O exchangeable), 8.52 (s, 3H, D₂O exchangeable), 8.48 – 8.45 (m, 1H), 8.45 – 8.35 (m, 2H),

7.81 – 7.74 (m, 1H), 7.65 – 7.57 (m, 2H), 7.45 – 7.35 (m, 2H), 7.34 – 7.24 (m, 2H), 4.27 – 4.13 (m, 2H), 3.78 (s, 2H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -112.09; MS (ES $^+$) 420.3 (M+1); (ES $^-$) 418.4 (M-1); HPLC purity, 98.34%.

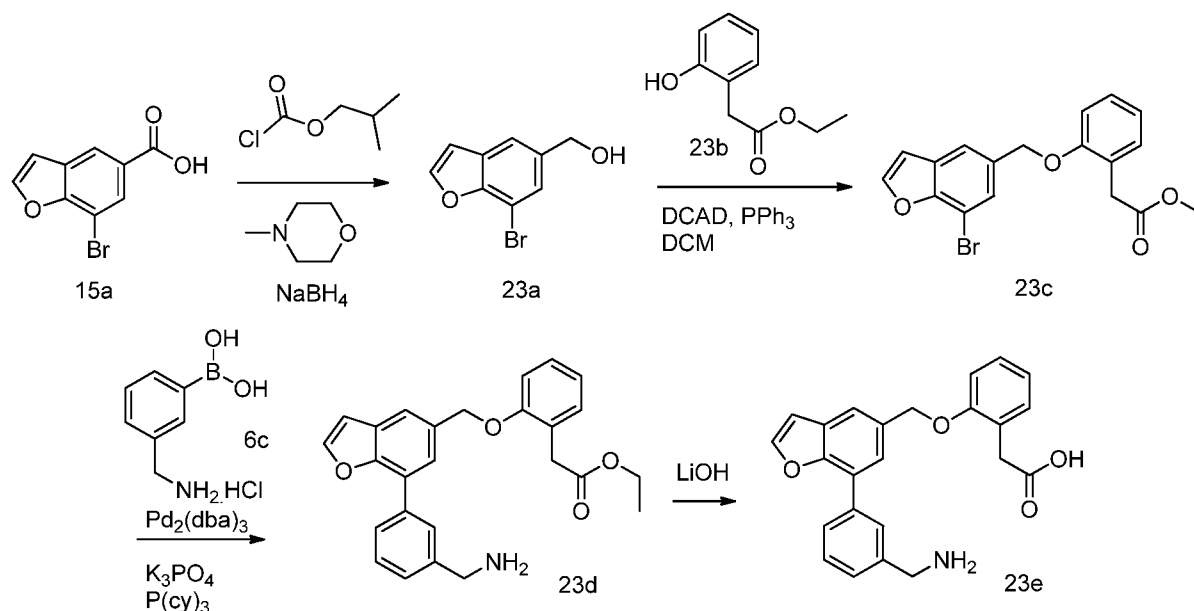
Scheme-22



Preparation of 2-(2-((4-(2-(aminomethyl)-3-fluoropyridin-4-yl)-1-(methylsulfonyl)-1H-indol-6-yl)methoxy)phenyl)acetic acid (**22a**)

Compound **22a** was prepared according to the procedure reported in step-6 of Scheme-1 from ethyl 2-(2-((4-(2-(aminomethyl)-3-fluoropyridin-4-yl)-1-(methylsulfonyl)-1H-indol-6-yl)methoxy)phenyl)acetate (**12b**) (0.1 g, 0.20 mmol) in MeOH/THF (4 mL, each) using lithium hydroxide hydrate (8 mg, 0.2 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((4-(2-(aminomethyl)-3-fluoropyridin-4-yl)-1-(methylsulfonyl)-1H-indol-6-yl)methoxy)phenyl)acetic acid (**22a**) (0.03 g, 36 % yield) HCl salt as a yellow solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.60 (d, J = 4.9 Hz, 1H), 8.53 (s, 3H), 8.12 (s, 1H), 7.75 (d, J = 3.8 Hz, 1H), 7.71 – 7.64 (m, 1H), 7.57 (d, J = 1.2 Hz, 1H), 7.29 – 7.18 (m, 2H), 7.16 – 7.07 (m, 1H), 6.92 (td, J = 7.4, 1.1 Hz, 1H), 6.76 (t, J = 3.3 Hz, 1H), 5.34 (s, 2H), 4.37 (d, J = 6.0 Hz, 2H), 3.59 (s, 2H), 3.55 (s, 3H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -128.61; MS (ES $^+$): 484.9 (M+1); MS (ES $^-$): 482.9 (M-1). HPLC purity: 93.84 %.

Scheme-23



Preparation of 2-(2-((7-(3-(aminomethyl) phenyl) benzofuran-5-yl) methoxy) phenyl) acetic acid (**23e**)

Step-1: Preparation of (7-bromobenzofuran-5-yl) methanol (**23a**)

To the stirred solution of 7-bromobenzofuran-5-carboxylic acid (**15a**) (10 g, 41.5 mmol) and N-methylmorpholine (5.47 mL, 49.8 mmol) in THF (200 mL) at -5°C was added isobutyl chloroformate (6.54 mL, 49.8 mmol). The reaction mixture was stirred for 15 min, filtered over a Celite pad and the precipitate was washed with THF (3×20 mL). The filtrate was cooled to 0°C and added carefully (gas released rapidly) a solution of NaBH₄ (4.71 g, 124 mmol) in water (10 mL). The reaction mixture was stirred for 30 mins, diluted with water (20 mL), washed with ethyl acetate ($3 \times$). The organic layers were combined, dried, filtered and concentrated in vacuum to afford (7-bromobenzofuran-5-yl)methanol (**23a**) (9 g, 96 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.09 (d, $J = 2.2$ Hz, 1H), 7.59 (d, $J = 1.4$ Hz, 1H), 7.49 (d, $J = 1.4$ Hz, 1H), 7.07 (d, $J = 2.2$ Hz, 1H), 5.34 (t, $J = 5.8$ Hz, 1H), 4.57 (d, $J = 5.8$ Hz, 2H).

Step-2: Preparation of ethyl 2-(2-((7-bromobenzofuran-5-yl) methoxy) phenyl) acetate (**23c**)

To a solution of (7-bromobenzofuran-5-yl) methanol (**23a**) (9 g, 39.6 mmol), triphenylphosphine (11.44 g, 43.6 mmol) and ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (7.86 g, 43.6 mmol; CAS # 41873-65-8) in DCM (180 mL) at 0°C was added dropwise a solution of bis(4-chlorobenzyl)azodicarboxylate (DCAD, 16.01 g, 43.6 mmol; CAS#: 916320-82-6) in DCM (40 mL). The resulting mixture was stirred at RT for 30 min and filtered to remove solid. The filtrate was concentrated in vacuum and residue obtained was purified by flash column chromatography [silica (80 g), eluting with EtOAc in hexane from 0-50%] to give

ethyl 2-(2-((7-bromobenzofuran-5-yl)methoxy)phenyl)acetate (**23c**) (11.5 g, 75 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.15 (d, $J = 2.2$ Hz, 1H), 7.72 (s, 1H), 7.60 (s, 1H), 7.30 – 7.19 (m, 2H), 7.11 (d, $J = 2.2$ Hz, 1H), 7.07 (d, $J = 8.1$ Hz, 1H), 6.91 (td, $J = 7.4$, 1.1 Hz, 1H), 5.18 (s, 2H), 4.01 (q, $J = 7.1$ Hz, 2H), 3.62 (s, 2H), 1.07 (t, $J = 7.1$ Hz, 3H).

Step-3: Preparation of ethyl 2-(2-((7-(3-(aminomethyl) phenyl) benzofuran-5-yl) methoxy) phenyl) acetate (**23d**)

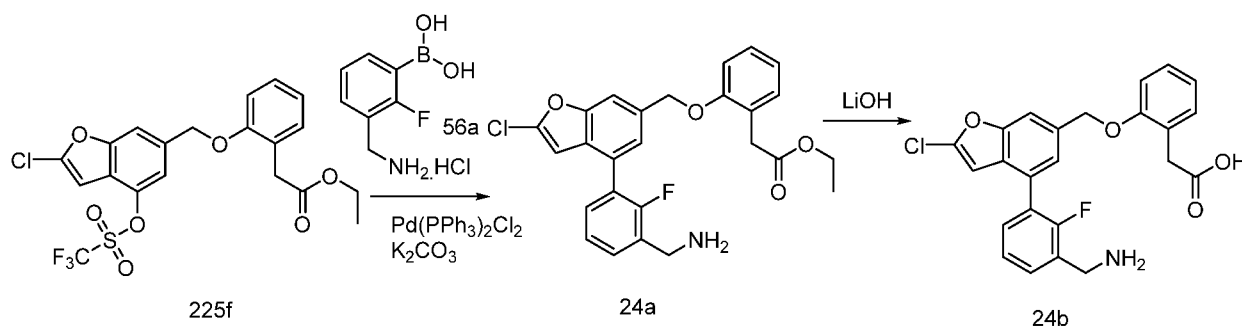
Compound **23d** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-bromobenzofuran-5-yl)methoxy)phenyl)acetate (**23c**) (300 mg, 0.77 mmol) in dioxane (6 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (217 mg, 1.16 mmol), tripotassium phosphate (1.3 M solution) (0.77 mL, 2.31 mmol), tricyclohexylphosphine (65 mg, 0.23 mmol) and $\text{Pd}_2(\text{dba})_3$ (71 mg, 0.077 mmol) under an Ar atmosphere and heating at 125 °C for 45 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-60%] followed by purification by reverse phase column [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(3-(aminomethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**23d**) (107 mg, 33 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.20 (s, 3H, D_2O exchangeable), 8.14 – 8.09 (m, 1H), 7.98 (s, 1H), 7.91 (d, $J = 7.3$ Hz, 1H), 7.81 – 7.71 (m, 1H), 7.67 – 7.47 (m, 3H), 7.34 – 7.19 (m, 2H), 7.17 – 7.06 (m, 2H), 6.92 (t, $J = 7.5$ Hz, 1H), 5.25 (s, 2H), 4.13 (s, 2H), 4.01 – 3.86 (m, 2H), 3.63 (s, 2H), 1.04 – 0.93 (m, 3H); MS (ES⁺): 416.3 (M+1); 831.5 (2M+1); MS (ES⁻): 450.4 (M+Cl); HPLC purity: 96.49%

Step-4: Preparation of 2-(2-((7-(3-(aminomethyl) phenyl) benzofuran-5-yl) methoxy) phenyl) acetic acid (**23e**)

Compound **23e** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(aminomethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**23d**) (2.25 g, 5.42 mmol) in MeOH/THF (30 mL) using a solution of lithium hydroxide hydrate (682 mg, 16.25 mmol) in water (5 mL) This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**23e**) (1.5 g, 72 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.25 (s, 1H, D_2O exchangeable), 8.53 (s, 3H, D_2O exchangeable), 8.11 (d, $J = 2.2$ Hz, 1H), 8.04 – 7.99 (m, 1H), 7.97 – 7.89 (m, 1H), 7.77 (d, $J = 1.6$ Hz, 1H), 7.66 (d, $J = 1.7$ Hz, 1H), 7.61 – 7.54 (m, 2H), 7.23 (d, $J = 7.4$ Hz, 2H), 7.13 – 7.04 (m, 2H), 6.91 (td, $J = 7.4$, 1.1 Hz, 1H), 5.27 (s,

2H), 4.13 (s, 2H), 3.61 (s, 2H); MS (ES⁺): 388.3 (M+1); (ES⁻): 386.3 (M-1); 422.3 (M+Cl); HPLC purity: 99.44%.

Scheme-24



Preparation of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-2-chlorobenzofuran-6-yl)methoxy)phenyl)acetic acid (**24b**)

Step-1: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-2-chlorobenzofuran-6-yl)methoxy)phenyl)acetate (**24a**)

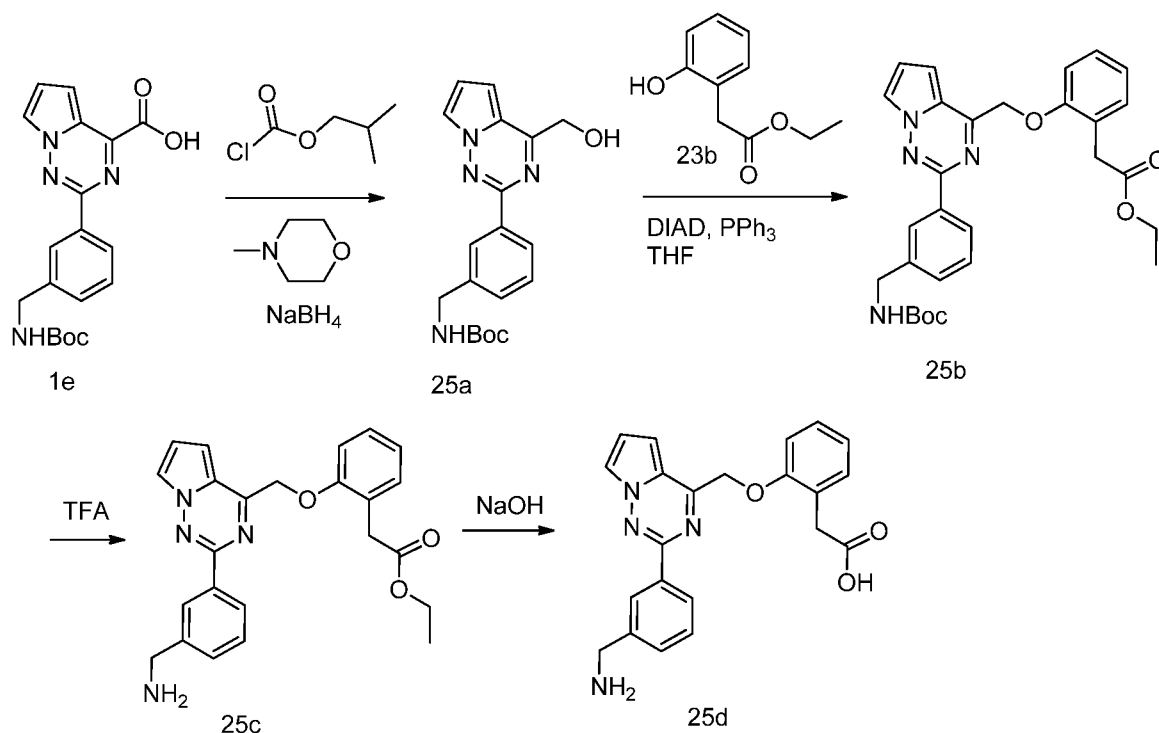
Compound **24a** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((2-chloro-4-((trifluoromethyl)sulfonyl)oxy)benzofuran-6-yl)methoxy)phenyl)acetate (**225f**) (191 mg, 0.388 mmol) in dioxane (5 mL) using (3-(aminomethyl)-2-fluorophenyl)boronic acid hydrochloride (**56a**) (117 mg, 0.692 mmol), a solution of K₂CO₃ (186 mg, 1.346 mmol) in water (0.5 mL), Pd(PPh₃)₂Cl₂ (55 mg, 0.078 mmol) and heating under an Ar atmosphere at 100 °C for 3 h. This gave after workup, purification by flash column chromatography (silica gel 12 g, eluting with DMA80 in DCM from 0-50%) ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-2-chlorobenzofuran-6-yl)methoxy)phenyl)acetate (**24a**) (181 mg, 100 % yield) as a pale-yellow oil. MS (ES⁺): 467.9 (M+1).

Step-2: Preparation of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-2-chlorobenzofuran-6-yl)methoxy)phenyl)acetic acid (**24b**)

Compound **24b** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-2-chlorobenzofuran-6-yl)methoxy)phenyl)acetate (**24a**) (205 mg, 0.438 mmol) in MeOH/THF (6 mL) using a solution of lithium hydroxide (132 mg, 3.15 mmol) in water (2 mL). This gave after workup and purification by reverse phase column (C18, 100 g, 0-60% MeCN in H₂O containing 0.1% HCl) 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-2-chlorobenzofuran-6-yl)methoxy)phenyl)acetic acid (**24b**) (60 mg, 31 % yield) HCl salt as a white solid. ¹H NMR

(300 MHz, DMSO- d_6) δ 8.59 (s, 2H), 7.70 (s, 1H), 7.62 (t, J = 7.1 Hz, 1H), 7.54 (t, J = 7.4 Hz, 1H), 7.42 (s, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 7.4 Hz, 2H), 7.02 (dd, J = 13.9, 5.9 Hz, 2H), 6.84 (t, J = 7.3 Hz, 1H), 5.23 (s, 2H), 4.09 (s, 2H), 3.53 (s, 2H). MS (ES⁺): 439.9 (M+1); MS(ES⁻): 437.9 (M-1).

Scheme-25



Preparation of 2-(2-((2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)methoxy)phenyl)acetic acid (**25d**)

Step-1: Preparation of *tert*-butyl 3-(4-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl)benzylcarbamate (**25a**)

Compound **25a** was prepared according to the procedure reported in step-1 of Scheme-23, from 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**1e**) (570 mg, 1.55 mmol) in THF (30 mL), using N-methylmorpholine (0.2 mL, 1.86 mmol), isobutyl chloroformate (0.24 mL, 1.86 mmol) and NaBH₄ (176 mg, 4.64 mmol) in water (0.8 mL). This gave after workup *tert*-butyl 3-(4-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl)benzylcarbamate (**25a**) (100 mg, 18% yield) as a yellow oil; ¹H NMR (300 MHz, DMSO- d_6) δ 8.23 – 8.17 (m, 2H), 8.12 (s, 1H), 7.57 – 7.43 (m, 2H), 7.38 (d, J = 7.6 Hz, 1H), 7.20 (d, J = 4.5 Hz, 1H), 7.02 (dd, J = 4.5, 2.5 Hz, 1H), 5.77 (d, J = 5.7 Hz, 1H), 4.87 (d, J = 6.1 Hz, 2H), 4.22 (d, J = 6.2 Hz, 2H), 1.42 (s, 9H); MS (ES⁺): 355.3 (M+1), 377.3 (M+Na), (ES⁻): 353.4 (M-1).

Step-2: Preparation of ethyl 2-(2-((2-(3-(((tert-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)methoxy)phenyl)acetate (**25b**)

Compound **25b** was prepared according to the procedure reported in step-2 of Scheme-23, from *tert*-butyl 3-(4-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-2-yl)benzylcarbamate (**25a**) (95 mg, 0.27 mmol) in THF (5 mL) using triphenylphosphine (91 mg, 0.35 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (63 mg, 0.35 mmol) and diisopropyl azodicarboxylate (DIAD, 71 mg, 0.35 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-40%] ethyl 2-(2-((2-(3-(((tert-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)methoxy)phenyl)acetate (**25b**) (42 mg, 30% yield) as a solid; MS (ES⁺): 539.4, 540.5 (M+Na), (ES⁻): 515.4, 516.5 (M-1).

Step-3: Preparation of ethyl 2-(2-((2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)methoxy)phenyl)acetate (**25c**)

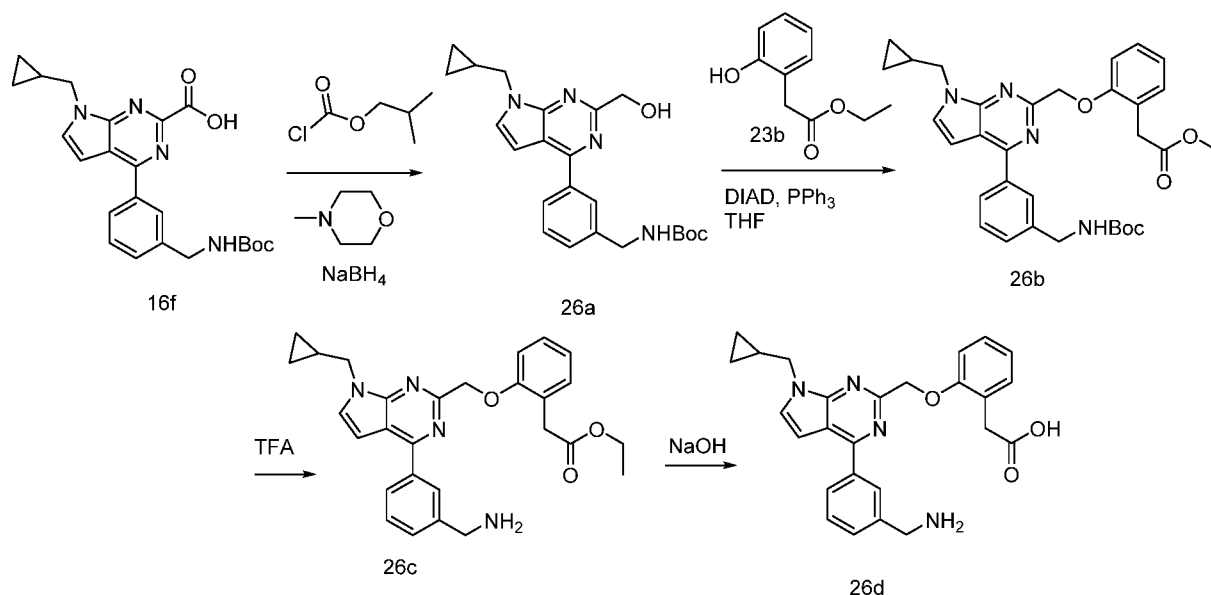
Compound **25c** was prepared according to the procedure reported in step-5 of Scheme-1, from ethyl 2-(2-((2-(3-(((tert-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)methoxy)phenyl)acetate (**25b**) (140 mg, 0.27 mmol) using TFA (0.21 mL, 2.71 mmol) in DCM (5 mL). This gave after workup followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)methoxy)phenyl)acetate (**25c**) (26 mg, 23 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.45 – 8.40 (m, 1H), 8.40 – 8.27 (m, 4H, partially D₂O exchangeable), 8.22 – 8.16 (m, 1H), 7.68 – 7.54 (m, 2H), 7.30 – 7.20 (m, 2H), 7.20 – 7.14 (m, 2H), 7.12 – 7.07 (m, 1H), 7.00 – 6.91 (m, 1H), 5.54 (s, 2H), 4.21 – 4.08 (m, 2H), 3.97 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 2H), 1.04 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 417.3 (M+1); 439.3 (M+Na); HPLC purity: 97.50%.

Step-4: Preparation of 2-(2-((2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)methoxy)phenyl)acetic acid (**25d**)

Compound **25d** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-((2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)methoxy)phenyl)acetate (**25c**) (38 mg, 0.09 mmol) in MeOH (5 mL) using sodium hydroxide (15.49 mg, 0.39 mmol) in water (0.5 mL). This gave after workup and purification by reverse phase column chromatography [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)methoxy)phenyl)acetic acid (**25d**) (3.6 mg, 12 % yield) as a yellow solid; ¹H NMR (300

MHz, Methanol-*d*₄) δ 8.50 (s, 1H), 8.44 – 8.36 (m, 1H), 8.08 – 8.03 (m, 1H), 7.63 – 7.56 (m, 2H), 7.31 – 7.19 (m, 3H), 7.11 – 7.02 (m, 2H), 7.01 – 6.92 (m, 1H), 5.58 (s, 2H), 4.23 (s, 2H), 3.75 (s, 2H); MS (ES⁺): 389.3 (M+1); 411.3 (M+Na); (ES⁻): 387.2 (M-1); 423.4 (M+Cl); HPLC, purity, 87.71%.

Scheme-26



Preparation of 2-(2-((4-(3-(aminomethyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)methoxy)phenyl)acetic acid (**26d**)

Step-1: Preparation of *tert*-butyl 3-(7-(cyclopropylmethyl)-2-(hydroxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzylcarbamate (**26a**)

Compound **26a** was prepared according to the procedure reported in step-1 of Scheme-23, from 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidine-2-carboxylic acid (**16f**) (500 mg, 1.18 mmol) in THF (30 mL), using N-methylmorpholine (0.14 mL, 1.3 mmol), isobutyl chloroformate (0.17 mL, 1.3 mmol) and NaBH₄ (90 mg, 2.37 mmol) in water (0.8 mL). This gave after workup *tert*-butyl 3-(7-(cyclopropylmethyl)-2-(hydroxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzylcarbamate (**26a**) (330 mg, 68% yield) as a yellow oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.10 – 8.03 (m, 2H), 7.78 (d, *J* = 3.6 Hz, 1H), 7.61 – 7.48 (m, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 3.6 Hz, 1H), 5.17 (t, *J* = 6.1 Hz, 1H), 4.71 (d, *J* = 6.1 Hz, 2H), 4.25 (d, *J* = 6.3 Hz, 2H), 4.16 (d, *J* = 7.2 Hz, 2H), 1.41 (s, 9H), 1.34 – 1.21 (m, 1H), 0.58 – 0.40 (m, 4H); ¹H NMR (300 MHz, DMSO-*d*₆/D₂O) δ 8.05 – 7.96 (m, 2H), 7.70 (d, *J* = 3.6 Hz, 1H), 7.57 – 7.43 (m, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 3.6 Hz, 1H), 4.69 (s, 2H), 4.23 (d, *J* = 4.8 Hz, 2H), 4.13 (d, *J* = 7.2 Hz, 2H), 1.37 (s, 9H), 1.31 – 1.17 (m, 1H), 0.54 – 0.36 (m, 4H).

Step-2: Preparation of ethyl 2-(2-((4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)methoxy)phenyl)acetate (**26b**)

Compound **26b** was prepared according to the procedure reported in step-2 of Scheme-23, from *tert*-butyl 3-(7-(cyclopropylmethyl)-2-(hydroxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzylcarbamate (**26a**) (327 mg, 0.8 mmol) in THF (8 mL) using triphenylphosphine (273 mg, 1.04 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (188 mg, 1.04 mmol) and (E)-diisopropyl diazene-1,2-dicarboxylate (DIAD, 210 mg, 1.04 mmol). This gave after workup and by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] ethyl 2-(2-((4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)methoxy)phenyl)acetate (**26b**) (352 mg, 77% yield) as an off white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.90 (s, 2H), 8.08 – 7.98 (m, 2H), 7.82 (d, *J* = 3.6 Hz, 1H), 7.58 – 7.48 (m, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.24 – 7.13 (m, 3H), 6.96 – 6.83 (m, 2H), 5.35 (s, 2H), 4.25 (d, *J* = 6.2 Hz, 2H), 4.13 (d, *J* = 7.2 Hz, 2H), 3.96 (q, *J* = 7.1 Hz, 2H), 1.40 (s, 9H), 1.34 – 1.19 (m, 1H), 1.01 (t, *J* = 7.1 Hz, 3H), 0.51 – 0.34 (m, 4H).

Step-3: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)methoxy)phenyl)acetate (**26c**)

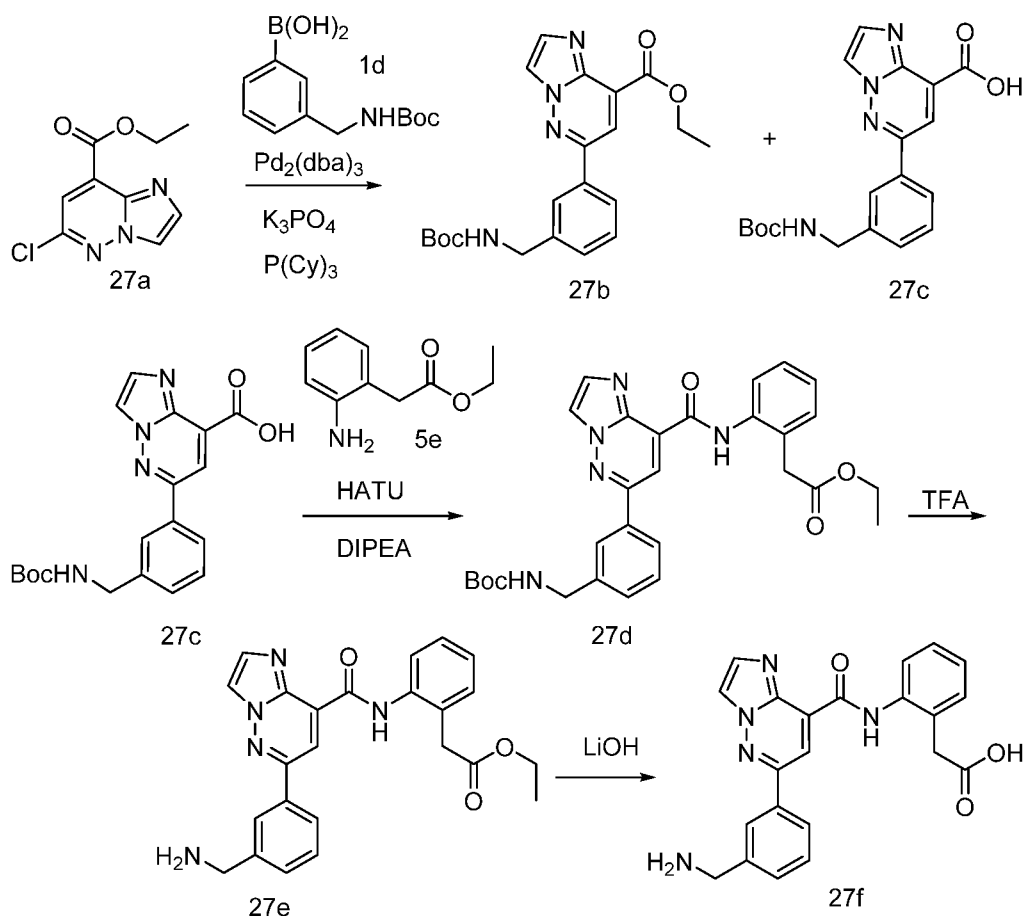
Compound **26c** was prepared according to the procedure reported in step-5 of Scheme-1, from ethyl 2-(2-((4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)methoxy)phenyl)acetate (**26b**) (350 mg, 0.61 mmol) using TFA (0.47 mL, 6.13 mmol) in DCM (25 mL). This gave after workup followed by purification by flash column chromatography [silica (12 g), eluting with DMA-80 in DCM from 0-100%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((4-(3-(aminomethyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)methoxy)phenyl)acetate (**26c**) (256 mg, 89 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.54 (s, 3H, D₂O exchangeable), 8.27 (s, 1H), 8.18 (dt, *J* = 7.4, 1.6 Hz, 1H), 7.88 (d, *J* = 3.6 Hz, 1H), 7.75 – 7.59 (m, 2H), 7.27 – 7.10 (m, 4H), 6.90 (td, *J* = 7.2, 1.3 Hz, 1H), 5.38 (s, 2H), 4.16 (t, *J* = 7.1 Hz, 4H), 3.97 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 2H), 1.36 – 1.19 (m, 1H), 1.02 (t, *J* = 7.1 Hz, 3H), 0.55 – 0.34 (m, 4H); MS (ES⁺): 471.4 (M+1); 493.4 (M+Na); (ES⁻): 505.4 (M+Cl); HPLC purity: 99.60%.

Step-4: Preparation of 2-(2-((4-(3-(aminomethyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)methoxy)phenyl)acetic acid (**26d**)

Compound **26d** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-((4-(3-(aminomethyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-

2-yl)methoxy)phenyl)acetate (**26c**) (105 mg, 0.22 mmol) in MeOH (10 mL) using sodium hydroxide (44.6 mg, 1.12 mmol) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((4-(3-(aminomethyl)phenyl)-7-(cyclopropylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)methoxy)phenyl)acetic acid (**26d**) (23 mg, 23 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.54 (s, 3H, D $_2$ O exchangeable), 8.26 (d, J = 2.1 Hz, 1H), 8.18 (dd, J = 7.6, 1.6 Hz, 1H), 7.87 (d, J = 3.6 Hz, 1H), 7.73 – 7.58 (m, 2H), 7.25 – 7.09 (m, 4H), 6.92 – 6.84 (m, 1H), 5.40 (s, 2H), 4.22 – 4.09 (m, 4H), 3.67 (s, 2H), 1.32 – 1.21 (m, 1H), 0.52 – 0.31 (m, 4H); MS (ES $^+$): 443.4 (M $^+$); 465.4 (M+Na); (ES $^-$): 441.5 (M-1); 477.4 (M+Cl); HPLC purity: 99.44%

Scheme-27



Preparation of 2-(2-(6-(3-(aminomethyl)phenyl)imidazo[1,2-b]pyridazine-8-carboxamido)phenyl)acetic acid (**27f**)

Step-1: Preparation of 6-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)imidazo[1,2-b]pyridazine-8-carboxylic acid (**27c**)

Compound **27c** was prepared according to the procedure reported in step-3 of Scheme-1, from ethyl 6-chloroimidazo[1,2-b]pyridazine-8-carboxylate (**27a**) (500 mg, 2.22 mmol; CAS

1161847-33-1) in dioxane (6 mL) using 3-(((*tert*-butoxycarbonylamino)methyl)phenyl)boronic acid (**1d**) (835 mg, 3.32 mmol), tripotassium phosphate (1.5 mL, 4.43 mmol, 1.3 M aqueous solution), tricyclohexylphosphine (186 mg, 0.67 mmol) and Pd₂(dba)₃ (203 mg, 0.22 mmol) under a nitrogen atmosphere by heating at 120 °C for 1 h in a microwave. This gave after workup and purification by flash column chromatography [silica (40 g), eluting with hexanes in ethyl acetate 0-100%] ethyl 6-(3-(((*tert*-butoxycarbonylamino)methyl)phenyl)imidazo[1,2-*b*]pyridazine-8-carboxylate (**27b**) (123 mg, 14% yield) as a colorless gum; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.47 (d, *J* = 1.2 Hz, 1H), 8.09 (s, 1H), 7.99 – 7.94 (m, 2H), 7.92 (d, *J* = 1.2 Hz, 1H), 7.58 – 7.39 (m, 3H), 4.47 (q, *J* = 7.1 Hz, 2H), 4.24 (d, *J* = 6.2 Hz, 2H), 1.43 – 1.30 (m, 12H); MS (ES⁺): 397.3 (M+1), further elution gave 6-(3-(((*tert*-butoxycarbonylamino)methyl)phenyl)imidazo[1,2-*b*]pyridazine-8-carboxylic acid (**27c**) (60 mg, 7 % yield) as an oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.47 (s, 1H), 8.05 (s, 1H), 8.00 – 7.94 (m, 2H), 7.91 (d, *J* = 1.3 Hz, 1H), 7.59 – 7.38 (m, 3H), 4.24 (d, *J* = 6.2 Hz, 2H), 1.41 (s, 9H).

Step-2: Preparation of ethyl 2-(2-(6-(3-(((*tert*-butoxycarbonylamino)methyl)phenyl)imidazo[1,2-*b*]pyridazine-8-carboxamido)phenyl)acetate (**27d**)

Compound **27d** was prepared according to the procedure reported in step-4 of Scheme-1, from 6-(3-(((*tert*-butoxycarbonylamino)methyl)phenyl)imidazo[1,2-*b*]pyridazine-8-carboxylic acid (**27c**) (180 mg, 0.489 mmol) using ethyl 2-(2-aminophenyl)acetate (**5e**) (153 mg, 0.86 mmol), DIPEA (0.26 mL, 1.47 mmol) and HATU (325 mg, 0.87 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane from 0-100%] ethyl 2-(2-(6-(3-(((*tert*-butoxycarbonylamino)methyl)phenyl)imidazo[1,2-*b*]pyridazine-8-carboxamido)phenyl)acetate (**27d**) (140 mg, 54 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.76 (s, 1H), 8.59 (s, 1H), 8.34 (s, 1H), 8.20 – 8.13 (m, 1H), 8.05 – 7.97 (m, 2H), 7.93 (s, 1H), 7.62 – 7.52 (m, 2H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.41 (s, 1H), 7.38 (s, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 4.26 (d, *J* = 6.2 Hz, 2H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 2H), 1.41 (s, 9H), 1.10 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 530.4 (M+1).

Step-3: Preparation of ethyl 2-(2-(6-(3-(aminomethyl)phenyl)imidazo[1,2-*b*]pyridazine-8-carboxamido)phenyl)acetate (**27e**)

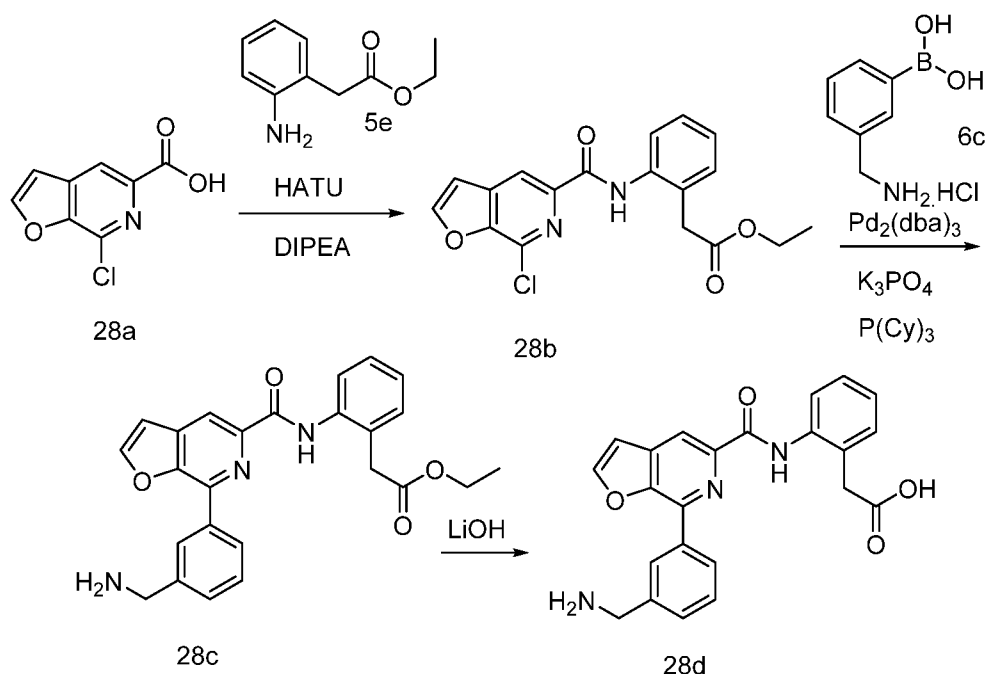
Compound **27e** was prepared according to the procedure reported in step-5 of Scheme-1, from ethyl 2-(2-(6-(3-(((*tert*-butoxycarbonylamino)methyl)phenyl)imidazo[1,2-*b*]pyridazine-8-carboxamido)phenyl)acetate (**27d**) (125 mg, 0.24 mmol) using TFA (0.18

mL, 2.36 mmol) in DCM (5 mL). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-100%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(6-(3-(aminomethyl)phenyl)imidazo[1,2-b]pyridazine-8-carboxamido)phenyl)acetate (**27e**) (100 mg, 99 % yield) as a pale yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.78 (s, 1H, D₂O exchangeable), 8.61 (d, *J* = 1.4 Hz, 1H), 8.51 – 8.35 (m, 4H, 3H D₂O exchangeable), 8.31 (s, 1H), 8.18 (dd, *J* = 7.9, 4.2 Hz, 2H), 7.97 (d, *J* = 1.4 Hz, 1H), 7.75 – 7.61 (m, 2H), 7.47 – 7.37 (m, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 4.20 (q, *J* = 5.9 Hz, 2H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.99 (s, 2H), 1.10 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 430.5 (M+1), 452.4 (M+Na), (ES⁻): 464.5 (M+Cl); HPLC purity: 97.66 %.

Step-4: Preparation of 2-(2-(6-(3-(aminomethyl)phenyl)imidazo[1,2-b]pyridazine-8-carboxamido)phenyl)acetic acid (**27f**)

Compound **27f** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-(6-(3-(aminomethyl)phenyl)imidazo[1,2-b]pyridazine-8-carboxamido)phenyl)acetate (**27e**) (61 mg, 0.142 mmol) in THF (5 mL) using a solution of lithium hydroxide hydrate (10 mg, 0.43 mmol) in water (1 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(6-(3-(aminomethyl)phenyl)imidazo[1,2-b]pyridazine-8-carboxamido)phenyl)acetic acid (**27f**) (65 mg, 100 % yield) as a light yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.87 (s, 1H, D₂O exchangeable), 8.61 (d, *J* = 1.4 Hz, 1H), 8.58 – 8.43 (m, 4H, 3H D₂O exchangeable), 8.32 (d, *J* = 1.9 Hz, 1H), 8.22 – 8.10 (m, 2H), 8.00 (d, *J* = 1.4 Hz, 1H), 7.75 – 7.62 (m, 2H), 7.39 (m, 2H), 7.22 (td, *J* = 7.5, 1.3 Hz, 1H), 4.18 (q, *J* = 5.5 Hz, 2H), 3.90 (s, 2H); MS (ES⁺): 402.4 (M+1), 424.4 (M+Na); (ES⁻): 400.5 (M-1); HPLC purity: 97.80 %.

Scheme-28



Preparation of 2-(2-(7-(3-(aminomethyl)phenyl)furo[2,3-c]pyridine-5-carboxamido)phenyl)acetic acid (**28d**)

Step-1: Preparation of ethyl 2-(2-(7-chlorofuro[2,3-c]pyridine-5-carboxamido)phenyl)acetate (**28b**)

Compound **28b** was prepared according to the procedure reported in step-4 of Scheme-1 from 7-chlorofuro[2,3-c]pyridine-5-carboxylic acid (**28a**) (500 mg, 2.53 mmol; CAS# 478148-53-7) in DMF (4 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (794 mg, 4.43 mmol), DIPEA (1.33 mL, 7.59 mmol) and HATU (1684 mg, 4.43 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane from 0-60%] ethyl 2-(2-(7-chlorofuro[2,3-c]pyridine-5-carboxamido)phenyl)acetate (**28b**) (500 mg, 55 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 10.26 (s, 1H), 8.53 (s, 1H), 8.49 (d, $J = 2.1$ Hz, 1H), 7.79 – 7.72 (m, 1H), 7.39 – 7.32 (m, 3H), 7.25 – 7.15 (m, 1H), 4.08 (q, $J = 7.1$ Hz, 2H), 3.79 (s, 2H), 1.11 (t, $J = 7.1$ Hz, 3H); MS (ES⁺): 359.2 (M+1); (ES⁻) 357.3 (M-1).

Step-2: Preparation of ethyl 2-(2-(7-(3-(aminomethyl)phenyl)furo[2,3-c]pyridine-5-carboxamido)phenyl)acetate (**28c**)

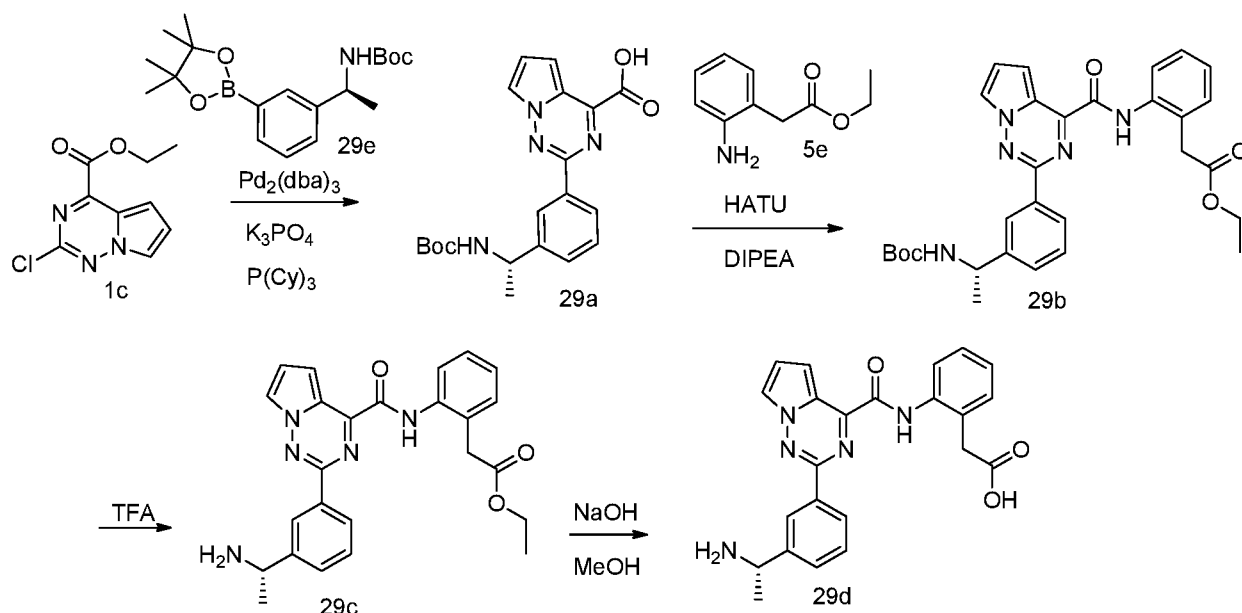
Compound **28c** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(7-chlorofuro[2,3-c]pyridine-5-carboxamido)phenyl)acetate (**28b**) (500 mg, 1.394 mmol) in dioxane (11 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (261 mg, 1.394 mmol), tripotassium phosphate (1.3 M solution) (1.394 mL, 4.18 mmol), tricyclohexylphosphine (117 mg, 0.418 mmol) and $\text{Pd}_2(\text{dba})_3$ (128 mg, 0.139 mmol) under an

Ar atmosphere and heating at 125 °C for 1 h in a microwave. This gave after workup, purification by flash column chromatography [silica (40 g), eluting with ethyl acetate in hexanes from 0-100%] ethyl 2-(2-(7-(3-(aminomethyl)phenyl)furo[2,3-c]pyridine-5-carboxamido)phenyl)acetate (**28c**) (0.304 g, 51 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.60 (s, 1H), 8.69 (s, 1H), 8.61 – 8.56 (m, 1H), 8.54 (d, *J* = 1.2 Hz, 1H), 8.49 (d, *J* = 2.2 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 4.6 Hz, 2H), 7.44 – 7.33 (m, 3H), 7.27 – 7.18 (m, 1H), 4.20 (s, 2H), 3.93 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 2H), 0.93 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 430.3 (M+1); MS (ES⁻): 428.3 (M-1), 474.4 (M+Cl); HPLC purity: 96.63 %.

Step-3: Preparation of 2-(2-(7-(3-(aminomethyl)phenyl)furo[2,3-c]pyridine-5-carboxamido)phenyl)acetic acid (**28d**)

Compound **28d** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-(7-(3-(aminomethyl)phenyl)furo[2,3-c]pyridine-5-carboxamido)phenyl)acetate (**28c**) (61 mg, 0.142 mmol) in THF (8 mL) using a solution of lithium hydroxide hydrate (41 mg, 1.71 mmol) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(7-(3-(aminomethyl)phenyl)furo[2,3-c]pyridine-5-carboxamido)phenyl)acetic acid (**28d**) (140 mgs, 61% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.78 (s, 1H), 10.75 (s, 1H), 8.69 (s, 1H), 8.59 – 8.56 (m, 1H), 8.55 (s, 1H), 8.50 (d, *J* = 2.2 Hz, 1H), 8.43 (s, 3H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.71 – 7.66 (m, 2H), 7.41 – 7.34 (m, 3H), 7.24 – 7.17 (m, 1H), 4.21 (d, *J* = 5.7 Hz, 2H), 3.78 (s, 2H); MS (ES⁺): 402.3 (M+1); 424.3 (M+Na), (ES⁻): 400.3 (M-1); HPLC purity 98.75.

Scheme-29



Preparation of (S)-2-(2-(2-(3-(1-aminoethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**29d**)

Step-1: Preparation of (S)-2-(3-(1-((*tert*-butoxycarbonyl)amino)ethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**29a**)

Compound **29a** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-chloropyrrolo[2,1-f][1,2,4]triazine-4-carboxylate (**1c**) (300 mg, 1.33 mmol) in dioxane (6 mL) using (S)-*tert*-butyl 1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethylcarbamate (**29e**) (693 mg, 1.99 mmol; CAS# 887254-65-1, prepared according to procedure reported in PCT Int. Appl., 2015009977, 22 Jan 2015), tripotassium phosphate (0.753 mL, 2.26 mmol, 3 M aqueous solution) tricyclohexylphosphine (112 mg, 0.4 mmol) and Pd₂(dba)₃ (122 mg, 0.13 mmol) in argon atmosphere and heating at 125 °C for 1 h in a microwave. This gave after workup and purification by flash column chromatography [silica (12 g), eluting with MeOH in DCM from 0-30%] (S)-2-(3-(1-((*tert*-butoxycarbonyl)amino)ethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**29a**) (110 mg, 15 % yield) as a solid; MS (ES⁻): 381.4, 382.4 (M-1).

Step-2: Preparation of (S)-ethyl 2-(2-(2-(3-(1-((*tert*-butoxycarbonyl)amino)ethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetate (**29b**)

Compound **29b** was prepared according to the procedure reported in step-4 of Scheme-1 from (S)-2-(3-(1-((*tert*-butoxycarbonyl)amino)ethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**29a**) (110 mg, 0.29 mmol) in DMF (5 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (77 mg, 0.43 mmol), DIPEA (0.1 mL, 0.575 mmol) and HATU

(164 mg, 0.431 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc/MeOH (9:1) in hexane from 0-100%] (S)-ethyl 2-(2-(2-(3-(1-((*tert*-butoxycarbonyl)amino)ethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetate (**29b**) (103 mg, 66 % yield) as a white solid; MS (ES⁺): 566.4 (M+Na); (ES⁻) 542.5, 543.5 (M-1).

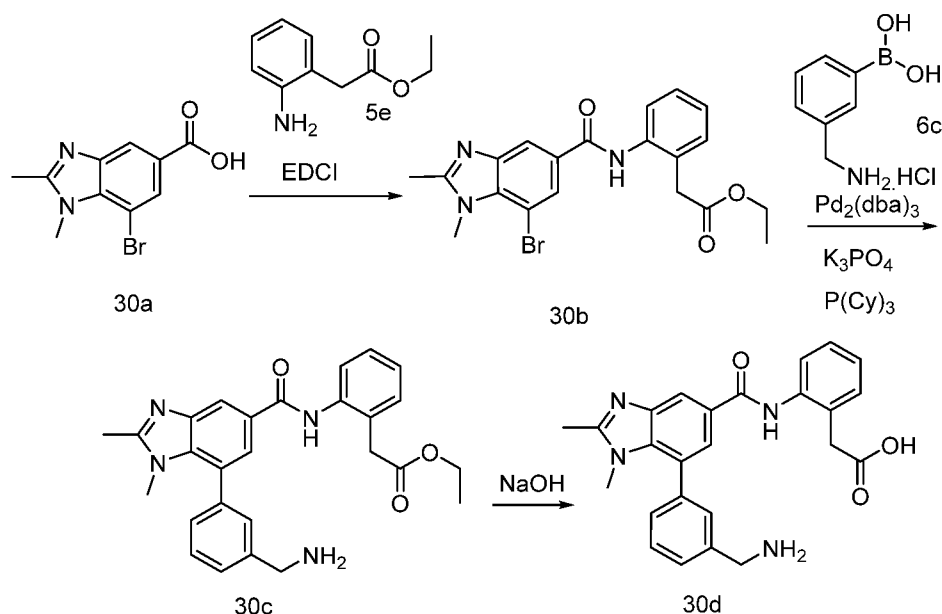
Step-3: Preparation of (S)-ethyl 2-(2-(2-(3-(1-aminoethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetate (**29c**)

Compound **29c** was prepared according to the procedure reported in step-5 of Scheme-1 from (S)-ethyl 2-(2-(2-(3-(1-((*tert*-butoxycarbonyl)amino)ethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetate (**29b**) (103 mg, 0.19 mmol) in DCM (5 mL) using TFA (0.15 mL, 1.90 mmol). This gave after workup (S)-ethyl 2-(2-(2-(3-(1-aminoethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetate (**29c**) (29 mg, 35% yield) as a yellow solid, MS (ES⁺): 444.4 (M+1).

Step-4: Preparation of (S)-2-(2-(2-(3-(1-aminoethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**29d**)

Compound **29d** was prepared according to the procedure reported in step-4 of Scheme-4 from (S)-ethyl 2-(2-(2-(3-(1-aminoethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetate (**29c**) (29 mg, 0.065 mmol) in MeOH (5 mL) using a solution of NaOH (38 mg, 0.95 mmol) in water (0.5 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] (S)-2-(2-(2-(3-(1-aminoethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**29d**) (28 mg, 35 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.77 (s, 1H, D₂O exchangeable), 10.91 (s, 1H), 8.66 (s, 1H), 8.60 (s, 3H, D₂O exchangeable), 8.55 – 8.50 (m, 1H), 8.39 (dd, *J* = 2.5, 1.4 Hz, 1H), 7.90 – 7.80 (m, 1H), 7.77 – 7.71 (m, 1H), 7.70 – 7.57 (m, 2H), 7.48 – 7.35 (m, 2H), 7.34 – 7.21 (m, 2H), 4.67 – 4.45 (m, 1H), 3.81 (s, 2H), 1.61 (d, *J* = 6.7 Hz, 3H); MS (ES⁺): 416.3 (M+1); (ES⁻): 414.4 (M-1); 450.4 (M+Cl); HPLC purity; 99.56%.

Scheme-30



Preparation of 2-(2-(7-(3-(aminomethyl)phenyl)-1,2-dimethyl-1H-benzo[d]imidazole-5-carboxamido)phenyl)acetic acid (**30d**)

Step-1: Preparation of ethyl 2-(2-(7-bromo-1,2-dimethyl-1H-benzo[d]imidazole-5-carboxamido)phenyl)acetate (**30b**)

Compound **30b** was prepared according to the procedure reported in step-1 of Scheme-7 from 7-bromo-1,2-dimethyl-1H-benzo[d]imidazole-5-carboxylic acid (**30a**) (500 mg, 2.53 mmol; CAS# 1420800-25-4) in MeOH (10 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (549 mg, 3.07 mmol) and EDCI (641 mg, 3.34 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] ethyl 2-(2-(7-bromo-1,2-dimethyl-1H-benzo[d]imidazole-5-carboxamido)phenyl)acetate (**30b**) (300 mg, 28% yield) as an off white solid. MS (ES⁺): 432.3 (M+1); (ES⁻) 464.3, 466.3 (M+Cl).

Step-2: Preparation of ethyl 2-(2-(7-(3-(aminomethyl)phenyl)-1,2-dimethyl-1H-benzo[d]imidazole-5-carboxamido)phenyl)acetate (**30c**)

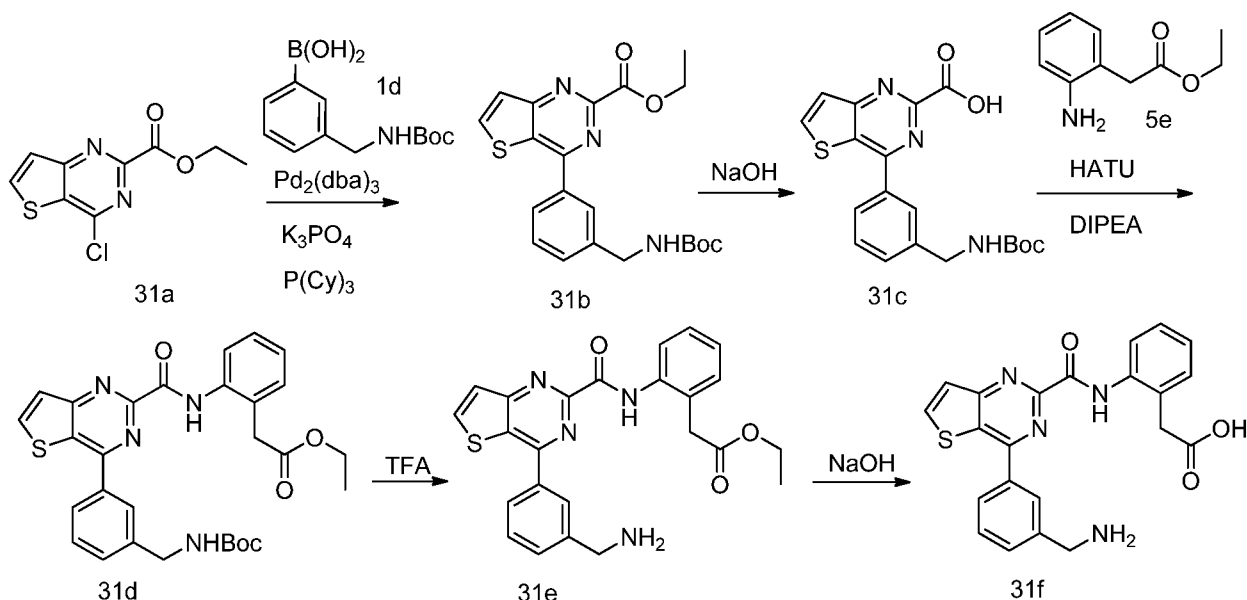
Compound **30c** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(7-bromo-1,2-dimethyl-1H-benzo[d]imidazole-5-carboxamido)phenyl)acetate (**30b**) (300 mg, 0.697 mmol) in dioxane (3 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (196 mg, 1.046 mmol), tripotassium phosphate (1.3 M solution) (0.697 mL, 2.092 mmol), tricyclohexylphosphine (59 mg, 0.209 mmol) and Pd₂(dba)₃ (64 mg, 0.07 mmol) under an Ar atmosphere and heating at 125 °C for 45 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-60%] followed by reverse phase column chromatography [C18 (50

g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(7-(3-(aminomethyl)phenyl)-1,2-dimethyl-1H-benzo[d]imidazole-5-carboxamido)phenyl)acetate (**30c**) (220 mg, 69 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 10.46 (s, 1H), 8.70 (s, 3H), 8.43 (d, $J = 1.6$ Hz, 1H), 7.97 (d, $J = 1.5$ Hz, 1H), 7.75 (d, $J = 1.8$ Hz, 1H), 7.72 – 7.51 (m, 3H), 7.41 – 7.21 (m, 4H), 4.13 (d, $J = 5.8$ Hz, 3H), 3.93 (q, $J = 7.1$ Hz, 2H), 2.84 (s, 3H), 3.45 (s, 3H), 0.97 (t, $J = 7.1$ Hz, 3H).

Step-3: Preparation of 2-(2-(7-(3-(aminomethyl)phenyl)-1,2-dimethyl-1H-benzo[d]imidazole-5-carboxamido)phenyl)acetic acid (**30d**)

Compound **30d** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-(7-(3-(aminomethyl)phenyl)-1,2-dimethyl-1H-benzo[d]imidazole-5-carboxamido)phenyl)acetate (**30c**) (125 mg, 0.27 mmol) in MeOH (10 mL) using a solution of sodium hydroxide (110 mg, 2.74 mmol) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(7-(3-(aminomethyl)phenyl)-1,2-dimethyl-1H-benzo[d]imidazole-5-carboxamido)phenyl)acetic acid (**30d**) (81 mg, 69 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 10.49 (s, 1H, D $_2$ O exchangeable), 8.71 (s, 3H, D $_2$ O exchangeable), 8.45 (d, $J = 1.6$ Hz, 1H), 7.99 (d, $J = 1.6$ Hz, 1H), 7.77 (d, $J = 2.1$ Hz, 1H), 7.74 – 7.68 (m, 1H), 7.67 – 7.54 (m, 2H), 7.43 – 7.20 (m, 4H), 4.13 (q, $J = 5.9$ Hz, 2H), 3.68 (s, 2H), 3.46 (s, 3H), 2.85 (s, 3H); MS (ES $^+$): 429.4 (M+1); (ES $^-$): 427.4 (M-1); 463.4 (M+Cl); HPLC purity: 100%.

Scheme-31



Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)thieno[3,2-d]pyrimidine-2-carboxamido)phenyl)acetic acid (**31f**)

Step-1: Preparation of ethyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)thieno[3,2-d]pyrimidine-2-carboxylate (**31b**)

Compound **31b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 4-chlorothieno[3,2-d]pyrimidine-2-carboxylate (**31a**) (350 mg, 1.44 mmol; CAS# 319442-18-7) in dioxane (3 mL) using (3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)boronic acid (**1d**) (543 mg, 2.16 mmol), tripotassium phosphate (0.82 mL, 2.452 mmol, 3 M aqueous solution), tricyclohexylphosphine (81 mg, 0.288 mmol) and Pd₂(dba)₃ (73 mg, 0.079 mmol) in argon atmosphere and heating at 125 °C for 30 min in a microwave. This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-70%] ethyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)thieno[3,2-d]pyrimidine-2-carboxylate (**31b**) (400 mg, 67 % yield) as a yellow solid.

Step-2: Preparation of 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)thieno[3,2-d]pyrimidine-2-carboxylic acid (**31c**)

Compound **31c** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)thieno[3,2-d]pyrimidine-2-carboxylate (**31b**) (400 mg, 0.97 mmol) in MeOH (10 mL) using a solution of NaOH (193 mg, 4.84 mmol) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)thieno[3,2-d]pyrimidine-2-carboxylic acid (**31c**) (365 mg, 98 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.46 (s, 1H), 8.72 (d, *J* = 5.6 Hz, 1H), 8.19 – 7.99 (m, 2H), 7.86 (d, *J* = 5.6 Hz, 1H), 7.69 – 7.47 (m, 3H), 4.28 (d, *J* = 6.2 Hz, 2H), 1.41 (s, 9H).

Step-3: Preparation of ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)thieno[3,2-d]pyrimidine-2-carboxamido)phenyl)acetate (**31d**)

Compound **31d** was prepared according to the procedure reported in step-4 of Scheme-1 from 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)thieno[3,2-d]pyrimidine-2-carboxylic acid (**31c**) (365 mg, 0.95 mmol) in DMF (5 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (204 mg, 1.14 mmol), DIPEA (0.331 mL, 1.894 mmol) and HATU (432 mg, 1.14 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc/MeOH (9:1) in hexane from 0-100%] ethyl 2-(2-(4-(3-(((*tert*-

butoxycarbonyl)amino)methyl)phenyl)thieno[3,2-d]pyrimidine-2-carboxamido)phenyl)acetate (**31d**) (425 mg, 82 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.72 (s, 1H), 8.77 (d, *J* = 5.5 Hz, 1H), 8.27 – 8.19 (m, 2H), 7.90 (d, *J* = 5.5 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.70 – 7.61 (m, 1H), 7.60 – 7.51 (m, 2H), 7.44 – 7.34 (m, 2H), 7.28 – 7.19 (m, 1H), 4.30 (d, *J* = 6.2 Hz, 2H), 3.98 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 2H), 1.40 (s, 9H), 0.98 (t, *J* = 7.1 Hz, 3H).

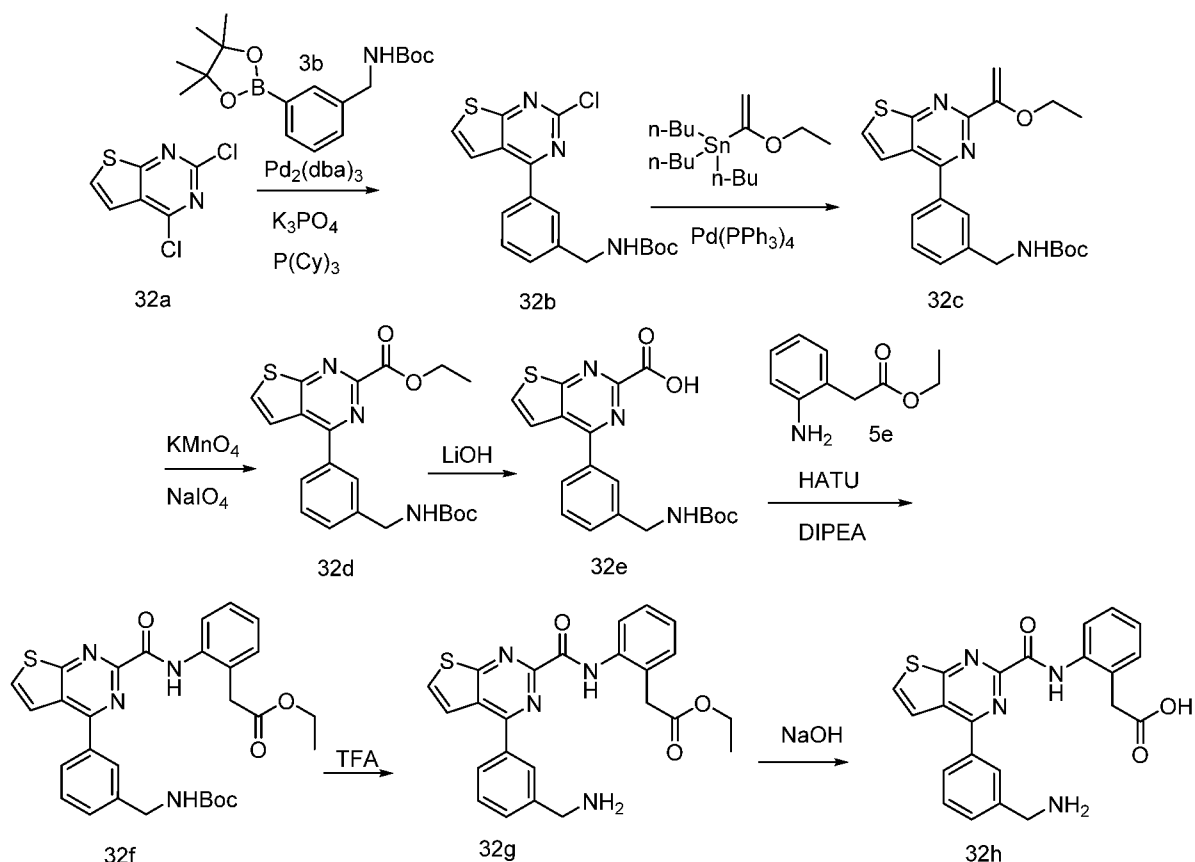
Step-4: Preparation of ethyl 2-(2-(4-(3-(aminomethyl)phenyl)thieno[3,2-d]pyrimidine-2-carboxamido)phenyl)acetate (**31e**)

Compound **31e** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)thieno[3,2-d]pyrimidine-2-carboxamido)phenyl)acetate (**31d**) (400 mg, 0.73 mmol) in DCM (5 mL) using TFA (0.56 mL, 7.32 mmol). This gave after workup and purification by reverse phase column purification [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(4-(3-(aminomethyl)phenyl)thieno[3,2-d]pyrimidine-2-carboxamido)phenyl)acetate (**31e**) (308 mg, 94 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.72 (s, 1H, D₂O exchangeable), 8.80 (d, *J* = 5.4 Hz, 1H), 8.60 (s, 3H, D₂O exchangeable), 8.51 (s, 1H), 8.39 – 8.31 (m, 1H), 7.93 (d, *J* = 5.5 Hz, 1H), 7.89 – 7.72 (m, 3H), 7.45 – 7.35 (m, 2H), 7.32 – 7.21 (m, 1H), 4.22 (s, 2H), 3.98 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 2H), 1.00 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 447.3 (M+1); (ES⁻): 481.3 (M+Cl); HPLC purity, 99.72%.

Step-5: Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)thieno[3,2-d]pyrimidine-2-carboxamido)phenyl)acetic acid (**31f**)

Compound **31f** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(4-(3-(aminomethyl)phenyl)thieno[3,2-d]pyrimidine-2-carboxamido)phenyl)acetate (**31e**) (256 mg, 0.57 mmol) in MeOH/THF (10 mL, 1:1) using a solution of NaOH (92 mg, 2.29 mmol) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(4-(3-(aminomethyl)phenyl)thieno[3,2-d]pyrimidine-2-carboxamido)phenyl)acetic acid (**31f**) (112 mg, 47% yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.82 (s, 1H, D₂O exchangeable), 8.80 (d, *J* = 5.5 Hz, 1H), 8.60 – 8.42 (m, 4H, partially D₂O exchangeable), 8.39 – 8.30 (m, 1H), 7.95 – 7.70 (m, 4H), 7.45 – 7.33 (m, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 4.27 – 4.20 (m, 2H), 3.79 (s, 2H); MS (ES⁺) 419.3 (M+1); 441.3 (M+Na); (ES⁻) 417.3 (M-1), 453.3 (M+Cl); HPLC, 0.395 min, 98.46%.

Scheme-32



Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)thieno[2,3-d]pyrimidine-2-carboxamido)phenyl)acetic acid (**32h**)

Step-1: Preparation of *tert*-butyl 3-(2-(4-(3-(aminomethyl)phenyl)thieno[2,3-d]pyrimidin-4-yl)benzylcarbamate (**32b**)

Compound **32b** was prepared according to the procedure reported in step-3 of Scheme-1 from 2,4-dichloro-5-(4-(3-(aminomethyl)phenyl)thieno[2,3-d]pyrimidin-2-carboxamido)phenyl)acetic acid (**32a**) (4.5 g, 21.94 mmol; CAS #18740-39-1) in dioxane (100 mL) using *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylcarbamate (**3b**) (5.63 g, 16.88 mmol), tripotassium phosphate (22.07 mL, 28.7 mmol) in water (1 mL), tricyclohexylphosphine (0.95 g, 3.38 mmol) and $\text{Pd}_2(\text{dba})_3$ (0.85 g, 0.93 mmol) in argon atmosphere and heating in an oil bath at 120 °C for 1h. This gave after workup and purification by flash column chromatography [silica (80 g), eluting with EtOAc in hexane from 0-70%] *tert*-butyl 3-(2-(4-(3-(aminomethyl)phenyl)thieno[2,3-d]pyrimidin-4-yl)benzylcarbamate (**32b**) (4.5 g, 71 % yield) as a yellow solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.08 (d, $J = 6.0$ Hz, 1H), 7.89 – 7.83 (m, 2H), 7.74 (d, $J = 6.1$ Hz, 1H), 7.62 – 7.47 (m, 3H), 4.25 (d, $J = 6.2$ Hz, 2H), 1.40 (s, 9H).

Step-2: Preparation of *tert*-butyl 3-(2-(1-ethoxyvinyl)thieno[2,3-d]pyrimidin-4-yl)benzylcarbamate (**32c**)

Compound **32c** was prepared according to the procedure reported in step-1 of Scheme-1 from

tert-butyl 3-(2-chlorothieno[2,3-d]pyrimidin-4-yl)benzylcarbamate (**32b**) (4.5 g, 11.97 mmol) in DMF (60 mL) using 1-ethoxyvinyltri-*n*-butyltin (4.89 mL, 14.37 mmol) and Pd(PPh₃)₄ (0.692 g, 0.599 mmol) in argon atmosphere and heating at 110 °C for 10 h. This gave after workup and purification by flash column chromatography [silica (80 g), eluting with EtOAc in hexane from 0-70%] *tert*-butyl 3-(2-(1-ethoxyvinyl)thieno[2,3-d]pyrimidin-4-yl)benzylcarbamate (**32c**) (4.4 g, 89 % yield) as a yellow solid; MS (ES⁺): 412.2 (M+1).

Step-3: Preparation of ethyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)thieno[2,3-d]pyrimidine-2-carboxylate (**32d**)

Compound **32d** was prepared according to the procedure reported in step-2 of Scheme-1 from *tert*-butyl 3-(2-(1-ethoxyvinyl)thieno[2,3-d]pyrimidin-4-yl)benzylcarbamate (**32c**) (4.4 g, 10.69 mmol) in 1,4-dioxane (50 mL) using sodium periodate solution (4.57 g, 21.38 mmol) in water (20 mL) and KMnO₄ (0.676 g, 4.28 mmol, and second dosing of 0.338 g, 2.138 mmol after 12 h). This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-60%] ethyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)thieno[2,3-d]pyrimidine-2-carboxylate (**32d**) (1.6 g, 36 % yield) as a yellow solid; MS (ES⁺): 414.2 (M+1), 436.1 (M+Na).

Step-4: Preparation of 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)thieno[2,3-d]pyrimidine-2-carboxylic acid (**32e**)

Compound **32e** was prepared according to the procedure reported in step-6 of Scheme-1 from ethyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)thieno[2,3-d]pyrimidine-2-carboxylate (**32d**) (1.6 g, 3.87 mmol) in THF/MeOH (30 mL, 1:1) using lithium hydroxide hydrate (0.812 g, 19.35 mmol) in water (5 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)thieno[2,3-d]pyrimidine-2-carboxylic acid (**32e**) (0.55 g, 37 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.62 (s, 1H), 8.26 (d, *J* = 6.0 Hz, 1H), 7.93 – 7.87 (m, 2H), 7.82 (d, *J* = 6.1 Hz, 1H), 7.64 – 7.44 (m, 3H), 4.26 (d, *J* = 6.2 Hz, 2H), 1.40 (s, 9H).

Step-5: Preparation of ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)thieno[2,3-d]pyrimidine-2-carboxamido)phenyl)acetate (**32f**)

Compound **32f** was prepared according to the procedure reported in step-4 of Scheme-1 from 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)thieno[2,3-d]pyrimidine-2-carboxylic acid (**32e**) (547 mg, 1.42 mmol) in DMF (5 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (305

mg, 1.703 mmol), DIPEA (0.5 mL, 2.84 mmol) and HATU (648 mg, 1.703 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc/MeOH (9:1) in hexane from 0-100%] ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)thieno[2,3-*d*]pyrimidine-2-carboxamido)phenyl)acetate (**32f**) (620 mg, 1.134 mmol, 80 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.71 (s, 1H), 8.29 (d, *J* = 6.1 Hz, 1H), 8.12 – 7.99 (m, 2H), 7.89 (d, *J* = 6.1 Hz, 1H), 7.86 – 7.78 (m, 1H), 7.65 – 7.48 (m, 3H), 7.38 (d, *J* = 7.5 Hz, 2H), 7.29 – 7.18 (m, 1H), 4.29 (d, *J* = 6.1 Hz, 2H), 3.96 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 2H), 1.40 (s, 9H), 0.98 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 569.4 (M+Na); (ES⁻): 545.5 (M-1).

Step-6: Preparation of ethyl 2-(2-(4-(3-(aminomethyl)phenyl)thieno[2,3-*d*]pyrimidine-2-carboxamido)phenyl)acetate (**32g**)

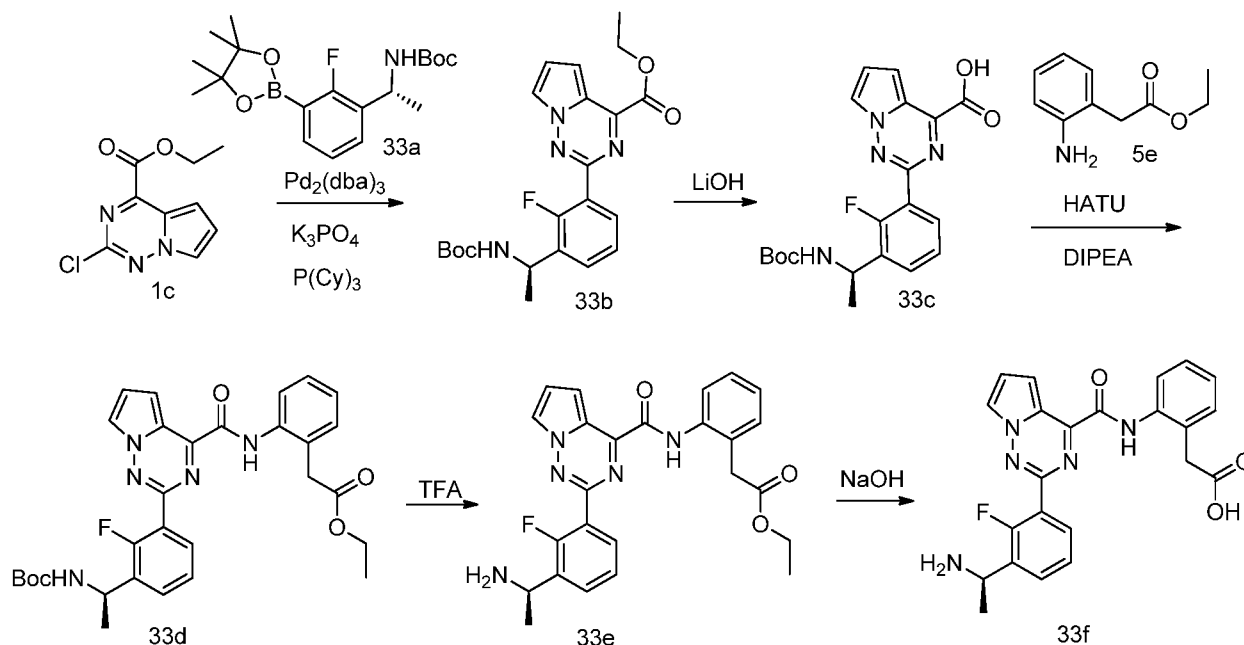
Compound **32g** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)thieno[2,3-*d*]pyrimidine-2-carboxamido)phenyl)acetate (**32f**) (600 mg, 1.10 mmol) in DCM (10 mL) using TFA (0.85 mL, 10.98 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(4-(3-(aminomethyl)phenyl)thieno[2,3-*d*]pyrimidine-2-carboxamido)phenyl)acetate (**32g**) (385 mg, 79 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.72 (s, 1H, D₂O exchangeable), 8.58 (s, 3H, D₂O exchangeable), 8.35 – 8.27 (m, 2H), 8.24 (d, *J* = 7.6 Hz, 1H), 8.10 (d, *J* = 6.1 Hz, 1H), 7.84 – 7.75 (m, 2H), 7.75 – 7.68 (m, 1H), 7.42 – 7.34 (m, 2H), 7.29 – 7.20 (m, 1H), 4.30 – 4.14 (m, 2H), 3.98 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 2H), 1.01 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 447.3 (M+1); (ES⁻): 481.3 (M+Cl); HPLC purity, 99.41%.

Step-7: Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)thieno[2,3-*d*]pyrimidine-2-carboxamido)phenyl)acetic acid (**32h**)

Compound **32h** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(4-(3-(aminomethyl)phenyl)thieno[2,3-*d*]pyrimidine-2-carboxamido)phenyl)acetate (**32g**) (200 mg, 0.448 mmol) in MeOH/THF (10 mL, 1:1) using a solution of NaOH (72 mg, 1.79 mmol) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(4-(3-(aminomethyl)phenyl)thieno[2,3-*d*]pyrimidine-2-carboxamido)phenyl)acetic acid (**32h**) (150 mg, 80 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.79 (s, 1H, D₂O exchangeable), 10.81 (s, 1H, D₂O

exchangeable), 8.60 (s, 3H, D₂O exchangeable), 8.35 – 8.27 (m, 2H), 8.27 – 8.20 (m, 1H), 8.17 – 8.07 (m, 1H), 7.95 – 7.84 (m, 1H), 7.83 – 7.77 (m, 1H), 7.77 – 7.67 (m, 1H), 7.44 – 7.33 (m, 2H), 7.29 – 7.17 (m, 1H), 4.26 – 4.17 (m, 2H), 3.78 (s, 2H); MS (ES⁺): 419.3 (M+1); 441.3 (M+Na); (ES⁻): 417.3 (M-1), 453.3 (M+Cl); HPLC, 0.406 min, 100%.

Scheme-33



Preparation of (R)-2-(2-(2-(3-(1-aminoethyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**33f**)

Step-1: Preparation of (R)-ethyl 2-(3-(1-((tert-butoxycarbonyl)amino)ethyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylate (**33b**)

Compound **33b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-chloropyrrolo[2,1-f][1,2,4]triazine-4-carboxylate (**1c**) (450 mg, 1.99 mmol) in dioxane (15 mL) using (R)-tert-butyl (1-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)carbamate (**33a**) (1.093 g, 2.99 mmol; CAS# 1645556-74-2, prepared according to procedure reported in PCT Int. Appl., 2015009977, 22 Jan 2015), 3 M aqueous solution of tripotassium phosphate (1.33 mL, 3.99 mmol), tricyclohexylphosphine (112 mg, 0.4 mmol) and Pd₂(dba)₃ (183 mg, 0.2 mmol) in argon atmosphere and heating at 125 °C for 45 min in a microwave. This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc in DCM from 0-50%] (R)-ethyl 2-(3-(1-((tert-butoxycarbonyl)amino)ethyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylate (**33b**) (0.73 g, 85 % yield) as an orange solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.44 – 8.37 (m, 1H), 7.88 – 7.79 (m, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.60 – 7.52 (m, 1H), 7.41

– 7.32 (m, 2H), 7.29 (dd, $J = 4.6, 2.6$ Hz, 1H), 5.07 – 4.91 (m, 1H), 4.50 (q, $J = 7.1$ Hz, 2H), 1.45 – 1.27 (m, 15H); MS (ES⁺): 429.3 (M+1); (ES⁻): 427.3 (M-1).

Step-2: Preparation of (R)-2-(3-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylic acid (**33c**)

Compound **33c** was prepared according to the procedure reported in step-6 of Scheme-1 from (R)-ethyl 2-(3-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylate (**33b**) (0.73 g, 1.704 mmol) in THF (15 mL) using lithium hydroxide hydrate (0.107 g, 2.56 mmol) in water (3 mL). This gave after workup (R)-2-(3-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylic acid (**33c**) (0.67 g, 98 % yield) as a light orange foam; ¹H NMR (300 MHz, DMSO-*d*₆) δ 14.37 (s, 1H), 8.39 – 8.34 (m, 1H), 7.87 (t, $J = 7.2$ Hz, 1H), 7.63 (d, $J = 8.0$ Hz, 1H), 7.59 – 7.51 (m, 1H), 7.40 – 7.31 (m, 2H), 7.25 (dd, $J = 4.6, 2.6$ Hz, 1H), 4.99 (t, $J = 7.4$ Hz, 1H), 1.46 – 1.24 (m, 12H); MS (ES⁺): 423.3 (M+Na); (ES⁻): 399.4 (M-1).

Step-3: Preparation of (R)-ethyl 2-(2-(2-(3-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**33d**)

Compound **33d** was prepared according to the procedure reported in step-4 of Scheme-1 from (R)-2-(3-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylic acid (**33c**) (200 mg, 0.499 mmol) in DMF (3 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (134 mg, 0.75 mmol), DIPEA (0.174 mL, 1.00 mmol) and HATU (228 mg, 0.6 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-100%] (R)-ethyl 2-(2-(2-(3-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**33d**) (0.22 g, 78 % yield) as an orange solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.67 (s, 1H), 8.42 (d, $J = 2.4$ Hz, 1H), 8.16 (t, $J = 7.4$ Hz, 1H), 7.78 (d, $J = 8.1$ Hz, 1H), 7.64 (d, $J = 8.1$ Hz, 1H), 7.61 – 7.51 (m, 2H), 7.44 – 7.32 (m, 3H), 7.32 – 7.20 (m, 2H), 5.09 – 4.93 (m, 1H), 3.95 (q, $J = 7.1$ Hz, 2H), 3.83 (s, 2H), 1.43 – 1.19 (m, 12H), 1.02 – 0.90 (m, 3H); MS (ES⁺): 584.4 (M+Na); (ES⁻): 560.5 (M-1).

Step-4: Preparation of (R)-ethyl 2-(2-(2-(3-(1-aminoethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**33e**)

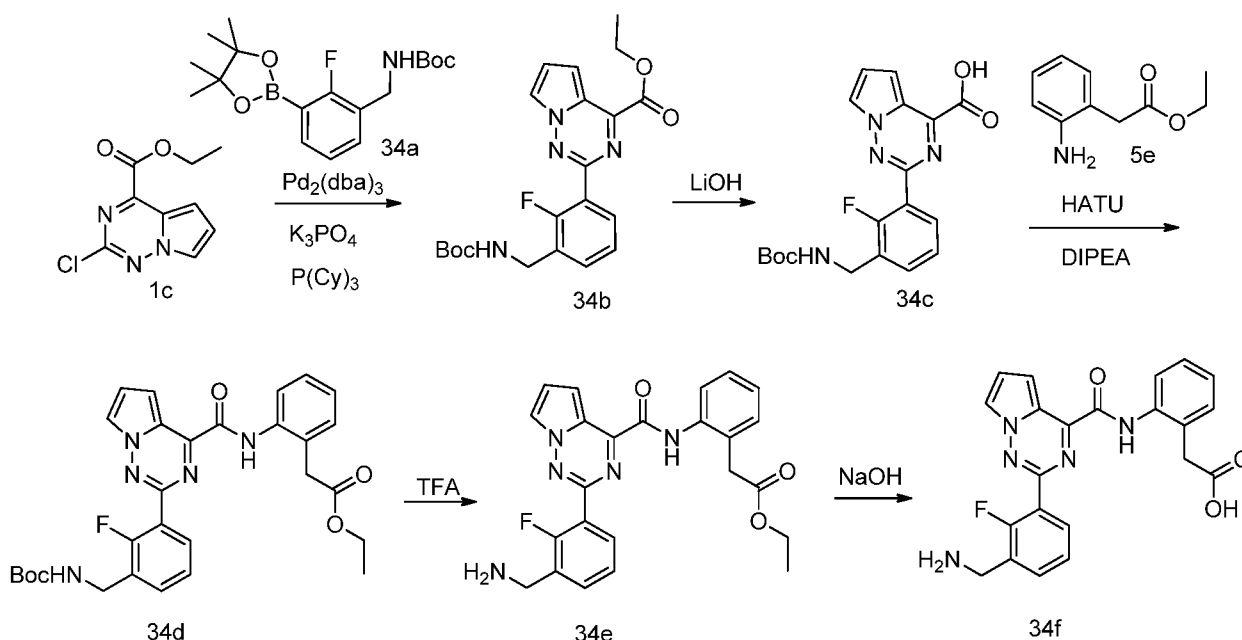
Compound **33e** was prepared according to the procedure reported in step-5 of Scheme-1 from (R)-ethyl 2-(2-(2-(3-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**33d**) (200 mg, 0.356 mmol) in DCM (2 mL) using TFA (0.274 mL, 3.56 mmol). This gave after workup and purification by reverse column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl)] from

0-100%] (R)-ethyl 2-(2-(2-(3-(1-aminoethyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetate (**33e**) (0.164 g, 100 % yield) HCl salt as an orange solid. ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 10.71 (s, 1H), 8.48 – 8.35 (m, 5H), 7.83 – 7.72 (m, 2H), 7.64 – 7.57 (m, 1H), 7.50 (t, $J = 7.8$ Hz, 1H), 7.46 – 7.36 (m, 2H), 7.36 – 7.23 (m, 2H), 4.85 – 4.69 (m, 1H), 3.97 (q, $J = 7.1$ Hz, 2H), 3.84 (s, 2H), 1.58 (d, $J = 6.7$ Hz, 3H), 0.98 (t, $J = 7.1$ Hz, 3H); ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ -118.34; MS (ES+): 462.3 (M+1), 484.3 (M+Na); HPLC purity 99.38 %

Step-5: Preparation of (R)-2-(2-(2-(3-(1-aminoethyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**33f**)

Compound **33f** was prepared according to the procedure reported in step-4 of Scheme-4 from (R)-ethyl 2-(2-(2-(3-(1-aminoethyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetate (**33e**) (120 mg, 0.26 mmol) in THF (4 mL) using a 2 M aqueous solution of NaOH (0.52 mL, 1.04 mmol). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] (R)-2-(2-(2-(3-(1-aminoethyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**33f**) (0.06 g, 53 % yield) HCl salt as an orange solid; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 12.73 (s, 1H), 10.74 (s, 1H), 8.62 (s, 3H), 8.46 – 8.32 (m, 2H), 7.92 – 7.78 (m, 2H), 7.66 – 7.58 (m, 1H), 7.50 (t, $J = 7.8$ Hz, 1H), 7.44 – 7.35 (m, 2H), 7.32 (dd, $J = 4.6, 2.6$ Hz, 1H), 7.25 (t, $J = 7.5$ Hz, 1H), 4.84 – 4.70 (m, 1H), 3.76 (s, 2H), 1.60 (d, $J = 6.7$ Hz, 3H); ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ -118.36; MS (ES+): 434.3 (M+1), MS (ES-): 432.4 (M-1); HPLC purity 99.62 %.

Scheme-34



Preparation of 2-(2-(2-(3-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**34f**)

Step-1: Preparation of ethyl 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylate (**34b**)

Compound **34b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-chloropyrrolo[2,1-f][1,2,4]triazine-4-carboxylate (**1c**) (400 mg, 1.77 mmol) in dioxane (15 mL) using *tert*-butyl 2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylcarbamate (**34a**) (1.093 g, 2.99 mmol; CAS# 1360819-53-9), 3 M aqueous solution of tripotassium phosphate (1.18 mL, 3.55 mmol), tricyclohexylphosphine (99 mg, 0.36 mmol) and Pd₂(dba)₃ (162 mg, 0.18 mmol) in argon atmosphere and heating at 125 °C for 45 min in a microwave. This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-50%] ethyl 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylate (**34b**) (0.61 g, 83 % yield) as an orange solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.40 (dd, J = 2.6, 1.4 Hz, 1H), 7.91 - 7.83 (m, 1H), 7.57 - 7.42 (m, 2H), 7.41 - 7.31 (m, 2H), 7.29 (dd, J = 4.6, 2.5 Hz, 1H), 4.50 (q, J = 7.1 Hz, 2H), 4.26 (d, J = 6.0 Hz, 2H), 1.47 - 1.30 (m, 12H); MS (ES⁺): 415.3 (M+1); (ES⁻): 413.4 (M-1).

Step-2: Preparation of 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**34c**)

Compound **34c** was prepared according to the procedure reported in step-6 of Scheme-1 from ethyl 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylate (**34b**) (0.6 g, 1.448 mmol) in THF (15 mL) using lithium hydroxide hydrate (0.122 g, 2.90 mmol) in water (1 mL). This gave after workup 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**34c**) (0.54 g, 97 % yield) as a light orange foam; ¹H NMR (300 MHz, DMSO-*d*₆) δ 14.37 (s, 1H), 8.36 (dd, J = 2.6, 1.4 Hz, 1H), 7.95 - 7.87 (m, 1H), 7.57 - 7.42 (m, 2H), 7.39 - 7.31 (m, 2H), 7.25 (dd, J = 4.6, 2.5 Hz, 1H), 4.26 (d, J = 6.1 Hz, 2H), 1.40 (s, 9H); MS (ES⁻): 385.3 (M-1).

Step-3: Preparation of ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetate (**34d**)

Compound **34d** was prepared according to the procedure reported in step-4 of Scheme-1 from 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**34c**) (250 mg, 0.647 mmol) in DMF (4 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (125 mg, 0.7 mmol), DIPEA (0.23 mL, 1.29 mmol) and HATU

(295 mg, 0.776 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-100%] ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**34d**) (0.31 g, 87 % yield) as an orange solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.68 (s, 1H), 8.40 (dd, *J* = 2.7, 1.4 Hz, 1H), 8.22 (t, *J* = 7.5 Hz, 1H), 7.81 - 7.75 (m, 1H), 7.61 - 7.55 (m, 2H), 7.50 (dt, *J* = 13.5, 6.3 Hz, 1H), 7.44 - 7.32 (m, 3H), 7.32 - 7.21 (m, 2H), 4.28 (d, *J* = 6.1 Hz, 2H), 3.96 (q, *J* = 7.0 Hz, 2H), 3.83 (s, 2H), 1.41 (s, 9H), 0.97 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 570.4 (M+Na); (ES⁻): 546.5 (M-1).

Step-4: Preparation of ethyl 2-(2-(2-(3-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**34e**)

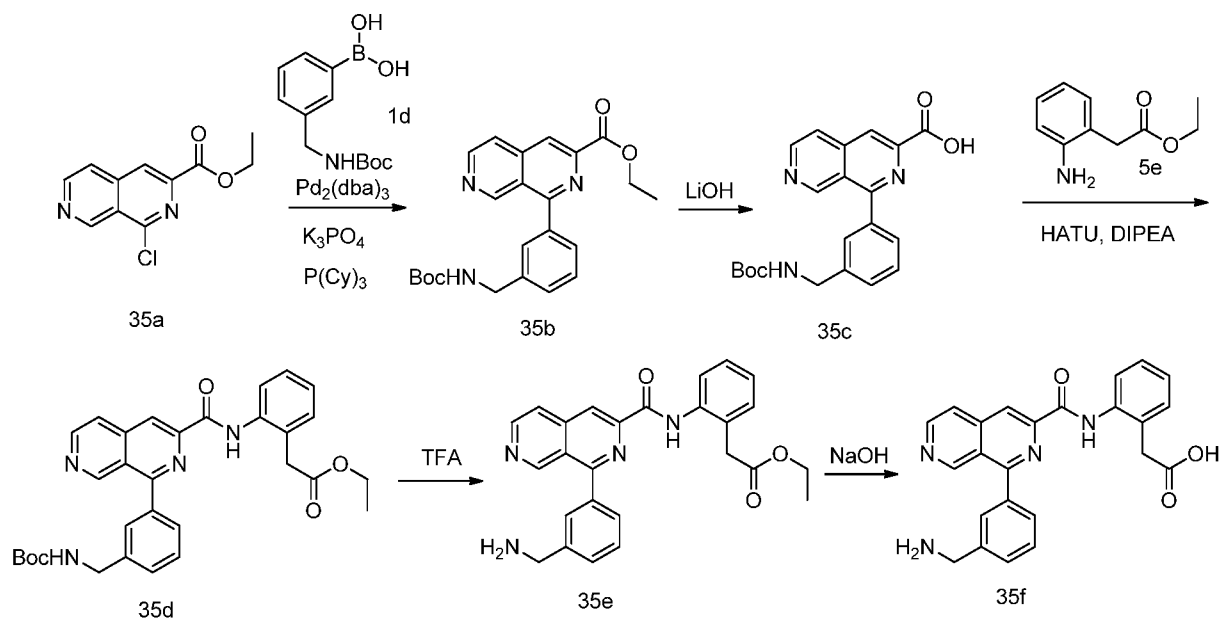
Compound **34e** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**34d**) (200 mg, 0.365 mmol) in DCM (5 mL) using TFA (0.281 mL, 3.65 mmol). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(2-(3-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**34e**) (0.16 g, 98 % yield) as a HCl salt; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.72 (s, 1H), 8.53 - 8.36 (m, 5H), 7.81 - 7.71 (m, 2H), 7.60 (dd, *J* = 4.6, 1.4 Hz, 1H), 7.52 - 7.36 (m, 3H), 7.34 - 7.23 (m, 2H), 4.20 (s, 2H), 3.97 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 2H), 0.99 (t, *J* = 7.1 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -116.67; MS (ES⁺): 448.3 (M+1), MS (ES⁻): 482.4 (M+Cl); HPLC purity 98.75 %

Step-5: Preparation of 2-(2-(2-(3-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**34f**)

Compound **34f** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(2-(3-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**34e**) (110 mg, 0.246 mmol) in THF (4 mL) using a 2 M aqueous solution of NaOH (0.62 mL, 1.23 mmol). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-40%] 2-(2-(2-(3-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**34f**) (0.072 g, 70 % yield) as a HCl salt; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.75 (s, 1H), 10.76 (s, 1H), 8.57 - 8.34 (m, 5H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.76 (t, *J* = 7.1 Hz, 1H), 7.62 (d, *J* = 4.5 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.45 - 7.33 (m, 2H), 7.32 (dd, *J* = 4.6, 2.6 Hz, 1H), 7.25 (t, *J* = 7.4 Hz, 1H), 4.20 (s, 2H), 3.76 (s,

2H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -116.66; MS (ES⁺): 420.3 (M+1), MS (ES⁻): 418.3 (M-1); HPLC purity 99.49 %.

Scheme-35



Preparation of 2-(2-(1-(3-(aminomethyl)phenyl)-2,7-naphthyridine-3-carboxamido)phenyl)acetic acid (**35f**)

Step-1: Preparation of ethyl 1-(3-(((tert-butoxycarbonyl)amino)methyl)phenyl)-2,7-naphthyridine-3-carboxylate (**35b**)

Compound **35b** was prepared according to the procedure reported in step-3 of Scheme-1, from ethyl 1-chloro-2,7-naphthyridine-3-carboxylate (**35a**) (1000 mg, 4.23 mmol; CAS # 263881-19-2) in DMF (11 mL) using 3-((tert-butoxycarbonylamino)methyl)phenylboronic acid (**1d**) (1.59 g, 6.34 mmol), tripotassium phosphate (1.3 M solution, 2.82 mL, 8.45 mmol), tricyclohexylphosphine (355 mg, 1.27 mmol) and $\text{Pd}_2(\text{dba})_3$ (387 mg, 0.42 mmol) under a nitrogen atmosphere by heating at 120 °C for 1 h in a microwave. This gave after workup and purification by flash column chromatography [silica (40 g), eluting with hexanes/ethyl acetate 0% to 100%] ethyl 1-(3-(((tert-butoxycarbonyl)amino)methyl)phenyl)-2,7-naphthyridine-3-carboxylate (**35b**) (1.32 g, 77 % yield) as an oil; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.42 (s, 1H), 8.88 (d, J = 5.7 Hz, 1H), 8.67 (s, 1H), 8.21 (dd, J = 5.7, 1.0 Hz, 1H), 7.68 – 7.45 (m, 5H), 4.43 (q, J = 7.1 Hz, 2H), 4.27 (d, J = 6.2 Hz, 2H), 1.40 – 1.28 (m, 12H).

Step-2: Preparation of 1-(3-(((tert-butoxycarbonyl)amino)methyl)phenyl)-2,7-naphthyridine-3-carboxylic acid (**35c**)

Compound **35c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 1-(3-(((tert-butoxycarbonyl)amino)methyl)phenyl)-2,7-naphthyridine-3-

carboxylate (**35b**) (1250 mg, 3.07 mmol) in THF (20 mL) using a solution of lithium hydroxide hydrate (220 mg, 9.2 mmol) in water (4 mL). This gave after workup 1-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2,7-naphthyridine-3-carboxylic acid (**35c**) (300 mgs, 26%), which was used as such for next step; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.43 (s, 1H), 8.86 (d, *J* = 5.7 Hz, 1H), 8.62 (s, 1H), 8.17 (d, *J* = 5.8 Hz, 1H), 7.72 – 7.41 (m, 5H), 4.27 (d, *J* = 6.2 Hz, 2H), 1.38 (s, 9H).

Step-3: Preparation of ethyl 2-(2-(1-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2,7-naphthyridine-3-carboxamido)phenyl)acetate (**35d**)

Compound **35d** was prepared according to the procedure reported in step-4 of Scheme-1, from 1-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2,7-naphthyridine-3-carboxylic acid (**35c**) (300 mg, 0.79 mmol) in DMF (4 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (248 mg, 1.38 mmol), DIPEA (0.41 mL, 2.37 mmol) and HATU (526 mg, 1.38 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc/MeOH (9:1) in hexane from 0-100%] ethyl 2-(2-(1-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2,7-naphthyridine-3-carboxamido)phenyl)acetate (**35d**) (300 mg, 70 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.68 (s, 1H), 9.55 (s, 1H), 8.90 (d, *J* = 5.7 Hz, 1H), 8.74 (s, 1H), 8.26 (d, *J* = 5.7 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.80 (s, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.57 – 7.46 (m, 2H), 7.44 – 7.32 (m, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 4.29 (d, *J* = 6.2 Hz, 2H), 3.87 – 3.73 (m, 4H), 1.37 (s, 9H), 0.88 (t, *J* = 7.1 Hz, 3H).

Step-4: Preparation of ethyl 2-(2-(1-(3-(aminomethyl)phenyl)-2,7-naphthyridine-3-carboxamido)phenyl)acetate (**35e**)

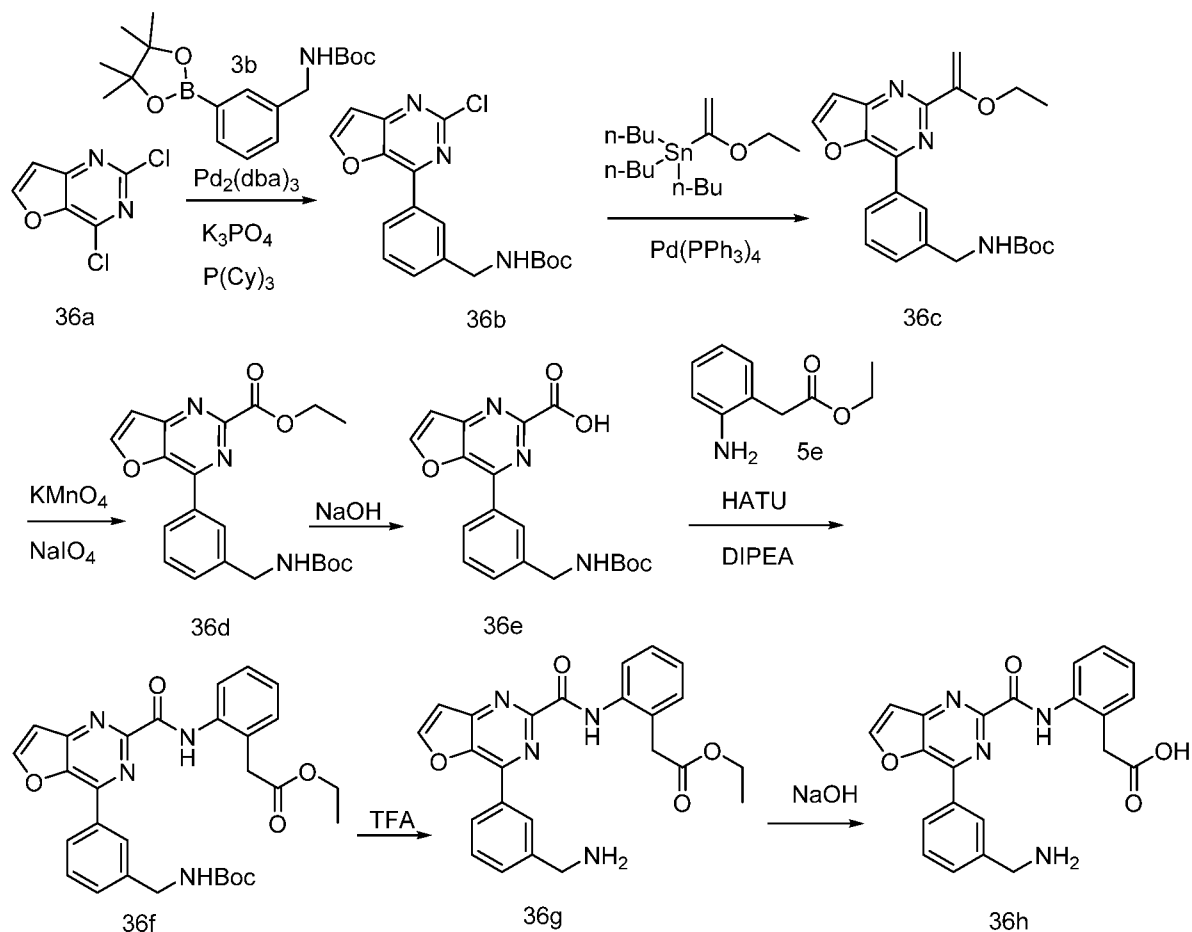
Compound **35e** was prepared according to the procedure reported in step-5 of Scheme-1, from ethyl 2-(2-(1-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2,7-naphthyridine-3-carboxamido)phenyl)acetate (**35d**) (300 mg, 0.56 mmol) using TFA (0.43 mL, 5.55 mmol) in DCM (5 mL). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(1-(3-(aminomethyl)phenyl)-2,7-naphthyridine-3-carboxamido)phenyl)acetate (**35e**) (0.21 g, 86 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.71 (s, 1H), 9.74 (s, 1H), 8.94 (d, *J* = 5.6 Hz, 1H), 8.81 (s, 1H), 8.64 (s, 2H), 8.39 (d, *J* = 5.7 Hz, 1H), 8.13 (s, 1H), 8.05 (d, *J* = 7.5 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 8.3 Hz, 2H), 7.23 (td, *J* = 7.3,

1.3 Hz, 1H), 4.19 (q, J = 5.8 Hz, 2H), 3.96 - 3.69 (m, 4H), 0.92 (t, J = 7.1 Hz, 3H); MS (ES+): 441.3 (M+1), 463.3 (M+Na); (ES-): 475.3 (M+Cl); HPLC purity: 98.24%.

Step-5: Preparation of 2-(2-(1-(3-(aminomethyl)phenyl)-2,7-naphthyridine-3-carboxamido)phenyl)acetic acid (**35f**)

Compound **35f** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-(1-(3-(aminomethyl)phenyl)-2,7-naphthyridine-3-carboxamido)phenyl)acetate (**35e**) (150 mg, 0.34 mmol) in MeOH/THF (10 mL, 1:1) using a solution of sodium hydroxide (54 mg, 1.36 mmol) in water (2 mL) This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(1-(3-(aminomethyl)phenyl)-2,7-naphthyridine-3-carboxamido)phenyl)acetic acid (**35f**) (0.12 g, 85 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.79 (s, 1H), 9.81 (s, 1H), 8.96 (s, 1H), 8.84 (s, 1H), 8.71 (d, J = 6.4 Hz, 3H), 8.47 (d, J = 5.5 Hz, 1H), 8.16 (s, 1H), 8.07 (d, J = 7.6 Hz, 1H), 8.02 – 7.92 (m, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H), 7.44 – 7.32 (m, 2H), 7.28 – 7.13 (m, 1H), 4.20 (q, J = 5.9 Hz, 2H), 3.74 (s, 2H); MS (ES+): 413.3 (M+1), 435.3 (M+Na); (ES-): 411.4 (M-1), 447.3 (M+Cl); HPLC purity: 94.81%.

Scheme-36



Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)furo[3,2-d]pyrimidine-2-carboxamido)phenyl)acetic acid (**36h**)

Step-1: Preparation of *tert*-butyl 3-(2-(4-(3-(aminomethyl)phenyl)furo[3,2-d]pyrimidin-4-yl)benzylcarbamate (**36b**)

Compound **36b** was prepared according to the procedure reported in step-3 of Scheme-1 from 2,4-dichlorofuro[3,2-d]pyrimidine (**36a**) (3 g, 15.87 mmol; CAS# 956034-07-4) in dioxane (100 mL) using *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylcarbamate (**3b**) (3.78 g, 11.34 mmol), tripotassium phosphate (8.31 mL, 24.94 mmol, 3 M aqueous solution) in water (1 mL), tricyclohexylphosphine (0.95 g, 3.38 mmol) and $\text{Pd}_2(\text{dba})_3$ (1.04 g, 1.13 mmol) in argon atmosphere and heating in an oil bath at 120 °C for 1.5 h. This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-70%] *tert*-butyl 3-(2-(4-(3-(aminomethyl)phenyl)furo[3,2-d]pyrimidin-4-yl)benzylcarbamate (**36b**) (2.65 g, 65 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.74 (d, $J = 2.3$ Hz, 1H), 8.29 (d, $J = 7.5$ Hz, 2H), 7.66 - 7.47 (m, 3H), 7.33 (d, $J = 2.3$ Hz, 1H), 4.26 (d, $J = 6.2$ Hz, 2H), 1.42 (s, 9H); MS (ES⁻): 358.3 & 360.3 (M-1).

Step-2: Preparation of *tert*-butyl 3-(2-(1-ethoxyvinyl)furo[3,2-d]pyrimidin-4-yl)benzylcarbamate (**36c**)

Compound **36c** was prepared according to the procedure reported in step-1 of Scheme-1 from *tert*-butyl 3-(2-chlorofuro[3,2-d]pyrimidin-4-yl)benzylcarbamate (**36b**) (2 g, 5.56 mmol) in DMF (30 mL) using 1-ethoxyvinyltri-*n*-butyltin (2.46 mL, 7.23 mmol) and Pd(PPh₃)₄ (0.64 g, 0.56 mmol) in argon atmosphere and heating at 110 °C for 4 h. This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-50%] *tert*-butyl 3-(2-(1-ethoxyvinyl)furo[3,2-d]pyrimidin-4-yl)benzylcarbamate (**36c**) (1.80 g, 82 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.63 (d, *J* = 2.2 Hz, 1H), 8.36 (d, *J* = 7.4 Hz, 2H), 7.66 – 7.46 (m, 3H), 7.35 (d, *J* = 2.2 Hz, 1H), 5.68 (d, *J* = 1.7 Hz, 1H), 4.68 (d, *J* = 1.7 Hz, 1H), 4.27 (d, *J* = 6.2 Hz, 2H), 3.99 (p, *J* = 7.0 Hz, 2H), 1.55 – 1.24 (m, 12H); MS (ES⁺): 396.3 (M+1); MS (ES⁻): 430.4 (M+Cl).

Step-3: Preparation of ethyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)furo[3,2-d]pyrimidine-2-carboxylate (**36d**)

Compound **36d** was prepared according to the procedure reported in step-2 of Scheme-1 from *tert*-butyl 3-(2-(1-ethoxyvinyl)furo[3,2-d]pyrimidin-4-yl)benzylcarbamate (**36c**) (1.7 g, 4.30 mmol) in 1,4-dioxane (100 mL) using sodium periodate solution (1.839 g, 8.60 mmol) in water (10 mL) and KMnO₄ (0.41 g, 2.58 mmol, and second dosing of 0.41 g, 2.58 mmol after 12 h). This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-60%] ethyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)furo[3,2-d]pyrimidine-2-carboxylate (**36d**) (0.55 g, 32 % yield) as a yellow solid; MS (ES⁻) 396.4 (M-1).

Step-4: Preparation of 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)furo[3,2-d]pyrimidine-2-carboxylic acid (**36e**)

Compound **36e** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)furo[3,2-d]pyrimidine-2-carboxylate (**36d**) (0.35 g, 0.88 mmol) in THF/MeOH (10 mL, 1:1) using sodium hydroxide (0.14 g, 3.52 mmol) in water (2 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)furo[3,2-d]pyrimidine-2-carboxylic acid (**36e**) (0.22 g, 68 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.53 (d, *J* = 2.3 Hz, 1H), 8.36 – 8.24 (m, 2H), 7.57 (dd, *J* = 9.4, 6.6 Hz, 2H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 2.3 Hz, 1H), 4.25 (d, *J* = 6.2 Hz, 2H), 1.40 (s, 9H); MS (ES⁻): 368.3 (M-1).

Step-5: Preparation of ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)furo[3,2-d]pyrimidine-2-carboxamido)phenyl)acetate (**36f**)

Compound **36f** was prepared according to the procedure reported in step-4 of Scheme-1 from 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)furo[3,2-*d*]pyrimidine-2-carboxylic acid (**36e**) (0.2 g, 0.54 mmol) in DMF (5 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (120 mg, 0.65 mmol), DIPEA (0.19 mL, 1.08 mmol) and HATU (250 mg, 0.65 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc/MeOH (9:1) in hexane from 0-100%] ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)furo[3,2-*d*]pyrimidine-2-carboxamido)phenyl)acetate (**36f**) (0.17 g, 59 % yield) as a white solid; MS (ES⁺): 553.5 (M+Na).

Step-6: Preparation of ethyl 2-(2-(4-(3-(aminomethyl)phenyl)furo[3,2-*d*]pyrimidine-2-carboxamido)phenyl)acetate (**36g**)

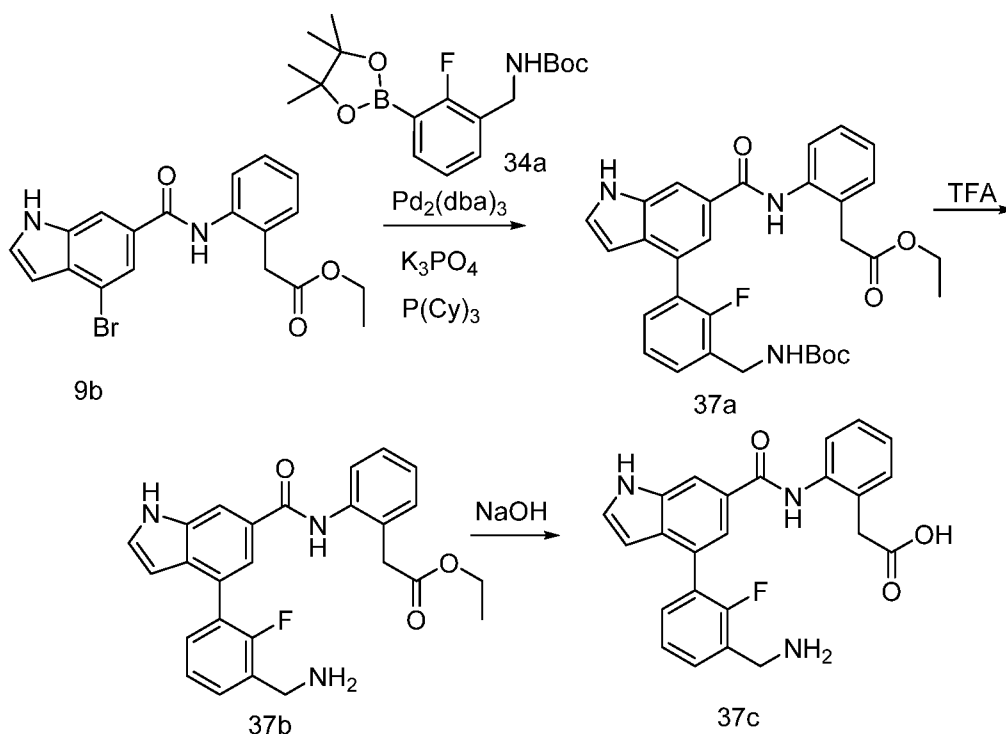
Compound **36g** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)furo[3,2-*d*]pyrimidine-2-carboxamido)phenyl)acetate (**36f**) (170 mg, 0.32 mmol) in DCM (5 mL) using TFA (0.25 mL, 3.2 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(4-(3-(aminomethyl)phenyl)furo[3,2-*d*]pyrimidine-2-carboxamido)phenyl)acetate (**36g**) (0.12 g, 87 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.68 (s, 1H), 8.88 – 8.77 (m, 2H), 8.69 (s, 2H), 8.66 – 8.61 (m, 1H), 7.85 (m, 1H), 7.80 – 7.69 (m, 2H), 7.53 – 7.46 (m, 1H), 7.43 – 7.35 (m, 2H), 7.30 – 7.21 (m, 1H), 4.20 (q, J = 5.8 Hz, 2H), 3.99 (q, J = 7.1 Hz, 2H), 3.87 (s, 2H), 1.00 (t, J = 7.1 Hz, 3H); MS (ES⁺): 431.3 (M+1); HPLC purity: 97.05%.

Step-7: Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)furo[3,2-*d*]pyrimidine-2-carboxamido)phenyl)acetic acid (**36h**)

Compound **36h** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(4-(3-(aminomethyl)phenyl)furo[3,2-*d*]pyrimidine-2-carboxamido)phenyl)acetate (**36g**) (600 mg, 0.14 mmol) in MeOH/THF (10 mL, 1:1) using a solution of NaOH (20 mg, 0.56 mmol) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(4-(3-(aminomethyl)phenyl)furo[3,2-*d*]pyrimidine-2-carboxamido)phenyl)acetic acid (**36h**) (0.03 g, 57 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.76 (s, 1H), 8.84 (d, J = 2.2 Hz, 1H), 8.75 (s, 1H), 8.63 (d, J = 7.6 Hz, 1H), 8.52 (s, 2H), 7.94 – 7.70 (m, 3H), 7.50 (d, J = 2.3 Hz, 1H), 7.38 (t, J = 7.0 Hz, 2H), 7.23

(t, J = 7.3 Hz, 1H), 4.22 (d, J = 5.8 Hz, 2H), 3.79 (s, 2H); MS (ES⁺): 403.3 (M+1), 425.3 (M+Na); MS (ES⁻): 401.3 (M-1), 437.3 (M+Cl).

Scheme-37



Preparation of 2-(2-(4-(3-(aminomethyl)-2-fluorophenyl)-1H-indole-6-carboxamido)phenyl)acetic acid (**37c**)

Step-1: Preparation of ethyl 2-(2-(4-(3-((tert-butoxycarbonyl)amino)methyl)-2-fluorophenyl)-1H-indole-6-carboxamido)phenyl)acetate (**37a**)

Compound **37a** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(4-bromo-1H-indole-6-carboxamido)phenyl)acetate (**9b**) (0.23 g, 0.57 mmol) in dioxane (30 mL) using *tert*-butyl 2-fluoro-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)benzylcarbamate (**34a**) (200 mg, 0.57 mmol), tripotassium phosphate (0.42 mL, 1.25 mmol, 3 M aqueous solution) in water (1 mL), tricyclohexylphosphine (0.05 g, 0.06 mmol) and Pd₂(dba)₃ (0.05 g, 0.06 mmol) in argon atmosphere and heating in an oil bath at 120 °C for 1 h. This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-70%] ethyl 2-(2-(4-(3-((tert-butoxycarbonyl)amino)methyl)-2-fluorophenyl)-1H-indole-6-carboxamido)phenyl)acetate (**37a**) (0.21 g, 68 % yield) as a white solid. MS (ES⁻): 544.5 (M-1).

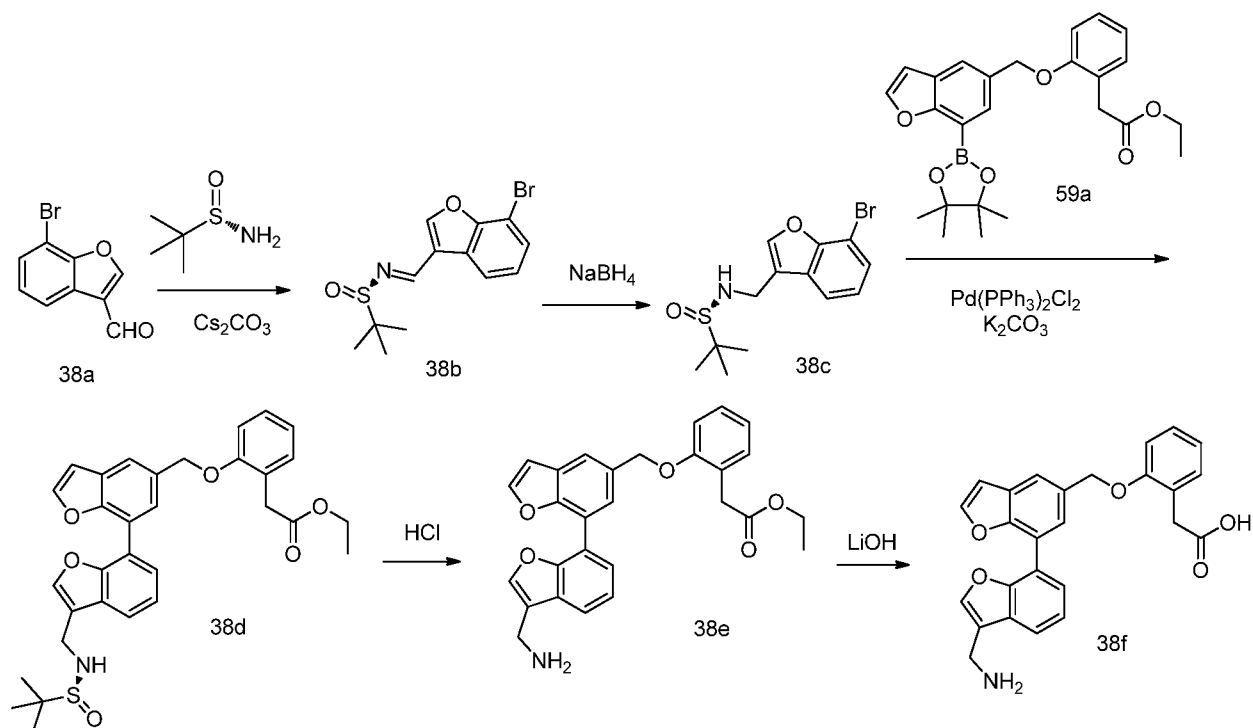
Step-2: Preparation of ethyl 2-(2-(4-(3-(aminomethyl)-2-fluorophenyl)-1H-indole-6-carboxamido)phenyl)acetate (**37b**)

Compound **37b** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)-1H-indole-6-carboxamido)phenyl)acetate (**37a**) (150 mg, 0.28 mmol) in DCM (5 mL) using TFA (0.21 mL, 2.75 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(4-(3-(aminomethyl)-2-fluorophenyl)-1H-indole-6-carboxamido)phenyl)acetate (**37b**) (0.09 g, 74 % yield) as a yellow solid; ^1H NMR (300 MHz, DMSO- d_6) δ 11.74 (s, 1H), 10.01 (s, 1H), 8.50 (s, 3H), 8.17 – 8.07 (m, 1H), 7.74 – 7.58 (m, 4H), 7.49 – 7.38 (m, 1H), 7.32 (m, 2H), 7.29 – 7.18 (m, 1H), 6.50 – 6.36 (m, 1H), 4.18 (d, J = 6.0 Hz, 2H), 4.02 – 3.90 (m, 2H), 3.75 (s, 2H), 1.14 – 0.86 (m, 3H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -118.67; MS (ES⁺): 446.3 (M+1), 448.3 (M+Na); MS (ES⁻): 480.4 (M+Cl). HPLC purity: 93.30%.

Step-3: Preparation of 2-(2-(4-(3-(aminomethyl)-2-fluorophenyl)-1H-indole-6-carboxamido)phenyl)acetic acid (**37c**)

Compound **37c** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(4-(3-(aminomethyl)-2-fluorophenyl)-1H-indole-6-carboxamido)phenyl)acetate (**37b**) (80 mg, 0.17 mmol) in MeOH/THF (5 mL, 1:1) using a solution of NaOH (30 mg, 0.67 mmol) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] of 2-(2-(4-(3-(aminomethyl)-2-fluorophenyl)-1H-indole-6-carboxamido)phenyl)acetic acid (**37c**) (0.04 g, 54 % yield) as a yellow solid; ^1H NMR (300 MHz, DMSO- d_6) δ 12.42 (s, 1H), 11.74 (s, 1H), 10.05 (s, 1H), 8.50 (s, 3H), 8.15 (s, 1H), 7.71 (s, 1H), 7.69 – 7.59 (m, 2H), 7.54 – 7.38 (m, 2H), 7.32 (m, 2H), 7.26 – 7.17 (m, 1H), 6.45 (d, J = 2.8 Hz, 1H), 4.18 (d, J = 5.9 Hz, 2H), 3.68 (s, 2H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -118.51; MS (ES⁺): 418.3 (M+1); MS (ES⁻): 416.4 (M-1), 452.3 (M+Cl). HPLC purity: 97.67%.

Scheme-38



Preparation of 2-(2-((3'-(aminomethyl)-[7,7'-bibenzofuran]-5-yl)methoxy)phenyl)acetic acid (**38f**)

Step-1: Preparation of (S)-N-((7-bromobenzofuran-3-yl)methylene)-2-methylpropane-2-sulfinamide (**38b**)

Compound **38b** was prepared according to the procedure reported in step-1 of Scheme-220 from 7-bromobenzofuran-3-carbaldehyde (**38a**) (110 mg, 0.489 mmol; CAS# 1368142-94-2) in DCM (20 mL) using Cs₂CO₃ (381 mg, 1.169 mmol) and (S)-2-methylpropane-2-sulfinamide (119 mg, 0.982 mmol). This gave after workup (S)-N-((7-bromobenzofuran-3-yl)methylene)-2-methylpropane-2-sulfinamide (**38b**) (160 mg, 100 % yield) which was used as such in next step without further purification. MS (ES⁺): 328.0 (M+1).

Step-2: Preparation of (S)-N-((7-bromobenzofuran-3-yl)methyl)-2-methylpropane-2-sulfinamide (**38c**)

Compound **38c** was prepared according to the procedure reported in step-2 of Scheme-220 from (S)-N-((7-bromobenzofuran-3-yl)methylene)-2-methylpropane-2-sulfinamide (**38b**) (160 mg, 0.487 mmol) in DCM (12 mL) and methanol (4 mL) using NaBH₄ (83 mg, 2.194 mmol). This gave after workup and purification by flash column chromatography (silica gel, 12 g, eluting with 30-100% ethyl acetate in hexanes) (S)-N-((7-bromobenzofuran-3-yl)methyl)-2-methylpropane-2-sulfinamide (**38c**) (120 mg, 75 % yield) as a colorless oil. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.05 (d, *J* = 1.1 Hz, 1H), 7.72 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.56

(dd, $J = 7.8, 1.0$ Hz, 1H), 7.23 (t, $J = 7.8$ Hz, 1H), 5.77 (t, $J = 5.5$ Hz, 1H), 4.28 (dt, $J = 5.6, 1.1$ Hz, 2H), 1.11 (s, 9H).

Step-3: Preparation of (S)-ethyl 2-(2-((3'-((1,1-dimethylethylsulfonamido)methyl)-[7,7'-bibenzofuran]-5-yl)methoxy)phenyl)acetate (**38d**)

Compound **38d** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (178 mg, 0.408 mmol) in dioxane (5 mL) using (S)-N-((7-bromobenzofuran-3-yl)methyl)-2-methylpropane-2-sulfonamide (**38c**) (120 mg, 0.363 mmol), bis(triphenylphosphine)palladium(II) chloride (45 mg, 0.064 mmol) and a solution of K_2CO_3 (158 mg, 1.143 mmol) in water (0.5 mL) under an Ar atmosphere and heating at 100 °C for 3 h on oil bath. This gave after workup, purification by flash column chromatography (silica gel 12 g, eluting with 30-100% hexanes in ethyl acetate) (S)-ethyl 2-(2-((3'-((1,1-dimethylethylsulfonamido)methyl)-[7,7'-bibenzofuran]-5-yl)methoxy)phenyl)acetate (**38d**) (189 mg, 83 % yield) as a pale-yellow oil. MS (ES⁺): 560.0 (M+1).

Step-4: Preparation of ethyl 2-(2-((3'-(aminomethyl)-[7,7'-bibenzofuran]-5-yl)methoxy)phenyl)acetate (**38e**)

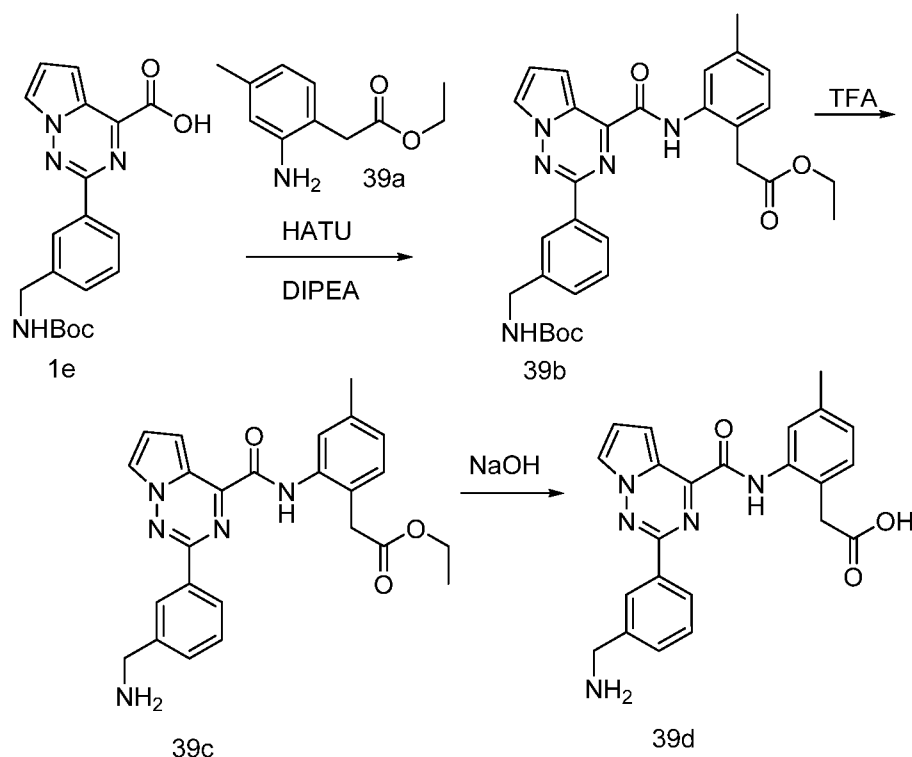
Compound **38e** was prepared according to the procedure reported in step-5 of Scheme-220 from (S)-ethyl 2-(2-((3'-((1,1-dimethylethylsulfonamido)methyl)-[7,7'-bibenzofuran]-5-yl)methoxy)phenyl)acetate (**38d**) (182 mg, 0.325 mmol) in methanol (8 mL) using hydrochloric acid (4 M in 1,4-dioxane, 0.35 mL, 1.400 mmol). This gave after workup, purification by flash column chromatography (silica gel 12 g, eluting with DMA80/DCM, from 0-80%) ethyl 2-(2-((3'-(aminomethyl)-[7,7'-bibenzofuran]-5-yl)methoxy)phenyl)acetate (**38e**) (96 mg, 45 % yield) as a yellow foam. (ES⁺): 456.0 (M+1).

Step-5: Preparation of 2-(2-((3'-(aminomethyl)-[7,7'-bibenzofuran]-5-yl)methoxy)phenyl)acetic acid (**38f**)

Compound **38f** was prepared according to the procedure reported in step-6 of Scheme-1 from ethyl 2-(2-((3'-(aminomethyl)-[7,7'-bibenzofuran]-5-yl)methoxy)phenyl)acetate (**38e**) (94 mg, 0.206 mmol) in THF/methanol (6 mL each) using lithium hydroxide hydrate (84 mg, 2.0 mmol) in water (2 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((3'-(aminomethyl)-[7,7'-bibenzofuran]-5-yl)methoxy)phenyl)acetic acid (**38f**) (61 mg, 69 % yield) HCl salt as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.64 (s, 2H), 8.12 (s, 1H), 8.00 (d, $J = 2.2$ Hz, 1H), 7.93 (dd, $J = 7.9, 1.2$ Hz, 1H), 7.76 (d, $J = 1.7$ Hz, 1H), 7.66 (dd, $J = 4.7, 3.0$ Hz, 2H), 7.42 (t, $J = 7.7$ Hz, 1H), 7.17 (dd, $J = 9.4, 6.7$ Hz, 2H), 7.05 (d, $J = 8.0$ Hz,

1H), 7.00 (d, $J = 2.2$ Hz, 1H), 6.83 (t, $J = 7.3$ Hz, 1H), 5.22 (s, 2H), 4.18 (s, 2H), 3.53 (s, 2H). MS (ES⁺): 427.9 (M+1); MS(ES⁻): 425.9 (M-1). HPLC purity 99.10%.

Scheme-39



Preparation of 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetic acid (**39d**)

Step-1: Preparation of ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetate (**39b**)

Compound **39b** was prepared according to the procedure reported in step-4 of Scheme-1 from 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**1e**) (0.15 g, 0.41 mmol) in DMF (3 mL) using ethyl 2-(2-amino-4-methylphenyl)acetate (**39a**) (118 mg, 0.611 mmol, CAS # 1261742-93-1), DIPEA (0.213 mL, 1.22 mmol) and HATU (186 mg, 0.489 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc in hexane] ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetate (**39b**) (0.18 g, 81 % yield) as an orange colored foam; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.76 (s, 1H), 8.44 (d, $J = 7.9$ Hz, 1H), 8.40 - 8.32 (m, 2H), 7.63 (d, $J = 1.6$ Hz, 1H), 7.60 - 7.47 (m, 3H), 7.43 (d, $J = 7.6$ Hz, 1H), 7.33 - 7.22 (m, 2H), 7.12 - 7.03

(m, 1H), 4.26 (d, $J = 6.1$ Hz, 2H), 4.00 (q, $J = 7.1$ Hz, 2H), 3.82 (s, 2H), 2.36 (s, 3H), 1.41 (s, 9H), 1.00 (t, $J = 7.1$ Hz, 3H); MS (ES⁺): 544.5 (M+1).

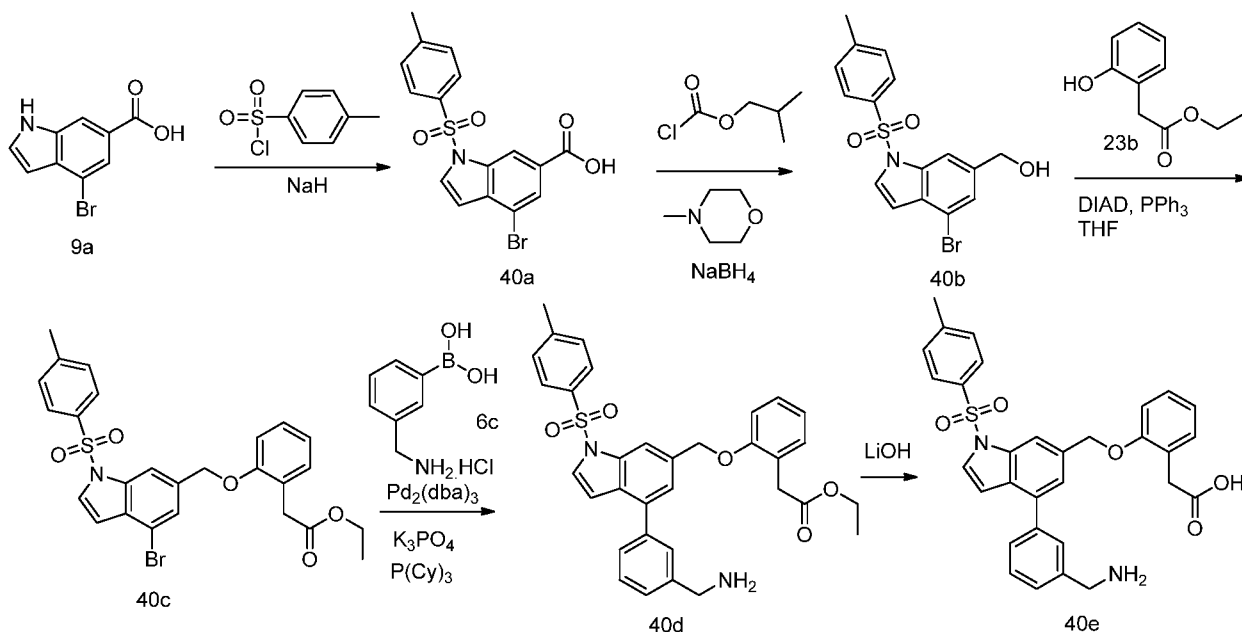
Step-2: Preparation of ethyl 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetate (**39c**)

Compound **39c** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetate (**39b**) (180 mg, 0.33 mmol) in DCM (5 mL) using TFA (0.255 mL, 3.31 mmol). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetate (**39c**) (0.055 g, 38 % yield) HCl salt as a solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.77 (s, 1H), 8.66 – 8.55 (m, 2H), 8.43 – 8.27 (m, 4H), 7.74 – 7.54 (m, 4H), 7.33 – 7.25 (m, 2H), 7.15 – 7.06 (m, 1H), 4.18 (s, 2H), 4.00 (q, $J = 7.1$ Hz, 2H), 3.82 (s, 2H), 2.36 (s, 3H), 1.00 (t, $J = 7.1$ Hz, 3H); MS (ES⁺) 444.4 (M+1), MS (ES⁻) 478.4 (M+Cl); HPLC purity: 94.27 %

Step-3: Preparation of 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetic acid (**39d**)

Compound **39d** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetate (**39c**) (0.11 g, 0.248 mmol) in THF (30 mL) using sodium hydroxide (0.62 mL, 1.24 mmol, 2 M aqueous). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetic acid (**39d**) (0.05 g, 48.5 % yield) HCl salt as a solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.76 (s, 1H), 10.85 (s, 1H), 8.61 (s, 1H), 8.54 (dt, $J = 7.1, 1.8$ Hz, 1H), 8.44 – 8.30 (m, 4H), 7.73 – 7.59 (m, 4H), 7.32 – 7.25 (m, 2H), 7.08 (dd, $J = 7.6, 1.7$ Hz, 1H), 4.24 – 4.12 (m, 2H), 3.74 (s, 2H), 2.36 (s, 3H). MS (ES⁺) 416.3 (M+1), MS (ES⁻) 414.4 (M-1), 829.7 (2M-1); HPLC purity: 97.48 %.

Scheme-40



Preparation of 2-(2-((4-(3-(aminomethyl)phenyl)-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**40e**)

Step-1: Preparation of 4-bromo-1-tosyl-1H-indole-6-carboxylic acid (**40a**)

To a solution of 4-bromo-1H-indole-6-carboxylic acid (**9a**) (1.5 g, 6.25 mmol) in DMF (9.5 mL) at 0 °C was added NaH (60% in mineral oil, 0.625 g, 15.62 mmol). After 15 min stirring at 0 °C, Tosyl-Cl (1.43 g, 7.50 mmol) was added in 1 g portions at 0 °C every 15 min and the reaction was warmed slowly in the ice bath to 10 °C. After stirring for 2 h, the mixture was dumped into H₂O and the mixture was acidified with 5 M HCl. The precipitate was collected by filtration, washed with water and dried to give 4-bromo-1-tosyl-1H-indole-6-carboxylic acid (**40a**) (1.85 g, 4.69 mmol, 75 % yield) as a tan solid, which was used in the next step without further purification; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.42 (s, 1H), 8.54 - 8.48 (m, 1H), 8.19 (d, *J* = 3.8 Hz, 1H), 8.01 - 7.94 (m, 1H), 7.93 - 7.84 (m, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 6.92 - 6.84 (m, 1H), 2.33 (s, 3H).

Step-2: Preparation of (4-bromo-1-tosyl-1H-indol-6-yl)methanol (**40b**)

Compound **40b** was prepared according to the procedure reported in step-1 of Scheme-23 from 4-bromo-1-tosyl-1H-indole-6-carboxylic acid (**40a**) (1.5 g, 3.8 mmol) using N-methylmorpholine (0.5 mL, 4.57 mmol) in THF (30 mL), isobutyl chloroformate (0.6 mL, 4.57 mmol) and NaBH₄ (0.43 g, 11.41 mmol) in water (0.8 mL). This gave after workup (4-bromo-1-tosyl-1H-indol-6-yl)methanol (**40b**) (1.2 g, 82% yield) as a clear oil which was used as such for next step without further purification; MS (ES⁺) 402.1, 404.1 (M+Na), (ES⁻) 378.2, 380.2 (M-1).

Step-3: Preparation of ethyl 2-(2-((4-bromo-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetate (**40c**)

Compound **40c** was prepared according to the procedure reported in step-2 of Scheme-23 from (4-bromo-1-tosyl-1H-indol-6-yl)methanol (**40b**) (1.2 g, 3.16 mmol) in THF (15 mL) using triphenylphosphine (1.07 g, 4.1 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (0.739 g, 4.1 mmol) and DIAD (0.83 g, 4.1 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] ethyl 2-(2-((4-bromo-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetate (**40c**) (0.4 g, 23 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.04 (s, 1H), 7.94 (d, *J* = 3.7 Hz, 1H), 7.89 (s, 1H), 7.87 (s, 1H), 7.54 (s, 1H), 7.36 (s, 1H), 7.33 (s, 1H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.81 – 6.69 (m, 4H), 5.26 (s, 2H), 4.07 – 4.01 (m, 2H), 3.66 (s, 2H), 2.31 (s, 3H), 1.03 (t, *J* = 7.1 Hz, 3H).

Step-4: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)phenyl)-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetate (**40d**)

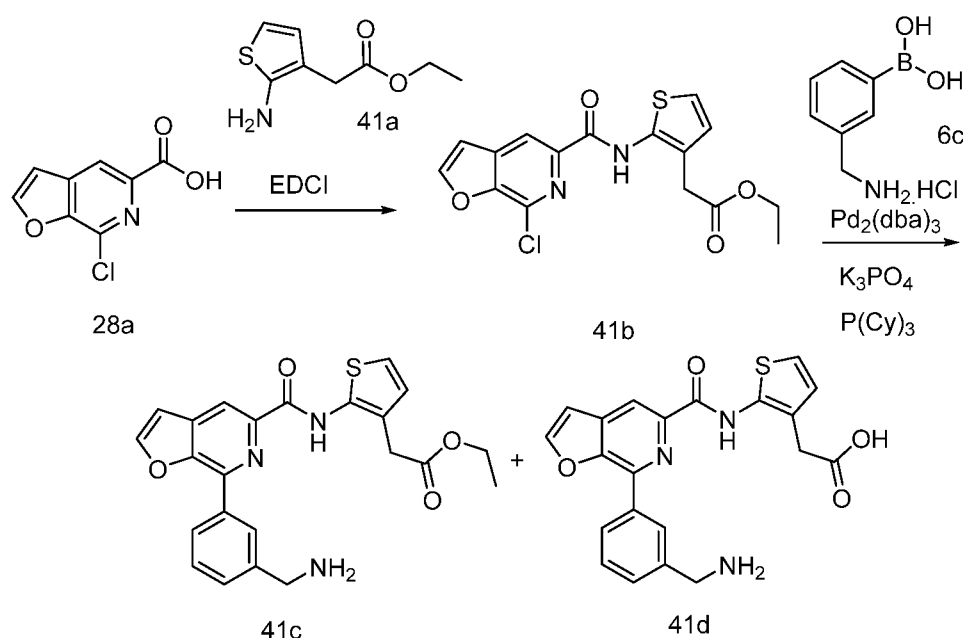
Compound **40d** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((4-bromo-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetate (**40c**) (400 mg, 0.74 mmol) in dioxane (3 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (207 mg, 1.11 mmol), tripotassium phosphate (1.3 M solution, 0.42 mL, 1.25 mmol), tricyclohexylphosphine (62 mg, 0.22 mmol) and Pd₂(dba)₃ (68 mg, 0.074 mmol) under an Ar atmosphere and heating at 125 °C for 20 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-70%] followed by purification by reverse phase column [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] of ethyl 2-(2-((4-(3-(aminomethyl)phenyl)-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetate (**40d**) (48 mg, 11 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.37 (s, 3H, D₂O exchangeable), 8.07 (s, 1H), 7.94 – 7.85 (m, 3H), 7.70 (s, 1H), 7.61 – 7.48 (m, 3H), 7.41 (s, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.28 – 7.19 (m, 2H), 7.12 – 7.04 (m, 1H), 7.00 (d, *J* = 3.8 Hz, 1H), 6.93 (t, *J* = 7.4 Hz, 1H), 5.32 (s, 2H), 4.15 – 4.04 (m, 2H), 3.90 (q, *J* = 7.1 Hz, 2H), 3.66 (s, 2H), 2.32 (s, 3H), 0.94 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 569.4 (M+1); 591.4 (M+Na); (ES⁻): 603.4 (M+Cl); HPLC purity: 95.30%.

Step-5: Preparation of 2-(2-((4-(3-(aminomethyl)phenyl)-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**40e**)

Compound **40e** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((4-(3-(aminomethyl)phenyl)-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetate (**40d**) (150 mg, 0.26 mmol) in MeOH/THF (10 mL, 1:1) using a solution of lithium

hydroxide hydrate (11 mg, 0.26 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((4-(3-(aminomethyl)phenyl)-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**40e**) (50 mg, 35% yield) HCl salt as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 12.24 (s, 1H, D $_2$ O exchangeable), 8.35 (s, 3H, D $_2$ O exchangeable), 8.08 (s, 1H), 7.94 – 7.89 (m, 2H), 7.88 (s, 1H), 7.70 (s, 1H), 7.61 – 7.48 (m, 3H), 7.45 (d, J = 1.3 Hz, 1H), 7.36 (d, J = 8.2 Hz, 2H), 7.29 – 7.18 (m, 2H), 7.09 – 7.02 (m, 1H), 6.99 (d, J = 3.8 Hz, 1H), 6.96 – 6.90 (m, 1H), 5.34 (s, 2H), 4.10 (s, 2H), 3.64 (s, 2H), 2.32 (s, 3H); MS (ES $^+$): 541.4 (M+1); 563.3 (M+Na); (ES $^-$): 539.4 (M-1), 575.4 (M+Cl).

Scheme-41



Preparation of 2-(2-(7-(3-(aminomethyl)phenyl)furo[2,3-c]pyridine-5-carboxamido)thiophen-3-yl)acetic acid (**41d**)

Step-1: Preparation of ethyl 2-(2-(7-chlorofuro[2,3-c]pyridine-5-carboxamido)thiophen-3-yl)acetate (**41b**)

Compound **41b** was prepared according to the procedure reported in step-1 of Scheme-6 from 7-chlorofuro[2,3-c]pyridine-5-carboxylic acid (**28a**) (200 mg, 1.01 mmol) in MeOH (10 mL) using ethyl 2-(2-aminothiophen-3-yl)acetate (**41a**) (225 mg, 1.22 mmol, CAS# 387390-67-2, prepared according to the procedure reported by Adrian Liam and Harris, William in PCT Int. Appl., 2002002567, 10 Jan 2002), and EDCI (233 mg, 1.22 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] ethyl 2-(2-(7-chlorofuro[2,3-c]pyridine-5-carboxamido)thiophen-3-yl)acetate (**41b**) (320 mg, 0.877 mmol, 87 % yield) as a yellow solid; ^1H NMR (300 MHz,

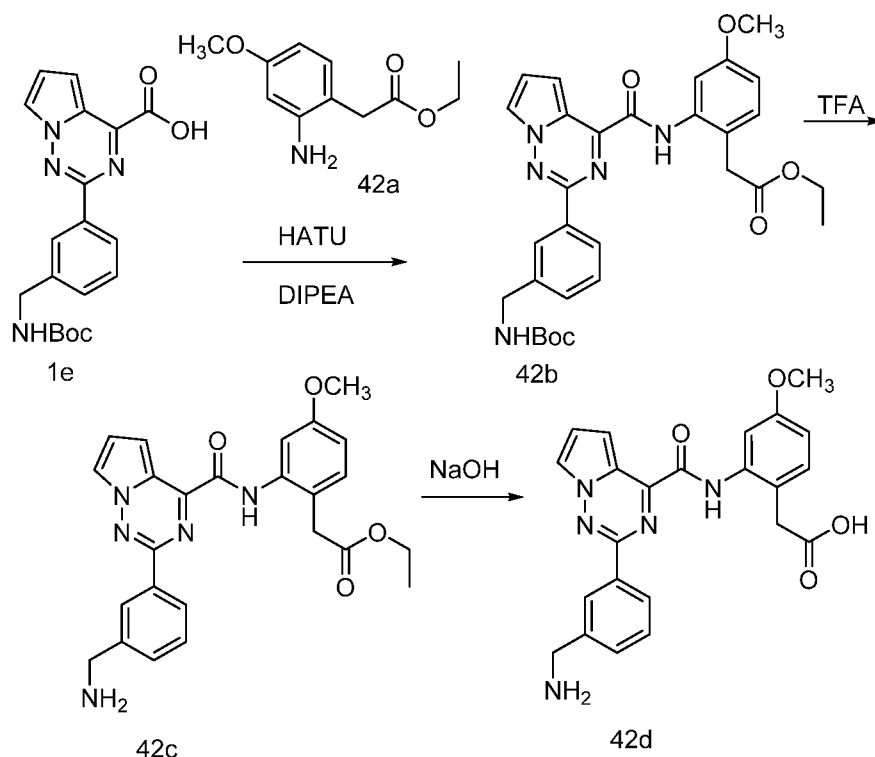
DMSO-*d*₆) δ 10.84 (s, 1H), 8.58 – 8.45 (m, 2H), 7.42 – 7.33 (m, 1H), 7.16 (d, *J* = 5.5 Hz, 1H), 6.91 (d, *J* = 5.5 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 2H), 1.21 (t, *J* = 7.1 Hz, 3H).

Step-2: Preparation of 2-(2-(7-(3-(aminomethyl)phenyl)furo[2,3-*c*]pyridine-5-carboxamido)thiophen-3-yl)acetic acid (**41d**)

Compound **41d** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(7-chlorofuro[2,3-*c*]pyridine-5-carboxamido)thiophen-3-yl)acetate (**41b**) (140 mg, 0.38 mmol) in dioxane (3 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (108 mg, 0.58 mmol), tripotassium phosphate (1.3 M solution, 0.22 mL, 0.65 mmol), tricyclohexylphosphine (32 mg, 0.12 mmol) and Pd₂(dba)₃ (35 mg, 0.038 mmol) under an Ar atmosphere and heating at 125 °C for 1 h in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-70%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(7-(3-(aminomethyl)phenyl)furo[2,3-*c*]pyridine-5-carboxamido)thiophen-3-yl)acetate (**41c**) (37 mg, 22% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.18 (s, 1H, D₂O exchangeable), 8.73 (s, 1H), 8.64 – 8.57 (m, 1H), 8.57 – 8.43 (m, 5H, partially D₂O exchangeable), 7.75 – 7.66 (m, 2H), 7.38 (d, *J* = 2.2 Hz, 1H), 7.17 (d, *J* = 5.5 Hz, 1H), 6.94 (d, *J* = 5.5 Hz, 1H), 6.55 (s, 1H), 4.19 (s, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 2H), 1.10 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 436.3 (M+1); (ES⁻): 470.3 (M+Cl); HPLC purity: 98.86%.

Followed by 2-(2-(7-(3-(aminomethyl)phenyl)furo[2,3-*c*]pyridine-5-carboxamido)thiophen-3-yl)acetic acid (**41d**) (19 mg, 12% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.84 (s, 1H, D₂O exchangeable), 11.28 (s, 1H, D₂O exchangeable), 8.73 (s, 1H), 8.65 – 8.57 (m, 1H), 8.56 – 8.37 (m, 5H, partially D₂O exchangeable), 7.75 – 7.65 (m, 2H), 7.38 (d, *J* = 2.2 Hz, 1H), 7.15 (d, *J* = 5.5 Hz, 1H), 6.93 (d, *J* = 5.5 Hz, 1H), 4.20 (q, *J* = 5.7 Hz, 2H), 3.79 (s, 2H); MS (ES⁺) 408.3 (M+1); (ES⁻) 406.3 (M-1), 442.3 (M+Cl); HPLC purity: 99.41%.

Scheme-42



Preparation of 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methoxyphenyl)acetic acid (**42d**)

Step-1: Preparation of ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methoxyphenyl)acetate (**42b**)

Compound **42b** was prepared according to the procedure reported in step-4 of Scheme-1 from 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**1e**) (0.18 g, 0.49 mmol) in DMF (4 mL) using ethyl 2-(2-amino-4-methoxyphenyl)acetate (**42a**) (123 mg, 0.586 mmol, CAS # 138344-20-4), DIPEA (0.26 mL, 1.47 mmol) and HATU (223 mg, 0.59 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-100% EtOAc in hexane] ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methoxyphenyl)acetate (**42b**) (0.19 g, 70 % yield) as an orange solid; ^1H NMR (300 MHz, DMSO- d_6) δ 10.79 (s, 1H), 8.44 (d, J = 7.8 Hz, 1H), 8.36 (d, J = 2.3 Hz, 2H), 7.61 – 7.39 (m, 5H), 7.32 (d, J = 8.5 Hz, 1H), 7.25 (dd, J = 4.6, 2.5 Hz, 1H), 6.86 (dd, J = 8.5, 2.7 Hz, 1H), 4.26 (d, J = 6.1 Hz, 2H), 4.01 (q, J = 7.1 Hz, 2H), 3.87 – 3.71 (m, 5H), 1.41 (s, 9H), 1.00 (t, J = 7.1 Hz, 3H); MS (ES $^+$): 560.4 (M+1), 582.4 (M+Na); (ES $^-$): 558.5 (M-1).

Step-2: Preparation of ethyl 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methoxyphenyl)acetate (**42c**)

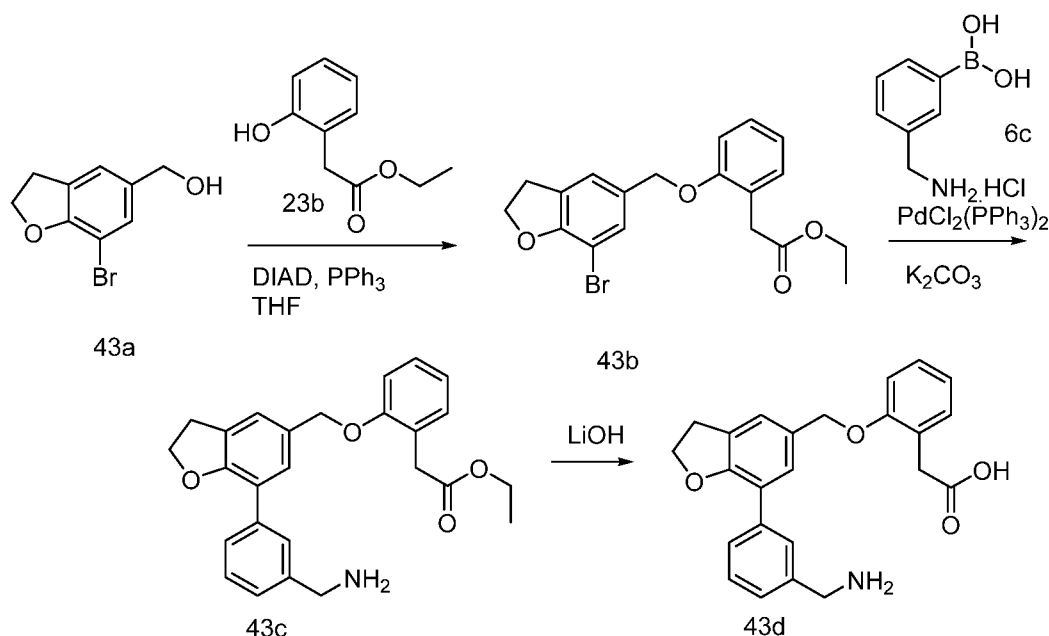
Compound **42c** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methoxyphenyl)acetate (**42b**) (190 mg, 0.34 mmol) in DCM (5 mL) using TFA (0.26 mL, 3.4 mmol). This gave after workup and purification by reverse phase column chromatography [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-60%] ethyl 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methoxyphenyl)acetate (**42c**) (0.05 g, 32.0 % yield) as a HCl salt; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.79 (s, 1H), 8.66 – 8.55 (m, 2H), 8.45 – 8.32 (m, 4H), 7.73 – 7.56 (m, 3H), 7.41 (d, *J* = 2.7 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 7.29 (dd, *J* = 4.6, 2.5 Hz, 1H), 6.88 (dd, *J* = 8.5, 2.7 Hz, 1H), 4.18 (s, 2H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.86 – 3.75 (m, 5H), 1.01 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 460.3 (M+1), MS (ES⁻): 494.3 (M+Cl); HPLC purity: 96.26 %

Step-3: Preparation of 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methoxyphenyl)acetic acid (**42d**)

Compound **42d** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methoxyphenyl)acetate (**42c**)

(0.11 g, 0.239 mmol) in THF (2 mL) using sodium hydroxide (0.24 mL, 0.48 mmol, 2 M aqueous). This gave after workup and purification by reverse phase column [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-40%] 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methoxyphenyl)acetic acid (**42d**) (0.045 g, 44 % yield) as a HCl salt; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.77 (s, 1H), 10.88 (s, 1H), 8.62 (s, 1H), 8.57 – 8.34 (m, 5H), 7.74 – 7.59 (m, 3H), 7.52 (d, *J* = 2.7 Hz, 1H), 7.36 – 7.25 (m, 2H), 6.85 (dd, *J* = 8.5, 2.7 Hz, 1H), 4.23 – 4.12 (m, 2H), 3.80 (s, 3H), 3.73 (s, 2H); MS (ES⁺): 432.3 (M+1); MS (ES⁻): 430.4 (M-1); HPLC purity: 98.05 %.

Scheme-43



Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2,3-dihydrobenzofuran-5-yl)methoxy)phenyl)acetic acid (**43d**)

Step-1: Preparation of ethyl 2-(2-((7-bromo-2,3-dihydrobenzofuran-5-yl)methoxy)phenyl)acetate (**43b**)

Compound **43b** was prepared according to the procedure reported in step-2 of Scheme-23 from (7-bromo-2,3-dihydrobenzofuran-5-yl)methanol (**43a**) (200 mg, 0.87 mmol; CAS # 501430-83-7) in THF (15 mL) using triphenylphosphine (0.30 g, 1.135 mmol) ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (205 mg, 1.14 mmol) and DIAD (0.23 g, 1.14 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] ethyl 2-(2-((7-bromo-2,3-dihydrobenzofuran-5-yl)methoxy)phenyl)acetate (**43b**) (0.27 g, 78 % yield) as colorless oil; MS (ES⁻): 389.3, 391.3 (M-1).

Step-2: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2,3-dihydrobenzofuran-5-yl)methoxy)phenyl)acetate (**43c**)

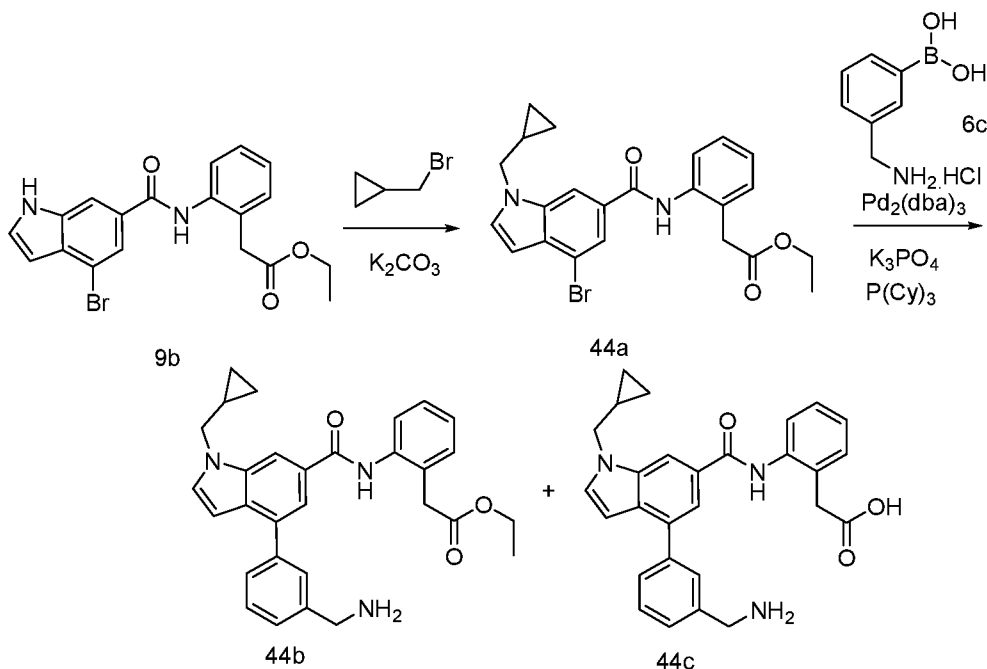
Compound **43c** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-bromo-2,3-dihydrobenzofuran-5-yl)methoxy)phenyl)acetate (**43b**) (0.52 g, 1.33 mmol) in dioxane (6 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (0.37 g, 2.0 mmol), a solution of potassium carbonate (0.55 g, 4.0 mmol) in water (2 mL), and PdCl₂(PPh₃)₂ (0.140 g, 0.2 mmol) under an Ar atmosphere and heating at 100 °C for 2 h on oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with MeOH in DCM from 0-20%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl

2-(2-((7-(3-(aminomethyl)phenyl)-2,3-dihydrobenzofuran-5-yl)methoxy)phenyl)acetate (**43c**) (0.23 g, 42 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.26 (s, 3H), 7.79 (s, 1H), 7.75 – 7.70 (m, 1H), 7.54 – 7.40 (m, 2H), 7.38 (s, 1H), 7.31 – 7.18 (m, 3H), 7.08 (d, J = 8.1 Hz, 1H), 6.90 (td, J = 7.4, 1.1 Hz, 1H), 5.05 (s, 2H), 4.60 (t, J = 8.7 Hz, 2H), 4.08 (s, 2H), 3.95 (q, J = 7.1 Hz, 2H), 3.60 (s, 2H), 3.25 (t, J = 8.7 Hz, 2H), 1.04 (t, J = 7.1 Hz, 3H); MS (ES⁺) 418.4 (M+1); (ES⁻) 416.4 (M-1).

Step-3: Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2,3-dihydrobenzofuran-5-yl)methoxy)phenyl)acetic acid (**43d**)

Compound **43d** was prepared according to the procedure reported in step-6 of Scheme-1 from ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2,3-dihydrobenzofuran-5-yl)methoxy)phenyl)acetate (**43c**) (0.12 g, 0.29 mmol) in THF/MeOH (4 mL) using lithium hydroxide hydrate (60 mg, 1.44 mmol) in water (0.8 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)phenyl)-2,3-dihydrobenzofuran-5-yl)methoxy)phenyl)acetic acid (**43d**) (40 mgs, 31 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.22 (s, 1H), 8.38 (s, 3H), 7.80 (s, 1H), 7.74 (dt, J = 7.2, 1.8 Hz, 1H), 7.52 – 7.41 (m, 3H), 7.32 (d, J = 1.6 Hz, 1H), 7.27 – 7.18 (m, 2H), 7.06 (dd, J = 8.2, 1.1 Hz, 1H), 6.89 (td, J = 7.4, 1.1 Hz, 1H), 5.07 (s, 2H), 4.60 (t, J = 8.7 Hz, 2H), 4.07 (d, J = 5.3 Hz, 2H), 3.56 (s, 2H), 3.25 (t, J = 8.7 Hz, 2H); MS (ES⁺): 390.4 (M+1); MS (ES⁻): 388.5 (M-1), 424.4 (M+Cl). HPLC purity: 91.28%.

Scheme-44



Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-1-(cyclopropylmethyl)-1H-indole-6-carboxamido)phenyl)acetic acid (**44c**)

Step-1: Preparation of ethyl 2-(2-(4-bromo-1-(cyclopropylmethyl)-1H-indole-6-carboxamido)phenyl)acetate (**44a**)

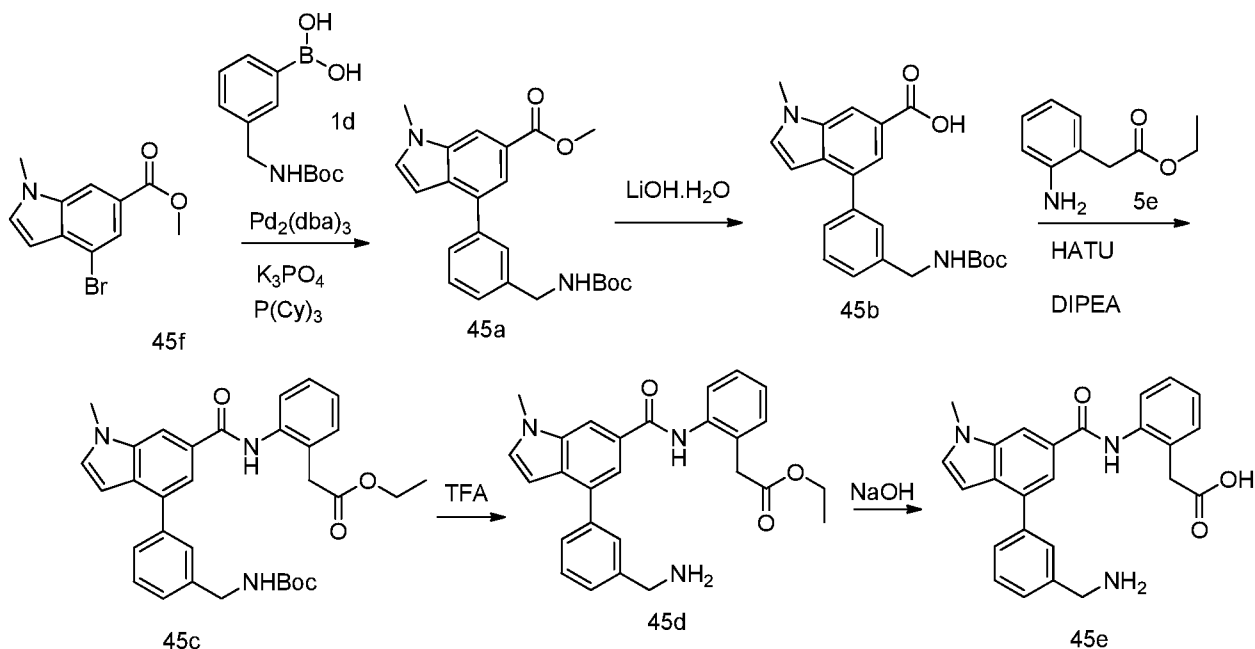
To a solution of ethyl 2-(2-(4-bromo-1H-indole-6-carboxamido)phenyl)acetate (**9b**) (0.2 g, 0.50 mmol) in DMF was added (bromomethyl)cyclopropane (0.07 mL, 0.75 mmol) and potassium carbonate (0.14 g, 1.0 mmol) and stirred at 60 °C overnight. The reaction mixture was diluted with EtOAc (100 mL), washed with water (3x), brine, dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] to give ethyl 2-(2-(4-bromo-1-(cyclopropylmethyl)-1H-indole-6-carboxamido)phenyl)acetate (**44a**) (0.15 g, 64 % yield); ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.02 (s, 1H), 8.24 (s, 1H), 7.85 (s, 1H), 7.78 (d, J = 3.1 Hz, 1H), 7.47 – 7.19 (m, 4H), 6.50 (d, J = 3.1 Hz, 1H), 4.15 (d, J = 7.1 Hz, 2H), 3.96 (m, 2H), 3.75 (s, 2H), 1.32 (m, 1H), 1.00 (t, J = 7.1 Hz, 3H), 0.58 – 0.31 (m, 4H). MS (ES⁺): 455.3 & 457.3 (M+1).

Step-2: Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-1-(cyclopropylmethyl)-1H-indole-6-carboxamido)phenyl)acetic acid (**44c**)

Compound **44c** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(4-bromo-1-(cyclopropylmethyl)-1H-indole-6-carboxamido)phenyl)acetate (**44a**) (140 mg, 0.31 mmol) in dioxane (3 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (90 mg, 0.46 mmol), tripotassium phosphate (1.3 M solution) (0.71 mL, 0.92 mmol), tricyclohexylphosphine (30 mg, 0.09 mmol) and Pd₂(dba)₃ (30 mg, 0.03 mmol) under an Ar atmosphere and heating at 125 °C for 45 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-60%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-1-(cyclopropylmethyl)-1H-indole-6-carboxamido)phenyl)acetate (**44b**) (0.06 g, 37 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.04 (s, 1H), 8.32 (s, 2H), 8.25 (s, 1H), 7.88 (s, 1H), 7.80 (d, J = 1.3 Hz, 1H), 7.77 (s, 1H), 7.75 (d, J = 3.0 Hz, 2H), 7.59 (t, J = 7.6 Hz, 1H), 7.55 – 7.40 (m, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.25 (td, J = 7.2, 1.5 Hz, 1H), 6.74 (d, J = 3.2 Hz, 1H), 4.18 (m, 2H), 4.15 (s, 2H), 3.95 (m, 2H), 3.78 (s, 2H), 1.37 (m, 1H), 0.98 (t, J = 7.1 Hz, 3H), 0.62 – 0.39 (m, 4H); MS (ES⁺): 482.4 (M+1); MS (ES⁻): 516.5 (M+Cl). HPLC purity: 96.64%; followed by 2-(2-(4-(3-(aminomethyl)phenyl)-1-(cyclopropylmethyl)-1H-indole-6-carboxamido)phenyl)acetic acid

(**44c**) (0.01 g, 7 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 8.37 (s, 2H), 8.24 (s, 1H), 7.91 (s, 1H), 7.85 (s, 1H), 7.79 (d, $J = 7.7$ Hz, 1H), 7.75 (d, $J = 3.2$ Hz, 1H), 7.58 (t, $J = 7.7$ Hz, 2H), 7.49 (d, $J = 7.7$ Hz, 1H), 7.32 (t, $J = 8.0$ Hz, 2H), 7.20 (t, $J = 7.4$ Hz, 1H), 6.74 (d, $J = 3.2$ Hz, 1H), 6.56 (s, 1H), 4.25 – 4.09 (m, 4H), 3.69 (s, 2H), 1.48 – 1.29 (m, 1H), 0.60 – 0.37 (m, 4H); MS (ES⁺): 454.4 (M+1); MS (ES⁻): 452.4 (M-1), 488.4 (M+Cl). HPLC purity: 97.36%.

Scheme-45



Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-1-methyl-1H-indole-6-carboxamido)phenyl)acetic acid (**45e**)

Step-1: Preparation of methyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1-methyl-1H-indole-6-carboxylate (**45a**)

Compound **45a** was prepared according to the procedure reported in step-3 of Scheme-1, from methyl 4-bromo-1-methyl-1H-indole-6-carboxylate (**45f**) (500 mg, 1.87 mmol; CAS#: 1246867-53-7) in dioxane (11 mL) using 3-(((*tert*-butoxycarbonyl)amino)methyl)phenylboronic acid (**1d**) (702 mg, 2.80 mmol), tripotassium phosphate (1.3 M solution, 1.1 mL, 3.17 mmol), tricyclohexylphosphine (157 mg, 0.56 mmol) and $\text{Pd}_2(\text{dba})_3$ (171 mg, 0.19 mmol) under a nitrogen atmosphere by heating at 120 °C for 45 min in a microwave. This gave after workup and purification by flash column chromatography [silica (12 g), eluting with hexanes/ethyl acetate 0% to 100%] methyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1-methyl-1H-indole-6-carboxylate (**45a**) (620 mg, 84 % yield) as a yellow solid; MS (ES⁺): 417.3 (M+Na).

Step-2: Preparation of 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1-methyl-1H-indole-6-carboxylic acid (**45b**)

Compound **45b** was prepared according to the procedure reported in step-6 of Scheme-1, from methyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1-methyl-1H-indole-6-carboxylate (**45a**) (600 mg, 1.52 mmol) in THF/MeOH (15 mL) using a solution of lithium hydroxide hydrate (383 mg, 9.13 mmol) in water (1 mL). This gave after workup 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1-methyl-1H-indole-6-carboxylic acid (**45b**) (500 mg, 86 % yield) as an off white solid, which was used in the next step without further purification. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.73 (s, 1H, D₂O exchangeable), 8.09 (s, 1H), 7.73 (d, *J* = 1.3 Hz, 1H), 7.63 (d, *J* = 3.1 Hz, 1H), 7.60 – 7.42 (m, 4H), 7.27 (d, *J* = 7.6 Hz, 1H), 6.63 (d, *J* = 3.2 Hz, 1H), 4.22 (d, *J* = 6.2 Hz, 2H), 3.91 (s, 3H), 1.40 (s, 9H).

Step-3: Preparation of ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1-methyl-1H-indole-6-carboxamido)phenyl)acetate (**45c**)

Compound **45c** was prepared according to the procedure reported in step-4 of Scheme-1, from 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1-methyl-1H-indole-6-carboxylic acid (**45b**) (300 mg, 0.79 mmol) in DMF (10 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (184 mg, 1.03 mmol), DIPEA (0.28 mL, 1.58 mmol) and HATU (360 mg, 0.79 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc in hexane] ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1-methyl-1H-indole-6-carboxamido)phenyl)acetate (**45c**) (211 mg, 49 % yield) as a pink semi-solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.02 (s, 1H, D₂O exchangeable), 8.11 (s, 1H), 7.77 (d, *J* = 1.4 Hz, 1H), 7.65 (s, 1H), 7.63 – 7.57 (m, 2H), 7.54 – 7.40 (m, 3H), 7.37 – 7.31 (m, 2H), 7.30 – 7.22 (m, 2H), 6.64 (d, *J* = 3.1 Hz, 1H), 4.23 (d, *J* = 6.2 Hz, 2H), 3.98 – 3.88 (m, 5H), 3.77 (s, 2H), 1.40 (s, 9H), 0.98 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 564.5 (M+Na); (ES⁻): 540.5 (M-1).

Step-4: Preparation of ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-1-methyl-1H-indole-6-carboxamido)phenyl)acetate (**45d**)

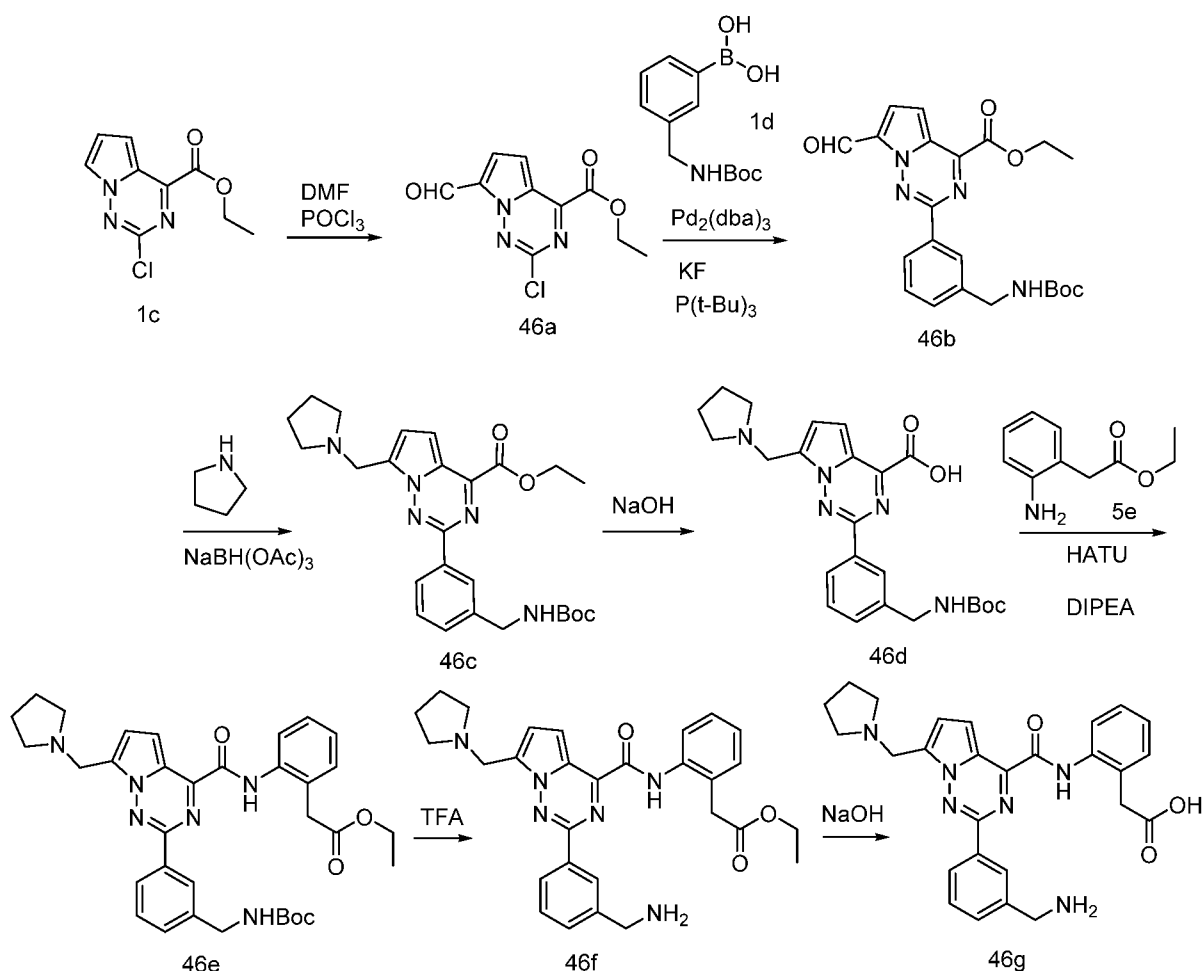
Compound **45d** was prepared according to the procedure reported in step-5 of Scheme-1, from ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1-methyl-1H-indole-6-carboxamido)phenyl)acetate (**45c**) (210 mg, 0.39 mmol) using TFA (0.3 mL, 3.88 mmol) in DCM (5 mL). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-1-methyl-1H-indole-6-

carboxamido)phenyl)acetate (**45d**) (114 mg, 67% yield) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.08 (s, 1H, D₂O exchangeable), 8.45 (s, 3H, D₂O exchangeable), 8.18 (s, 1H), 7.90 (d, *J* = 1.7 Hz, 1H), 7.84 (d, *J* = 1.4 Hz, 1H), 7.80 – 7.72 (m, 1H), 7.65 (d, *J* = 3.1 Hz, 1H), 7.62 – 7.49 (m, 2H), 7.44 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.25 (td, *J* = 7.1, 1.5 Hz, 1H), 6.75 (d, *J* = 3.1 Hz, 1H), 4.14 (s, 2H), 4.04 – 3.89 (m, 5H), 3.79 (s, 2H), 0.99 (t, *J* = 7.1 Hz, 3H).

Step-5: Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-1-methyl-1H-indole-6-carboxamido)phenyl)acetic acid (**45e**)

Compound **45e** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-1-methyl-1H-indole-6-carboxamido)phenyl)acetate (**45d**) (65 mg, 0.15 mmol) in MeOH/THF (10 mL, 1:1) using a solution of sodium hydroxide (35 mg, 0.88 mmol) in water (2 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(4-(3-(aminomethyl)phenyl)-1-methyl-1H-indole-6-carboxamido)phenyl)acetic acid (**45e**) (29 mg, 48% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.42 (s, 1H, D₂O exchangeable), 10.10 (s, 1H, D₂O exchangeable), 8.43 (s, 3H, D₂O exchangeable), 8.18 (s, 1H), 7.92 – 7.87 (m, 1H), 7.86 – 7.80 (m, 1H), 7.80 – 7.73 (m, 1H), 7.65 (d, *J* = 3.1 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.39 – 7.29 (m, 2H), 7.22 (td, *J* = 7.4, 1.4 Hz, 1H), 6.74 (d, *J* = 3.1 Hz, 1H), 4.14 (s, 2H), 3.93 (s, 3H), 3.71 (s, 2H); MS (ES⁺): 414.3 (M+1); 436.3 (M+Na); (ES⁻): 412.4 (M-1), 448.4 (M+Cl).

Scheme-46



Preparation of 2-(2-(2-(3-(aminomethyl)phenyl)-7-(pyrrolidin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**46g**)

Step-1: Preparation of ethyl 2-chloro-7-formylpyrrolo[2,1-f][1,2,4]triazine-4-carboxylate (**46a**)

To POCl₃ (1.239 mL, 13.30 mmol) in a sealed tube cooled with ice-water was added DMF (0.515 mL, 6.65 mmol) and stirred until the reaction mixture was homogeneous. The reaction mixture was warmed to room temperature and added ethyl 2-chloropyrrolo[2,1-f][1,2,4]triazine-4-carboxylate (**1c**) (300 mg, 1.33 mmol) and heated at 95 °C in a sealed tube for 5 h. The reaction mixture was cooled to room temperature and poured into an ice-cooled sat. aq. NaHCO₃ (60 mL), extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water (40 mL), brine (40 mL), dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica gel eluting with hexanes/ethyl acetate (1:0 to 9:1)] to afford ethyl 2-chloro-7-formylpyrrolo[2,1-f][1,2,4]triazine-4-carboxylate (**46a**) (224 mg, 66 % yield) as a yellow solid; ¹H NMR (300

MHz, DMSO-*d*₆) δ 10.38 (s, 1H), 7.78 (d, *J* = 5.1 Hz, 1H), 7.51 (d, *J* = 5.1 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

Step-2: Preparation of ethyl 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-formylpyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylate (**46b**)

Compound **46b** was prepared according to the procedure reported in step-3 of Scheme-1, from ethyl 2-chloro-7-formylpyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylate (**46a**) (250 mg, 0.99 mmol) in DMF (10 mL) using 3-(((*tert*-butoxycarbonyl)amino)methyl)phenylboronic acid (**1d**) (371 mg, 1.48 mmol), potassium fluoride (189 mg, 3.25 mmol), tri-*tert*-butylphosphine (1.281 mL, 1.28 mmol) and Pd₂(dba)₃ (90 mg, 0.099 mmol) under an argon atmosphere by heating at 120 °C overnight. This gave after workup and purification by flash column chromatography [silica (12 g), eluting with hexanes/ethyl acetate 0% to 50%] ethyl 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-formylpyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylate (**46b**) (339 mg, 81 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.62 (s, 1H), 8.34 – 8.27 (m, 2H), 7.73 (d, *J* = 5.0 Hz, 1H), 7.61 – 7.51 (m, 2H), 7.51 – 7.44 (m, 1H), 7.41 (d, *J* = 5.0 Hz, 1H), 4.54 (q, *J* = 7.1 Hz, 2H), 4.26 (d, *J* = 6.2 Hz, 2H), 1.49 – 1.39 (m, 12H); MS (ES⁺): 447.3 (M+1).

Step-3: Preparation of ethyl 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(pyrrolidin-1-ylmethyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylate (**46c**)

To a solution of ethyl 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-formylpyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylate (**46b**) (150 mg, 0.35 mmol) in DCE (10 mL) was added pyrrolidine (27.6 mg, 0.39 mmol) and acetic acid (0.020 mL, 0.35 mmol). The resulting mixture was stirred at RT for 2h followed by the addition of sodium triacetoxyborohydride (90 mg, 0.42 mmol). The resulting mixture was stirred at RT for 2h, diluted with EtOAc, washed with water, dried, filtered and concentrated in vacuum. The residue obtained was purified by chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] to give ethyl 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(pyrrolidin-1-ylmethyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylate (**46c**) (140 mg, 83 % yield) as a yellow semi-solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.23 (d, *J* = 6.2 Hz, 2H), 7.59 – 7.47 (m, 2H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 4.6 Hz, 1H), 7.20 (d, *J* = 4.6 Hz, 1H), 4.51 (q, *J* = 7.1 Hz, 2H), 4.25 (d, *J* = 6.2 Hz, 2H), 4.18 (s, 2H), 2.64 – 2.55 (m, 4H), 1.75 – 1.63 (m, 4H), 1.50 – 1.29 (m, 12H); MS (ES⁺): 480.4 (M+1); 502.4 (M+Na); (ES⁻): 478.5 (M-1).

Step-4: Preparation of 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(pyrrolidin-1-ylmethyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylic acid (**46d**)

Compound **46d** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(pyrrolidin-1-ylmethyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylate (**46c**) (140 mg, 1.52 mmol) in THF/MeOH (10 mL) using a solution of sodium hydroxide (70 mg, 1.75 mmol) in water (2 mL). This gave after workup followed by purification by flash column chromatography [silica (4 g), eluting with MeOH in DCM from 0-100%] 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(pyrrolidin-1-ylmethyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylic acid (**46d**) (60 mg, 46 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.40 – 8.27 (m, 2H), 7.60 – 7.49 (m, 2H), 7.46 – 7.30 (m, 3H), 4.95 (s, 2H), 4.26 (d, *J* = 6.1 Hz, 2H), 3.57 – 3.36 (m, 4H), 2.08 – 1.83 (m, 4H), 1.41 (s, 9H); MS (ES⁺): 452.4 (M+1); 474.4 (M+Na); (ES⁻): 450.4 (M-1); 486.4 (M+Cl).

Step-5: Preparation of ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(pyrrolidin-1-ylmethyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**46e**) Compound **46e** was prepared according to the procedure reported in step-4 of Scheme-1, from 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(pyrrolidin-1-ylmethyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylic acid (**46d**) (56 mg, 0.12 mmol) in DMF (10 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (29 mg, 0.16 mmol), DIPEA (0.043 mL, 0.25 mmol) and HATU (57 mg, 0.15 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc in hexane] ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(pyrrolidin-1-ylmethyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**46e**) (53 mg, 70 % yield) as a pink semi-solid; MS (ES⁺): 613.4 (M+1); 635.4 (M+Na); (ES⁻): 611.5 (M-1).

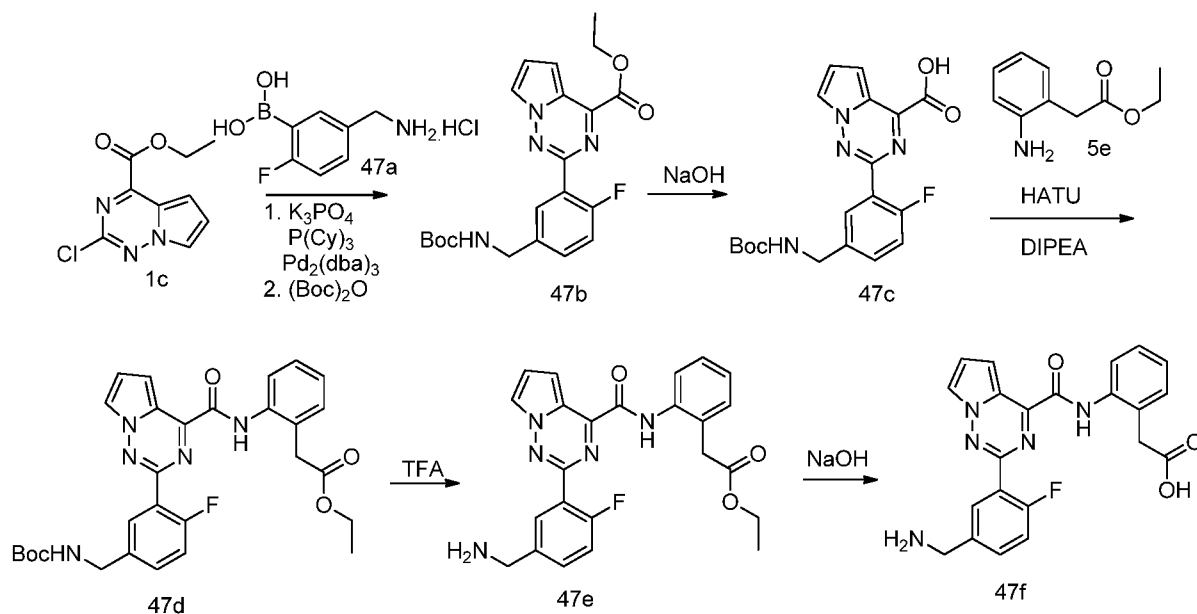
Step-6: Preparation of ethyl 2-(2-(2-(3-(aminomethyl)phenyl)-7-(pyrrolidin-1-ylmethyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**46f**) Compound **46f** was prepared according to the procedure reported in step-5 of Scheme-1, from ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-7-(pyrrolidin-1-ylmethyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**46e**) (53 mg, 0.086 mmol) using TFA (0.067 mL, 0.87 mmol) in DCM (5 mL). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] ethyl 2-(2-(2-(3-(aminomethyl)phenyl)-7-(pyrrolidin-1-ylmethyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**46f**) (27 mg, 61% yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.88 (s, 1H, D₂O exchangeable), 9.00 (s, 1H, D₂O exchangeable), 8.71 (d, *J* = 7.6 Hz, 3H), 7.72 (t, *J* = 7.9 Hz, 2H), 7.68 – 7.61 (m, 2H), 7.53 (d, *J* = 4.7 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 2H), 7.31 (td, *J* = 7.5, 7.1, 1.4 Hz, 1H), 5.07 (s, 2H),

4.19 (d, $J = 5.1$ Hz, 2H), 4.01 (q, $J = 7.1$ Hz, 2H), 3.88 (s, 2H), 3.58 – 3.43 (m, 2H), 3.33 – 3.25 (m, 2H), 2.14 – 1.97 (m, 2H), 1.95 – 1.80 (m, 2H), 1.02 (t, $J = 7.1$ Hz, 3H); MS (ES⁺): 513.4 (M+1); 535.4 (M+Na).

Step-7: Preparation of 2-(2-(2-(3-(aminomethyl)phenyl)-7-(pyrrolidin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**46g**)

Compound **46g** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-(2-(3-(aminomethyl)phenyl)-7-(pyrrolidin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetate (**46f**) (25 mg, 0.049 mmol) in MeOH/THF (10 mL, 1:1) using a solution of sodium hydroxide (12 mg, 0.29 mmol) in water (2 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(2-(3-(aminomethyl)phenyl)-7-(pyrrolidin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**46g**) (11 mg, 47 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.81 (s, 1H, D₂O exchangeable), 11.09 (s, 1H, D₂O exchangeable), 10.94 (s, 1H), 8.97 (d, $J = 1.7$ Hz, 1H), 8.80 – 8.60 (m, 4H, partially D₂O exchangeable), 7.83 (d, $J = 8.1$ Hz, 1H), 7.73 – 7.60 (m, 3H), 7.55 (d, $J = 4.7$ Hz, 1H), 7.47 – 7.37 (m, 2H), 7.28 (td, $J = 7.4, 1.3$ Hz, 1H), 5.08 (d, $J = 4.5$ Hz, 2H), 4.26 – 4.12 (m, 2H), 3.81 (s, 2H), 3.59 – 3.41 (m, 4H), 2.16 – 1.97 (m, 2H), 1.95 – 1.78 (m, 2H); MS (ES⁺) 485.4 (M+1); (ES⁻) 483.4 (M-1); HPLC purity, 93.69%.

Scheme-47



Preparation of 2-(2-(2-(5-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**47f**)

Step-1: Preparation of ethyl 2-(5-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylate (**47b**)

To a solution of ethyl 2-chloropyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylate (**1c**) (400 mg, 1.77 mmol) in dioxane (12 mL) was added (5-(aminomethyl)-2-fluorophenyl)boronic acid hydrochloride (**47a**) (546 mg, 2.66 mmol; CAS# 1072946-46-3), 3 M aqueous potassium triphosphate (1.182 mL, 3.55 mmol), tricyclohexylphosphine (99 mg, 0.355 mmol) and Pd₂(dba)₃ (162 mg, 0.177 mmol). The mixture was degassed and filled with Ar, then heated at 125 °C for 30 min in a microwave. The mixture was cooled to room temperature, diluted with water (60 mL) and EtOAc (60 mL). To the biphasic layer was added BOC-anhydride (580 mg, 2.66 mmol) and stirred at room temperature for 3 h. The organic layer was separated and aqueous layer was extracted with EtOAc (50 mL). The organic layers were combined washed with washed with water, brine, filtered and concentrated in vacuum to dryness. The residue obtained was purified by flash column chromatography [silica (12 g), eluting with EtOAc in hexanes 0 to 60%] to afford ethyl 2-(5-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylate (**47b**) (0.32 g, 0.772 mmol, 43.6 % yield) as an orange colored foam; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.40 (s, 1H), 7.87 (d, *J* = 7.3 Hz, 1H), 7.53 (t, *J* = 6.1 Hz, 1H), 7.49 – 7.24 (m, 4H), 4.50 (q, *J* = 7.1 Hz, 2H), 4.19 (d, *J* = 6.2 Hz, 2H), 1.44 – 1.33 (m, 12H); MS (ES⁺): 437.3 (M+Na)

Step-2: Preparation of 2-(5-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylic acid (**47c**)

Compound **47c** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(5-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylate (**47b**) (0.32 g, 0.772 mmol) in THF (10 mL) using sodium hydroxide (0.772 mL, 1.544 mmol, 2 M aqueous solution). This gave after workup 2-(5-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxylic acid (**47c**) (0.29 g, 97 % yield) as a light orange foam. ¹H NMR (300 MHz, DMSO-*d*₆) δ 14.43 (s, 1H), 8.36 (dd, *J* = 2.6, 1.4 Hz, 1H), 7.92 (dd, *J* = 7.5, 2.2 Hz, 1H), 7.53 (t, *J* = 6.1 Hz, 1H), 7.47 – 7.39 (m, 1H), 7.39 – 7.32 (m, 2H), 7.24 (dd, *J* = 4.6, 2.5 Hz, 1H), 4.19 (d, *J* = 6.2 Hz, 2H), 1.39 (s, 9H); MS (ES⁻): 385.3 (M-1).

Step-3: Preparation of ethyl 2-(2-(2-(5-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)phenyl)acetate (**47d**)

Compound **47d** was prepared according to the procedure reported in step-4 of Scheme-1 from 2-(5-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-

carboxylic acid (**47c**) (180 mg, 0.47 mmol) in DMF (3 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (125 mg, 0.7 mmol), DIPEA (0.24 mL, 1.4 mmol) and HATU (213 mg, 0.56 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] ethyl 2-(2-(2-(5-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetate (**47d**) (0.19 g, 75 % yield) as an orange colored foam; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.61 (s, 1H), 8.41 (dd, *J* = 2.6, 1.4 Hz, 1H), 8.18 (dd, *J* = 7.6, 2.2 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.59 (dd, *J* = 4.6, 1.4 Hz, 1H), 7.55 – 7.33 (m, 5H), 7.37 – 7.20 (m, 2H), 4.23 (d, *J* = 6.1 Hz, 2H), 3.94 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 2H), 1.38 (s, 9H), 0.96 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 548.3 (M+1), 570.3 (M+Na); (ES⁻): 582.4 (M+Cl).

Step-4: Preparation of ethyl 2-(2-(2-(5-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetate (**47e**)

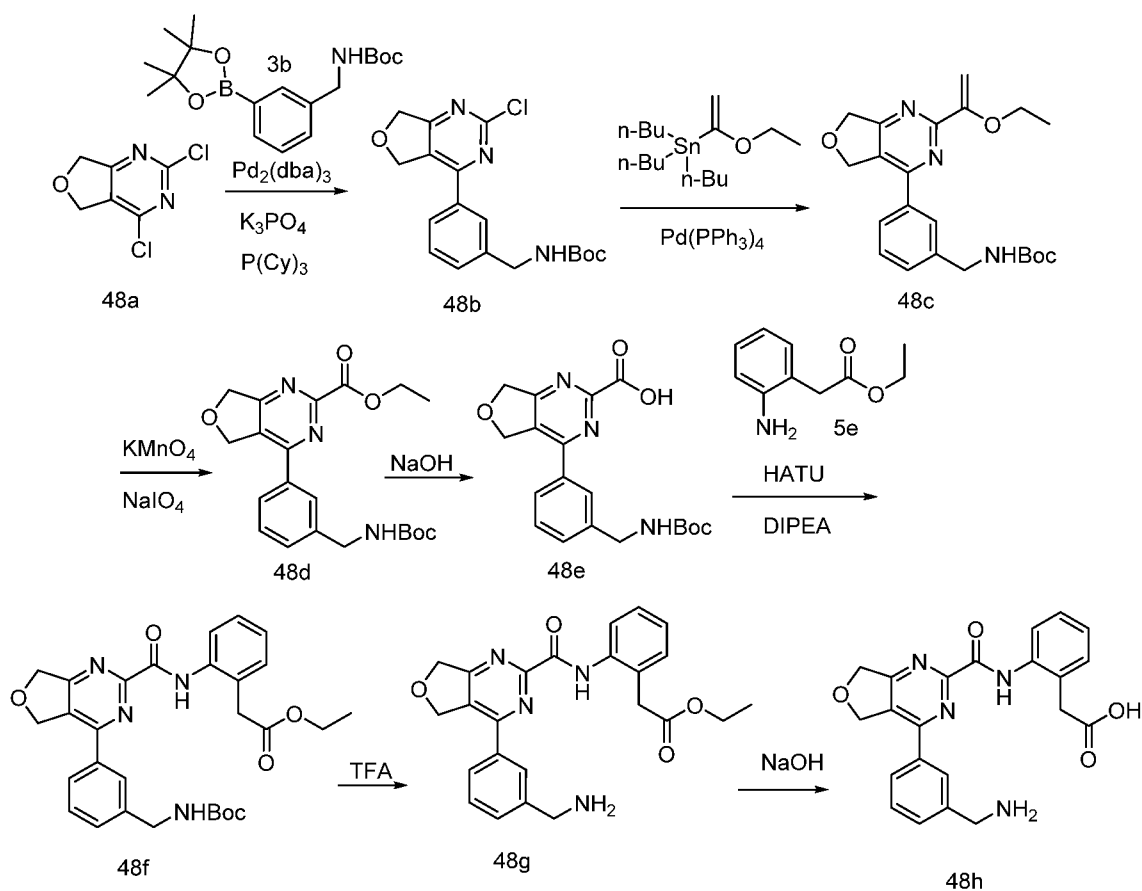
Compound **47e** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-(2-(5-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetate (**47d**) (180 mg, 0.329 mmol) in DCM (5 mL) using TFA (0.025 mL, 0.329 mmol). This gave after workup and purification by reverse phase column chromatography [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(2-(5-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetate (**47e**) (0.045 g, 31 % yield) as a HCl salt; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.61 (s, 1H), 8.53 (d, *J* = 7.1 Hz, 1H), 8.49 – 8.32 (m, 4H), 7.81 – 7.70 (m, 2H), 7.61 (dd, *J* = 4.6, 1.3 Hz, 1H), 7.51 (dd, *J* = 11.1, 8.5 Hz, 1H), 7.45 – 7.37 (m, 2H), 7.35 – 7.24 (m, 2H), 4.21 – 4.10 (m, 2H), 3.94 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 2H), 0.97 (t, *J* = 7.1 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -113.01; MS (ES⁺): 448.3 (M+1), MS (ES⁻): 482.3 (M+Cl); HPLC purity 94.88 %.

Step-5: Preparation of 2-(2-(2-(5-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**47f**)

Compound **47f** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(2-(5-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetate (**47e**) (110 mg, 0.246 mmol) in THF (4 mL) using a 2 M aqueous solution of NaOH (0.246 mL, 0.492 mmol). This gave after workup and purification by reverse phase column chromatography [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-40%] 2-(2-(2-(5-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)phenyl)acetic acid (**47f**) (0.045 g, 44 % yield) as a HCl salt; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.70 (s, 1H), 11.12 – 10.76 (m, 1H), 8.66-8.55 (m, 1H),

8.51 – 8.33 (m, 4H), 7.90 – 7.82 (m, 1H), 7.75--7.65 (m, 1H), 7.63 (dd, $J = 4.6, 1.3$ Hz, 1H), 7.49 (dd, $J = 11.1, 8.5$ Hz, 1H), 7.43-7.34 (m, 2H), 7.31 (dd, $J = 4.6, 2.6$ Hz, 1H), 7.24 (t, $J = 7.5$ Hz, 1H), 4.23-4.08 (m, 2H), 3.74 (s, 2H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -112.49; MS (ES+) 420.3 (M+1), MS (ES-) 418.3 (M-1); HPLC purity: 97.95 %.

Scheme-48



Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxamido)phenyl)acetic acid (**48h**)

Step-1: Preparation of *tert*-butyl 3-(2-chloro-5,7-dihydrofuro[3,4-d]pyrimidin-4-yl)benzylcarbamate (**48b**)

Compound **48b** was prepared according to the procedure reported in step-3 of Scheme-1 from 2,4-dichloro-5,7-dihydrofuro[3,4-d]pyrimidine (**48a**) (2 g, 10.47 mmol; CAS# 848398-41-4) in dioxane (100 mL) using *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylcarbamate (**3b**) (2.49 g, 7.48 mmol), tripotassium phosphate (5.48 mL, 16.45 mmol, 3 M aqueous solution), tricyclohexylphosphine (0.63 g, 2.24 mmol) and $\text{Pd}_2(\text{dba})_3$ (0.69 g, 0.75 mmol) in argon atmosphere and heating in an oil bath at 120 °C for 1.5 h. This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-70%] *tert*-butyl 3-(2-chloro-5,7-dihydrofuro[3,4-d]pyrimidin-4-

yl)benzylcarbamate (**48b**) (0.72 g, 27 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 7.81 (d, J = 2.0 Hz, 1H), 7.74 -7.68 (m, 1H), 7.59 - 7.44 (m, 3H), 5.40 (t, J = 1.8 Hz, 2H), 5.02 (d, J = 1.8 Hz, 2H), 4.22 (d, J = 6.2 Hz, 2H), 1.41 (s, 9H). MS (ES-): 360.4 & 362.3 (M-1).

Step-2: Preparation of *tert*-butyl 3-(2-(1-ethoxyvinyl)-5,7-dihydrofuro[3,4-d]pyrimidin-4-yl)benzylcarbamate (**48c**)

Compound **48c** was prepared according to the procedure reported in step-1 of Scheme-1 from *tert*-butyl 3-(2-chloro-5,7-dihydrofuro[3,4-d]pyrimidin-4-yl)benzylcarbamate (**48b**) (0.7 g, 1.94 mmol) in DMF (20 mL) using 1-ethoxyvinyltri-*n*-butyltin (0.86 mL, 2.52 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.22 g, 0.19 mmol) in argon atmosphere and heating at 110 °C for 4 h. This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-50%] *tert*-butyl 3-(2-(1-ethoxyvinyl)-5,7-dihydrofuro[3,4-d]pyrimidin-4-yl)benzylcarbamate (**48c**) (0.51 g, 66 % yield) as a white solid; MS (ES+): 398.4 (M+1), 420.3 (M+Na); MS (ES-): 396.4 (M-1), 432.4 (M+Cl).

Step-3: Preparation of ethyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxylate (**48d**)

Compound **48d** was prepared according to the procedure reported in step-2 of Scheme-1 from *tert*-butyl 3-(2-(1-ethoxyvinyl)-5,7-dihydrofuro[3,4-d]pyrimidin-4-yl)benzylcarbamate (**48c**) (0.5 g, 1.258 mmol) in 1,4-dioxane (100 mL) using sodium periodate solution (0.54 g, 2.52 mmol) in water (10 mL) and KMnO_4 (0.12 g, 0.76 mmol, and second dosing of 0.12 g, 0.76 mmol after 12 h). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] ethyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxylate (**48d**) (0.28 g, 56 % yield) as a yellow solid; MS (ES+): 400.3 (M+1), 422.3 (M+Na); MS (ES-): 398.4 (M-1).

Step-4: Preparation of 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxylic acid (**48e**)

Compound **48e** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxylate (**48d**) (0.28 g, 0.70 mmol) in THF/MeOH (5 mL, 1:1) using sodium hydroxide (0.11 g, 2.80 mmol) in water (2 mL). This gave after workup 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxylic acid (**48e**) (0.16 g, 62 % yield) as a yellow solid; ^1H NMR (300 MHz, DMSO- d_6) δ 7.86 (s, 1H),

7.81 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.7 Hz, 2H), 7.45 (d, J = 7.7 Hz, 1H), 5.47 (s, 2H), 5.08 (d, J = 1.8 Hz, 2H), 4.23 (d, J = 6.2 Hz, 2H), 1.41 (s, 9H); MS (ES⁻): 370.3 (M-1).

Step-5: Preparation of ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxamido)phenyl)acetate (**48f**)

Compound **48f** was prepared according to the procedure reported in step-4 of Scheme-1 from 4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxylic acid (**48e**) (0.16 g, 0.43 mmol) in DMF (5 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (0.09 g, 0.52 mmol), DIPEA (0.15 mL, 0.86 mmol) and HATU (0.20 g, 0.52 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc/MeOH (9:1) in hexane from 0-100%] ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxamido)phenyl)acetate (**48f**) (0.17 g, 72 % yield) as a white solid; MS (ES⁺): 555.3 (M+Na); MS (ES⁻): 531.6 (M-1).

Step-6: Preparation of ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxamido)phenyl)acetate (**48g**)

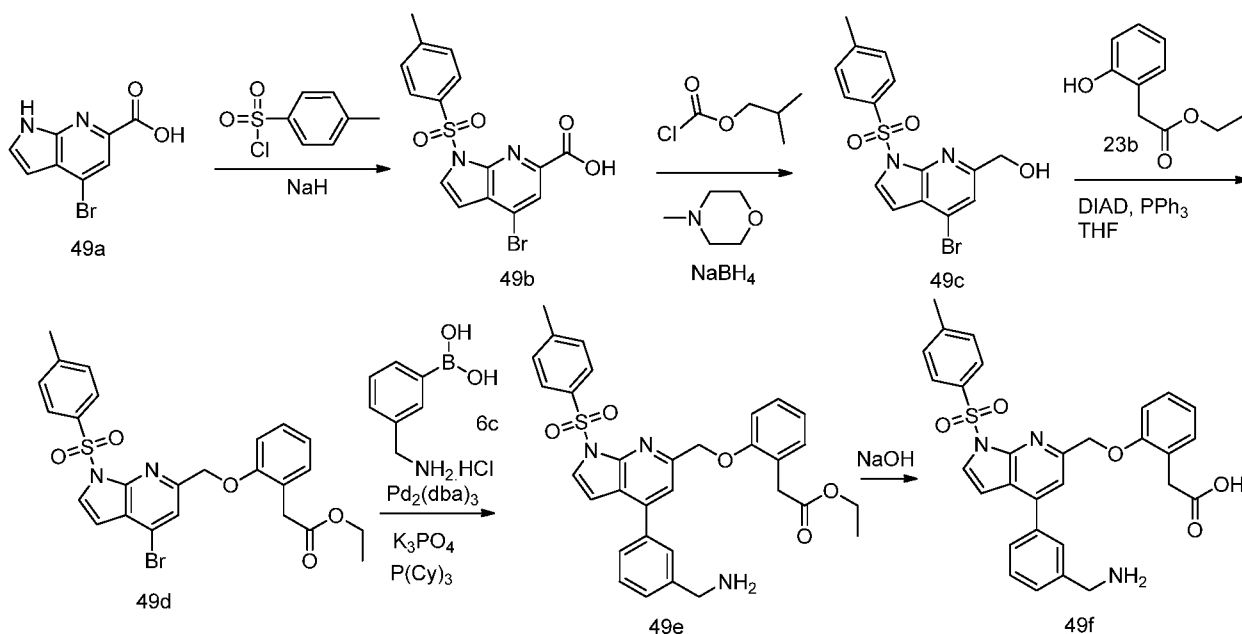
Compound **48g** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-(4-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxamido)phenyl)acetate (**48f**) (160 mg, 0.30 mmol) in DCM (5 mL) using TFA (0.23 mL, 3.0 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxamido)phenyl)acetate (**48g**) (0.11 g, 85 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.63 (s, 1H), 8.62 (s, 3H), 8.19 (m, 2H), 7.79 – 7.71 (m, 2H), 7.66 (t, J = 7.6 Hz, 1H), 7.38 (m, 2H), 7.24 (t, J = 7.2 Hz, 1H), 5.61 (s, 2H), 5.14 (s, 2H), 4.17 (d, J = 5.8 Hz, 2H), 3.98 (q, J = 7.0 Hz, 2H), 3.84 (s, 2H), 1.01 (t, J = 7.1 Hz, 3H); MS (ES⁺): 433.3 (M+1), 455.3 (M+Na). HPLC purity: 94.03%.

Step-7: Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxamido)phenyl)acetic acid (**48h**)

Compound **48h** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxamido)phenyl)acetate (**48g**) (50 mg, 0.116 mmol) in MeOH/THF (5 mL, 1:1) using a solution of NaOH (18 mg, 0.462 mmol) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in

water (containing 0.1% HCl) from 0-100%] 2-(2-(4-(3-(aminomethyl)phenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2-carboxamido)phenyl)acetic acid (**48h**) (0.016 g, 34 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.71 (s, 1H), 8.51 (s, 3H), 8.20 (s, 1H), 8.14 (d, *J* = 7.5, Hz, 1H), 7.82 (d, *J* = 7.5, Hz, 1H), 7.78 – 7.72 (m, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.38 (m, 2H), 7.27 – 7.18 (m, 1H), 5.60 (s, 2H), 5.15 (s, 2H), 4.18 (q, *J* = 5.8 Hz, 2H), 3.76 (s, 2H); MS (ES⁺): 405.3 (M+1), 427.3 (M+Na); MS (ES⁻): 403.3 (M-1), 439.3 (M+Cl). HPLC purity: 96.60%.

Scheme-49



Preparation of 2-(2-((4-(3-(aminomethyl)phenyl)-1-tosyl-1H-pyrrolo[2,3-b]pyridin-6-yl)methoxy)phenyl)acetic acid (**49f**)

Step-1: Preparation of 4-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylic acid (**49b**)

Compound **49b** was prepared according to the procedure reported in step-1 of Scheme-40 from 4-bromo-1H-pyrrolo[2,3-b]pyridine-6-carboxylic acid (**49a**) (0.7 g, 2.90 mmol; CAS#:1190321-81-3) in DMF (9.5 mL) using NaH (60% in mineral oil, 0.29 g, 7.26 mmol) and tosyl-Cl (0.66 g, 3.48 mmol). This gave after work up 4-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylic acid (**49b**) (0.79 g, 69 % yield) as a tan solid, which was used in the next step without further purification. MS (ES⁻): 393.2 & 395.1 (M-1).

Step-2: Preparation of (4-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridin-6-yl)methanol (**49c**)

Compound **49c** was prepared according to the procedure reported in step-1 of Scheme-23 from 4-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylic acid (**49b**) (0.6 g, 1.52 mmol) using N-methylmorpholine (0.20 mL, 1.82 mmol) in THF (30 mL), isobutyl chloroformate (0.24 mL, 1.82 mmol) and NaBH₄ (0.17 g, 4.55 mmol) in water (0.8 mL). This gave after

workup (4-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridin-6-yl)methanol (**49c**) (0.27 g, 49 % yield) as a clear oil.; MS (ES+): 382.5 (M+1); MS (ES-): 415.2 & 417.2 (M+Cl).

Step-3: Preparation of ethyl 2-(2-((4-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridin-6-yl)methoxy)phenyl)acetate (**49d**)

Compound **49d** was prepared according to the procedure reported in step-2 of Scheme-23 from (4-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridin-6-yl)methanol (**49c**) (0.28 g, 0.73 mmol) in THF (15 mL) using triphenylphosphine (0.25 g, 0.96 mmol), ethyl 2-(2-hydroxyphenyl)acetate (**23b**) (0.17 g, 0.96 mmol) and DIAD (0.19 mL, 0.96 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] ethyl 2-(2-((4-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridin-6-yl)methoxy)phenyl)acetate (**49d**) (0.31 g, 78 % yield) as colorless oil.; MS (ES+): 543.1 & 545.2 (M+1).

Step-4: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)phenyl)-1-tosyl-1H-pyrrolo[2,3-b]pyridin-6-yl)methoxy)phenyl)acetate (**49e**)

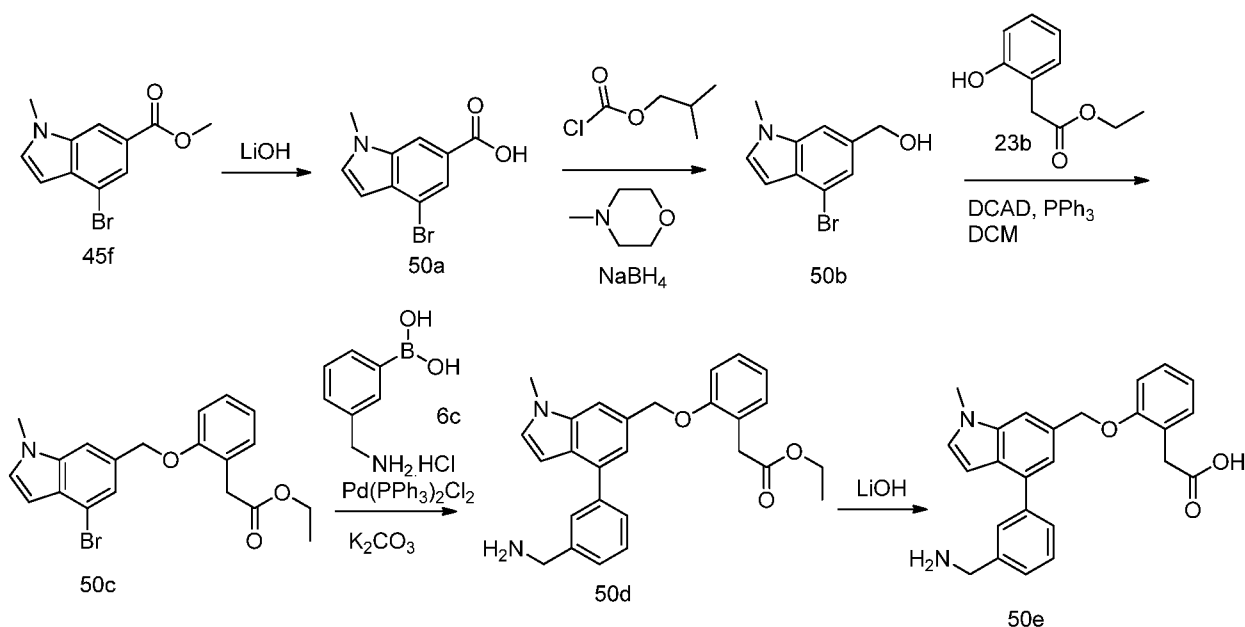
Compound **49e** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((4-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridin-6-yl)methoxy)phenyl)acetate (**49d**) (0.2 g, 0.368 mmol) in dioxane (3 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (0.103 g, 0.552 mmol), tripotassium phosphate (1.3 M solution, 0.849 mL, 1.104 mmol), tricyclohexylphosphine (0.031 g, 0.11 mmol) and Pd₂(dba)₃ (0.034 g, 0.037 mmol) under an Ar atmosphere and heating at 125 °C for 30 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-60%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((4-(3-(aminomethyl)phenyl)-1-tosyl-1H-pyrrolo[2,3-b]pyridin-6-yl)methoxy)phenyl)acetate (**49e**) (0.152 g, 73 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.51 (s, 3H), 8.16 – 8.05 (m, 2H), 8.00 (d, J = 4.1 Hz, 1H), 7.84 (s, 1H), 7.73 – 7.65 (m, 1H), 7.61 (m, 2H), 7.54 (s, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.29 – 7.14 (m, 2H), 7.11 (d, J = 4.1 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 6.92 (t, J = 7.4 Hz, 1H), 5.35 (s, 2H), 4.11 (q, J = 5.9 Hz, 2H), 3.88 (q, J = 7.1 Hz, 2H), 3.69 (s, 2H), 2.36 (s, 3H), 0.91 (t, J = 7.1 Hz, 3H); MS (ES+): 570.4 (M+1), 592.3 (M+Na); MS (ES-): 604.4 (M+Cl). HPLC purity: 90.90%.

Step-5: Preparation of 2-(2-((4-(3-(aminomethyl)phenyl)-1-tosyl-1H-pyrrolo[2,3-b]pyridin-6-yl)methoxy)phenyl)acetic acid (**49f**)

Compound **49f** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-((4-(3-(aminomethyl)phenyl)-1-tosyl-1H-pyrrolo[2,3-b]pyridin-6-

yl)methoxy)phenyl)acetate (**49e**) (0.05 g, 0.088 mmol) in MeOH/THF (5 mL, 1:1) using a solution of sodium hydroxide (4 mg, 0.088 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((4-(3-(aminomethyl)phenyl)-1-tosyl-1H-pyrrolo[2,3-b]pyridin-6-yl)methoxy)phenyl)acetic acid (**49f**) (0.01 g, 21 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 12.29 (s, 1H), 8.47 (s, 3H), 8.09 (d, J = 8.0 Hz, 2H), 8.00 (d, J = 4.1 Hz, 1H), 7.83 (s, 1H), 7.70 (d, J = 6.5 Hz, 1H), 7.59 (m, 3H), 7.43 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 7.3 Hz, 1H), 7.16 (t, J = 7.8 Hz, 1H), 7.10 (d, J = 4.1 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.91 (t, J = 7.3 Hz, 1H), 5.36 (s, 2H), 4.10 (d, J = 5.9 Hz, 2H), 3.64 (s, 2H), 2.35 (s, 3H); MS (ES $^{+}$): 542.3 (M+1), 564.3 (M+Na); MS (ES $^{-}$): 576.4 (M+Cl). HPLC purity: 88.38%.

Scheme-50



Preparation of 2-(2-((4-(3-(aminomethyl)phenyl)-1-methyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**50e**)

Step-1: Preparation of 4-bromo-1-methyl-1H-indole-6-carboxylic acid (**50a**)

Compound **50a** was prepared according to the procedure reported in step-6 of Scheme-1, from methyl 4-bromo-1-methyl-1H-indole-6-carboxylate (**45f**) (3 g, 11.19 mmol) in THF/MeOH (30 mL) using a solution of lithium hydroxide hydrate (2.82 g, 67.1 mmol) in water (3 mL). This gave after workup 4-bromo-1-methyl-1H-indole-6-carboxylic acid (**50a**) (2.2 g, 77 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 12.96 (s, 1H), 8.10 (s, 1H), 7.78 (s, 1H), 7.69 (d, J = 3.1 Hz, 1H), 6.52 - 6.42 (m, 1H), 3.89 (s, 3H). MS (ES $^{-}$): 252.1 (M-1).

Step-2: Preparation of (4-bromo-1-methyl-1H-indol-6-yl)methanol (**50b**)

Compound **50b** was prepared according to the procedure reported in step-1 of Scheme-23 from 4-bromo-1-methyl-1H-indole-6-carboxylic acid (**50a**) (3.7 g, 14.56 mmol) using N-methylmorpholine (1.92 mL, 17.47 mmol) in THF (100 mL), isobutyl chloroformate (2.30 mL, 17.47 mmol) and NaBH₄ (1.65 g, 43.7 mmol) in water. This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc/MeOH=9:1 in Hexane from 0-100%] (4-bromo-1-methyl-1H-indol-6-yl)methanol (**50b**) (2.1 g, 60 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.41 (d, J = 3.2 Hz, 2H), 7.22 (s, 1H), 6.34 (dd, J = 3.1, 0.9 Hz, 1H), 5.27 (t, J = 5.8 Hz, 1H), 4.59 (d, J = 5.7 Hz, 2H), 3.79 (s, 3H).

Step-3: Preparation of ethyl 2-(2-((4-bromo-1-methyl-1H-indol-6-yl)methoxy)phenyl)acetate (**50c**)

Compound **50c** was prepared according to the procedure reported in step-2 of Scheme-23 from (4-bromo-1-methyl-1H-indol-6-yl)methanol (**50b**) (1 g, 4.16 mmol) in DCM (50 mL) using triphenylphosphine (1.42 g, 5.41 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (0.98 g, 5.41 mmol) and di-(4-chlorobenzyl)azodicarboxylate (DCAD, 1.99 g, 5.41 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane from 0-60%] ethyl 2-(2-((4-bromo-1-methyl-1H-indol-6-yl)methoxy)phenyl)acetate (**50c**) (0.66 g, 39 % yield) as a colorless oil; MS (ES⁺): 424.2 & 426.1 (M+Na).

Step-4: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)phenyl)-1-methyl-1H-indol-6-yl)methoxy)phenyl)acetate (**50d**)

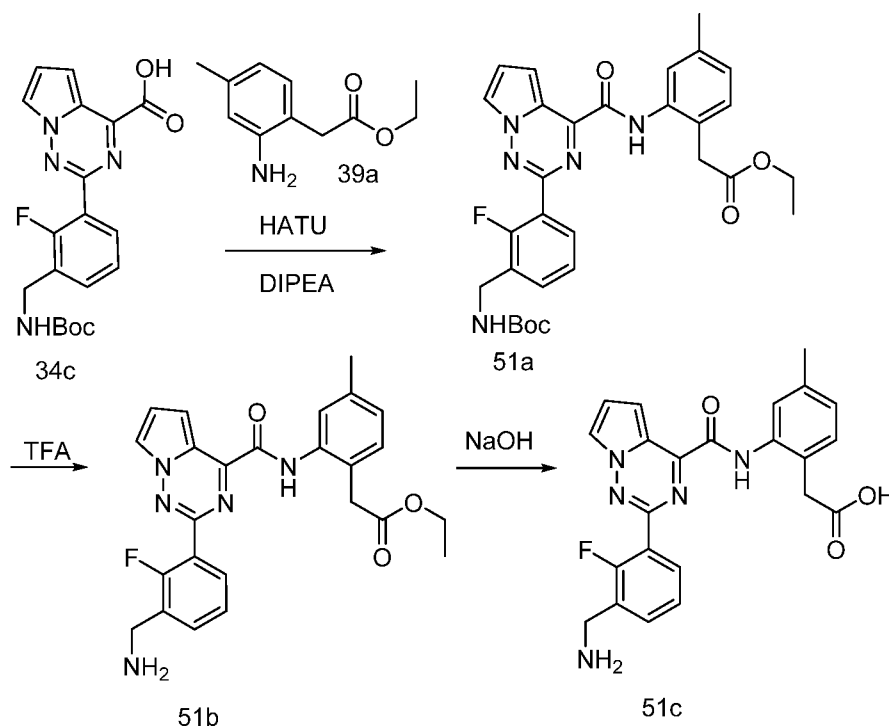
Compound **50d** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((4-bromo-1-methyl-1H-indol-6-yl)methoxy)phenyl)acetate (**50c**) (0.65 g, 1.62 mmol) in dioxane (15 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (0.45 g, 2.42 mmol), K₂CO₃ (0.67 g, 4.85 mmol) in water (2 mL) and bis(triphenylphosphine)Palladium(II) chloride (0.17 g, 0.24 mmol) under an Ar atmosphere and heating at 100 °C for 2 h in an oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] ethyl 2-(2-((4-(3-(aminomethyl)phenyl)-1-methyl-1H-indol-6-yl)methoxy)phenyl)acetate (**50d**) (0.16 g, 23 % yield) as a white solid; MS (ES⁺): 429.3 (M+1).

Step-5: Preparation of 2-(2-((4-(3-(aminomethyl)phenyl)-1-methyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**50e**)

Compound **50e** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((4-(3-(aminomethyl)phenyl)-1-methyl-1H-indol-6-

yl)methoxy)phenyl)acetate (**50d**) (0.16 g, 0.373 mmol) in THF/MeOH (8 mL) using a solution of lithium hydroxide hydrate (0.078 g, 1.867 mmol) in water (2 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((4-(3-(aminomethyl)phenyl)-1-methyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**50e**) (0.045 g, 30 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.34 (s, 3H), 7.81 (s, 1H), 7.72 – 7.65 (m, 1H), 7.59 (m, 2H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.45 (d, *J* = 3.1 Hz, 1H), 7.27 – 7.22 (m, 2H), 7.21 (s, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.93 – 6.86 (m, 1H), 6.64 (d, *J* = 3.2 Hz, 1H), 5.28 (s, 2H), 4.13 (s, 2H), 3.84 (s, 3H), 3.60 (s, 2H); MS (ES⁺): 401.3 (M+1), 423.3 (M+Na); MS (ES⁻): 399.3 (M-1), 435.3 (M+Cl). HPLC purity: 98.50 %.

Scheme-51



Preparation of 2-(2-(2-(3-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetic acid (**51c**)

Step-1: Preparation of ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetate (**51a**)

Compound **51a** was prepared according to the procedure reported in step-4 of Scheme-1 from 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**34c**) (0.1 g, 0.259 mmol) in DMF (3 mL) using ethyl 2-(2-amino-4-methylphenyl)acetate (**39a**) (118 mg, 0.611 mmol), DIPEA (0.136 mL, 0.776 mmol) and HATU (118 mg, 0.311 mmol). This gave after workup and purification by flash column

chromatography [silica (12 g), eluting with 0-60% EtOAc in hexane] ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetate (**51a**) (0.1 g, 69 % yield) as an orange colored foam; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.63 (s, 1H), 8.40 (d, *J* = 2.6 Hz, 1H), 8.26 - 8.17 (m, 1H), 7.65 - 7.61 (m, 1H), 7.59 (d, *J* = 4.6 Hz, 1H), 7.56 - 7.43 (m, 2H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.31 - 7.23 (m, 2H), 7.07 (dd, *J* = 7.8, 1.8 Hz, 1H), 4.28 (d, *J* = 6.1 Hz, 2H), 3.95 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 2H), 2.35 (s, 3H), 1.40 (s, 9H), 0.97 (t, *J* = 7.1 Hz, 3H).

Step-2: Preparation of ethyl 2-(2-(2-(3-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetate (**51b**)

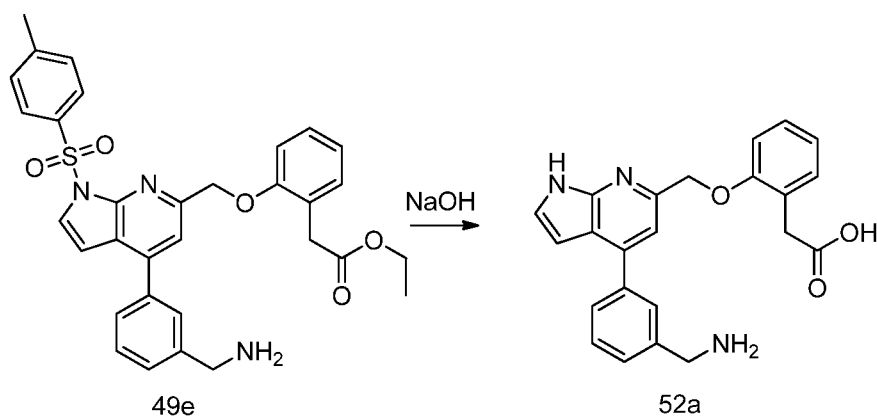
Compound **51b** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetate (**51a**) (0.1 g, 0.178 mmol) in DCM (3 mL) using TFA (0.137 mL, 1.78 mmol). This gave after workup and purification by reverse phase column chromatography [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(2-(3-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetate (**51b**) (0.028 g, 34 % yield) as a HCl salt; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.67 (s, 1H), 8.52 – 8.32 (m, 5H), 7.75 (t, *J* = 7.1 Hz, 1H), 7.63 – 7.58 (m, 2H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.32 (dd, *J* = 4.6, 2.5 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 4.20 (s, 2H), 3.96 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 2H), 2.35 (s, 3H), 0.99 (t, *J* = 7.1 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -116.69; MS (ES⁺): 462.3 (M+1), 484.3 (M+Na); MS (ES⁻): 460.4 (M-1), 496.4 (M+Cl); HPLC purity 99.65%

Step-3: Preparation of 2-(2-(2-(3-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetic acid (**51c**)

Compound **51c** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(2-(3-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetate (**51b**) (0.07 g, 0.152 mmol) in THF (4 mL) using sodium hydroxide (0.152 mL, 0.303 mmol, 2 M aqueous). This gave after workup and purification by reverse phase column [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(2-(3-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetic acid (**51c**) (0.025 g, 38.0 % yield) as a HCl salt; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.71 (s, 1H), 10.74 (s, 1H), 8.52 – 8.31 (m, 4H), 7.81 – 7.67 (m, 3H), 7.63 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.32 (dd, *J* = 4.6, 2.5 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.06 (dd, *J* = 7.8, 1.7 Hz, 1H), 4.20 (s, 2H), 3.69 (s, 2H), 2.35 (s, 3H); ¹⁹F NMR

(282 MHz, DMSO-*d*₆) δ -116.59; MS (ES⁺): 434.3 (M+1), MS (ES⁻): 432.3 (M+Cl); HPLC purity 97.76%.

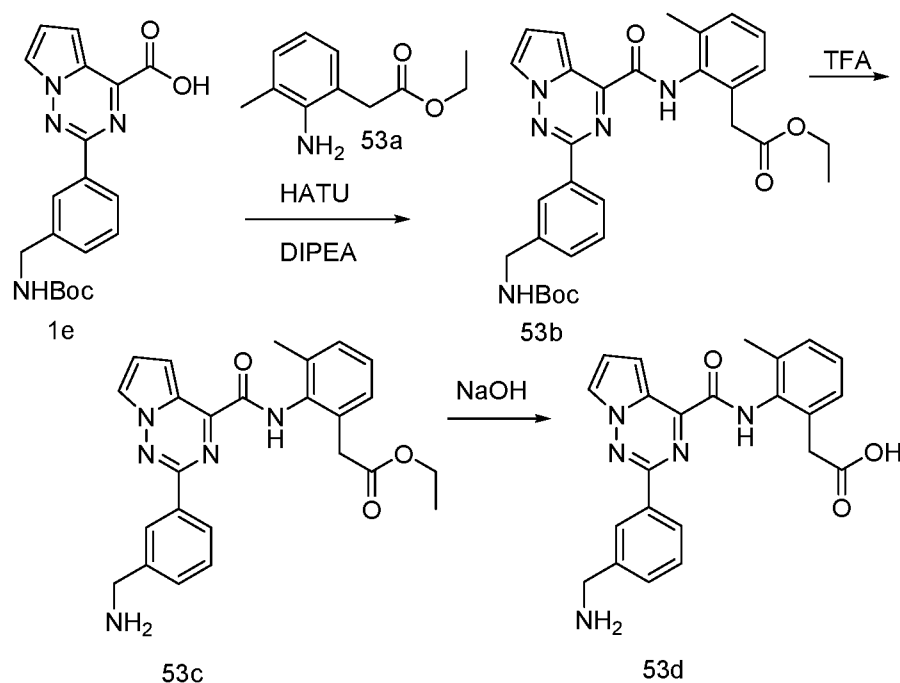
Scheme-52



Preparation of 2-(2-((4-(3-(aminomethyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)methoxy)phenyl)acetic acid (**52a**)

Compound **52a** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-((4-(3-(aminomethyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)methoxy)phenyl)acetate (**49e**) (0.04 g, 0.070 mmol) in THF (5 mL) using a solution of sodium hydroxide (0.028 g, 0.702 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((4-(3-(aminomethyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)methoxy)phenyl)acetic acid (**52a**) (0.012 g, 44 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.91 (s, 1H), 8.36 (s, 3H), 7.92 (s, 1H), 7.79 (dt, J = 6.9, 1.9 Hz, 1H), 7.59 (m, 3H), 7.42 (s, 1H), 7.22 (m, 2H), 7.08 (m, 1H), 6.90 (t, J = 7.3 Hz, 1H), 6.76 (m, 1H), 5.28 (s, 2H), 4.15 (d, J = 5.8 Hz, 2H), 3.63 (s, 2H); MS (ES⁺): 388.3 (M+1); MS (ES⁻): 386.4 (M-1), 422.3 (M+Cl). HPLC purity: 91.49%.

Scheme-53



Preparation of 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-3-methylphenyl)acetic acid (**53d**)

Step-1: Preparation of ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-3-methylphenyl)acetate (**53b**)

Compound **53b** was prepared according to the procedure reported in step-4 of Scheme-1 from 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**1e**) (0.18 g, 0.489 mmol) in DMF (3 mL) using ethyl 2-(2-amino-3-methylphenyl)acetate (**53a**) (113 mg, 0.586 mmol, CAS # 1261751-05-6), DIPEA (0.256 mL, 1.466 mmol) and HATU (223 mg, 0.586 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc in hexane] ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-3-methylphenyl)acetate (**53b**) (0.21 g, 79 % yield) as an orange colored foam; ^1H NMR (300 MHz, DMSO-*d*₆) δ 10.61 (s, 1H), 8.51 (d, *J* = 7.8 Hz, 1H), 8.40 (s, 1H), 8.37 - 8.32 (m, 1H), 7.56 - 7.47 (m, 3H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.32 - 7.20 (m, 4H), 4.26 (d, *J* = 6.2 Hz, 2H), 3.91 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 2H), 2.29 (s, 3H), 1.41 (s, 9H), 0.89 (t, *J* = 7.1 Hz, 3H).

Step-2: Preparation of ethyl 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-3-methylphenyl)acetate (**53c**)

Compound **53c** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-

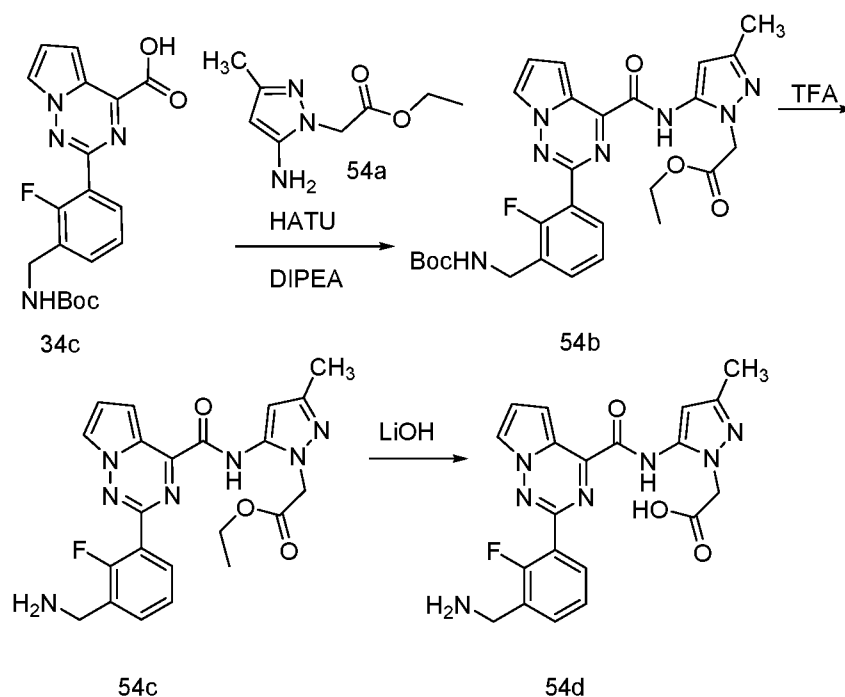
carboxamido)-3-methylphenyl)acetate (**53b**) (200 mg, 0.368 mmol) in DCM (5 mL) using TFA (0.283 mL, 3.68 mmol). This gave after workup and purification by reverse phase column chromatography [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-3-methylphenyl)acetate (**53c**) (0.035 g, 22 % yield) as a HCl salt; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.65 (s, 1H), 8.69 (d, *J* = 1.8 Hz, 1H), 8.67 - 8.60 (m, 1H), 8.47 (s, 4H), 8.36 (dt, *J* = 2.9, 1.5 Hz, 1H), 7.73 - 7.58 (m, 2H), 7.54 (dd, *J* = 4.6, 1.4 Hz, 1H), 7.32 - 7.22 (m, 3H), 4.23 - 4.10 (m, 2H), 3.95 - 3.84 (m, 2H), 3.74 (s, 2H), 2.29 (s, 3H), 0.93 - 0.84 (m, 3H).

Step-3: Preparation of 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-3-methylphenyl)acetic acid (**53d**)

Compound **53d** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-3-methylphenyl)acetate (**53c**)

(0.12 g, 0.271 mmol) in THF (4 mL) using sodium hydroxide (0.135 mL, 0.271 mmol, 2 M aqueous). This gave after workup and purification by reverse phase column [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(2-(3-(aminomethyl)phenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-3-methylphenyl)acetic acid (**53d**) (0.07 g, 0.168 mmol, 62.3 % yield) as a HCl salt; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.42 (s, 1H), 10.64 (s, 1H), 8.67 - 8.56 (m, 2H), 8.44 - 8.28 (m, 4H), 7.71 - 7.58 (m, 2H), 7.55 (dd, *J* = 4.6, 1.4 Hz, 1H), 7.31 - 7.23 (m, 4H), 4.23 - 4.13 (m, 2H), 3.68 (s, 2H), 2.29 (s, 3H). MS (ES⁺) 416.3 (M+1), MS (ES⁻) 414.4 (M-1); HPLC purity 98.00%.

Scheme-54



Preparation of 2-(5-(2-(3-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-3-methyl-1H-pyrazol-1-yl)acetic acid (**54d**)

Step-1: Preparation of ethyl 2-(5-(2-(3-((tert-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-3-methyl-1H-pyrazol-1-yl)acetate (**54b**)

Compound **54b** was prepared according to the procedure reported in step-4 of Scheme-1 from 2-(3-((tert-butoxycarbonyl)amino)methyl)-2-fluorophenylpyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**34c**) (150 mg, 0.388 mmol) in DMF (10 mL) using ethyl 2-(5-amino-3-methyl-1H-pyrazol-1-yl)acetate (**54a**) (75 mg, 0.388 mmol; CAS# 956440-82-7), DIPEA (0.203 mL, 1.165 mmol) and HATU (221 mg, 0.582 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DCM/methanol (1:0 to 19:1)] ethyl 2-(5-(2-(3-((tert-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-3-methyl-1H-pyrazol-1-yl)acetate (**54b**) (0.19 g, 89 % yield) as a brown solid; ^1H NMR (300 MHz, DMSO- d_6) δ 10.85 (s, 1H), 8.40 (s, 1H), 8.26 – 8.15 (m, 1H), 7.57 – 7.42 (m, 3H), 7.36 (t, $J = 7.7$ Hz, 1H), 7.32 – 7.24 (m, 1H), 6.29 (s, 1H), 5.01 (s, 2H), 4.28 (d, $J = 6.3$ Hz, 2H), 4.08 (q, $J = 7.1$ Hz, 2H), 2.17 (s, 3H), 1.40 (s, 9H), 1.11 (t, $J = 7.1$ Hz, 3H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -119.39; MS (ES+) 552.3 (M+1); (ES-) 550.4 (M-1).

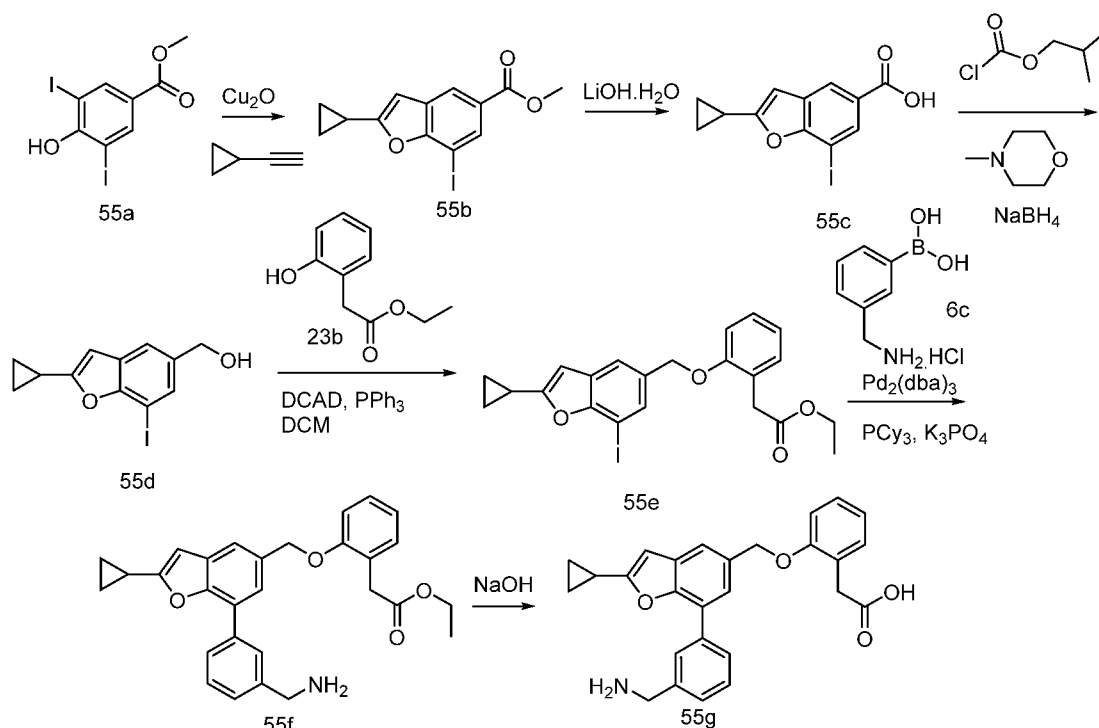
Step-2: Preparation of ethyl 2-(5-(2-(3-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-3-methyl-1H-pyrazol-1-yl)acetate (**54c**)

Compound **54c** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(5-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)-3-methyl-1H-pyrazol-1-yl)acetate (**54b**) (0.18 g, 0.326 mmol) in DCM (15 mL) using TFA (1.01 mL, 13.05 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DCM/methanol (1:0 to 9:1)] ethyl 2-(5-(2-(3-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)-3-methyl-1H-pyrazol-1-yl)acetate (**54c**) (0.14 g, 95 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.87 (s, 1H), 8.52 – 8.42 (m, 1H), 8.38 (d, *J* = 2.6 Hz, 1H), 8.29 (s, 3H), 7.77 – 7.67 (m, 1H), 7.52 – 7.44 (m, 2H), 7.32 (dd, *J* = 4.6, 2.6 Hz, 1H), 6.29 (s, 1H), 5.01 (s, 2H), 4.22 (s, 2H), 4.09 (q, *J* = 7.0 Hz, 2H), 2.18 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -116.54; MS (ES⁺): 452.3 (M+1), 474.3 (M+Na); MS (ES⁻): 450.4 (M-1).

Step-3: Preparation of 2-(5-(2-(3-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)-3-methyl-1H-pyrazol-1-yl)acetic acid (**54d**)

Compound **54d** was prepared according to the procedure reported in step-6 of Scheme-1 from ethyl 2-(5-(2-(3-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)-3-methyl-1H-pyrazol-1-yl)acetate (**54c**) (0.129 g, 0.286 mmol) in THF/MeOH (20 mL, 1:1) using lithium hydroxide hydrate (73.4 mg, 1.714 mmol) in water (10 mL). This gave after workup and purification by reverse phase column [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(5-(2-(3-(aminomethyl)-2-fluorophenyl)pyrrolo[2,1-*f*][1,2,4]triazine-4-carboxamido)-3-methyl-1H-pyrazol-1-yl)acetic acid (**54d**) (47 mg, 39% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.63 (s, 1H), 8.80 (s, 3H), 8.49 – 8.39 (m, 1H), 8.16 (t, *J* = 7.3 Hz, 1H), 7.71 (t, *J* = 7.0 Hz, 1H), 7.61 – 7.55 (m, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.32 (dd, *J* = 4.6, 2.6 Hz, 1H), 6.30 (s, 1H), 4.66 (s, 2H), 4.14 (s, 2H), 2.15 (s, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -115.10; MS (ES⁻): 422.4 (M-1).

Scheme-55



Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-cyclopropylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**55g**)

Step-1: Preparation of methyl 2-cyclopropyl-7-iodobenzofuran-5-carboxylate (**55b**)

To a solution of methyl 4-hydroxy-3,5-diiodobenzoate (**55a**) (3 g, 7.43 mmol, CAS # 3337-66-4) in pyridine (10 mL) was added ethynyl cyclopropane (0.49 g, 7.43 mmol, CAS# 6746-94-7) and copper(I) oxide (0.53 g, 3.71 mmol). The mixture was degassed, filled with Ar, stirred for 10 min at room temperature and heated at 125 °C for 3h in a sealed flask. The reaction was cooled to room temperature, diluted with EtOAc, washed with 1 N aqueous HCl (4 x 100mL), water and brine. The organic layer was dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-70%] to give methyl 2-cyclopropyl-7-iodobenzofuran-5-carboxylate (**55b**) (1.6 g, 63 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.12 (s, 2H), 6.85 (s, 1H), 2.24 – 2.14 (m, 1H), 1.11 – 1.03 (m, 2H), 0.97 – 0.90 (m, 2H); MS (ES⁺): 365.1 (M+Na); (ES⁻): 341.1 (M-1).

Step-2: Preparation of 2-cyclopropyl-7-iodobenzofuran-5-carboxylic acid (**55c**)

Compound **55c** was prepared according to the procedure reported in step-6 of Scheme-1, from methyl 2-cyclopropyl-7-iodobenzofuran-5-carboxylate (**55b**) (1.3 g, 3.80 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide hydrate (0.32 g, 7.60 mmol) in water (2 mL) This gave after workup 2-cyclopropyl-7-iodobenzofuran-5-carboxylic acid (**55c**) (1.19 g, 95 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 13.06 (s, 1H),

8.14 – 8.05 (m, 2H), 6.83 (s, 1H), 2.18 (m, 1H), 1.06 (dt, $J = 8.3, 3.1$ Hz, 2H), 0.97 – 0.87 (m, 2H).

Step-3: Preparation of (2-cyclopropyl-7-iodobenzofuran-5-yl)methanol (**55d**)

Compound **55d** was prepared according to the procedure reported in step-1 of Scheme-23 from 2-cyclopropyl-7-iodobenzofuran-5-carboxylic acid (**55c**) (1.16 g, 3.54 mmol) using N-methylmorpholine (0.47 mL, 4.2 mmol) in THF (50 mL), isobutyl chloroformate (0.56 mL, 4.24 mmol) and NaBH₄ (0.40 g, 10.61 mmol) in water (2.0 mL). This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-50%] (2-cyclopropyl-7-iodobenzofuran-5-yl)methanol (**55d**) (1.02 g, 92 % yield) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.52 (d, $J = 1.5$ Hz, 1H), 7.40 (d, $J = 1.4$ Hz, 1H), 6.68 (s, 1H), 5.25 (t, $J = 5.8$ Hz, 1H, D₂O exchangeable), 4.51 (d, $J = 5.8$ Hz, 2H), 2.19 – 2.07 (m, 1H), 1.09 – 0.98 (m, 2H), 0.93 – 0.85 (m, 2H); MS (ES⁺): 337.3 (M+Na).

Step-4: Preparation of ethyl 2-(2-((2-cyclopropyl-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**55e**)

Compound **55e** was prepared according to the procedure reported in step-2 of Scheme-23 from (2-cyclopropyl-7-iodobenzofuran-5-yl)methanol (**55d**) (850 mg, 2.71 mmol) in DCM (10 mL) using triphenylphosphine (781 mg, 2.98 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (536 mg, 2.98 mmol) and di-(4-chlorobenzyl)azodicarboxylate (DCAD, 1093 mg, 2.98 mmol). This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-50%] ethyl 2-(2-((2-cyclopropyl-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**55e**) (800 mg, 62 % yield) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.62 (d, $J = 1.5$ Hz, 1H), 7.52 (d, $J = 1.5$ Hz, 1H), 7.29 – 7.18 (m, 2H), 7.05 (d, $J = 8.1$ Hz, 1H), 6.91 (td, $J = 7.4, 1.0$ Hz, 1H), 6.72 (s, 1H), 5.11 (s, 2H), 4.03 (q, $J = 7.1$ Hz, 2H), 3.61 (s, 2H), 2.23 – 2.05 (m, 1H), 1.14 – 0.98 (m, 5H), 0.96 – 0.83 (m, 3H); MS (ES⁺): 499.1 (M+Na); (ES⁻): 475.3 (M-1).

Step-5: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-cyclopropylbenzofuran-5-yl)methoxy)phenyl)acetate (**55f**)

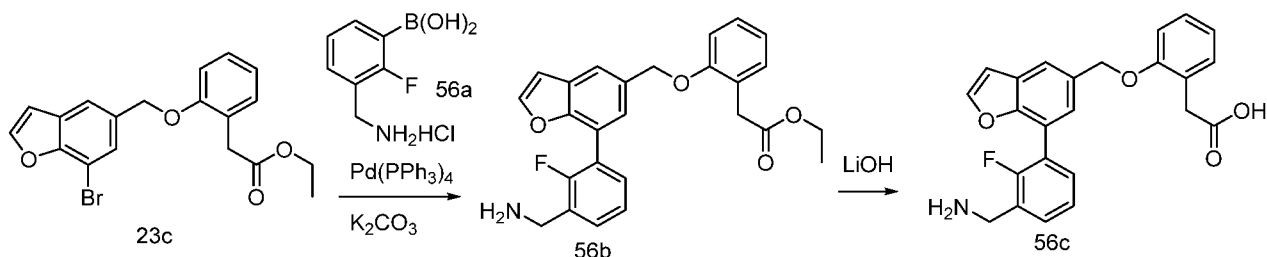
Compound **55f** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((2-cyclopropyl-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**55e**) (250 mg, 0.53 mmol) in dioxane (3 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (148 mg, 0.787 mmol), tripotassium phosphate (3 M aqueous solution, 0.30 mL, 0.89 mmol), tricyclohexylphosphine (44.2 mg, 0.16 mmol) and Pd₂(dba)₃ (48 mg, 0.052 mmol) under an Ar atmosphere and heating at 125 °C for 45 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1,

v/v) in hexane from 0-70%] ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-cyclopropylbenzofuran-5-yl)methoxy)phenyl)acetate (**55f**) (120 mg, 32% yield) as a free base. 70 mg of free base was further purified by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] to afford ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-cyclopropylbenzofuran-5-yl)methoxy)phenyl)acetate (**55f**) (25 mg, 30% yield) HCl salt as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.44 (s, 3H, D_2O exchangeable), 7.95 (s, 1H), 7.92 – 7.83 (m, 1H), 7.66 – 7.45 (m, 5H), 7.32 – 7.17 (m, 2H), 7.15 – 7.06 (m, 1H), 6.97 – 6.86 (m, 1H), 6.67 (s, 1H), 5.20 (s, 2H), 4.12 (s, 2H), 3.94 (q, $J = 7.1$ Hz, 2H), 3.62 (s, 2H), 2.22 – 2.09 (m, 1H), 1.07 – 0.96 (m, 5H), 0.96 – 0.90 (m, 2H); MS (ES⁺): 456.3 (M+1); (ES⁻): 490.3 (M+Cl).

Step-6: Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-cyclopropylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**55g**)

Compound **55g** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-cyclopropylbenzofuran-5-yl)methoxy)phenyl)acetate (**55f**) (50 mg, 0.11 mmol) in MeOH/THF (3 mL) using a solution of sodium hydroxide (21.9 mg, 0.55 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)phenyl)-2-cyclopropylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**55g**) (21 mg, 45 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.27 (s, 1H, D_2O exchangeable), 8.43 (s, 2H, D_2O exchangeable), 7.95 (d, $J = 1.6$ Hz, 1H), 7.90 (dt, $J = 7.5, 1.6$ Hz, 1H), 7.63 – 7.49 (m, 4H), 7.29 – 7.17 (m, 2H), 7.08 (d, $J = 8.1$ Hz, 1H), 6.94 – 6.85 (m, 1H), 6.66 (s, 1H), 5.23 (s, 2H), 4.13 (s, 2H), 3.59 (s, 2H), 2.22 – 2.12 (m, 1H), 1.10 – 0.97 (m, 2H), 0.97 – 0.88 (m, 2H); MS (ES⁺): 428.3 (M+1); 450.4 (M+Na); (ES⁻): 426.4 (M-1), 462.3 (M+Cl).

Scheme-56



Preparation of 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**56c**)

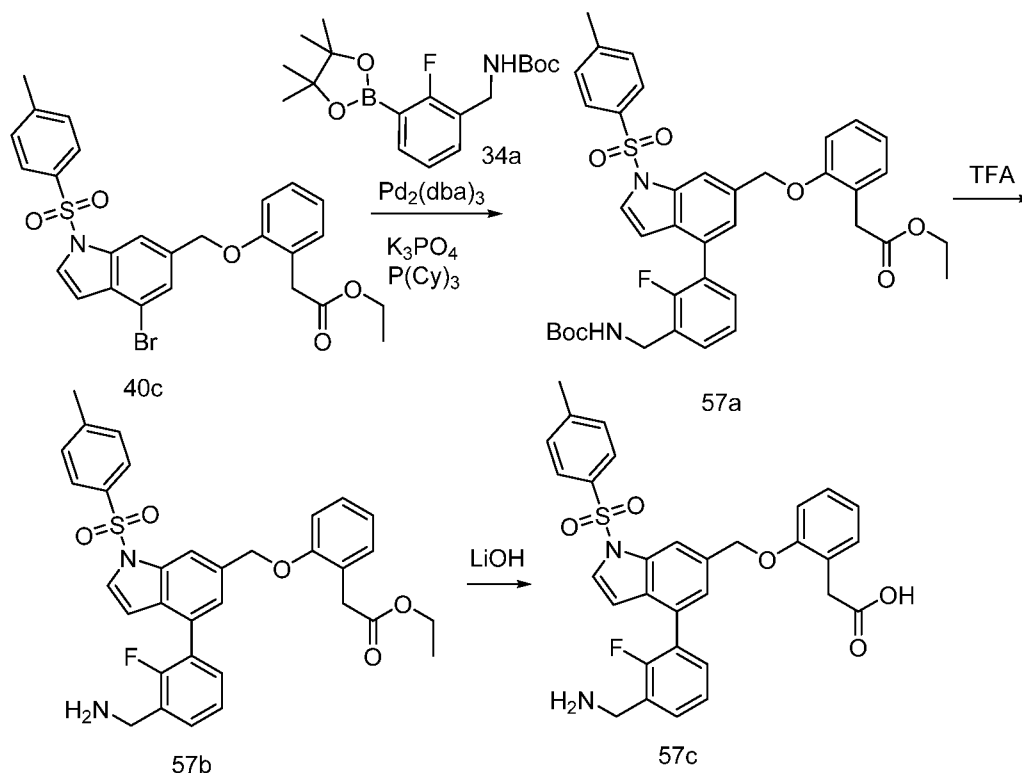
Step-1: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**56b**)

Compound **56b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-bromobenzofuran-5-yl)methoxy)phenyl)acetate (**23c**) (250 mg, 0.64 mmol) in dioxane (3 mL) using (3-(aminomethyl)-2-fluorophenyl)boronic acid hydrochloride (**56a**) (198 mg, 0.96 mmol; CAS# 1072946-44-1), tetrakis(triphenylphosphine)palladium(0) (148 mg, 0.128 mmol), potassium carbonate (266 mg, 1.93 mmol) in water (1 mL) under an Ar atmosphere and heating at 150 °C for 55 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1, v/v) in hexane from 0-100%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**56b**) (125 mg, 45% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.52 (s, 3H, D₂O exchangeable), 8.06 (d, *J* = 2.2 Hz, 1H), 7.79 (d, *J* = 1.6 Hz, 1H), 7.74 – 7.62 (m, 2H), 7.46 – 7.39 (m, 2H), 7.30 – 7.19 (m, 2H), 7.11 (d, *J* = 8.2 Hz, 1H), 7.08 (d, *J* = 2.2 Hz, 1H), 6.91 (td, *J* = 7.4, 1.0 Hz, 1H), 5.24 (s, 2H), 4.17 (s, 2H), 3.92 (q, *J* = 7.1 Hz, 2H), 3.62 (s, 2H), 0.99 (t, *J* = 7.1 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -118.52; MS (ES⁺): 434.3 (M+1).

Step-2: Preparation of 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**56c**)

Compound **56c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**56b**) (65 mg, 0.15 mmol) in MeOH/THF (3 mL) using a solution of lithium hydroxide hydrate (25.2 mg, 0.60 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**56c**) (26 mg, 43% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.13 – 8.08 (m, 1H, D₂O exchangeable), 8.06 (d, *J* = 2.2 Hz, 1H), 7.83 (d, *J* = 1.6 Hz, 1H), 7.73 – 7.61 (m, 2H), 7.50 – 7.39 (m, 2H), 7.28 – 7.18 (m, 2H), 7.12 – 7.02 (m, 2H), 6.90 (t, *J* = 7.4 Hz, 1H), 5.26 (s, 2H), 4.18 (s, 2H), 3.58 (s, 2H); MS (ES⁺): 406.3 (M+1); 428.3 (M+Na); (ES⁻): 404.4 (M-1), 440.3 (M+Cl).

Scheme-57



Preparation of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**57c**)

Step-1: Preparation of ethyl 2-(2-((4-(3-((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetate (**57a**)

Compound **57a** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((4-bromo-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetate (**40c**) (500 mg, 0.92 mmol) in dioxane (5 mL) using *tert*-butyl 2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylcarbamate (**34a**) (0.49 g, 1.38 mmol), 3 M aqueous solution of tripotassium phosphate (0.52 mL, 1.57 mmol), tricyclohexylphosphine (78 mg, 0.277 mmol) and $\text{Pd}_2(\text{dba})_3$ (80 mg, 0.09 mmol) in argon atmosphere and heating at 125 °C for 60 min in a microwave. This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-70%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((4-(3-((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetate (**57a**) (0.36 g, 57 % yield) as a white solid; MS (ES⁺): 709.4 (M+Na), MS (ES⁻): 685.4 (M-1), 721.5 (M+Cl).

Step-2: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetate (**57b**)

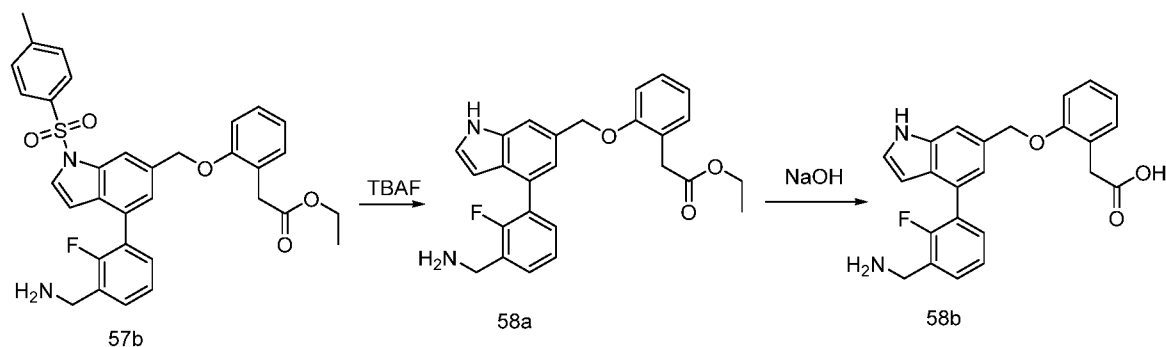
Compound **57b** was prepared according to the procedure reported in step-5 of Scheme-1 from

ethyl ethyl 2-(2-((4-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetate (**57a**) (0.35 g, 0.51 mmol) in DCM (5 mL) using TFA (0.39 mL, 5.1 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetate (**57b**) (0.15 g, 50 % yield) as a yellow solid; MS (ES⁺): 587.3 (M+1), MS (ES⁻): 621.4 (M+Cl).

Step-3: Preparation of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**57c**)

Compound **57c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetate (**57b**) (100 mg, 0.17 mmol) in MeOH/THF (10 mL, 1:1) using a solution of lithium hydroxide hydrate (40 mg, 1.02 mmol) in water (2 mL). This gave after workup 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**57c**) (0.02 g, 16 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.58 (s, 3H), 8.13 (m, 2H), 8.00 – 7.86 (m, 3H), 7.71 – 7.62 (m, 1H), 7.52 (m, 1H), 7.45 – 7.33 (m, 4H), 7.23 (m, 1H), 7.07 (m, 1H), 6.93 (t, J = 7.4 Hz, 1H), 6.82 – 6.68 (m, 1H), 5.34 (s, 2H), 4.11 (q, J = 5.9 Hz, 2H), 3.63 (s, 2H), 2.32 (s, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -118.79; MS (ES⁺): 559.2 (M+1), 581.3 (M+Na); MS (ES⁻): 557.4 (M-1).

Scheme-58



Preparation of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1H-indol-6-yl)methoxy)phenyl)acetic acid (**58b**)

Step-1: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1H-indol-6-yl)methoxy)phenyl)acetate (**58a**)

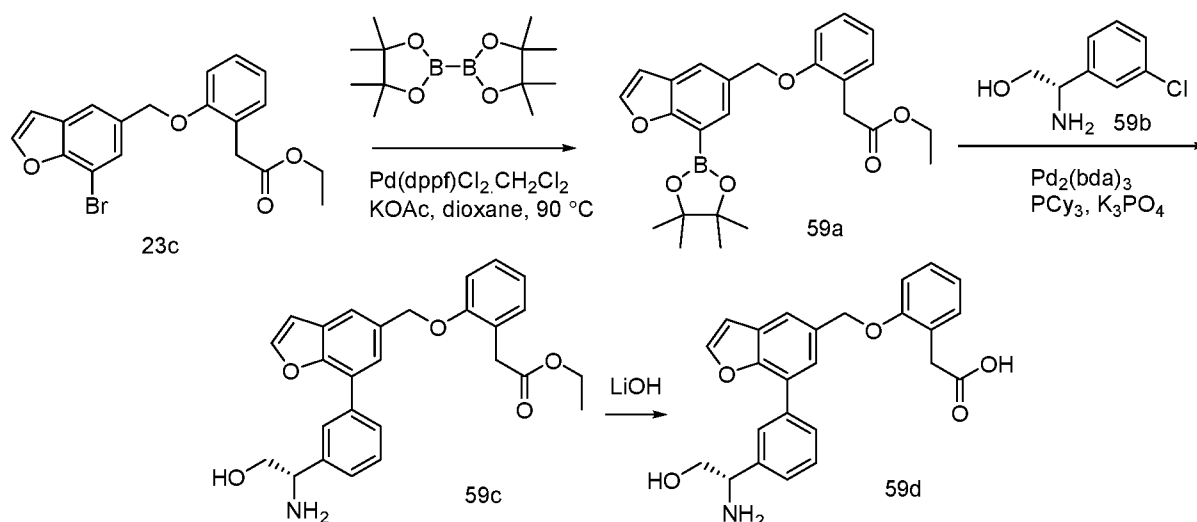
To a solution of ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-tosyl-1H-indol-6-yl)methoxy)phenyl)acetate (**57b**) (0.31 g, 0.53 mmol) in THF (5 mL) was added

tetrabutylammonium fluoride (1.38 g, 5.28 mmol). The mixture was heated at 90 °C in THF for 6 h cooled to room temperature, diluted with EtOAc (60 mL), washed with water (3x), brine, dried and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc/MeOH (9:1) in hexane from 0-100%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] to give ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1H-indol-6-yl)methoxy)phenyl)acetate (**58a**) (0.12 g, 53 % yield) as a purple solid; ^1H NMR (300 MHz, DMSO- d_6) δ 11.39 (s, 1H), 8.52 (bs, 3H), 7.61 (m, 2H), 7.53 (s, 1H), 7.42 (m, 1H), 7.37 (m, 1H), 7.30 – 7.17 (m, 2H), 7.13 (m, 2H), 6.90 (t, J = 7.3 Hz, 1H), 6.36 (t, J = 2.6 Hz, 1H), 5.22 (s, 2H), 4.15 (d, J = 5.5 Hz, 2H), 3.91 (q, J = 7.1 Hz, 2H), 3.60 (s, 2H), 0.97 (t, J = 7.1 Hz, 3H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -118.80; MS (ES $^+$): 433.3 (M+1), 455.3 (M+Na); MS (ES $^-$): 467.3 (M+Cl). HPLC purity: 92.85 %.

Step-2: Preparation of Preparation of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1H-indol-6-yl)methoxy)phenyl)acetic acid (**58b**)

Compound **58b** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1H-indol-6-yl)methoxy)phenyl)acetate (**58a**) (30 mg, 0.07 mmol) in MeOH/THF (5 mL, 1:1) using a solution of sodium hydroxide (10 mg, 0.28 mmol) in water (2 mL). This gave after workup and purification by flash column chromatography [silica (4 g), eluting with DMA80 in DCM from 0-100%] 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1H-indol-6-yl)methoxy)phenyl)acetic acid (**58b**) (0.01 g, 43 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 12.1082 (bs, 1 H); 11.31 (s, 1H), 8.34 (s, 3H), 7.65 – 7.57 (m, 2H), 7.56 (s, 1H), 7.50 – 7.33 (m, 2H), 7.21 (m, 2H), 7.18 – 7.07 (m, 2H), 6.89 (t, J = 7.3 Hz, 1H), 6.35 (s, 1H), 5.24 (s, 2H), 4.17 (s, 2H), 3.57 (s, 2H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -118.65; MS (ES $^+$) 405.3 (M+1), 427.2 (M+Na); MS (ES $^-$): 439.3 (M+Cl). HPLC purity: 94.55%.

Scheme-59



Preparation of (S)-2-(2-((7-(3-(1-amino-2-hydroxyethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**59d**)

Step-1: Preparation of ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**)

To a degassed solution of ethyl 2-(2-((7-bromobenzofuran-5-yl)methoxy)phenyl)acetate (**23c**) (8.9 g, 22.87 mmol), bis(pinacolato)diboron (8.71 g, 34.3 mmol, CAS#: 73183-34-3) and potassium acetate (6.73 g, 68.6 mmol) in anhydrous dioxane (150 mL) was added Pd(dppf)Cl₂·CH₂Cl₂ (1.87 g, 2.29 mmol). The resulting mixture was degassed, filled with Ar and stirred at 90 °C overnight. The reaction mixture was then diluted with EtOAc (400 mL) and washed with water (100 mL). The aqueous layer was re-extracted with EtOAc (100 mL x 2). The organic layers were combined washed with water (100 mL), brine (100 mL), dried and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica (80 g), eluting with EtOAc in hexane from 0-40%] to give ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (9 g, 90 % yield) as an off white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.05 (d, *J* = 2.2 Hz, 1H), 7.84 (d, *J* = 1.8 Hz, 1H), 7.65 (d, *J* = 1.8 Hz, 1H), 7.34 – 7.17 (m, 2H), 7.10 (d, *J* = 8.1 Hz, 1H), 6.98 – 6.87 (m, 2H), 5.17 (s, 2H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.59 (s, 2H), 1.34 (s, 12H), 1.05 (t, *J* = 7.1 Hz, 3H).

Step-2: Preparation of (S)-ethyl 2-(2-((7-(3-(1-amino-2-hydroxyethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**59c**)

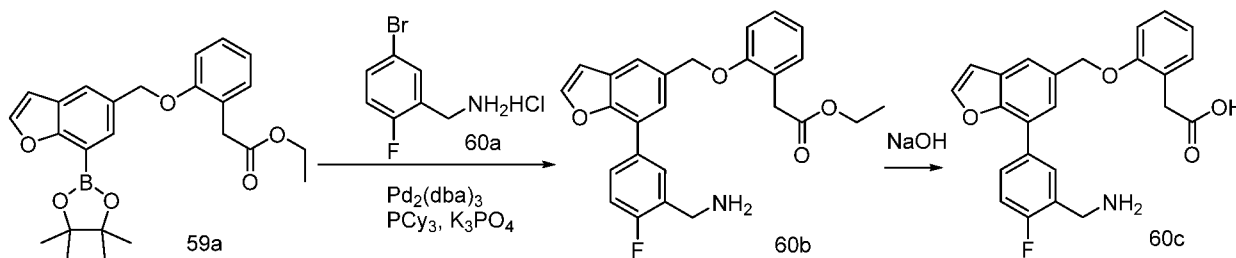
Compound **59c** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (450 mg, 1.03 mmol) in dioxane (6 mL) using (S)-2-amino-2-(3-chlorophenyl)ethanol (**59b**) (301 mg, 1.75 mmol; CAS# 663611-73-2), tripotassium

phosphate (3M aqueous, 0.58 mL, 1.75 mmol), tricyclohexylphosphine (87 mg, 0.31 mmol) and $\text{Pd}_2(\text{dba})_3$ (94 mg, 0.10 mmol) under an Ar atmosphere and heating at 125 °C for 60 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), DMA80 in DCM from 0-70%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] (S)-ethyl 2-(2-((7-(3-(1-amino-2-hydroxyethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**59c**) (253 mg, 55% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.74 (s, 3H, D_2O exchangeable), 8.13 (d, $J = 2.2$ Hz, 1H), 8.03 (d, $J = 2.0$ Hz, 1H), 7.93 (dt, $J = 6.9, 1.8$ Hz, 1H), 7.74 (d, $J = 1.6$ Hz, 1H), 7.70 – 7.54 (m, 3H), 7.34 – 7.19 (m, 2H), 7.13 (d, $J = 8.1$ Hz, 1H), 7.08 (d, $J = 2.2$ Hz, 1H), 6.97 – 6.87 (m, 1H), 5.66 (t, $J = 5.0$ Hz, 1H, D_2O exchangeable), 5.26 (s, 2H), 4.38 (t, $J = 6.0$ Hz, 1H), 3.94 (q, $J = 7.1$ Hz, 2H), 3.83 (t, $J = 5.6$ Hz, 2H), 3.64 (s, 2H), 0.99 (t, $J = 7.1$ Hz, 3H); MS (ES⁺): 446.3 (M+1); 468.4 (M+Na); (ES⁻): 480.3 (M+Cl).

Step-3: Preparation of (S)-2-(2-((7-(3-(1-amino-2-hydroxyethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**59d**)

Compound **59d** was prepared according to the procedure reported in step-6 of Scheme-1, from (S)-ethyl 2-(2-((7-(3-(1-amino-2-hydroxyethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**59c**) (96 mg, 0.22 mmol) in MeOH/THF (5 mL) using a solution of lithium hydroxide hydrate (36 mg, 0.86 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] (S)-2-(2-((7-(3-(1-amino-2-hydroxyethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**59d**) (65 mg, 72 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.25 (s, 1H, D_2O exchangeable), 8.59 (s, 3H, D_2O exchangeable), 8.11 (d, $J = 2.2$ Hz, 1H), 8.00 (d, $J = 1.8$ Hz, 1H), 7.97 – 7.87 (m, 1H), 7.77 (d, $J = 1.5$ Hz, 1H), 7.66 (d, $J = 1.6$ Hz, 1H), 7.64 – 7.54 (m, 2H), 7.28 – 7.20 (m, 2H), 7.14 – 7.03 (m, 2H), 6.97 – 6.78 (m, 1H), 5.62 (bs, 1H, D_2O exchangeable), 5.28 (s, 2H), 4.46 – 4.33 (m, 1H), 3.86 – 3.73 (m, 2H), 3.60 (s, 2H); MS (ES⁺): 418.3 (M+1); 440.3 (M+Na); (ES⁻): 416.4 (M-1), 452.3 (M+Cl).

Scheme-60



Preparation of 2-(2-((7-(3-(aminomethyl)-4-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**60c**)

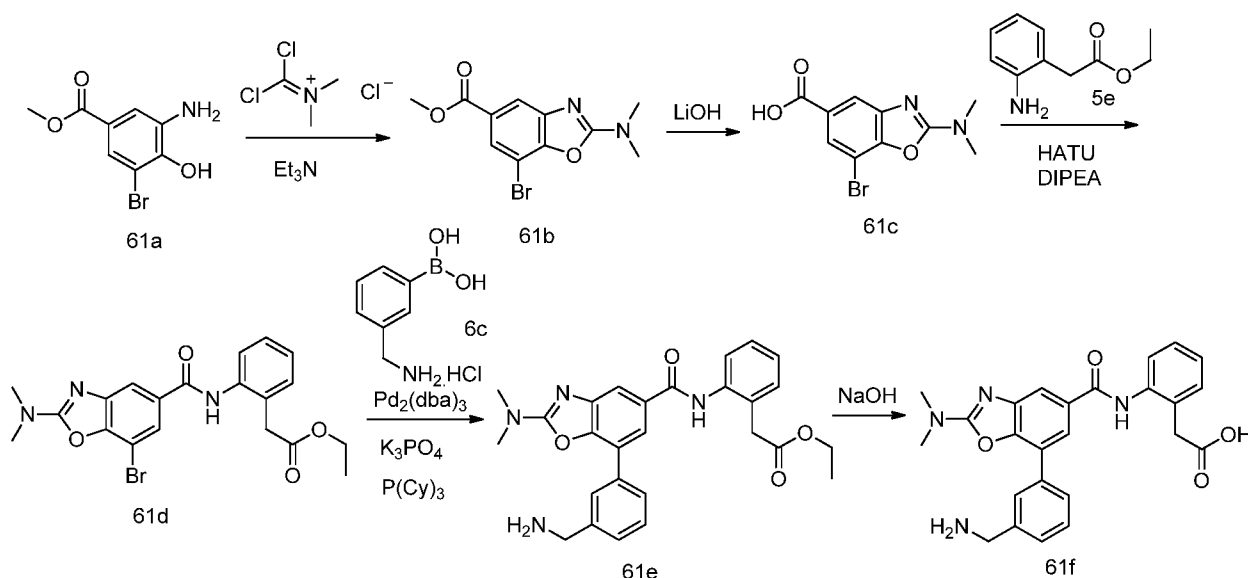
Step-1: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)-4-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**60b**)

Compound **60b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (300 mg, 0.69 mmol) in dioxane (3 mL) using (5-bromo-2-fluorophenyl)methanamine hydrochloride (**60a**) (248 mg, 1.03 mmol, CAS# 202865-69-8), tripotassium phosphate (3M aqueous, 0.85 mL, 2.54 mmol), tricyclohexylphosphine (58 mg, 0.21 mmol) and Pd₂(dba)₃ (63 mg, 0.069 mmol) under an Ar atmosphere and heating at 125 °C for 90 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), EtOAc in hexane from 0-70%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(3-(aminomethyl)-4-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**60b**) (165 mg, 55 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.54 (s, 3H, D₂O exchangeable), 8.16 – 8.07 (m, 2H), 8.03 – 7.92 (m, 1H), 7.76 – 7.70 (m, 1H), 7.65 – 7.58 (m, 1H), 7.52 – 7.41 (m, 1H), 7.30 – 7.19 (m, 2H), 7.15 – 7.05 (m, 2H), 6.96 – 6.87 (m, 1H), 5.24 (s, 2H), 4.16 (s, 2H), 3.94 (q, *J* = 7.1 Hz, 2H), 3.63 (s, 2H), 0.99 (t, *J* = 7.1 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -117.93; MS (ES⁺): 434.3 (M+1); 476.4 (M+Na); (ES⁻): 468.3 (M+Cl).

Step-2: Preparation of 2-(2-((7-(3-(aminomethyl)-4-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**60c**)

Compound **60c** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-((7-(3-(aminomethyl)-4-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**60b**) (65 mg, 0.15 mmol) in MeOH/THF (3 mL) using a solution of sodium hydroxide (24 mg, 0.6 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)-4-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**60c**) (36 mg, 59% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.61 (s, 3H, D₂O exchangeable), 8.18 – 8.10 (m, 2H), 8.05 – 7.96 (m, 1H), 7.77 (d, *J* = 1.5 Hz, 1H), 7.66 (d, *J* = 1.6 Hz, 1H), 7.52 – 7.41 (m, 1H), 7.29 – 7.19 (m, 2H), 7.14 – 7.05 (m, 2H), 6.96 – 6.87 (m, 1H), 5.27 (s, 2H), 4.17 (s, 2H), 3.60 (s, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -118.03; MS (ES⁺): 406.3 (M+1); (ES⁻): 404.3 (M-1); 440.3 (M+Cl).

Scheme-61



Preparation of 2-(2-(7-(3-(aminomethyl)phenyl)-2-(dimethylamino)benzo[d]oxazole-5-carboxamido)phenyl)acetic acid (**61f**)

Step-1: Preparation of methyl 7-bromo-2-(dimethylamino)benzo[d]oxazole-5-carboxylate (**61b**)

To a solution of methyl 3-amino-5-bromo-4-hydroxybenzoate (**61a**) (0.2 g, 0.81 mmol; CAS# 260249-10-3) in DCM (10 mL) was added N-(dichloromethylene)-N-methylmethanaminium chloride (0.26 g, 1.63 mmol) and triethylamine (0.34 mL, 2.44 mmol). The reaction mixture was heated reflux for 2 h, cooled to room temperature and concentrated in vacuum. The residue obtained was dissolved in EtOAc, washed with water, dried and concentrated. The residue obtained was purified by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] to give methyl 7-bromo-2-(dimethylamino)benzo[d]oxazole-5-carboxylate (**61b**) (0.22 g, 90 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 7.72 (d, J = 1.5 Hz, 1H), 7.70 (d, J = 1.5 Hz, 1H), 3.85 (s, 3H), 3.15 (s, 6H); MS (ES $^+$): 299.1 & 301.1 (M+1).

Step-2: Preparation of 7-bromo-2-(dimethylamino)benzo[d]oxazole-5-carboxylic acid (**61c**)

Compound **61c** was prepared according to the procedure reported in step-6 of Scheme-1, from methyl 7-bromo-2-(dimethylamino)benzo[d]oxazole-5-carboxylate (**61b**) (220 mg, 0.735 mmol) in MeOH (10 mL) using a solution of lithium hydroxide hydrate (0.185 g, 4.41 mmol) in water (2 mL). This gave after workup 7-bromo-2-(dimethylamino)benzo[d]oxazole-5-carboxylic acid (**61c**) (0.18 g, 86 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 13.14 (s, 1H), 7.73 (d, J = 1.5 Hz, 1H), 7.71 (d, J = 1.5 Hz, 1H), 3.16 (s, 6H); MS (ES $^-$): 283.1 (M-1).

Step-3: Preparation of ethyl 2-(2-(7-bromo-2-(dimethylamino)benzo[d]oxazole-5-carboxamido)phenyl)acetate (**61d**)

Compound **61d** was prepared according to the procedure reported in step-4 of Scheme-1 from 7-bromo-2-(dimethylamino)benzo[d]oxazole-5-carboxylic acid (**61c**) (180 mg, 0.76 mmol) in DMF (5 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (0.14 g, 0.76 mmol), HATU (0.29 g, 0.76 mmol) and DIPEA (0.22 mL, 1.26 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] ethyl 2-(2-(7-bromo-2-(dimethylamino)benzo[d]oxazole-5-carboxamido)phenyl)acetate (**61d**) (0.17 g, 60 % yield) as a white solid; MS (ES⁻): 444.3 & 446.2 (M-1), 482.2 & 484.1 (M+Cl).

Step-4: Preparation of ethyl 2-(2-(7-(3-(aminomethyl)phenyl)-2-(dimethylamino)benzo[d]oxazole-5-carboxamido)phenyl)acetate (**61e**)

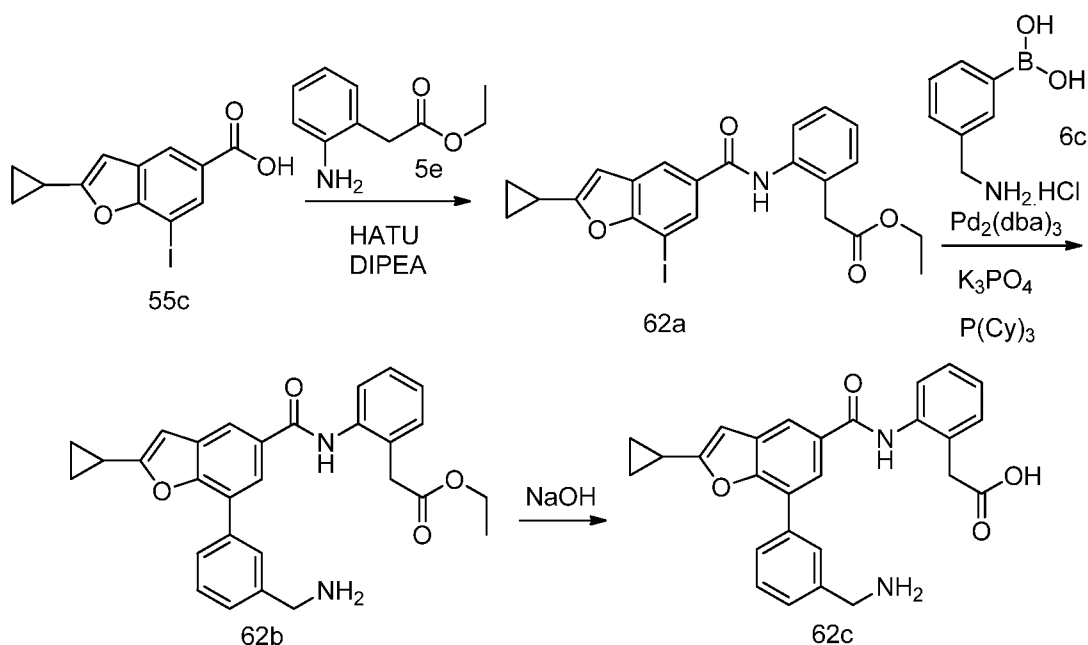
Compound **61e** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(7-bromo-2-(dimethylamino)benzo[d]oxazole-5-carboxamido)phenyl)acetate (**61d**) (90 mg, 0.2 mmol) in dioxane (3 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (60 mg, 0.3 mmol), tripotassium phosphate (3M aqueous, 0.2 mL, 0.61 mmol), tricyclohexylphosphine (20 mg, 0.06 mmol) and Pd₂(dba)₃ (20 mg, 0.06 mmol) under an Ar atmosphere and heating at 125 °C for 90 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-60%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(7-(3-(aminomethyl)phenyl)-2-(dimethylamino)benzo[d]oxazole-5-carboxamido)phenyl)acetate (**61e**) (0.03 g, 30 % yield) as a white solid; MS (ES⁺): 473.3 (M+1), MS (ES⁻): 471.4 (M-1).

Step-5: Preparation of 2-(2-(7-(3-(aminomethyl)phenyl)-2-(dimethylamino)benzo[d]oxazole-5-carboxamido)phenyl)acetic acid (**61f**)

Compound **61f** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-(7-(3-(aminomethyl)phenyl)-2-(dimethylamino)benzo[d]oxazole-5-carboxamido)phenyl)acetate (**61e**) (20 mg, 0.04 mmol) in MeOH (5 mL) using a solution of sodium hydroxide (7 mg, 0.17 mmol) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(7-(3-(aminomethyl)phenyl)-2-(dimethylamino)benzo[d]oxazole-5-carboxamido)phenyl)acetic acid (**61f**) (0.01 g, 59 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.12 (s, 1H), 8.60 (s, 3H), 8.08 (s, 1H), 7.99 (d, J = 1.6 Hz, 1H), 7.94 (dd, J = 5.3, 2.8 Hz, 1H), 7.85 (d, J = 1.5 Hz, 1H), 7.60 (m, 2H), 7.49 (d, J = 7.7 Hz, 1H), 7.38 – 7.28 (m, 2H), 7.22 (m, 1H), 4.14 (q, J = 5.8 Hz, 2H),

3.71 (s, 2H), 3.21 (s, 6H); MS (ES⁺): 445.3 (M+1), 467.3 (M+Na); MS (ES⁻): 443.3 (M-1), 439.3 (M+Cl). HPLC purity: 98.13%.

Scheme-62



Preparation of 2-(2-(7-(3-(aminomethyl)phenyl)-2-cyclopropylbenzofuran-5-carboxamido)phenyl)acetic acid (**62c**)

Step-1: Preparation of ethyl 2-(2-(2-cyclopropyl-7-iodobenzofuran-5-carboxamido)phenyl)acetate (**62a**)

Compound **62a** was prepared according to the procedure reported in step-4 of Scheme-1 from 2-cyclopropyl-7-iodobenzofuran-5-carboxylic acid (**55c**) (185 mg, 0.56 mmol) in DMF (10 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (121 mg, 0.68 mmol), HATU (257 mg, 0.68 mmol) and DIPEA (0.20 mL, 1.13 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] ethyl 2-(2-(2-cyclopropyl-7-iodobenzofuran-5-carboxamido)phenyl)acetate (**62a**) (145 mg, 53 % yield) as a semisolid; MS (ES⁺): 490.2 (M+1); 512.2 (M+Na); (ES⁻): 488.2 (M-1).

Step-2: Preparation of ethyl 2-(2-(7-(3-(aminomethyl)phenyl)-2-cyclopropylbenzofuran-5-carboxamido)phenyl)acetate (**62b**)

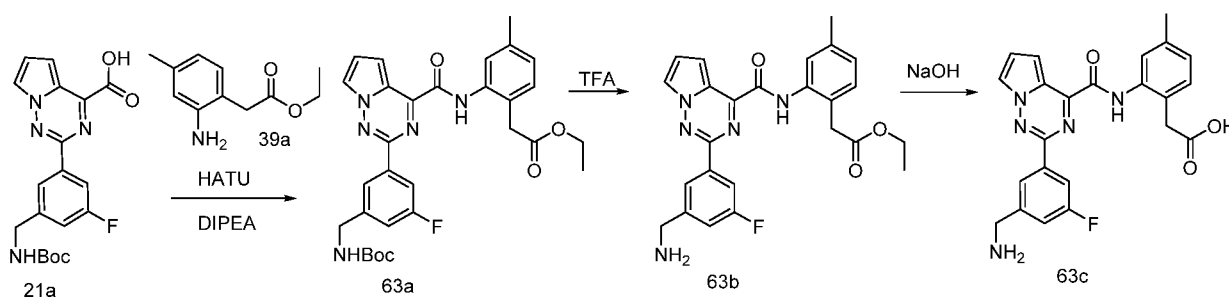
Compound **62b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(2-cyclopropyl-7-iodobenzofuran-5-carboxamido)phenyl)acetate (**62a**) (160 mg, 0.33 mmol) in dioxane (3 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (92 mg, 0.49 mmol), tripotassium phosphate (3M aqueous, 0.40 mL, 1.21 mmol), tricyclohexylphosphine (28 mg, 0.098 mmol) and Pd₂(dba)₃ (30 mg, 0.033 mmol) under an Ar atmosphere and heating at 125 °C for 60 min in a microwave. This gave after workup,

purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-70%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(7-(3-(aminomethyl)phenyl)-2-cyclopropylbenzofuran-5-carboxamido)phenyl)acetate (**62b**) (86 mg, 56 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.12 (s, 1H, D_2O exchangeable), 8.44 (s, 3H, D_2O exchangeable), 8.15 – 8.11 (m, 1H), 8.11 – 8.07 (m, 1H), 8.04 (s, 1H), 7.99 – 7.92 (m, 1H), 7.68 – 7.52 (m, 2H), 7.44 – 7.38 (m, 1H), 7.38 – 7.30 (m, 2H), 7.29 – 7.21 (m, 1H), 6.82 (s, 1H), 4.15 (s, 2H), 3.95 (q, $J = 7.1$ Hz, 2H), 3.78 (s, 2H), 2.28 – 2.16 (m, 1H), 1.12 – 1.03 (m, 2H), 1.03 – 0.93 (m, 5H); MS (ES⁺): 469.3 (M+1); (ES⁻): 503.4 (M+Cl).

Step-3: Preparation of 2-(2-(7-(3-(aminomethyl)phenyl)-2-cyclopropylbenzofuran-5-carboxamido)phenyl)acetic acid (**62c**)

Compound **62c** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-(7-(3-(aminomethyl)phenyl)-2-cyclopropylbenzofuran-5-carboxamido)phenyl)acetate (**62b**) (53 mg, 0.11 mmol) in MeOH/THF (3 mL) using a solution of sodium hydroxide (18 mg, 0.45 mmol) in water (1 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(7-(3-(aminomethyl)phenyl)-2-cyclopropylbenzofuran-5-carboxamido)phenyl)acetic acid (**62c**) (15 mg, 31 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.37 (s, 1H, D_2O exchangeable), 10.17 (s, 1H, D_2O exchangeable), 8.41 (s, 3H, D_2O exchangeable), 8.14 (d, $J = 1.7$ Hz, 1H), 8.08 (d, $J = 1.8$ Hz, 1H), 8.05 – 8.00 (m, 1H), 8.00 – 7.92 (m, 1H), 7.67 – 7.52 (m, 2H), 7.51 – 7.44 (m, 1H), 7.37 – 7.28 (m, 2H), 7.22 (td, $J = 7.4, 1.4$ Hz, 1H), 6.81 (s, 1H), 4.15 (s, 2H), 3.69 (s, 2H), 2.28 – 2.13 (m, 1H), 1.11 – 1.01 (m, 2H), 1.01 – 0.92 (m, 2H); MS (ES⁺): 441.3 (M+1); 463.3 (M+Na); (ES⁻): 439.4 (M-1); HPLC purity: 98.99%.

Scheme-63



Preparation of 2-(2-(2-(3-(aminomethyl)-5-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetic acid (**63c**)

Step-1: Preparation of ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetate (**63a**)

Compound **63a** was prepared according to the procedure reported in step-4 of Scheme-1 from 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxylic acid (**21a**) (0.15 g, 0.388 mmol) in DMF (3 mL) using ethyl 2-(2-amino-4-methylphenyl)acetate (**39a**) (90 mg, 0.466 mmol), DIPEA (0.20 mL, 1.165 mmol) and HATU (0.177 g, 0.466 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc in hexane] ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetate (**63a**) (0.17 g, 78 % yield) as an orange colored foam; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.85 (s, 1H), 8.37 (d, *J* = 2.6 Hz, 1H), 8.33 (d, *J* = 10.3 Hz, 1H), 8.19 (s, 1H), 7.62 – 7.54 (m, 3H), 7.33 – 7.19 (m, 3H), 7.13 – 7.06 (m, 1H), 4.27 (d, *J* = 6.2 Hz, 2H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 2H), 2.36 (s, 3H), 1.42 (s, 9H), 1.00 (t, *J* = 7.1 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -113.24; MS (ES⁺): 562.4 (M+1), 584.3 (M+Na), (ES⁻): 560.5 (M-1).

Step-2: Preparation of ethyl 2-(2-(2-(3-(aminomethyl)-5-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetate (**63b**)

Compound **63b** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetate (**63a**) (0.17 g, 0.303 mmol) in DCM (3 mL) using TFA (0.02 mL, 0.30 mmol). This gave after workup and purification by reverse phase column chromatography [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(2-(3-(aminomethyl)-5-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetate (**63b**) (0.036 g, 26 % yield) as a HCl salt; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.87 (s, 1H), 8.58 – 8.47 (m, 1H), 8.45 – 8.34 (m, 2H), 8.27 (s, 3H), 7.63 (dd, *J* = 4.6, 1.4 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.34 – 7.27 (m, 2H), 7.11 (d, *J* = 7.7 Hz, 1H), 4.20 (s, 2H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 2H), 2.36 (s, 3H), 0.99 (t, *J* = 7.1 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -112.48; MS (ES⁺): 462.3 (M+1); MS (ES⁻): 496.3 (M+Cl).

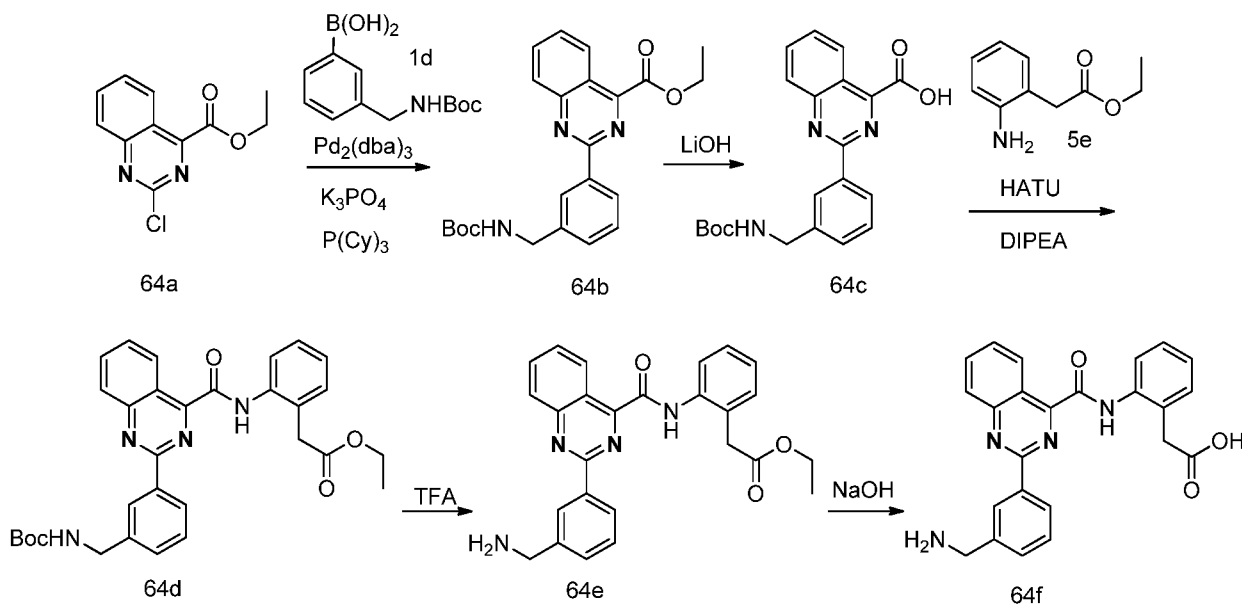
Step-3: Preparation of 2-(2-(2-(3-(aminomethyl)-5-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetic acid (**63c**)

Compound **63c** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(2-(3-(aminomethyl)-5-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetate (**63b**) (0.08 g, 0.173 mmol) in THF (2 mL) using sodium hydroxide

(0.173 mL, 0.347 mmol, 2 M aqueous). This gave after workup and purification by reverse phase column [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(2-(3-(aminomethyl)-5-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-carboxamido)-4-methylphenyl)acetic acid (**63c**)

(0.026 g, 35 % yield) as a HCl salt; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 12.64 (s, 1H), 10.93 (s, 1H), 8.51 – 8.35 (m, 6H), 7.66 – 7.60 (m, 2H), 7.60 – 7.54 (m, 1H), 7.34 – 7.25 (m, 2H), 7.09 (dd, $J = 7.8, 1.8$ Hz, 1H), 4.26 – 4.15 (m, 2H), 3.72 (s, 2H), 2.36 (s, 3H); ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ -112.08; MS (ES+) 434.3 (M+1); MS (ES-) 432.4 (M-1); HPLC purity: 94.02%.

Scheme-64



Preparation of 2-(2-(2-(3-(aminomethyl)phenyl)quinazoline-4-carboxamido)phenyl)acetic acid (**64f**)

Step-1: Preparation of ethyl 2-(3-(((tert-butoxycarbonyl)amino)methyl)phenyl)quinazoline-4-carboxylate (**64b**)

Compound **64b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-chloroquinazoline-4-carboxylate (**64a**) (0.4 g, 1.69 mmol; CAS# 1092352-52-7) in dioxane (5 mL) using 3-(((tert-butoxycarbonyl)amino)methyl)phenylboronic acid (**1d**) (0.64 g, 2.54 mmol), tripotassium phosphate (3M aqueous, 0.96 mL, 2.87 mmol), tricyclohexylphosphine 100 mg, 0.34 mmol) and $\text{Pd}_2(\text{dba})_3$ (90 mg, 0.09 mmol) under an Ar atmosphere and heating at 125 °C for 60 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane

from 0-70%] ethyl 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)quinazoline-4-carboxylate (**64b**) (0.6 g, 87 % yield) as a yellow solid; MS (ES⁺): 430.3 (M+Na), MS (ES⁻): 406.4 (M-1).

Step-2: Preparation of 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)quinazoline-4-carboxylic acid (**64c**)

Compound **64c** was prepared according to the procedure reported in step-6 of Scheme-1 from ethyl 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)quinazoline-4-carboxylate (**64b**) (0.6 g, 1.47 mmol) in THF/MeOH (5 mL) using lithium hydroxide (0.35 g, 14.73 mmol) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)quinazoline-4-carboxylic acid (**64c**) (0.44 g, 79 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 14.56 (s, 1H), 8.44 (d, J = 8.0 Hz, 2H), 8.37 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 7.0 Hz, 2H), 7.80 (t, J = 7.3 Hz, 1H), 7.55 (m, 2H), 7.44 (d, J = 7.5 Hz, 1H), 4.26 (d, J = 6.0 Hz, 2H), 1.43 (s, 9H); MS (ES⁻): 378.4 (M-1).

Step-3: Preparation of ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)quinazoline-4-carboxamido)phenyl)acetate (**64d**)

Compound **64d** was prepared according to the procedure reported in step-4 of Scheme-1 from 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)quinazoline-4-carboxylic acid (**64c**) (0.2 g, 0.53 mmol) in DMF (5 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (0.11 g, 0.63 mmol), DIPEA (0.18 mL, 1.05 mmol) and HATU (0.24 g, 0.63 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc/MeOH (9:1) in hexane from 0-100%] ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)quinazoline-4-carboxamido)phenyl)acetate (**64d**) (0.26 g, 91 % yield) as a white solid; MS (ES⁺): 541.4 (M-1); MS (ES⁻): 539.5 (M-1).

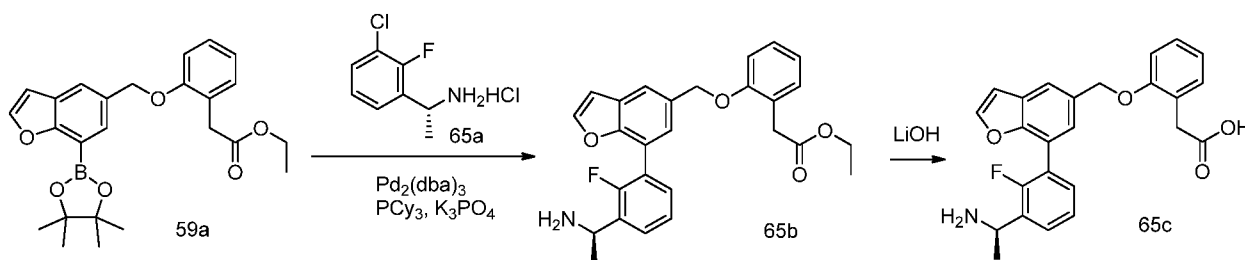
Step-4: Preparation of ethyl 2-(2-(2-(3-(aminomethyl)phenyl)quinazoline-4-carboxamido)phenyl)acetate (**64e**)

Compound **64e** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-(2-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)quinazoline-4-carboxamido)phenyl)acetate (**64d**) (0.13 g, 0.24 mmol) in DCM (5 mL) using TFA (0.19 mL, 2.41 mmol). This gave after workup and purification by reverse column chromatography [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(2-(3-(aminomethyl)phenyl)quinazoline-4-carboxamido)phenyl)acetate (**64e**) (0.1 g, 94 % yield) as a yellow solid; MS (ES⁺): 441.4 (M+1).

Step-5: Preparation of 2-(2-(2-(3-(aminomethyl)phenyl)quinazoline-4-carboxamido)phenyl)acetic acid (**64f**)

Compound **64f** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(2-(3-(aminomethyl)phenyl)quinazoline-4-carboxamido)phenyl)acetate (**64e**) (100 mg, 0.227 mmol) in MeOH/THF (5 mL) using a solution of NaOH ((0.036 g, 0.908 mmol) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-40%] 2-(2-(2-(3-(aminomethyl)phenyl)quinazoline-4-carboxamido)phenyl)acetic acid (**64f**) (0.042 g, 45 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.85 (d, *J* = 2.9 Hz, 1H), 9.07 – 8.94 (m, 1H), 8.82 (t, *J* = 1.8 Hz, 1H), 8.73 (d, *J* = 7.7 Hz, 1H), 8.54 (s, 3H), 8.24 – 8.08 (m, 2H), 7.84 (m, 2H), 7.74 (m, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.41 (m, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 4.20 (q, *J* = 5.8 Hz, 2H), 3.83 (s, 2H); MS (ES⁺): 413.2 (M+1); MS (ES⁻): 411.3 (M-1). HPLC purity: 96.86%.

Scheme-65



Preparation of (R)-2-(2-((7-(3-(1-aminoethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**65c**)

Step-1: Preparation of (R)-ethyl 2-(2-((7-(3-(1-aminoethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**65b**)

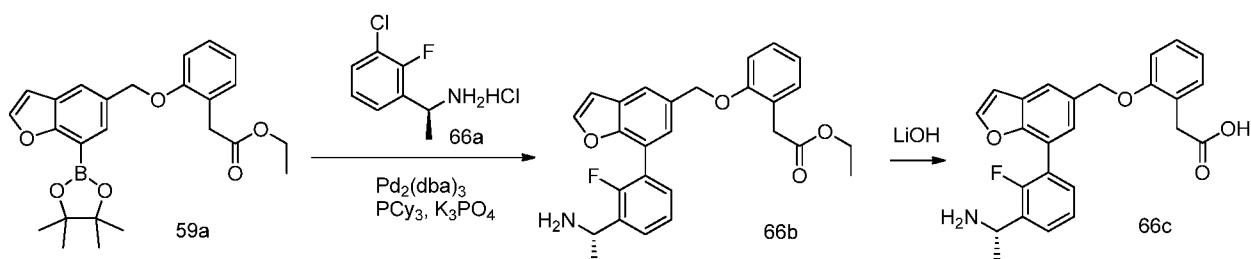
Compound **65b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (300 mg, 0.69 mmol) in dioxane (5 mL) using (R)-1-(3-chloro-2-fluorophenyl)ethanamine hydrochloride (**65a**) (289 mg, 1.38 mmol, CAS# 1253792-97-0), tripotassium phosphate (3M aqueous, 0.92 mL, 2.75 mmol), tricyclohexylphosphine (58 mg, 0.21 mmol) and $\text{Pd}_2(\text{dba})_3$ (63 mg, 0.069 mmol) under an Ar atmosphere and heating at 130 °C for 30 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), EtOAc in hexane from 0-70%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] (R)-ethyl 2-(2-((7-(3-(1-aminoethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**65b**) (256 mg, 83 % yield) as a white solid; ¹H NMR (300 MHz,

DMSO-*d*₆) δ 8.73 (s, 3H, D₂O exchangeable), 8.07 (d, J = 2.2 Hz, 1H), 7.84 – 7.74 (m, 2H), 7.66 (td, J = 7.4, 1.7 Hz, 1H), 7.51 – 7.41 (m, 2H), 7.31 – 7.20 (m, 2H), 7.16 – 7.09 (m, 1H), 7.08 (d, J = 2.2 Hz, 1H), 6.92 (td, J = 7.4, 1.1 Hz, 1H), 5.24 (s, 2H), 4.79 – 4.62 (m, 1H), 3.92 (q, J = 7.1 Hz, 2H), 3.62 (s, 2H), 1.59 (d, J = 6.8 Hz, 3H), 0.99 (t, J = 7.1 Hz, 3H); MS (ES⁺): 448.3 (M+1); (ES⁻): 482.4 (M+Cl).

Step-2: Preparation of (R)-2-(2-((7-(3-(1-aminoethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**65c**)

Compound **65c** was prepared according to the procedure reported in step-6 of Scheme-1, from (R)-ethyl 2-(2-((7-(3-(1-aminoethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**65b**) (58 mg, 0.13 mmol) in MeOH/THF (3 mL) using a solution of lithium hydroxide monohydrate (21.76 mg, 0.52 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] (R)-2-(2-((7-(3-(1-aminoethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**65c**) (17 mg, 31 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.22 (s, 1H, D₂O exchangeable), 8.68 (s, 3H, D₂O exchangeable), 8.06 (d, J = 2.2 Hz, 1H), 7.85 – 7.73 (m, 2H), 7.71 – 7.61 (m, 1H), 7.51 – 7.41 (m, 2H), 7.27 – 7.18 (m, 2H), 7.13 – 7.02 (m, 2H), 6.90 (t, J = 7.4 Hz, 1H), 5.26 (s, 2H), 4.71 (d, J = 7.2 Hz, 1H), 3.58 (s, 2H), 1.59 (d, J = 6.8 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -119.76; MS (ES⁺): 420.3 (M+1); (ES⁻): 418.3 (M-1); 454.3 (M+Cl).

Scheme-66



Preparation of (S)-2-(2-((7-(3-(1-aminoethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**66c**)

Step-1: Preparation of (S)-ethyl 2-(2-((7-(3-(1-aminoethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**66b**)

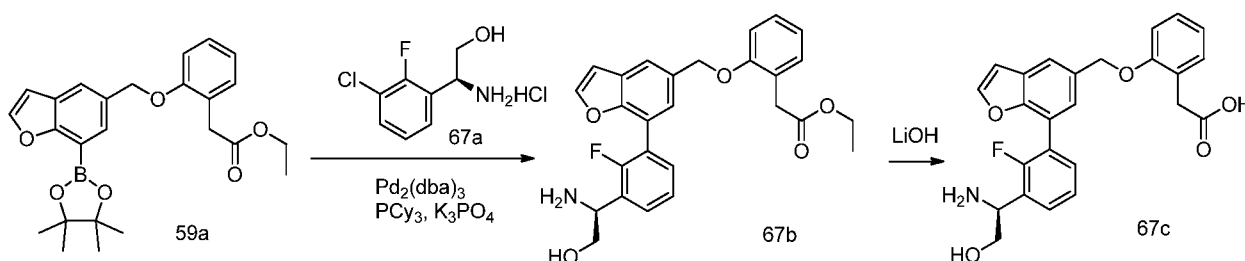
Compound **66b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (300 mg, 0.69 mmol) in dioxane (5 mL) using (S)-1-(3-chloro-2-fluorophenyl)ethanamine hydrochloride (**66a**) (253 mg, 1.20 mmol, CAS# 1313593-59-7), tripotassium phosphate (3M aqueous, 0.92 mL, 2.75 mmol), tricyclohexylphosphine

(58 mg, 0.21 mmol) and $\text{Pd}_2(\text{dba})_3$ (63 mg, 0.069 mmol) under an Ar atmosphere and heating at 130 °C for 60 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), DMA80 in DCM from 0-70%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] (S)-ethyl 2-(2-((7-(3-(1-aminoethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**66b**) (130 mg, 42 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.79 (s, 3H, D_2O exchangeable), 8.07 (d, $J = 2.2$ Hz, 1H), 7.88 – 7.75 (m, 2H), 7.69 – 7.59 (m, 1H), 7.51 – 7.39 (m, 2H), 7.30 – 7.19 (m, 2H), 7.16 – 7.03 (m, 2H), 6.91 (t, $J = 7.3$ Hz, 1H), 5.24 (s, 2H), 4.70 (q, $J = 6.5$ Hz, 1H), 3.91 (q, $J = 7.1$ Hz, 2H), 3.62 (s, 2H), 1.59 (d, $J = 6.8$ Hz, 3H), 0.98 (t, $J = 7.1$ Hz, 3H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -120.02; MS (ES+): 448.3 (M+1); (ES-): 482.3 (M+Cl); HPLC purity: 98.77%.

Step-2: Preparation of (S)-2-(2-((7-(3-(1-aminoethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**66c**)

Compound **66c** was prepared according to the procedure reported in step-6 of Scheme-1, from (S)-ethyl 2-(2-((7-(3-(1-aminoethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**66b**) (72 mg, 0.16 mmol) in MeOH/THF (3 mL) using a solution of lithium hydroxide monohydrate (27 mg, 0.64 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] (S)-2-(2-((7-(3-(1-aminoethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**66c**) (26 mg, 39 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.78 (s, 2H, D_2O exchangeable), 8.06 (d, $J = 2.2$ Hz, 1H), 7.82 (d, $J = 1.6$ Hz, 1H), 7.77 (t, $J = 7.2$ Hz, 1H), 7.66 (t, $J = 7.4$ Hz, 1H), 7.51 – 7.38 (m, 2H), 7.30 – 7.16 (m, 2H), 7.14 – 7.02 (m, 2H), 6.90 (t, $J = 7.4$ Hz, 1H), 5.26 (s, 2H), 4.72 (q, $J = 6.8$ Hz, 1H), 3.58 (s, 2H), 1.59 (d, $J = 6.7$ Hz, 3H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -119.75; MS (ES+): 420.3 (M+1); (ES-): 418.3 (M-1), 454.3 (M+Cl); HPLC purity: 99.82%.

Scheme-67



Preparation of (S)-2-(2-((7-(3-(1-amino-2-hydroxyethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**67c**)

Step-1: Preparation of (S)-ethyl 2-(2-((7-(3-(1-amino-2-hydroxyethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**67b**)

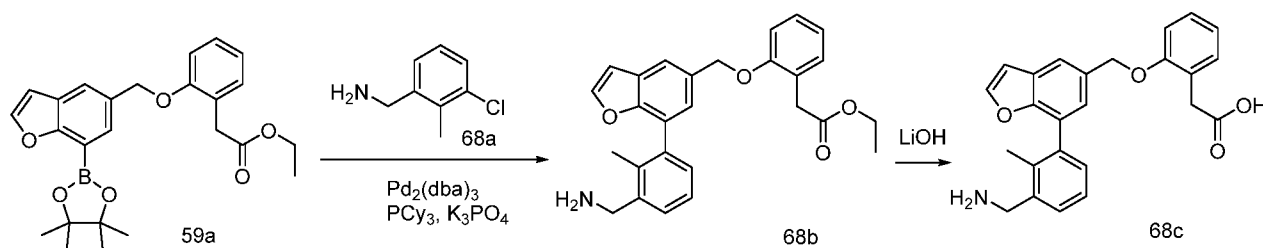
Compound **67b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (316 mg, 0.72 mmol) in dioxane (5 mL) using (S)-2-amino-2-(3-chloro-2-fluorophenyl)ethanol hydrochloride (**67a**) (327 mg, 1.45 mmol, CAS# 1391506-22-1), tripotassium phosphate (3M aqueous, 0.41 mL, 1.23 mmol), tricyclohexylphosphine (61 mg, 0.22 mmol) and Pd₂(dba)₃ (66 mg, 0.072 mmol) under an Ar atmosphere and heating at 125 °C for 60 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), DMA80 in DCM from 0-70%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] (S)-ethyl 2-(2-((7-(3-(1-amino-2-hydroxyethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**67b**) (142 mg, 42% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.70 (s, 3H, D₂O exchangeable), 8.07 (d, *J* = 2.1 Hz, 1H), 7.83 – 7.72 (m, 2H), 7.67 (td, *J* = 7.4, 1.6 Hz, 1H), 7.52 – 7.41 (m, 2H), 7.31 – 7.18 (m, 2H), 7.12 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.08 (d, *J* = 2.2 Hz, 1H), 6.92 (td, *J* = 7.4, 1.1 Hz, 1H), 5.68 (t, *J* = 5.2 Hz, 1H, D₂O exchangeable), 5.24 (s, 2H), 4.60 (t, *J* = 5.9 Hz, 1H), 3.92 (q, *J* = 7.1 Hz, 2H), 3.85 – 3.72 (m, 2H), 3.62 (s, 2H), 0.99 (t, *J* = 7.1 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -119.52; MS (ES⁺): 464.3 (M+1); 486.3 (M+Na); (ES⁻): 498.3 (M+Cl); HPLC purity: 98.65%.

Step-2: Preparation of (S)-2-(2-((7-(3-(1-amino-2-hydroxyethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**67c**)

Compound **67c** was prepared according to the procedure reported in step-6 of Scheme-1, from (S)-ethyl 2-(2-((7-(3-(1-amino-2-hydroxyethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**67b**) (65 mg, 0.14 mmol) in MeOH/THF (5 mL) using a solution of lithium hydroxide monohydrate (24 mg, 0.56 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] (S)-2-(2-((7-(3-(1-amino-2-hydroxyethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**67c**) (31 mg, 51 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.75 (s, 2H, D₂O exchangeable), 8.07 (d, *J* = 2.2 Hz, 1H), 7.85 – 7.80 (m, 1H), 7.76 (t, *J* = 7.3 Hz, 1H), 7.67 (t, *J* = 7.3 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.27 – 7.17 (m, 2H), 7.13 – 7.04 (m, 2H), 6.95 – 6.86 (m, 1H), 5.67 (s, 1H, D₂O exchangeable), 5.27 (s, 2H), 4.60 (t, *J* = 5.7 Hz, 1H), 3.87 – 3.71 (m, 2H), 3.58 (s, 2H);

^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ -119.34; MS (ES^+) 436.3 ($\text{M}+1$); (ES^-), 434.3 ($\text{M}-1$); 470.3 ($\text{M}+\text{Cl}$); HPLC purity: 99.26%.

Scheme-68



Preparation of 2-(2-((7-(3-(aminomethyl)-2-methylphenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**68c**)

Step-1: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)-2-methylphenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**68b**)

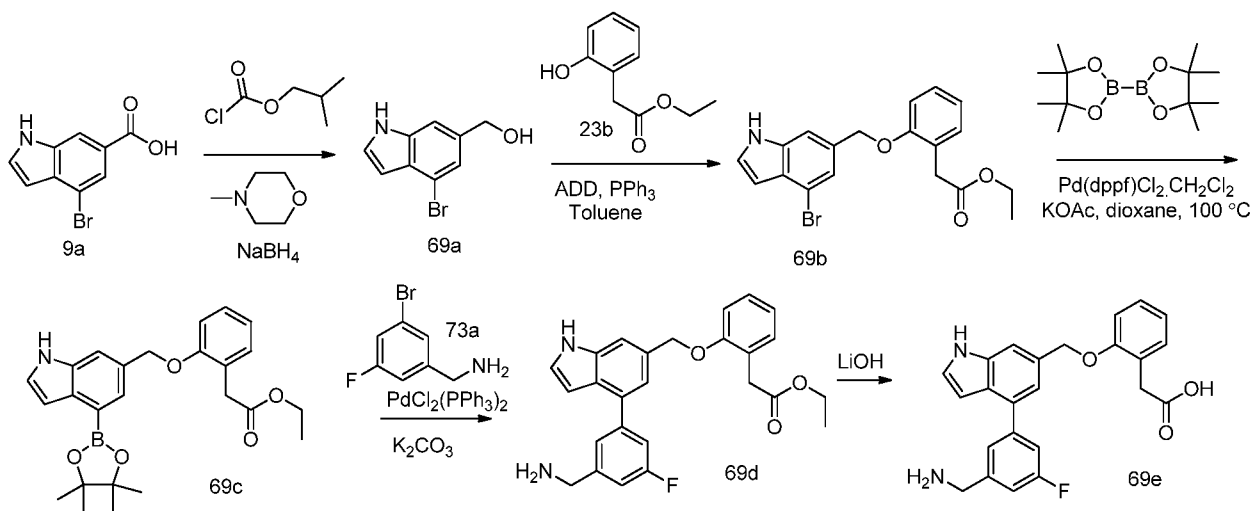
Compound **68b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (315 mg, 0.72 mmol) in dioxane (5 mL) using (3-chloro-2-methylphenyl)methanamine (**68a**) (225 mg, 1.44 mmol, CAS# 226565-61-3), tripotassium phosphate (3M aqueous, 0.41 mL, 1.23 mmol), tricyclohexylphosphine (61 mg, 0.22 mmol) and $\text{Pd}_2(\text{dba})_3$ (66 mg, 0.072 mmol) under an Ar atmosphere and heating at 130 °C for 60 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), DMA80 in DCM from 0-70%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(3-(aminomethyl)-2-methylphenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**68b**) (188 mg, 61% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 8.49 (s, 3H, D_2O exchangeable), 7.99 (d, $J = 2.2$ Hz, 1H), 7.74 (d, $J = 1.6$ Hz, 1H), 7.52 (dd, $J = 7.4, 1.7$ Hz, 1H), 7.42 – 7.31 (m, 2H), 7.31 – 7.17 (m, 3H), 7.12 (d, $J = 8.0$ Hz, 1H), 7.05 (d, $J = 2.2$ Hz, 1H), 6.97 – 6.86 (m, 1H), 5.23 (s, 2H), 4.13 (s, 2H), 3.91 (q, $J = 7.1$ Hz, 2H), 3.62 (s, 2H), 2.11 (s, 3H), 0.99 (t, $J = 7.1$ Hz, 3H); MS (ES^+): 430.4 ($\text{M}+1$); 452.3 ($\text{M}+\text{Na}$).

Step-2: Preparation of 2-(2-((7-(3-(aminomethyl)-2-methylphenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**68c**)

Compound **68c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(aminomethyl)-2-methylphenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**68b**) (55 mg, 0.13 mmol) in MeOH/THF (5 mL) using a solution of lithium hydroxide monohydrate (22 mg, 0.51 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water

(containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)-2-methylphenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**68c**) (23 mg, 45 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.59 (s, 1H, D $_2$ O exchangeable), 7.98 (d, J = 2.2 Hz, 1H), 7.78 (d, J = 1.6 Hz, 1H), 7.51 (dd, J = 7.0, 1.9 Hz, 1H), 7.42 – 7.29 (m, 2H), 7.27 – 7.18 (m, 3H), 7.09 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 2.2 Hz, 1H), 6.90 (t, J = 7.4 Hz, 1H), 5.25 (s, 2H), 4.12 (s, 2H), 3.57 (s, 2H), 2.11 (s, 3H); MS (ES $^+$): 402.3 (M+1); 424.3 (M+Na); (ES $^-$): 400.4 (M-1), 436.4 (M+Cl).

Scheme-69



Preparation of 2-(2-((4-(3-(aminomethyl)-5-fluorophenyl)-1H-indol-6-yl)methoxy)phenyl)acetic acid (**69e**)

Step-1: Preparation of (4-bromo-1H-indol-6-yl)methanol (**69a**)

Compound **69a** was prepared according to the procedure reported in step-1 of Scheme-23 from 4-bromo-1H-indole-6-carboxylic acid (**9a**) (10 g, 41.7 mmol) in THF (100 mL), using N-methylmorpholine (5.50 mL, 50.0 mmol), isobutyl chloroformate (6.56 mL, 50.0 mmol) and NaBH $_4$ (4.73 g, 125 mmol) in water (0.8 mL). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with ethyl acetate/MeOH (9:1) in hexane from 0-100%] (4-bromo-1H-indol-6-yl)methanol (**69a**) (6.1 g, 65 % yield) as a yellow solid; ^1H NMR (300 MHz, DMSO- d_6) δ 11.41 (s, 1H), 7.42 (t, J = 2.8 Hz, 1H), 7.36 (t, J = 1.1 Hz, 1H), 7.18 (d, J = 1.2 Hz, 1H), 6.35 (m, 1H), 5.22 (t, J = 5.9 Hz, 1H), 4.56 (d, J = 5.6 Hz, 2H).

Step-2: Preparation of ethyl 2-(2-((4-bromo-1H-indol-6-yl)methoxy)phenyl)acetate (**69b**)

Compound **69b** was prepared according to the procedure reported in step-2 of Scheme-23 from (4-bromo-1H-indol-6-yl)methanol (**69a**) (3 g, 13.27 mmol) in toluene (50 mL) using triphenylphosphine (4.52 g, 17.25 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (3.11 g, 17.25 mmol) and a solution of (E)-diazene-1,2-diylbis(piperidin-1-ylmethanone) (ADD, 4.35

g, 17.25 mmol) in toluene (50 mL). This gave after workup and purification by flash column chromatography [silica (48 g), eluting with EtOAc/MeOH (9:1) in hexane from 0-10% for 40 min, then 10%-50%] ethyl 2-(2-((4-bromo-1H-indol-6-yl)methoxy)phenyl)acetate (**69b**) (1.3 g, 25 % yield) as a yellow oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.54 (s, 1H), 7.51 – 7.44 (m, 2H), 7.27 (d, *J* = 1.2 Hz, 1H), 7.26 – 7.18 (m, 2H), 7.08 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.90 (td, *J* = 7.4, 1.1 Hz, 1H), 6.39 (m, 1H), 5.16 (s, 2H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.60 (s, 2H), 1.07 (t, *J* = 7.1 Hz, 3H).

Step-3: Preparation of ethyl 2-(2-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-6-yl)methoxy)phenyl)acetate (**69c**)

Compound **69c** was prepared according to the procedure reported in step-1 of Scheme-59 from ethyl 2-(2-((4-bromo-1H-indol-6-yl)methoxy)phenyl)acetate (**69b**) (1.3 g, 3.35 mmol) in anhydrous dioxane (20 mL), using bis(pinacolato)diboron (1.28 g, 5.02 mmol), potassium acetate (0.986 g, 10.04 mmol), Pd(dppf)Cl₂-CH₂Cl₂ (0.41 g, 0.50 mmol) and heating under an argon atmosphere at 90 °C overnight. This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc/MeOH=9:1 in hexane from 0-10%] ethyl 2-(2-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-6-yl)methoxy)phenyl)acetate (**69c**) (0.98 g, 67 % yield) as a yellow oil; MS (ES⁺) 458.2 (M+Na).

Step-4: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)-5-fluorophenyl)-1H-indol-6-yl)methoxy)phenyl)acetate (**69d**)

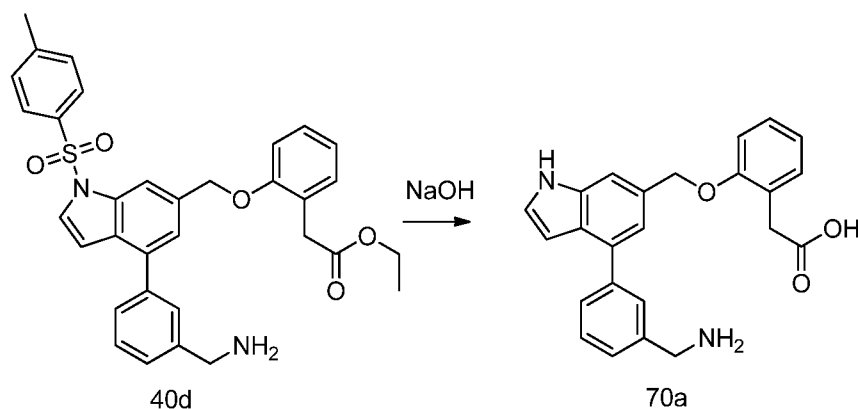
Compound **69d** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-6-yl)methoxy)phenyl)acetate (**69c**) (0.98 g, 2.25 mmol) in dioxane (7 mL) using (3-bromo-5-fluorophenyl)methanamine (**73a**) (0.20 mL, 1.50 mmol), a solution of potassium carbonate (0.52 g, 3.75 mmol) in water (0.7 mL), bis(triphenylphosphine)Palladium(II)chloride (0.16 g, 0.23 mmol) under an Ar atmosphere and heating at 100 °C for 2 h in an oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with MeOH in DCM from 0-50%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((4-(3-(aminomethyl)-5-fluorophenyl)-1H-indol-6-yl)methoxy)phenyl)acetate (**69d**) (0.19 g, 29 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.44 (s, 1H), 8.34 (s, 3H), 7.68 (d, *J* = 1.5 Hz, 1H), 7.54 – 7.45 (m, 3H), 7.37 (d, *J* = 9.7 Hz, 1H), 7.28 – 7.18 (m, 3H), 7.12 (d, *J* = 8.1 Hz, 1H), 6.91 (dd, *J* = 7.4, 1.1 Hz, 1H), 6.68 (d, *J* = 2.9 Hz, 1H), 5.23 (s, 2H), 4.15 (d, *J* = 5.8 Hz, 2H), 3.94 (q, *J* = 7.1 Hz, 2H),

3.61 (s, 2H), 0.98 (t, $J = 7.1$ Hz, 3H); ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ -112.87; MS (ES^+) 433.2 ($\text{M}+1$); MS (ES^-) 431.3 ($\text{M}-1$). HPLC: 97.87 %.

Step-5: Preparation of 2-(2-((4-(3-(aminomethyl)-5-fluorophenyl)-1H-indol-6-yl)methoxy)phenyl)acetic acid (**69e**)

Compound **69e** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((4-(3-(aminomethyl)-5-fluorophenyl)-1H-indol-6-yl)methoxy)phenyl)acetate (**69d**) (0.15 g, 0.35 mmol) in MeOH/THF (4 mL) using a solution of lithium hydroxide hydrate (73 mg, 1.73 mmol) in water (0.8 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((4-(3-(aminomethyl)-5-fluorophenyl)-1H-indol-6-yl)methoxy)phenyl)acetic acid (**69e**) (0.02 g, 15 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 12.14 (s, 1H), 11.41 (s, 1H), 8.41 (s, 3H), 7.68 (s, 1H), 7.57 – 7.43 (m, 3H), 7.37 (d, $J = 9.4$ Hz, 1H), 7.26 (d, $J = 1.3$ Hz, 1H), 7.22 (s, 1H), 7.20 (s, 1H), 7.10 (d, $J = 8.0$ Hz, 1H), 6.89 (t, $J = 7.3$ Hz, 1H), 6.67 (d, $J = 2.6$ Hz, 1H), 5.25 (s, 2H), 4.15 (s, 2H), 3.58 (s, 2H).; ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ -112.73; MS (ES^+) 405.1 ($\text{M}+1$). HPLC purity: 95.81 %.

Scheme-70

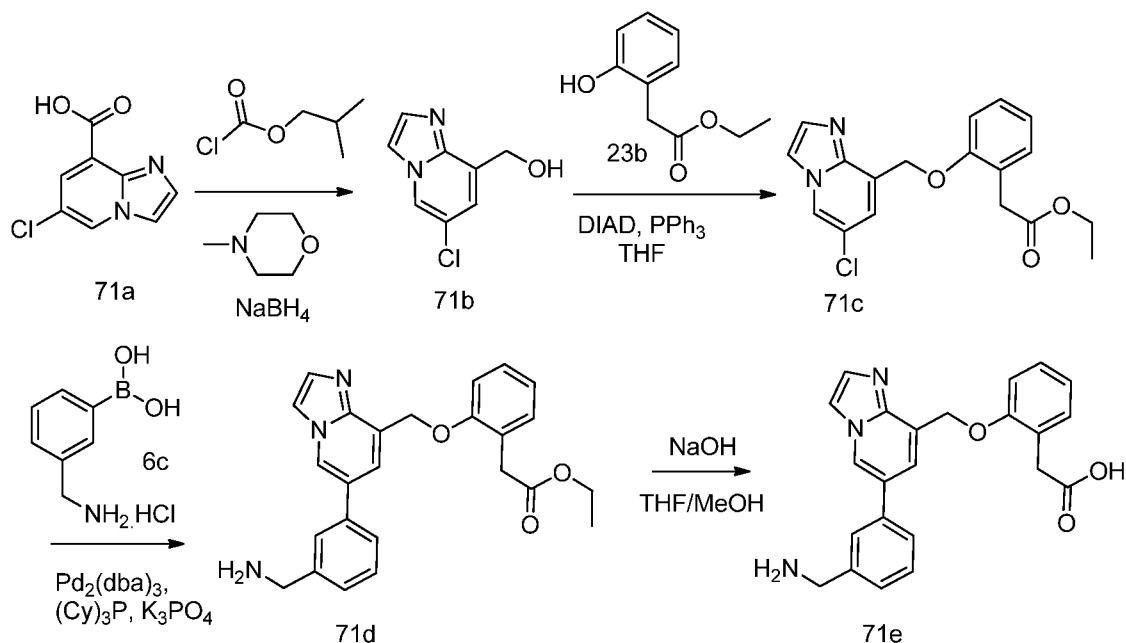


Preparation of 2-(2-((4-(3-(aminomethyl)phenyl)-1H-indol-6-yl)methoxy)phenyl)acetic acid (**70a**)

Compound **70a** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-((4-(3-(aminomethyl)phenyl)-1H-indol-6-yl)methoxy)phenyl)acetate (**40d**) (0.08 g, 0.141 mmol) in MeOH/THF (5 mL, 1:1) using a solution of sodium hydroxide (56 mg, 1.41 mmol) in water (2 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((4-(3-(aminomethyl)phenyl)-1H-indol-6-yl)methoxy)phenyl)acetic acid (**70a**) (0.021 g, 39 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 12.19 (s, 1H), 11.37 (s, 1H), 8.34 (s, 4H), 7.82 (t, $J = 1.7$ Hz, 1H), 7.70 (dt, $J = 7.7, 1.5$ Hz, 1H), 7.56 (m, 1H), 7.51 (m,

1H), 7.48 – 7.43 (m, 1H), 7.27 – 7.17 (m, 2H), 7.11 (d, J = 8.1 Hz, 1H), 6.89 (td, J = 7.4, 1.2 Hz, 1H), 6.66 (d, J = 2.7 Hz, 1H), 5.25 (s, 2H), 4.13 (s, 2H), 3.58 (s, 2H); MS (ES⁺): 387.3 (M+1); MS (ES⁻): 421.4 (M+Cl).

Scheme-71



Preparation of 2-(2-((6-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridin-8-yl)methoxy)phenyl)acetic acid (**71e**)

Step-1: Preparation of (6-chloroimidazo[1,2-a]pyridin-8-yl)methanol (**71b**)

Compound **71b** was prepared according to the procedure reported in step-1 of Scheme-23 from 6-chloroimidazo[1,2-a]pyridine-8-carboxylic acid (**71a**) (1.0 g, 5.09 mmol; CAS# 155735-02-7) using N-methylmorpholine (0.615 mL, 5.60 mmol) in THF (20 mL), isobutyl chloroformate (0.735 mL, 5.60 mmol) and NaBH₄ (0.289 g, 7.63 mmol) in water. This gave after workup and purification by flash column chromatography [silica (12 g), eluting with ethyl acetate in hexane from 0-100%] (6-chloroimidazo[1,2-a]pyridin-8-yl)methanol (**71b**) (0.401 g, 43 % yield) as a pale yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.76 - 8.73 (m, 1H), 7.99 - 7.91 (m, 1H), 7.60 - 7.54 (m, 1H), 7.28 - 7.13 (m, 1H), 5.54 (s, 1H, D₂O exchangeable), 4.84 (s, 2H).

Step-2: Preparation of ethyl 2-(2-((6-chloroimidazo[1,2-a]pyridin-8-yl)methoxy)phenyl)acetate (**71c**)

Compound **71c** was prepared according to the procedure reported in step-2 of Scheme-23 from (6-chloroimidazo[1,2-a]pyridin-8-yl)methanol (**71b**) (0.4 g, 2.19 mmol) in THF (25 mL) using triphenylphosphine (0.747 g, 2.85 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (0.513 g, 2.85 mmol) and DIAD (0.554 mL, 2.85 mmol). This gave after workup and

purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-100%] ethyl 2-(2-((6-chloroimidazo[1,2-a]pyridin-8-yl)methoxy)phenyl)acetate (**71c**) (0.66 g, 87 % yield) as a yellow solid.

MS (ES⁺): 367.2 (M+Na).

Step-3: Preparation of ethyl 2-(2-((6-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridin-8-yl)methoxy)phenyl)acetate (**71d**)

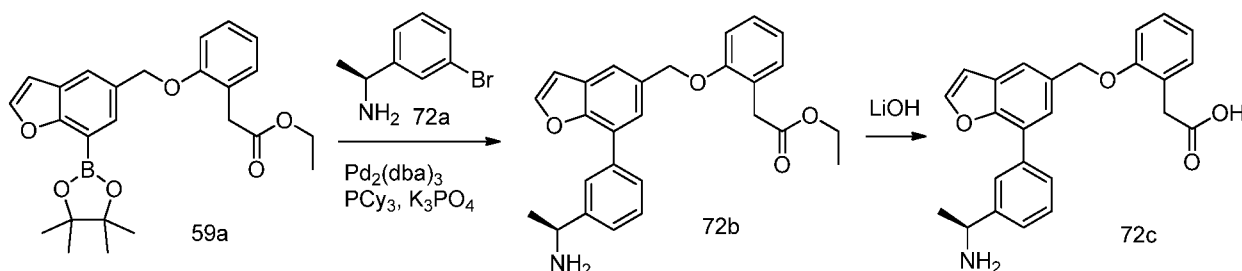
Compound **71d** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((6-chloroimidazo[1,2-a]pyridin-8-yl)methoxy)phenyl)acetate (**71c**) (0.65 g, 1.89 mmol) in dioxane (6 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (0.530 g, 2.83 mmol), tripotassium phosphate (1.3M, 1.885 mL, 5.66 mmol), tricyclohexylphosphine (0.159 g, 0.566 mmol) and Pd₂(dba)₃ (0.173 g, 0.189 mmol) under an Ar atmosphere and heating at 125 °C for 45 min in an oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-60%] ethyl 2-(2-((6-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridin-8-yl)methoxy)phenyl)acetate (**71d**) (0.151 g, 19 % yield) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.39 – 9.35 (m, 1H), 8.64 (s, 3H, D₂O exchangeable), 8.42 (d, *J* = 2.0 Hz, 1H), 8.40 – 8.26 (m, 2H), 8.05 (s, 1H), 7.90 – 7.76 (m, 1H), 7.69 – 7.58 (m, 2H), 7.38 – 7.18 (m, 3H), 7.05 – 6.93 (m, 1H), 5.58 (s, 2H), 4.21 – 4.03 (m, 2H), 3.86 (q, *J* = 7.1 Hz, 2H), 3.69 (s, 2H), 0.91 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 416.3 (M+1); MS (ES⁻): 450.4 (M+Cl); HPLC purity: 97.21%. Analysis Calculated for: C₂₅H₂₅N₃O₃·3H₂O·2HCl: C, 55.35; H, 6.13; Cl, 13.07; N, 7.75; Found: C, 55.41; H, 5.96; Cl, 13.01; N, 7.79

Step-4: Preparation of 2-(2-((6-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridin-8-yl)methoxy)phenyl)acetic acid (**71e**)

Compound **71e** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-((6-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridin-8-yl)methoxy)phenyl)acetate (**71d**) (0.040 g, 0.096 mmol) in THF (4 mL) and methanol (8 mL) using a 2 M aqueous solution of sodium hydroxide (0.193 mL, 0.385 mmol). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((6-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridin-8-yl)methoxy)phenyl)acetic acid (**71e**) (0.026 g, 70 % yield) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.35 (s, 1H), 8.62 (s, 3H, D₂O exchangeable, 2H), 8.45 – 8.39 (m, 1H), 8.33 (d, *J* = 12.0 Hz, 2H), 8.05 (s, 1H), 7.88 – 7.76 (m, 1H), 7.64 (d, *J* = 4.7 Hz, 2H), 7.40 – 7.16 (m, 3H), 7.04 – 6.94 (m, 1H), 5.58 (s, 2H), 4.20 – 4.02 (m, 2H), 3.72 (s, 2H); MS (ES⁺): 388.3 (M+1); MS (ES⁻): 386.4 (M-1); 422.3 (M+Cl); Analysis

calculated for: $C_{23}H_{21}N_3O_3 \cdot 2.0H_2O \cdot 2.0HCl$: C, 55.65; H, 5.48; N, 8.47; Found: C, 55.53; H, 5.71; N, 8.15.

Scheme-72



Preparation of (S)-2-(2-((7-(3-(1-aminoethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**72c**)

Step-1: Preparation of (S)-ethyl 2-(2-((7-(3-(1-aminoethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**72b**)

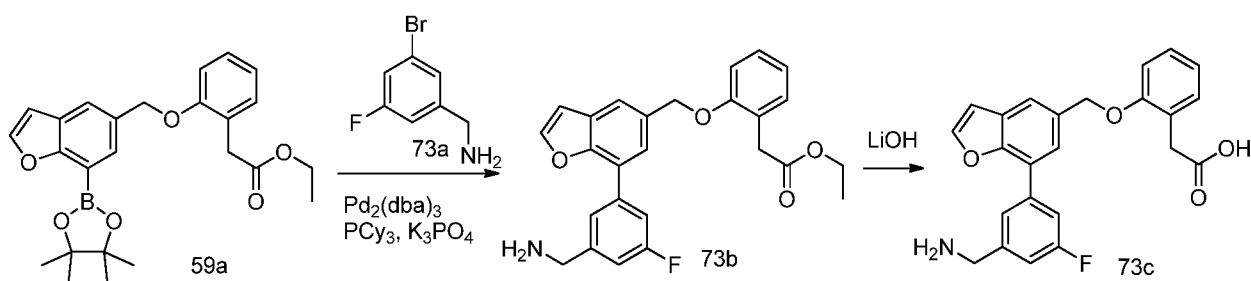
Compound **72b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (450 mg, 1.03 mmol) in dioxane (6 mL) using (S)-1-(3-bromophenyl)ethanamine (**72a**) (351 mg, 1.75 mmol; CAS# 139305-96-7), tripotassium phosphate (3M aqueous, 0.58 mL, 1.75 mmol), tricyclohexylphosphine (87 mg, 0.31 mmol) and $Pd_2(dba)_3$ (94 mg, 0.10 mmol) under an Ar atmosphere and heating at 120 °C for 90 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), DMA80 in DCM from 0-70%] followed by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] (S)-ethyl 2-(2-((7-(3-(1-aminoethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**72b**) (312 mg, 70% yield) HCl salt as a white solid; ^1H NMR (300 MHz, $DMSO-d_6$) δ 8.65 (s, 3H, D_2O exchangeable), 8.12 (d, $J = 2.2$ Hz, 1H), 8.02 (d, $J = 2.0$ Hz, 1H), 7.96 – 7.85 (m, 1H), 7.74 (d, $J = 1.5$ Hz, 1H), 7.67 – 7.58 (m, 3H), 7.31 – 7.19 (m, 2H), 7.17 – 7.10 (m, 1H), 7.08 (d, $J = 2.2$ Hz, 1H), 6.92 (td, $J = 7.4, 1.0$ Hz, 1H), 5.25 (s, 2H), 4.50 (q, $J = 6.7$ Hz, 1H), 3.93 (q, $J = 7.1$ Hz, 2H), 3.64 (s, 2H), 1.60 (d, $J = 6.7$ Hz, 3H), 0.98 (t, $J = 7.1$ Hz, 3H); MS (ES⁺): 430.3 (M+1); (ES⁻): 464.3 (M+Cl).

Step-2: Preparation of (S)-2-(2-((7-(3-(1-aminoethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**72c**)

Compound **72c** was prepared according to the procedure reported in step-6 of Scheme-1, from (S)-ethyl 2-(2-((7-(3-(1-aminoethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**72b**) (145 mg, 0.34 mmol) in MeOH/THF (5 mL) using a solution of lithium hydroxide

monohydrate (57 mg, 1.35 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] (S)-2-(2-((7-(3-(1-aminoethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**72c**) (114 mg, 84 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 12.26 (s, 1H, D $_2$ O exchangeable), 8.66 (s, 3H, D $_2$ O exchangeable), 8.11 (d, J = 2.2 Hz, 1H), 8.02 (s, 1H), 7.96 – 7.86 (m, 1H), 7.76 (d, J = 1.5 Hz, 1H), 7.68 (d, J = 1.6 Hz, 1H), 7.65 – 7.54 (m, 2H), 7.30 – 7.16 (m, 2H), 7.15 – 7.03 (m, 2H), 6.90 (t, J = 7.3 Hz, 1H), 5.27 (s, 2H), 4.57 – 4.41 (m, 1H), 3.60 (s, 2H), 1.60 (d, J = 6.7 Hz, 3H); MS (ES $^+$): 402.3 (M+1); 424.3 (M+Na); (ES $^-$): 400.4 (M-1), 436.3 (M+Cl).

Scheme-73



Preparation of 2-(2-((7-(3-(aminomethyl)-5-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**73c**)

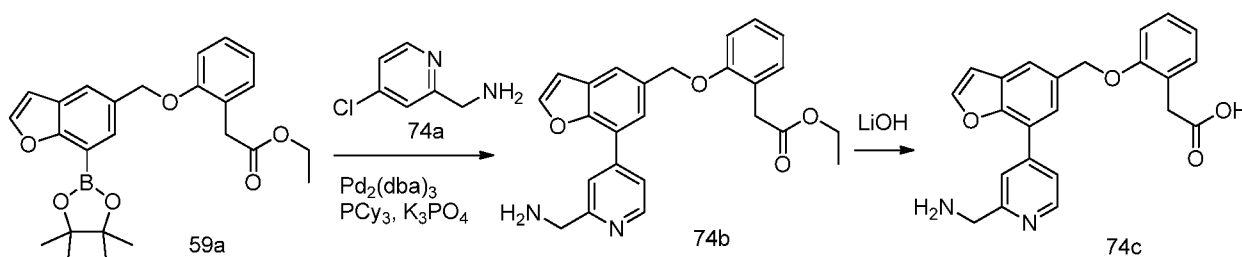
Step-1: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)-5-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**73b**)

Compound **73b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (400 mg, 0.92 mmol) in dioxane (5 mL) using (3-bromo-5-fluorophenyl)methanamine (**73a**) (374 mg, 1.83 mmol; CAS# 1094555-68-6), tripotassium phosphate (3M aqueous, 0.52 mL, 1.56 mmol), tricyclohexylphosphine (77 mg, 0.28 mmol) and $\text{Pd}_2(\text{dba})_3$ (84 mg, 0.092 mmol) under an Ar atmosphere and heating at 120 °C for 90 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), DMA80 in DCM from 0-70%] ethyl 2-(2-((7-(3-(aminomethyl)-5-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**73b**) (223 mg, 56 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.62 (s, 3H, D $_2$ O exchangeable), 8.14 (d, J = 2.2 Hz, 1H), 7.91 (d, J = 1.7 Hz, 1H), 7.80 – 7.72 (m, 2H), 7.68 (d, J = 1.6 Hz, 1H), 7.54 – 7.46 (m, 1H), 7.30 – 7.19 (m, 2H), 7.14 – 7.06 (m, 2H), 6.95 – 6.87 (m, 1H), 5.25 (s, 2H), 4.15 (s, 2H), 3.95 (q, J = 7.1 Hz, 2H), 3.64 (s, 2H), 1.00 (t, J = 7.1 Hz, 3H); MS (ES $^+$): 434.3 (M+1); (ES $^-$): 468.3 (M+Cl);

Step-2: Preparation of 2-(2-((7-(3-(aminomethyl)-5-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**73c**)

Compound **73c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(aminomethyl)-5-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**73b**) (89 mg, 0.21 mmol) in MeOH/THF (5 mL) using a solution of lithium hydroxide monohydrate (35 mg, 0.82 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)-5-fluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**73c**) (64 mg, 77 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 12.26 (s, 1H, D $_2$ O exchangeable), 8.59 (s, 3H, D $_2$ O exchangeable), 8.13 (d, J = 2.1 Hz, 1H), 7.90 (d, J = 1.8 Hz, 1H), 7.83 – 7.74 (m, 2H), 7.72 (d, J = 1.6 Hz, 1H), 7.54 – 7.45 (m, 1H), 7.28 – 7.18 (m, 2H), 7.13 – 7.04 (m, 2H), 6.90 (t, J = 7.3 Hz, 1H), 5.27 (s, 2H), 4.16 (s, 2H), 3.60 (s, 2H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -112.57; MS (ES $^+$): 406.3 (M+1); (ES $^-$): 404.4 (M-1), 440.3 (M+Cl).

Scheme-74



Preparation of 2-(2-((7-(2-(aminomethyl)pyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**74c**)

Step-1: Preparation of ethyl 2-(2-((7-(2-(aminomethyl)pyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**74b**)

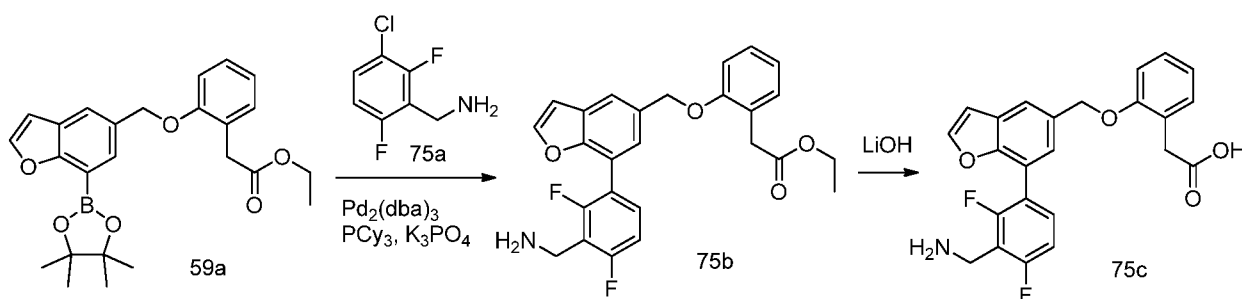
Compound **74b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (300 mg, 0.69 mmol) in dioxane (3 mL) using (4-chloropyridin-2-yl)methanamine (**74a**) (196 mg, 1.38 mmol; CAS# 180748-30-5), tripotassium phosphate (3M aqueous, 0.39 mL, 1.169 mmol), tricyclohexylphosphine (58 mg, 0.21 mmol) and $\text{Pd}_2(\text{dba})_3$ (63 mg, 0.069 mmol) under an Ar atmosphere and heating at 120 °C for 90 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), DMA80 in DCM from 0-70%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(2-(aminomethyl)pyridin-4-yl)benzofuran-5-

yl)methoxy)phenyl)acetate (**74b**) (98 mg, 34% yield) HCl salt as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.82 (d, J = 5.4 Hz, 1H), 8.74 (s, 3H, D $_2$ O exchangeable), 8.25 (s, 1H), 8.19 (d, J = 2.2 Hz, 1H), 8.08 (dd, J = 5.5, 1.8 Hz, 1H), 7.89 – 7.81 (m, 2H), 7.31 – 7.18 (m, 2H), 7.17 – 7.07 (m, 2H), 6.91 (t, J = 7.4 Hz, 1H), 5.27 (s, 2H), 4.34 (q, J = 5.8 Hz, 2H), 3.94 (q, J = 7.1 Hz, 2H), 3.64 (s, 2H), 0.98 (t, J = 7.1 Hz, 3H); MS (ES $^+$): 417.3 (M+1); 439.3 (M+Na); (ES $^-$): 451.3 (M+Cl).

Step-2: Preparation of 2-(2-((7-(2-(aminomethyl)pyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**74c**)

Compound **74c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(2-(aminomethyl)pyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**74b**) (66 mg, 0.16 mmol) in MeOH/THF (5 mL) using a solution of lithium hydroxide monohydrate (27 mg, 0.63 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(2-(aminomethyl)pyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**74c**) (36 mg, 59 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.89 – 8.70 (m, 4H, D $_2$ O exchangeable), 8.33 (d, J = 1.6 Hz, 1H), 8.19 (d, J = 2.1 Hz, 1H), 8.15 (dd, J = 5.6, 1.7 Hz, 1H), 7.91 (s, 2H), 7.22 (d, J = 7.4 Hz, 2H), 7.16 – 7.04 (m, 2H), 6.90 (t, J = 7.3 Hz, 1H), 5.29 (s, 2H), 4.38 (d, J = 5.4 Hz, 2H), 3.61 (s, 2H); MS (ES $^+$): 489.3 (M+1); 411.3 (M+Na); (ES $^-$): 387.3 (M-1), 423.3 (M+Cl).

Scheme-75



Preparation of 2-(2-((7-(3-(aminomethyl)-2,4-difluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**75c**)

Step-1: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)-2,4-difluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**75b**)

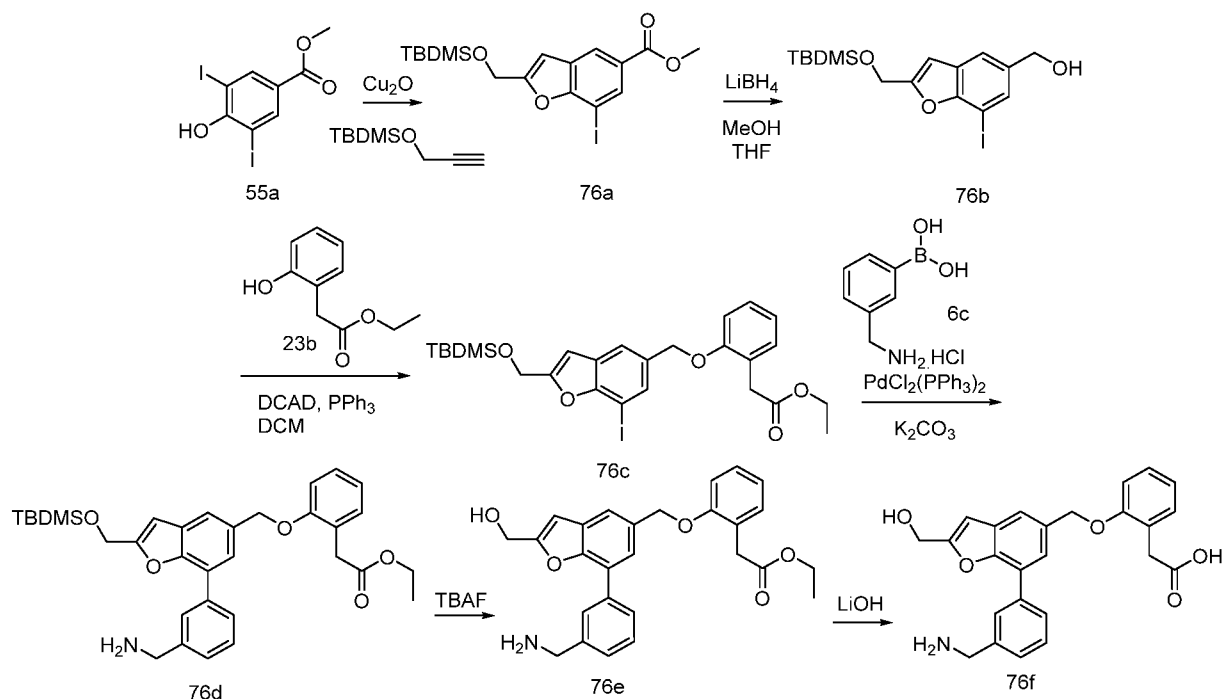
Compound **75b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (400 mg, 0.917 mmol) in dioxane (6 mL) using (3-chloro-2,6-difluorophenyl)methanamine (**75a**) (244 mg, 1.38 mmol; CAS# 261762-46-3),

tripotassium phosphate (3M aqueous, 0.52 mL, 1.56 mmol), tricyclohexylphosphine (77 mg, 0.28 mmol) and $\text{Pd}_2(\text{dba})_3$ (84 mg, 0.092 mmol) under an Ar atmosphere and heating at 120 °C for 90 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-70%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(3-(aminomethyl)-2,4-difluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**75b**) (96.8 mg) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.58 (s, 3H, D_2O exchangeable), 8.08 (d, $J = 2.2$ Hz, 1H), 7.84 – 7.73 (m, 2H), 7.46 – 7.37 (m, 2H), 7.32 – 7.19 (m, 2H), 7.17 – 7.06 (m, 2H), 6.97 – 6.88 (m, 1H), 5.24 (s, 2H), 4.16 (s, 2H), 3.94 (q, $J = 7.1$ Hz, 2H), 3.63 (s, 2H), 1.00 (t, $J = 7.1$ Hz, 3H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -112.50, -113.05; MS (ES+): 452.3 (M+1); (ES-): 486.3(M+Cl).

Step-2: Preparation of 2-(2-((7-(3-(aminomethyl)-2,4-difluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**75c**)

Compound **75c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(aminomethyl)-2,4-difluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**75b**) (130 mg, 0.29 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (36 mg, 0.86 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)-2,4-difluorophenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**75c**) (79 mg, 65 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.89 (s, 2H, D_2O exchangeable), 8.07 (d, $J = 2.2$ Hz, 1H), 7.84 (d, $J = 1.6$ Hz, 1H), 7.82 – 7.73 (m, 1H), 7.47 (s, 1H), 7.44 – 7.34 (m, 1H), 7.27 – 7.18 (m, 2H), 7.13 – 7.04 (m, 2H), 6.95 – 6.86 (m, 1H), 5.27 (s, 2H), 4.16 (s, 2H), 3.59 (s, 2H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -112.64, -112.92; MS (ES+): 424.3 (M+1); 446.3 (M+Na); (ES-): 422.3 (M-1), 458.3 (M+Cl).

Scheme-76



Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-(hydroxymethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (76f)

Step-1: Preparation of methyl 2-(((tert-butyldimethylsilyl)oxy)methyl)-7-iodobenzofuran-5-carboxylate (76a)

Compound **76a** was prepared according to the procedure reported in step-1 of Scheme-55, from methyl 4-hydroxy-3,5-diiodobenzoate (**55a**) (5 g, 12.38 mmol) in pyridine (10 mL) using *tert*-butyldimethyl(prop-2-ynyloxy)silane (2.11 g, 12.38 mmol; CAS# 76782-82-6) and copper(I) oxide (0.89 g, 6.19 mmol). This gave after workup and purification by flash column chromatography [silica (80 g), eluting with EtOAc in hexane from 0-70%] methyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-iodobenzofuran-5-carboxylate (**76a**) (3.2 g, 58 % yield) as a clear oil; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.13 (d, $J = 1.6$ Hz, 1H), 8.07 (d, $J = 1.6$ Hz, 1H), 6.95 (s, 1H), 4.72 (s, 2H), 3.74 (s, 3H), 0.76 (s, 9H), -0.00 (s, 6H); MS (ES⁺): 469.1 (M+Na).

Step-2: Preparation of (2-(((tert-butyldimethylsilyl)oxy)methyl)-7-iodobenzofuran-5-yl)methanol (76b)

To a solution of methyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-iodobenzofuran-5-carboxylate (**76a**) (12 g, 26.9 mmol) in THF (150 mL) at -78°C was added LiBH_4 (26.9 mL, 53.8 mmol, 2 M solution in THF) and MeOH (2.2 mL, 53.8 mmol). The reaction mixture was stirred at RT for 24 h, quenched with saturated aqueous NH_4Cl solution and extracted with

EtOAc. The organic layer was washed with brine, dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica (80 g), eluting with EtOAc in hexane from 0-60%] to afford (2-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-iodobenzofuran-5-yl)methanol (**76b**) (10.4 g, 92 % yield) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.62 (d, *J* = 1.5 Hz, 1H), 7.52 (d, *J* = 1.4 Hz, 1H), 6.92 (d, *J* = 1.2 Hz, 1H), 5.25 (t, *J* = 5.8, 1.2 Hz, 1H, D₂O exchangeable), 4.81 (s, 2H), 4.53 (d, *J* = 5.8 Hz, 2H), 0.89 (s, 9H), 0.12 (s, 6H); MS (ES⁺): 441.2 (M⁺Na); (ES⁻): 417.2 (M-1).

Step-3: Preparation of ethyl 2-(2-((2-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**76c**)

Compound **76c** was prepared according to the procedure reported in step-2 of Scheme-23 from (2-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-iodobenzofuran-5-yl)methanol (**76b**) (2.6 g, 6.22 mmol) in DCM (50 mL) using triphenylphosphine (1.79 g, 6.84 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (1.23 g, 6.84 mmol) and di-(4-chlorobenzyl)azodicarboxylate (DCAD, 2.51 g, 6.84 mmol) in DCM (20 mL). This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-50%] ethyl 2-(2-((2-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**76c**) (2.86 g, 79 % yield) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.71 (d, *J* = 1.5 Hz, 1H), 7.64 (d, *J* = 1.5 Hz, 1H), 7.28 – 7.18 (m, 2H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.96 (s, 1H), 6.95 – 6.87 (m, 1H), 5.13 (s, 2H), 4.82 (s, 2H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.61 (s, 2H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.12 (s, 6H).

Step-4: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)benzofuran-5-yl)methoxy)phenyl)acetate (**76d**)

Compound **76d** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((2-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**76c**) (1.2 g, 2.07 mmol) in dioxane (20 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (0.58 g, 3.10 mmol), a solution of K₂CO₃ (0.86 g, 6.20 mmol) in water (4 mL), bis(triphenylphosphine)palladium(II) chloride (0.218 g, 0.310 mmol) and heating at 100 °C for 3h on oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1, v/v) in hexane from 0-70%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(((*tert*-

butyldimethylsilyl)oxy)methyl)benzofuran-5-yl)methoxy)phenyl)acetate (**76d**) (1.01 g, 87 % yield) as a white solid; MS (ES⁺): 560.4 (M+1).

Step-5: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(hydroxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**76e**)

To a solution of ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-((*tert*-butyldimethylsilyl)oxy)methyl)benzofuran-5-yl)methoxy)phenyl)acetate (**76d**)

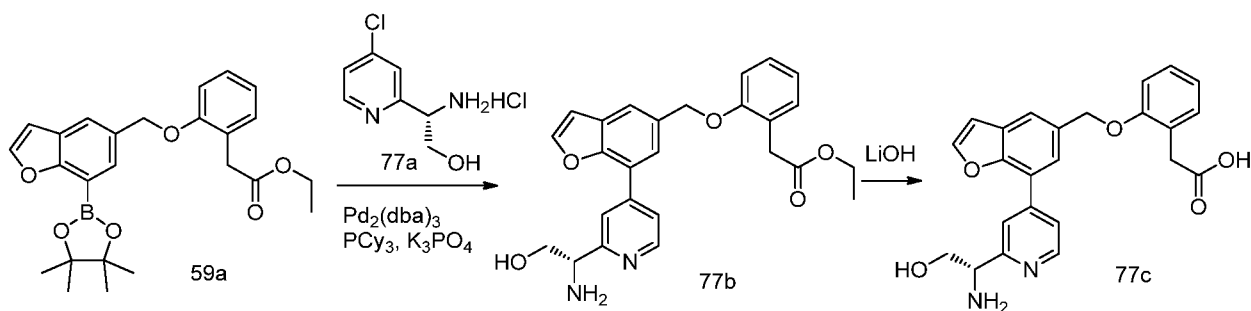
(175 mg, 0.31 mmol) in THF (20 mL) at 0 °C was added TBAF (102 mg, 0.39 mmol). The reaction mixture was allowed to warm to RT over a period of 1h and quenched with saturated aqueous NH₄Cl solution. The reaction mixture was extracted with EtOAc and the combined organic layers were dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-70%] followed by purification using reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] to afford ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(hydroxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**76e**) (70 mg, 50 % yield) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.41 (s, 3H, D₂O exchangeable), 7.98 (s, 1H), 7.92 (dt, *J* = 7.5, 1.7 Hz, 1H), 7.66 (d, *J* = 1.6 Hz, 1H), 7.64 – 7.51 (m, 3H), 7.31 – 7.18 (m, 2H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.96 – 6.87 (m, 1H), 6.85 (s, 1H), 5.55 (t, *J* = 5.9 Hz, 1H, D₂O exchangeable), 5.23 (s, 2H), 4.61 (d, *J* = 5.9 Hz, 2H), 4.13 (s, 2H), 3.94 (q, *J* = 7.1 Hz, 2H), 3.63 (s, 2H), 1.00 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 446.3 (M+1); 468.3 (M+Na); (ES⁻): 480.4 (M+Cl).

Step-6: Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-(hydroxymethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**76f**)

Compound **76f** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(hydroxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**76e**) (700 mg, 1.57 mmol) in MeOH/THF (30 mL) using a solution of lithium hydroxide monohydrate (165 mg, 3.93 mmol) in water (3.0 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)phenyl)-2-(hydroxymethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**76f**) (455 mg, 69 % yield) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.21 (s, 1H, D₂O exchangeable), 8.61 (s, 3H, D₂O exchangeable), 8.02 (s, 1H), 7.96 – 7.89 (m, 1H), 7.69 (d, *J* = 1.6 Hz, 1H), 7.62 (d, *J* = 1.7 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.28 – 7.18 (m, 2H), 7.09 (d, *J* = 8.1 Hz, 1H),

6.90 (t, $J = 7.4$ Hz, 1H), 6.84 (s, 1H), 5.66 – 5.49 (m, 1H, D₂O exchangeable), 5.25 (s, 2H), 4.62 (d, $J = 4.2$ Hz, 2H), 4.13 (s, 2H), 3.60 (s, 2H); MS (ES⁺): 418.3 (M+1); (ES⁻): 416.3 (M-1), 452.3 (M+Cl).

Scheme-77



Preparation of (S)-2-(2-((7-(2-(1-amino-2-hydroxyethyl)pyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**77c**)

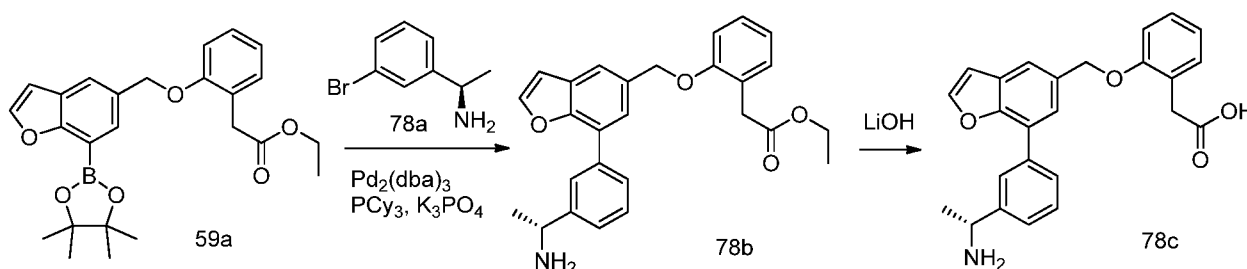
Step-1: Preparation of (S)-ethyl 2-(2-((7-(2-(1-amino-2-hydroxyethyl)pyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**77b**)

Compound **77b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (400 mg, 0.917 mmol) in dioxane (6 mL) using (S)-2-amino-2-(4-chloropyridin-2-yl)ethanol hydrochloride (**77a**) (288 mg, 1.38 mmol; CAS# 1213411-99-4), tripotassium phosphate (3M aqueous, 1.13 mL, 3.39 mmol), tricyclohexylphosphine (77 mg, 0.28 mmol) and Pd₂(dba)₃ (84 mg, 0.092 mmol) under an Ar atmosphere and heating at 120 °C for 90 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-70%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] (S)-ethyl 2-(2-((7-(2-(1-amino-2-hydroxyethyl)pyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**77b**) (215 mg, 53 % yield) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.79 (d, $J = 5.3$ Hz, 1H), 8.64 (d, $J = 5.4$ Hz, 3H, D₂O exchangeable), 8.19 (d, $J = 2.2$ Hz, 1H), 8.15 (d, $J = 1.6$ Hz, 1H), 8.03 (dd, $J = 5.3, 1.6$ Hz, 1H), 7.88 – 7.80 (m, 2H), 7.32 – 7.19 (m, 2H), 7.16 – 7.09 (m, 2H), 6.92 (t, $J = 7.4$ Hz, 1H), 5.27 (s, 2H), 4.61 – 4.49 (m, 1H), 3.99 – 3.82 (m, 4H), 3.65 (s, 2H), 0.99 (t, $J = 7.1$ Hz, 3H); MS (ES⁺): 447.3 (M+1); 469.3 (M+Na); (ES⁻): 481.3 (M+Cl).

Step-2: Preparation of (S)-2-(2-((7-(2-(1-amino-2-hydroxyethyl)pyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**77c**)

Compound **77c** was prepared according to the procedure reported in step-6 of Scheme-1, from (S)-ethyl 2-(2-((7-(2-(1-amino-2-hydroxyethyl)pyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**77b**) (88 mg, 0.20 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (25 mg, 0.59 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] (S)-2-(2-((7-(2-(1-amino-2-hydroxyethyl)pyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**77c**) (31 mg, 38 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.77 (d, J = 5.3 Hz, 1H), 8.63 – 8.41 (m, 3H, D $_2$ O exchangeable), 8.17 (d, J = 2.1 Hz, 1H), 8.10 (s, 1H), 8.00 (dd, J = 5.3, 1.6 Hz, 1H), 7.88 (s, 1H), 7.83 (d, J = 1.6 Hz, 1H), 7.28 – 7.19 (m, 2H), 7.14 – 7.05 (m, 2H), 6.91 (t, J = 7.3 Hz, 1H), 5.29 (s, 2H), 4.60 – 4.51 (m, 1H), 3.91 – 3.85 (m, 2H), 3.60 (s, 2H); MS (ES $^+$): 419.3 (M+1); 441.3 (M+Na); (ES $^-$): 417.3 (M-1), 453.3 (M+Cl).

Scheme-78



Preparation of (R)-2-(2-((7-(3-(1-aminoethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**78c**)

Step-1: Preparation of (R)-ethyl 2-(2-((7-(3-(1-aminoethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**78b**)

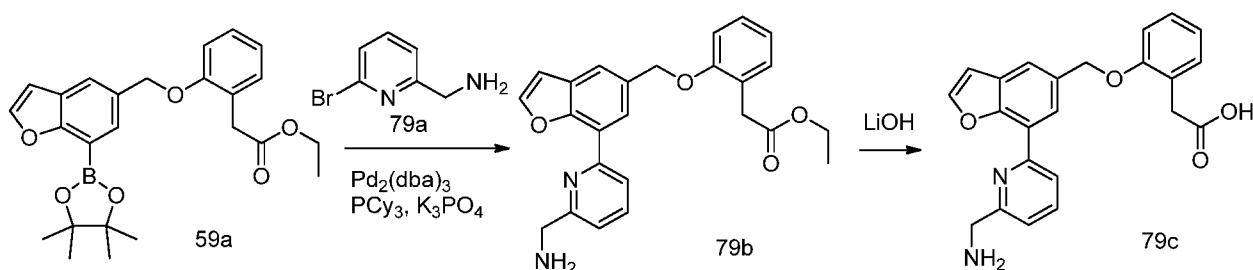
Compound **78b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (450 mg, 1.03 mmol) in dioxane (6 mL) using (R)-1-(3-bromophenyl)ethanamine (**78a**) (351 mg, 1.75 mmol; CAS# 176707-77-0), tripotassium phosphate (3M aqueous, 0.58 mL, 1.75 mmol), tricyclohexylphosphine (87 mg, 0.31 mmol) and $\text{Pd}_2(\text{dba})_3$ (94 mg, 0.10 mmol) under an Ar atmosphere and heating at 120 °C for 90 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-70%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] (R)-ethyl 2-(2-((7-(3-(1-aminoethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**78b**) (300 mg, 68 % yield) HCl salt as a white solid; ^1H NMR

(300 MHz, DMSO- d_6) δ 8.60 (s, 3H, D₂O exchangeable), 8.12 (d, J = 2.2 Hz, 1H), 8.01 (s, 1H), 7.94 – 7.87 (m, 1H), 7.74 (d, J = 1.5 Hz, 1H), 7.67 – 7.55 (m, 3H), 7.31 – 7.20 (m, 2H), 7.16 – 7.10 (m, 1H), 7.08 (d, J = 2.2 Hz, 1H), 6.92 (td, J = 7.4, 1.1 Hz, 1H), 5.25 (s, 2H), 4.57 – 4.43 (m, 1H), 3.93 (q, J = 7.1 Hz, 2H), 3.64 (s, 2H), 1.59 (d, J = 6.8 Hz, 3H), 0.98 (t, J = 7.1 Hz, 3H); MS (ES⁺): 430.3 (M+1); 452.3 (M+Na); (ES⁻): 464.4 (M+Cl).

Step-2: Preparation of (R)-2-(2-((7-(3-(1-aminoethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**78c**)

Compound **78c** was prepared according to the procedure reported in step-6 of Scheme-1, from (R)-ethyl 2-(2-((7-(3-(1-aminoethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**78b**) (156 mg, 0.36 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (46 mg, 1.09 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] (R)-2-(2-((7-(3-(1-aminoethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**78c**) (108 mg, 74 % yield) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO- d_6) δ 12.24 (s, 1H, D₂O exchangeable), 8.62 (s, 3H, D₂O exchangeable), 8.11 (d, J = 2.2 Hz, 1H), 8.02 (s, 1H), 7.95 – 7.88 (m, 1H), 7.76 (d, J = 1.5 Hz, 1H), 7.68 (d, J = 1.6 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.28 – 7.18 (m, 2H), 7.10 (d, J = 8.1 Hz, 1H), 7.06 (d, J = 2.2 Hz, 1H), 6.90 (t, J = 7.3 Hz, 1H), 5.27 (s, 2H), 4.50 (q, J = 5.9 Hz, 1H), 3.60 (s, 2H), 1.60 (d, J = 6.7 Hz, 3H); MS (ES⁺): 402.3 (M+1); (ES⁻): 400.4 (M-1), 436.3 (M+Cl).

Scheme-79



Preparation of 2-(2-((7-(6-(aminomethyl)pyridin-2-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**79c**)

Step-1: Preparation of ethyl 2-(2-((7-(6-(aminomethyl)pyridin-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**79b**)

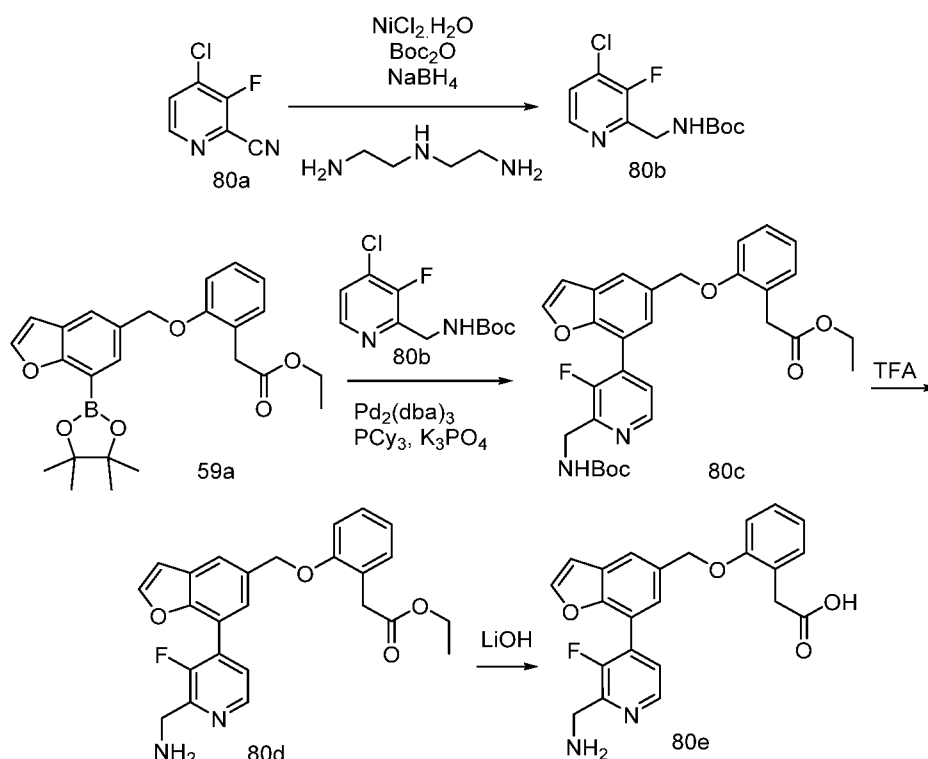
Compound **79b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (450 mg, 1.03 mmol) in dioxane (6 mL) using (6-bromopyridin-2-yl)methanamine (**79a**) (289 mg, 1.55 mmol; CAS# 188637-63-0),

tripotassium phosphate (3M aqueous, 0.58 mL, 1.75 mmol), tricyclohexylphosphine (87 mg, 0.31 mmol) and $\text{Pd}_2(\text{dba})_3$ (94 mg, 0.10 mmol) under an Ar atmosphere and heating at 120 °C for 45 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-70%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(6-(aminomethyl)pyridin-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**79b**) (146 mg, 34 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.69 (s, 3H, D_2O exchangeable), 8.50 (d, $J = 1.6$ Hz, 1H), 8.39 – 8.31 (m, 1H), 8.17 (d, $J = 2.1$ Hz, 1H), 8.06 (t, $J = 7.8$ Hz, 1H), 7.82 (d, $J = 1.7$ Hz, 1H), 7.55 (d, $J = 7.7$ Hz, 1H), 7.32 – 7.19 (m, 2H), 7.17 – 7.06 (m, 2H), 6.92 (t, $J = 7.4$ Hz, 1H), 5.28 (s, 2H), 4.30 (q, $J = 5.9$ Hz, 2H), 3.97 (q, $J = 7.1$ Hz, 2H), 3.64 (s, 2H), 1.01 (t, $J = 7.1$ Hz, 3H); MS (ES⁺): 417.3 (M+1); 439.3 (M+Na).

Step-2: Preparation of 2-(2-((7-(6-(aminomethyl)pyridin-2-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**79c**)

Compound **79c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(6-(aminomethyl)pyridin-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**79b**) (66 mg, 0.16 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (20 mg, 0.48 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(6-(aminomethyl)pyridin-2-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**79c**) (36 mg, 59 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.56 (s, 3H, D_2O exchangeable), 8.48 (d, $J = 1.7$ Hz, 1H), 8.35 (d, $J = 7.9$ Hz, 1H), 8.16 (d, $J = 2.2$ Hz, 1H), 8.05 (t, $J = 7.8$ Hz, 1H), 7.86 (d, $J = 1.7$ Hz, 1H), 7.53 (d, $J = 7.7$ Hz, 1H), 7.29 – 7.19 (m, 2H), 7.14 – 7.05 (m, 2H), 6.91 (t, $J = 7.4$, 1.1 Hz, 1H), 5.30 (s, 2H), 4.35 – 4.28 (m, 2H), 3.61 (s, 2H); MS (ES⁺): 389.3 (M+1); (ES⁻): 387.3.3 (M-1); 423.3 (M+Cl).

Scheme-80



Preparation of 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**80e**)

Step-1: Preparation of *tert*-butyl ((4-chloro-3-fluoropyridin-2-yl)methyl)carbamate (**80b**)

To a solution of 4-chloro-3-fluoropicolonitrile (**80a**) (0.26 g, 1.661 mmol; CAS# 1155847-43-0) in Methanol (15 mL) was added BOC-Anhydride (0.54 g, 2.49 mmol), nickel(II) chloride hydrate (0.025 g, 0.17 mmol). To the reaction mixture was added sodium borohydride (0.19 g, 4.98 mmol) over a period of 2 h. The reaction mixture was quenched with N1-(2-aminoethyl)ethane-1,2-diamine (0.9 mL, 8.30 mmol) and continued stirring at RT for 2 h. The reaction mixture was concentrated in vacuum and the residue obtained was partitioned between water (60 mL) and EtOAc (60 mL). The organic layer was separated and aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine, dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica gel 12 g, eluting with EtOAc in hexanes 0 to 60%] to afford *tert*-butyl ((4-chloro-3-fluoropyridin-2-yl)methyl)carbamate (**80b**) (0.26 g, 60 % yield) as a crystalline solid.

Step-2: Preparation of ethyl 2-(2-((7-(2-(((*tert*-butoxycarbonyl)amino)methyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**80c**)

Compound **80c** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-

yl)methoxy)phenyl)acetate (**59a**) (243 mg, 0.56 mmol) in dioxane (6 mL) using *tert*-butyl ((4-chloro-3-fluoropyridin-2-yl)methyl)carbamate (**80b**) (145 mg, 0.56 mmol), tripotassium phosphate (3M aqueous, 0.32 mL, 0.95 mmol), tricyclohexylphosphine (47 mg, 0.17 mmol) and Pd₂(dba)₃ (51 mg, 0.056 mmol) under an Ar atmosphere and heating at 120 °C for 90 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-70%] ethyl 2-(2-((7-(2-(((*tert*-butoxycarbonyl)amino)methyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**80c**) (185 mg, 62 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.50 (d, *J* = 5.0 Hz, 1H), 8.11 (d, *J* = 2.1 Hz, 1H), 7.85 (d, *J* = 1.5 Hz, 1H), 7.63 (t, *J* = 5.3 Hz, 1H), 7.53 (s, 1H), 7.34 – 7.28 (m, 1H), 7.28 – 7.19 (m, 2H), 7.15 – 7.08 (m, 2H), 6.91 (td, *J* = 7.3, 1.3 Hz, 1H), 5.25 (s, 2H), 3.95 – 3.86 (m, 2H), 3.62 (s, 2H), 3.34 (s, 2H), 1.39 (s, 9H), 1.00 – 0.92 (m, 3H); MS (ES⁺): 535.4 (M+1); 557.4 (M+Na); (ES⁻): 534.3 (M-1).

Step-3: Preparation of ethyl 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**80d**)

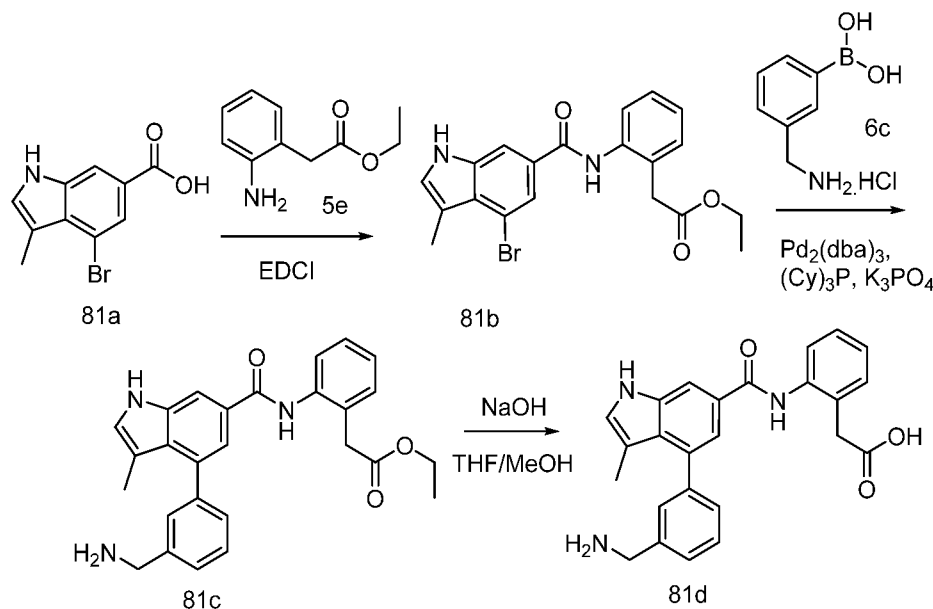
Compound **80d** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-((7-(2-(((*tert*-butoxycarbonyl)amino)methyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**80c**) (182 mg, 0.34 mmol) in DCM (5 mL) using TFA (0.26 mL, 3.40 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] followed by reverse phase column purification [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**80d**) (136 mg, 92 % yield) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.63 (d, *J* = 5.0 Hz, 4H, partially D₂O exchangeable), 8.12 (d, *J* = 2.2 Hz, 1H), 7.89 (d, *J* = 1.6 Hz, 1H), 7.80 (t, *J* = 5.3 Hz, 1H), 7.57 (s, 1H), 7.31 – 7.19 (m, 2H), 7.16 – 7.09 (m, 2H), 6.92 (td, *J* = 7.4, 1.1 Hz, 1H), 5.27 (s, 2H), 4.36 (s, 2H), 3.94 (q, *J* = 7.1, 1.3 Hz, 2H), 3.63 (s, 2H), 1.00 (t, *J* = 7.1, 1.3 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -128.52; MS (ES⁺): 435.3 (M+1); (ES⁻): 469.3 (M+Cl).

Step-4: Preparation of 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**80e**)

Compound **80e** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**80d**) (61 mg, 0.14 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (18 mg, 0.42 mmol) in water (1 mL). This gave

after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**80e**) (32 mg, 56 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 8.73 – 8.58 (m, 4H, partially D_2O exchangeable), 8.11 (d, $J = 2.1$ Hz, 1H), 7.92 (d, $J = 1.6$ Hz, 1H), 7.80 (t, $J = 5.3$ Hz, 1H), 7.61 (s, 1H), 7.28 – 7.19 (m, 2H), 7.14 – 7.06 (m, 2H), 6.91 (t, $J = 7.3$ Hz, 1H), 5.29 (s, 2H), 4.39 – 4.33 (m, 2H), 3.59 (s, 2H); ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ -128.34; MS (ES⁺): 407.2 (M+1); 429.2 (M+Na); (ES⁻): 405.3 (M-1); 441.3 (M+Cl).

Scheme-81



Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-3-methyl-1H-indole-6-carboxamido)phenyl)acetic acid (**81d**)

Step-1: Preparation of ethyl 2-(2-(4-bromo-3-methyl-1H-indole-6-carboxamido)phenyl)acetate (**81b**)

Compound **81b** was prepared according to the procedure reported in step-4 of Scheme-1 from 4-bromo-3-methyl-1H-indole-6-carboxylic acid (**81a**) (0.3 g, 1.18 mmol; CAS# 1360890-98-7) in methanol (10 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (233 mg, 1.30 mmol) and EDCI.HCl (272 mg, 1.42 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc/MeOH (9:1) in hexane from 0-100%] ethyl 2-(2-(4-bromo-3-methyl-1H-indole-6-carboxamido)phenyl)acetate (**81b**) (0.11 g, 22 % yield) as an off white solid; MS (ES⁺): 437.1 & 439.1 (M+Na), MS (ES⁻): 449.2 & 451.1 (M+Cl).

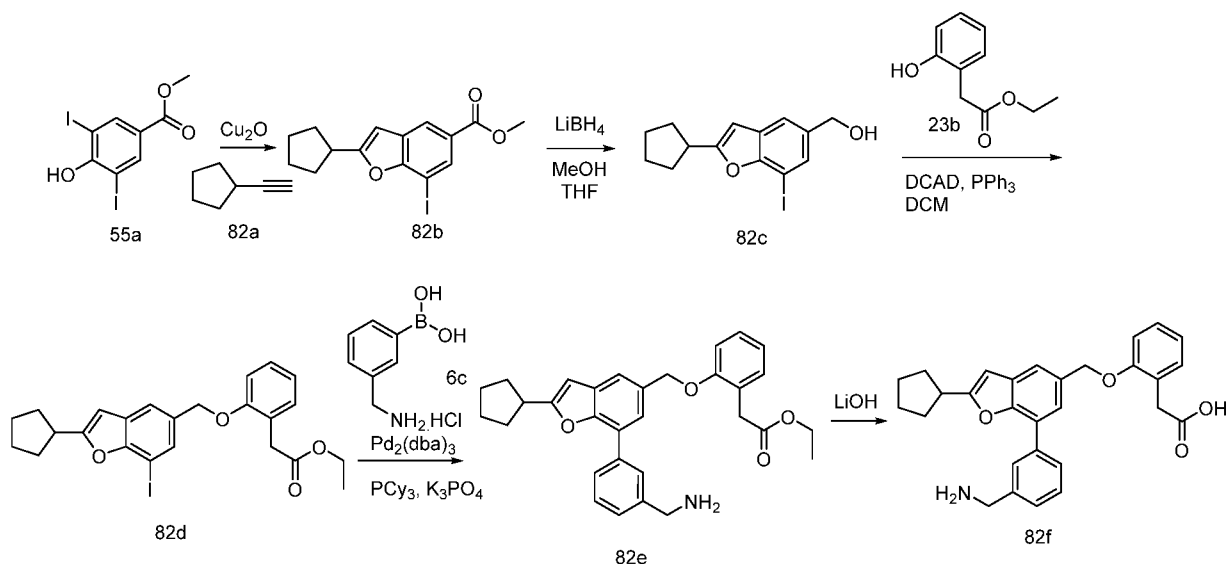
Step-2: Preparation of ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-3-methyl-1H-indole-6-carboxamido)phenyl)acetate (**81c**)

Compound **81c** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(4-bromo-3-methyl-1H-indole-6-carboxamido)phenyl)acetate (**81b**) (60 mg, 0.14 mmol) in dioxane (3 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (41 mg, 0.22 mmol), tripotassium phosphate (1.3M, 0.33 mL, 0.43 mmol), tricyclohexylphosphine (12 mg, 0.04 mmol) and Pd₂(dba)₃ (13 mg, 0.01 mmol) under an Ar atmosphere and heating at 125 °C for 90 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-60%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-3-methyl-1H-indole-6-carboxamido)phenyl)acetate (**81c**) (0.03 g, 39 % yield) HCl salt as a white solid; MS (ES⁺): 442.3 (M+1), MS (ES⁻): 440.4 (M-1).

Step-3: Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-3-methyl-1H-indole-6-carboxamido)phenyl)acetic acid (**81d**)

Compound **81d** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-3-methyl-1H-indole-6-carboxamido)phenyl)acetate (**81c**) (0.02 g, 0.05 mmol) in THF/MeOH (5 mL) using a solution of sodium hydroxide (0.02 g, 0.45 mmol) in water (2 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(4-(3-(aminomethyl)phenyl)-3-methyl-1H-indole-6-carboxamido)phenyl)acetic acid (**81d**) (0.01 g, 43 % yield) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.33 (s, 1H), 11.38 (s, 1H), 9.98 (s, 1H), 8.25 (bs, 3H), 8.06 (s, 1H), 7.57 (m, 1H), 7.54 – 7.44 (m, 4H), 7.39 – 7.24 (m, 3H), 7.21 (m, 1H), 4.13 (d, J = 5.5 Hz, 2H), 3.66 (s, 2H), 1.85 (s, 3H); MS (ES⁺): 414.3 (M+1), 436.3 (M+Na); MS (ES⁻): 412.4 (M-1), 448.3 (M+Cl). HPLC purity: 97.98 %.

Scheme-82



Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-cyclopentylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**82f**)

Step-1: Preparation of methyl 2-cyclopentyl-7-iodobenzofuran-5-carboxylate (**82b**)

Compound **82b** was prepared according to the procedure reported in step-1 of Scheme-55, from methyl 4-hydroxy-3,5-diiodobenzoate (**55a**) (6 g, 14.85 mmol) in pyridine (20 mL) using ethynyl cyclopentane (**82a**) (1.4 g, 14.85 mmol; CAS# 930-51-8) and copper(I) oxide (1.063 g, 7.43 mmol). This gave after workup and purification by flash column chromatography [silica (120g), eluting with EtOAc in hexane from 0-15%] methyl 2-cyclopentyl-7-iodobenzofuran-5-carboxylate (**82b**) (5.1 g, 93 % yield) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.16 (d, *J* = 1.5 Hz, 1H), 8.14 (d, *J* = 1.6 Hz, 1H), 6.90 (d, *J* = 1.0 Hz, 1H), 3.86 (s, 3H), 3.33 – 3.24 (m, 1H), 2.19 – 1.56 (m, 8H).

Step-2: Preparation of (2-cyclopentyl-7-iodobenzofuran-5-yl)methanol (**82c**)

Compound **82c** was prepared according to the procedure reported in step-2 of Scheme-76 from methyl 2-cyclopentyl-7-iodobenzofuran-5-carboxylate (**82b**) (4.48 g, 12.10 mmol) in THF (30 mL) using LiBH₄ (18.15 mL, 36.3 mmol, 2 M solution in THF) and MeOH (1.47 mL, 36.3 mmol). This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-60%] (2-cyclopentyl-7-iodobenzofuran-5-yl)methanol (**82c**) (3.4 g, 82 % yield) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.55 (d, *J* = 1.5 Hz, 1H), 7.44 (d, *J* = 1.4 Hz, 1H), 6.72 (d, *J* = 1.0 Hz, 1H), 5.27 (t, *J* = 5.8 Hz, 1H, D₂O exchangeable), 4.52 (d, *J* = 5.8 Hz, 2H), 3.31 – 3.18 (m, 1H), 2.11 – 2.00 (m, 2H), 1.79 – 1.64 (m, 6H).

Step-3: Preparation of ethyl 2-(2-((2-cyclopentyl-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**82d**)

Compound **82d** was prepared according to the procedure reported in step-2 of Scheme-23 from (2-cyclopentyl-7-iodobenzofuran-5-yl)methanol (**82c**) (3.4 g, 9.94 mmol) in DCM (15 mL) using triphenylphosphine (2.87 g, 10.93 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (1.970 g, 10.93 mmol) and di-(4-chlorobenzyl)azodicarboxylate di-(4-chlorobenzyl)azodicarboxylate (DCAD, 4.01 g, 10.93 mmol) in DCM (20 mL). This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-50%] ethyl 2-(2-((2-cyclopentyl-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**82d**) (3.2 g, 64% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.64 (d, *J* = 1.5 Hz, 1H), 7.56 (d, *J* = 1.5 Hz, 1H), 7.28 – 7.19 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.91 (td, *J* = 7.4, 1.0 Hz, 1H), 6.76 (d, *J* = 1.0 Hz, 1H), 5.12 (s, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.61 (s, 2H), 3.31 – 3.20 (m, 1H), 2.12 – 1.98 (m, 2H), 1.80 – 1.64 (m, 6H), 1.09 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 527.2 (M+Na); (ES⁻): 503.3 (M-1).

Step-4: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-cyclopentylbenzofuran-5-yl)methoxy)phenyl)acetate (**82e**)

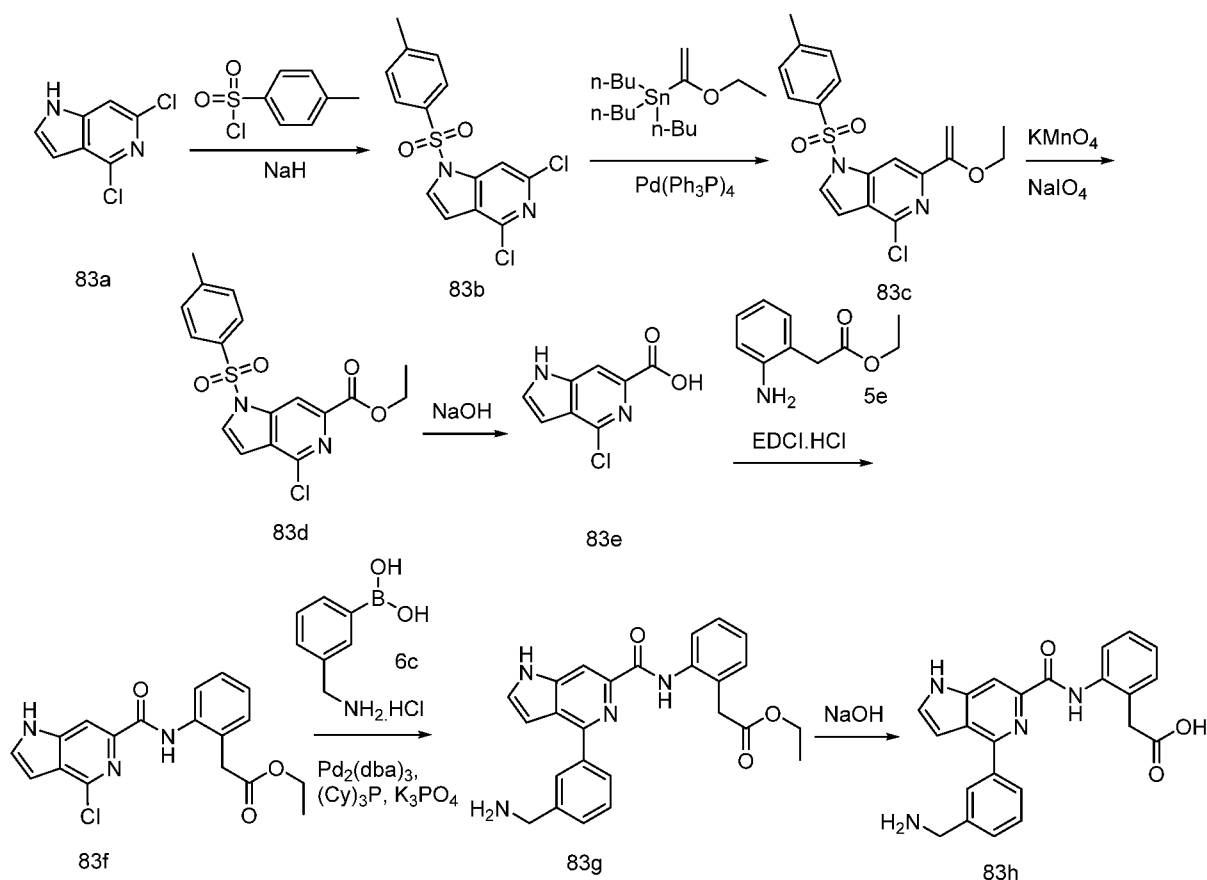
Compound **82e** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((2-cyclopentyl-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**82d**) (500 mg, 0.99 mmol) in dioxane (20 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (279 mg, 1.49 mmol), a 3 M solution of tripotassium phosphate (1.223 mL, 3.67 mmol) in water (1 mL), tricyclohexylphosphine (83 mg, 0.30 mmol) and Pd₂(dba)₃ (91 mg, 0.1 mmol) and heating at 125 °C for 60 min on a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-70%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-cyclopentylbenzofuran-5-yl)methoxy)phenyl)acetate (**82e**) (223 mg, 47 % yield) HCl salt as an off white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.47 (s, 3H, D₂O exchangeable), 7.99 – 7.95 (m, 1H), 7.92 (dt, *J* = 7.3, 1.8 Hz, 1H), 7.63 – 7.51 (m, 4H), 7.29 – 7.18 (m, 2H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.91 (t, *J* = 7.3 Hz, 1H), 6.71 – 6.66 (m, 1H), 5.22 (s, 2H), 4.12 (s, 2H), 3.95 (q, *J* = 7.1 Hz, 2H), 3.62 (s, 2H), 2.13 – 1.98 (m, 2H), 1.85 – 1.59 (m, 7H), 1.01 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 484.4 (M+1).

Step-5: Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-cyclopentylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**82f**)

Compound **82f** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-cyclopentylbenzofuran-5-yl)methoxy)phenyl)acetate (**82e**) (150 mg, 0.31 mmol) in MeOH/THF (10 mL) using a

solution of lithium hydroxide monohydrate (39 mg, 0.93 mmol) in water (1.0 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)phenyl)-2-cyclopentylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**82f**) (52 mg, 37% yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 12.13 (s, 1H, D $_2$ O exchangeable), 8.40 (s, 2H, D $_2$ O exchangeable), 7.98 – 7.89 (m, 2H), 7.64 – 7.60 (m, 1H), 7.60 – 7.50 (m, 3H), 7.22 (d, J = 7.4 Hz, 2H), 7.08 (d, J = 8.1 Hz, 1H), 6.90 (t, J = 7.3 Hz, 1H), 6.68 (s, 1H), 5.23 (s, 2H), 4.13 (s, 2H), 3.59 (s, 2H), 2.50 – 2.49 (m, 1H), 2.13 – 1.98 (m, 2H), 1.83 – 1.61 (m, 6H); MS (ES $^+$): 456.3 (M+1); (ES $^-$): 454.3 (M-1); 490.3 (M+Cl).

Scheme-83



Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-1H-pyrrolo[3,2-c]pyridine-6-carboxamido)phenyl)acetic acid (**83h**)

Step-1: Preparation of 4,6-dichloro-1-tosyl-1H-pyrrolo[3,2-c]pyridine (**83b**)

Compound **83b** was prepared according to the procedure reported in step-1 of Scheme-40 from 4,6-dichloro-1H-pyrrolo[3,2-c]pyridine (**83a**) (4 g, 21.39 mmol; CAS #67139-79-1) in DMF (30 mL) using NaH (60% in mineral oil, 2.14 g, 53.5 mmol) and tosyl-Cl (4.89 g, 25.7 mmol). This gave after workup 4,6-dichloro-1-tosyl-1H-pyrrolo[3,2-c]pyridine (**83b**) (6.8 g,

93 % yield) as a tan solid, which was used in the next step without further purification. ^1H NMR (300 MHz, DMSO-*d*₆) δ 8.11 (d, *J* = 3.8 Hz, 1H), 8.09 - 8.02 (d, *J* = 8.4 Hz, 2H), 7.98 (s, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 6.96 (d, *J* = 3.8 Hz, 1H), 2.36 (s, 3H).

Step-2: Preparation of 4-chloro-6-(1-ethoxyvinyl)-1-tosyl-1H-pyrrolo[3,2-*c*]pyridine (**83c**)

Compound **83c** was prepared according to the procedure reported in step-1 of Scheme-1 from 4,6-dichloro-1-tosyl-1H-pyrrolo[3,2-*c*]pyridine (**83b**) (3 g, 8.79 mmol) in DMF (20 mL) using 1-ethoxyvinyltri-*n*-butyltin (3.89 mL, 11.43 mmol) and Pd(Ph₃P)₄ (1.02 g, 0.88 mmol) in argon atmosphere and heating at 110 °C for 2 h. This gave after workup and purification by flash column chromatography [silica (80 g), eluting with EtOAc in hexane from 0-50%] 4-chloro-6-(1-ethoxyvinyl)-1-tosyl-1H-pyrrolo[3,2-*c*]pyridine (**83c**) (1.6 g, 48 % yield) as a white solid; MS (ES⁺): 377.2 (M+1), 399.2 (M+Na).

Step-3: Preparation of ethyl 4-chloro-1-tosyl-1H-pyrrolo[3,2-*c*]pyridine-6-carboxylate (**83d**)

Compound **83d** was prepared according to the procedure reported in step-2 of Scheme-1 from 4-chloro-6-(1-ethoxyvinyl)-1-tosyl-1H-pyrrolo[3,2-*c*]pyridine (**83c**) (1 g, 2.65 mmol) in 1,4-dioxane (100 mL) using sodium periodate solution (1.14 g, 5.31 mmol) in water (10 mL) and KMnO₄ (0.252 g, 1.592 mmol, and second dosing of 0.25 g, 1.59 mmol after 12 h). This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-60%] ethyl 4-chloro-1-tosyl-1H-pyrrolo[3,2-*c*]pyridine-6-carboxylate (**83d**) (0.21 g, 21 % yield) as a yellow solid; MS (ES⁺): 379.1 (M+1), 401.2 (M+Na).

Step-4: Preparation of 4-chloro-1H-pyrrolo[3,2-*c*]pyridine-6-carboxylic acid (**83e**)

Compound **83e** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 4-chloro-1-tosyl-1H-pyrrolo[3,2-*c*]pyridine-6-carboxylate (**83d**) (0.2 g, 0.53 mmol) in THF/MeOH (5 mL) using sodium hydroxide (0.13 g, 3.17 mmol) in water (2 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 4-chloro-1H-pyrrolo[3,2-*c*]pyridine-6-carboxylic acid (**83e**) (0.07 g, 63 % yield) HCl salt as a yellow solid; ^1H NMR (300 MHz, DMSO-*d*₆) δ 13.22 (s, 1H), 11.93 (s, 1H), 7.66 (s, 2H), 6.97 (s, 1H). MS (ES⁻): 195.1 (M-1), 231.1 (M+Cl).

Step-5: Preparation of ethyl 2-(2-(4-chloro-1H-pyrrolo[3,2-*c*]pyridine-6-carboxamido)phenyl)acetate (**83f**)

Compound **83f** was prepared according to the procedure reported in step-4 of Scheme-1 from 4-chloro-1H-pyrrolo[3,2-*c*]pyridine-6-carboxylic acid (**83e**) (0.06 g, 0.31 mmol) in MeOH (5 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (0.06 g, 0.34 mmol), and EDCl.HCl (0.07 g,

0.37 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] ethyl 2-(2-(4-chloro-1H-pyrrolo[3,2-c]pyridine-6-carboxamido)phenyl)acetate (**83f**) (0.02 g, 18 % yield) as an off white solid; MS (ES⁺): 358.3 (M+1), 380.2 (M+Na); MS (ES⁻): 356.2 (M-1), 392.3 (M+Cl).

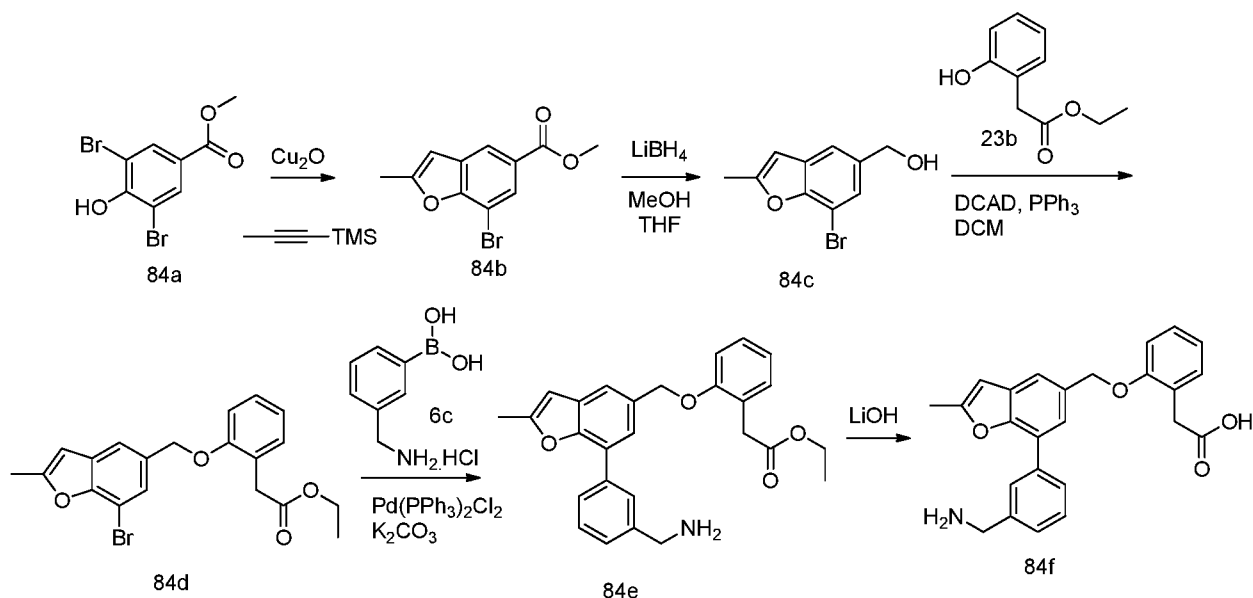
Step-6: Preparation of ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-1H-pyrrolo[3,2-c]pyridine-6-carboxamido)phenyl)acetate (**83g**)

Compound **83g** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-(4-chloro-1H-pyrrolo[3,2-c]pyridine-6-carboxamido)phenyl)acetate (**83f**) (0.02 g, 0.06 mmol) in dioxane (4 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (0.02 g, 0.08 mmol), tripotassium phosphate (1.3M, 0.03 mL, 0.10 mmol), tricyclohexylphosphine (5 mg, 0.02 mmol) and Pd₂(dba)₃ (5 mg, 5.59 μmol) under an Ar atmosphere and heating at 125 °C for 90 min in a microwave. This gave after workup, purification by flash column chromatography [silica (24 g), eluting with hexane in ethyl acetate from 0-70%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-1H-pyrrolo[3,2-c]pyridine-6-carboxamido)phenyl)acetate (**83g**) (0.02 g, 84 % yield) as a white solid; MS (ES⁺): 429.3 (M+1); MS (ES⁻): 427.4 (M-1), 463.5 (M+Cl).

Step-7: Preparation of 2-(2-(4-(3-(aminomethyl)phenyl)-1H-pyrrolo[3,2-c]pyridine-6-carboxamido)phenyl)acetic acid (**83h**)

Compound **83h** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(4-(3-(aminomethyl)phenyl)-1H-pyrrolo[3,2-c]pyridine-6-carboxamido)phenyl)acetate (**83g**) (0.02 g, 0.05 mmol) in MeOH/THF (5 mL) using a solution of NaOH (0.15 mL, 0.37 mmol, 2.5 M) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(4-(3-(aminomethyl)phenyl)-1H-pyrrolo[3,2-c]pyridine-6-carboxamido)phenyl)acetic acid (**83h**) (0.01 g, 59 % yield) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.24 (s, 1H), 10.80 (s, 1H), 8.69 (s, 3H), 8.47 (s, 1H), 8.26 (t, J = 5.0 Hz, 1H), 8.23 (s, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.68 (t, J = 2.7 Hz, 1H), 7.55 (m, 2H), 7.37 (m, 2H), 7.23 (s, 1H), 7.18 (t, J = 7.3 Hz, 1H), 4.15 (d, J = 5.8 Hz, 2H), 3.80 (s, 2H); MS (ES⁺): 401.3 (M+1), 423.3 (M+Na); MS (ES⁻): 399.4 (M-1), 435.3 (M+Cl). HPLC purity: 98.19%.

Scheme-84



Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**84f**)

Step-1: Preparation of methyl 7-bromo-2-methylbenzofuran-5-carboxylate (**84b**)

Compound **84b** was prepared according to the procedure reported in step-1 of Scheme-55, from methyl 3,5-dibromo-4-hydroxybenzoate (**84a**) (150 g, 484 mmol; CAS# 41727-47-3) in pyridine (500 mL) using 1-(trimethylsilyl)-1-propyne (54.3 g, 484 mmol; CAS# 6224-91-5) and copper(I) oxide (69.3 g, 484 mmol). This gave after workup and purification by flash column chromatography [silica (330g), eluting with EtOAc in hexane from 0-70%] methyl 7-bromo-2-methylbenzofuran-5-carboxylate (**84b**) (76 g, 58 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.18 (d, *J* = 1.5 Hz, 1H), 7.97 (d, *J* = 1.5 Hz, 1H), 6.85 (d, *J* = 1.3 Hz, 1H), 3.88 (s, 3H), 2.52 (s, 3H).

Step-2: Preparation of (7-bromo-2-methylbenzofuran-5-yl)methanol (**84c**)

Compound **84c** was prepared according to the procedure reported in step-2 of Scheme-76 from methyl 7-bromo-2-methylbenzofuran-5-carboxylate (**84b**) (67 g, 249 mmol) in THF (500 mL) using LiBH₄ (2 M in THF, 311 mL, 622 mmol) and MeOH (25.2 mL, 622 mmol). This gave after workup (7-bromo-2-methylbenzofuran-5-yl)methanol (**84c**) (60 g, 100 % yield) as a clear oil, which turned into a white solid after standing at RT. This compound was used in the next step without further purification; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.46 (d, *J* = 1.4 Hz, 1H), 7.39 (d, *J* = 1.5 Hz, 1H), 6.68 (d, *J* = 1.3 Hz, 1H), 5.31 (t, *J* = 5.8 Hz, 1H), 4.55 (d, *J* = 5.7 Hz, 2H), 2.48 (s, 3H).

Step-3: Preparation of ethyl 2-(2-((7-bromo-2-methylbenzofuran-5-yl)methoxy)phenyl)acetate (**84d**)

Compound **84d** was prepared according to the procedure reported in step-2 of Scheme-23 from (7-bromo-2-methylbenzofuran-5-yl)methanol (**84c**) (2.2 g, 9.13 mmol) in DCM (15 mL) using triphenylphosphine (2.87 g, 10.93 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (1.81 g, 10.04 mmol) and di-(4-chlorobenzyl)azodicarboxylate (DCAD, 3.69 g, 10.04 mmol) in DCM (20 mL). This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-50%] ethyl 2-(2-((7-bromo-2-methylbenzofuran-5-yl)methoxy)phenyl)acetate (**84d**) (2.2 g, 60 % yield) as a white solid; ¹H NMR (300 MHz, Chloroform-*d*) δ 7.50 – 7.43 (m, 2H), 7.31 – 7.19 (m, 2H), 7.03 – 6.91 (m, 2H), 6.49 – 6.41 (m, 1H), 5.12 (s, 2H), 4.15 (q, $J = 7.1$ Hz, 2H), 3.69 (s, 2H), 2.53 (d, $J = 1.1$ Hz, 3H), 1.22 (t, $J = 7.1$ Hz, 3H).

Step-4: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetate (**84e**)

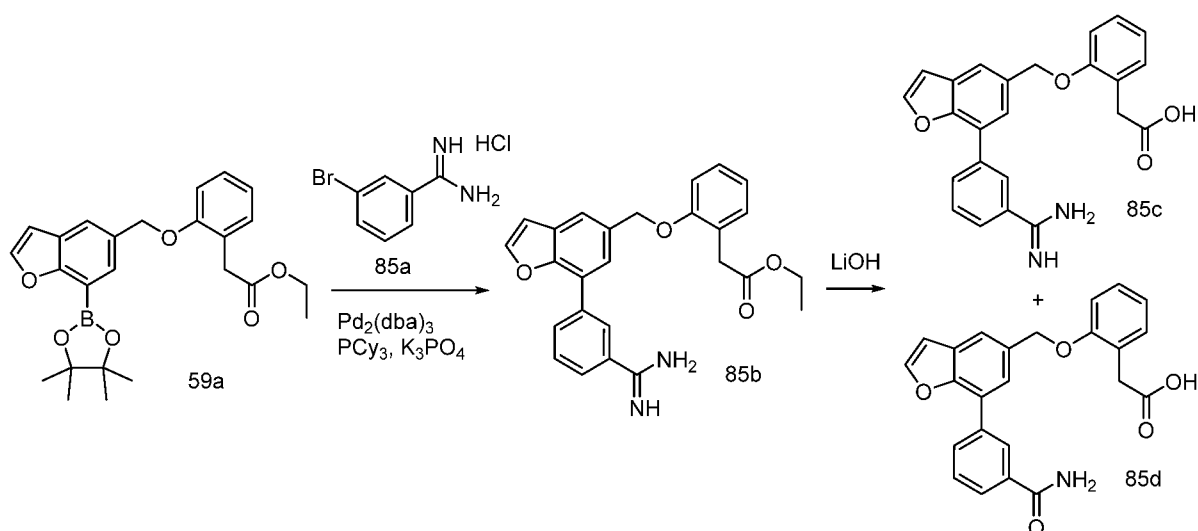
Compound **84e** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-bromo-2-methylbenzofuran-5-yl)methoxy)phenyl)acetate (**84d**) (500 mg, 1.24 mmol) in dioxane (15 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (302 mg, 1.61 mmol), bis(triphenylphosphine)palladium(II) chloride (131 mg, 0.186 mmol), a solution of K₂CO₃ (514 mg, 3.72 mmol) in water (3 mL) and heating under an argon atmosphere at 100 °C for 3h on an oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetate (**84e**) (160 mg, 30 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.45 (s, 3H, D₂O exchangeable), 7.99 – 7.93 (m, 1H), 7.93 – 7.85 (m, 1H), 7.62 – 7.53 (m, 3H), 7.52 – 7.48 (m, 1H), 7.30 – 7.19 (m, 2H), 7.17 – 7.07 (m, 1H), 6.97 – 6.86 (m, 1H), 6.67 (d, $J = 1.4$ Hz, 1H), 5.21 (s, 2H), 4.13 (s, 2H), 3.95 (q, $J = 7.1$ Hz, 2H), 3.69 (s, 2H), 2.49 (s, 3H), 1.01 (t, $J = 7.1, 1.6$ Hz, 3H); MS (ES⁺): 430.3 (M+1).

Step-5: Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**84f**)

Compound **84f** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetate (**84e**) (46 mg, 0.11 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (14 mg, 0.32 mmol) in water (1.0 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)phenyl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetic

acid (**84f**) (17 mg, 40% yield) HCl salt as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.21 (s, 1H, D_2O exchangeable), 8.40 (s, 3H, D_2O exchangeable), 8.02 – 7.86 (m, 2H), 7.65 – 7.50 (m, 4H), 7.29 – 7.17 (m, 2H), 7.09 (d, $J = 8.1$ Hz, 1H), 6.90 (t, $J = 7.4$ Hz, 1H), 6.66 (s, 1H), 5.23 (s, 2H), 4.14 (s, 2H), 3.59 (s, 2H), 2.50 (s, 3H); MS (ES⁺): 402.3 (M+1); (ES⁻): 400.4 (M-1), 436.3 (M+Cl).

Scheme-85



Preparation of 2-(2-((7-(3-carbamimidoylphenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**85c**) and 2-(2-((7-(3-carbamoylphenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**85d**)

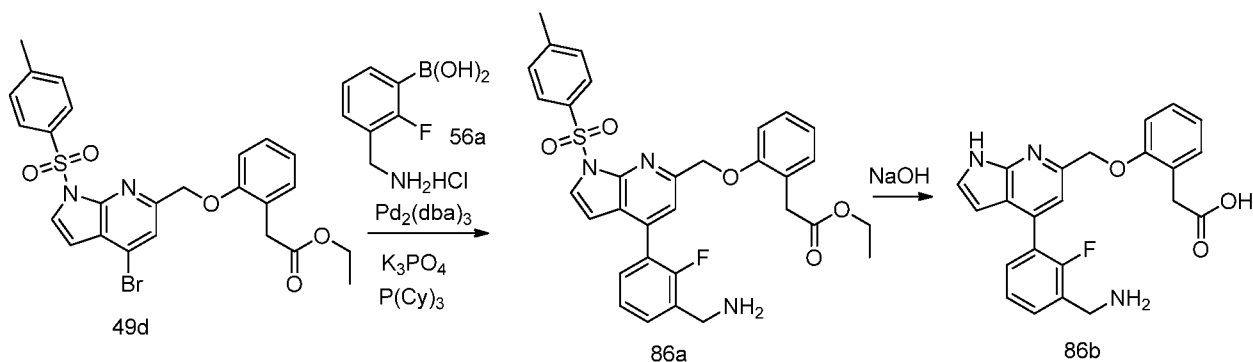
Step-1: Preparation of ethyl 2-(2-((7-(3-carbamimidoylphenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**85b**)

Compound **85b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (400 mg, 0.92 mmol) in dioxane (6 mL) using 3-bromobenzimidamide hydrochloride (**85a**) (367 mg, 1.56 mmol; CAS# 16796-52-4), tripotassium phosphate (3M aqueous, 0.92 mL, 2.75 mmol), tricyclohexylphosphine (77 mg, 0.28 mmol) and $\text{Pd}_2(\text{dba})_3$ (84 mg, 0.092 mmol) under an Ar atmosphere and heating at 120 °C for 90 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-70%] ethyl 2-(2-((7-(3-carbamimidoylphenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**85b**) (120 mg, 31 % yield) as a yellow solid; MS (ES⁺): 429.3 (M+1).

Step-2: Preparation of 2-(2-((7-(3-carbamimidoylphenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**85c**) and 2-(2-((7-(3-carbamoylphenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**85d**)

Compounds **85c** and **85d** were prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-carbamimidoylphenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**85b**) (120 mg, 0.28 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (35 mg, 0.84 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-carbamimidoylphenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**85c**) (10 mg, 9 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 12.20 (s, 1H, D₂O exchangeable), 9.45 (s, 2H, D₂O exchangeable), 9.19 (s, 2H, D₂O exchangeable), 8.35 – 8.21 (m, 2H), 8.12 (d, J = 2.2 Hz, 1H), 7.92 – 7.83 (m, 1H), 7.83 – 7.74 (m, 3H), 7.29 – 7.17 (m, 2H), 7.16 – 7.03 (m, 2H), 6.91 (t, J = 7.3 Hz, 1H), 5.29 (s, 2H), 3.60 (s, 2H); MS (ES⁺): 401.3 (M+1); 423.3 (M+Na); (ES⁻): 435.4 (M+Cl); and 2-(2-((7-(3-carbamoylphenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**85d**) (37 mg, 33 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 12.19 (s, 1H, D₂O exchangeable), 8.38 (t, J = 1.8 Hz, 1H), 8.11 (d, J = 2.2 Hz, 1H), 8.09 – 8.02 (m, 2H, D₂O exchangeable, 1H), 7.97 – 7.88 (m, 1H), 7.77 (d, J = 1.6 Hz, 1H), 7.69 (d, J = 1.6 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.47 (s, 1H), 7.28 – 7.17 (m, 2H), 7.11 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 2.2 Hz, 1H), 6.96 – 6.84 (m, 1H), 5.28 (s, 2H), 3.60 (s, 2H); MS (ES⁺) 402.2 (M+1); 424.3 (M+Na); (ES⁻) 400.3 (M-1), 436.3 (M+Cl).

Scheme-86



Preparation of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)methoxy)phenyl)acetic acid (**86b**)

Step-1: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-tosyl-1H-pyrrolo[2,3-b]pyridin-6-yl)methoxy)phenyl)acetate (**86a**)

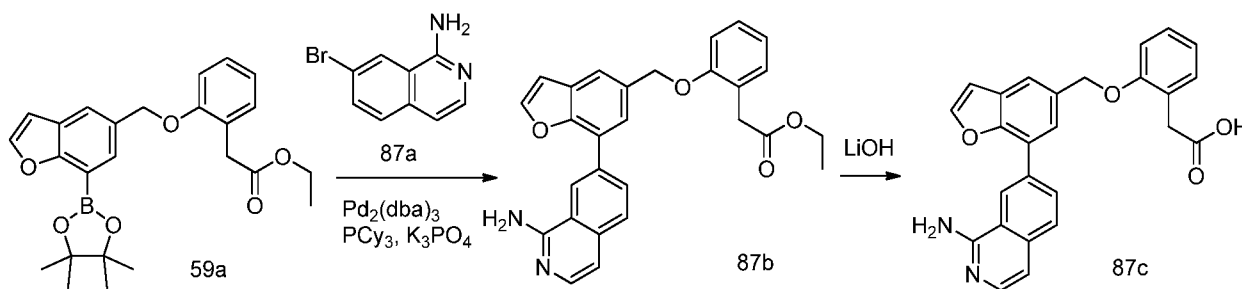
Compound **86a** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((4-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridin-6-yl)methoxy)phenyl)acetate (**49d**) (0.08 g, 0.15 mmol) in dioxane (4 mL) using 3-(aminomethyl)-2-fluorophenylboronic acid hydrochloride (**56a**) (0.045 g, 0.221 mmol), tripotassium phosphate (1.3 M solution, 0.08 mL,

0.25 mmol), tricyclohexylphosphine (0.01 g, 0.04 mmol) and $\text{Pd}_2(\text{dba})_3$ (0.01 g, 0.02 mmol) under an Ar atmosphere and heating at 125 °C for 90 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-60%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-tosyl-1H-pyrrolo[2,3-b]pyridin-6-yl)methoxy)phenyl)acetate (**86a**) (0.06 g, 71 % yield) as a white solid, which was used as such for next step.

Step-2: Preparation of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)methoxy)phenyl)acetic acid (**86b**)

Compound **86b** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-tosyl-1H-pyrrolo[2,3-b]pyridin-6-yl)methoxy)phenyl)acetate (**86a**) (0.06 g, 0.10 mmol) in MeOH/THF (6 mL, 1:1) using a solution of sodium hydroxide (0.41 mL, 1.02 mmol, 2.5 M) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)methoxy)phenyl)acetic acid (**86b**) (0.02 g, 44 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 11.89 (s, 1H), 8.55 (s, 3H), 7.67 (m, 2H), 7.56 (t, $J = 2.9$ Hz, 1H), 7.44 (m, 1H), 7.34 (s, 1H), 7.21 (m, 2H), 7.09 (m, 1H), 6.90 (t, $J = 7.3$ Hz, 1H), 6.45 (q, $J = 2.7$ Hz, 1H), 5.29 (s, 2H), 4.16 (q, $J = 5.9$ Hz, 2H), 3.60 (s, 2H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -118.12; MS (ES⁺): 406.3 (M+1); MS (ES⁻): 404.3 (M-1), 440.3 (M+Cl). HPLC purity: 98.61%.

Scheme-87



Preparation of 2-(2-((7-(1-aminoisoquinolin-7-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**87c**)

Step-1: Preparation of ethyl 2-(2-((7-(1-aminoisoquinolin-7-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**87b**)

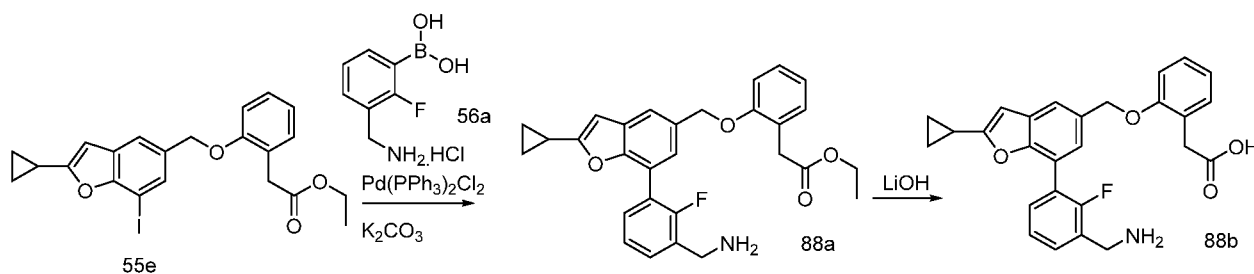
Compound **87b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-

yl)methoxy)phenyl)acetate (**59a**) (400 mg, 0.92 mmol) in dioxane (3 mL) using 7-bromoisoquinolin-1-amine (**87a**) (307 mg, 1.38 mmol; CAS# 215453-53-5), tripotassium phosphate (3M aqueous, 0.52 mL, 1.56 mmol), tricyclohexylphosphine (77 mg, 0.28 mmol) and $\text{Pd}_2(\text{dba})_3$ (84 mg, 0.092 mmol) under an Ar atmosphere and heating at 120 °C for 60 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-70%] ethyl 2-(2-((7-(1-aminoisoquinolin-7-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**87b**) (154 mg, 37 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 13.39 (s, 1H, D_2O exchangeable), 9.21 (s, 2H, D_2O exchangeable), 9.05 (d, $J = 1.7$ Hz, 1H), 8.50 (dd, $J = 8.5, 1.6$ Hz, 1H), 8.17 – 8.09 (m, 2H), 7.84 – 7.78 (m, 2H), 7.75 (d, $J = 6.8$ Hz, 1H), 7.31 (d, $J = 6.8$ Hz, 1H), 7.29 – 7.20 (m, 2H), 7.14 (d, $J = 8.5$ Hz, 1H), 7.12 – 7.10 (m, 1H), 6.92 (t, $J = 7.4, 1.1$ Hz, 1H), 5.29 (s, 2H), 3.90 (q, $J = 7.1, 1.5$ Hz, 2H), 3.65 (s, 2H), 0.94 (t, $J = 7.1, 1.4$ Hz, 3H); MS (ES⁺): 453.3 (M+1); (ES⁻): 487.3 (M+Cl).

Step-2: Preparation of 2-(2-((7-(1-aminoisoquinolin-7-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**87c**)

Compound **87c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(1-aminoisoquinolin-7-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**87b**) (114 mg, 0.25 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (32 mg, 0.76 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(1-aminoisoquinolin-7-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**87c**) (32 mg, 30% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 13.28 (s, 1H, D_2O exchangeable), 12.20 (s, 1H, D_2O exchangeable), 9.10 (s, 2H, D_2O exchangeable), 9.02 (s, 1H), 8.49 (dd, $J = 8.4, 1.6$ Hz, 1H), 8.17 – 8.06 (m, 2H), 7.86 – 7.78 (m, 2H), 7.74 (d, $J = 6.9$ Hz, 1H), 7.34 – 7.26 (m, 1H), 7.23 (d, $J = 7.6$ Hz, 2H), 7.17 – 7.06 (m, 2H), 6.91 (t, $J = 7.2$ Hz, 1H), 5.31 (s, 2H), 3.61 (s, 2H); MS (ES⁺): 425.3 (M+1); (ES⁻): 423.3 (M-1), 459.3 (M+Cl).

Scheme-88



Preparation of 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-cyclopropylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**88b**)

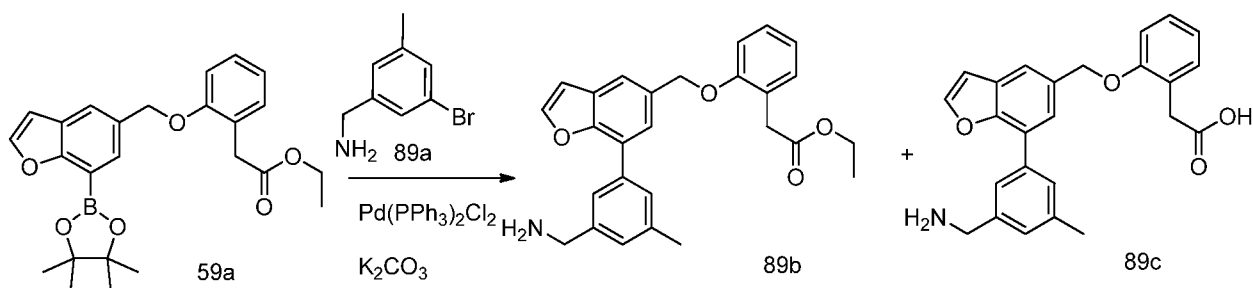
Step-1: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-cyclopropylbenzofuran-5-yl)methoxy)phenyl)acetate (**88a**)

Compound **88a** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((2-cyclopropyl-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**55e**) (500 mg, 1.05 mmol) in dioxane (15 mL) using 3-(aminomethyl)-2-fluorophenylboronic acid hydrochloride (**56a**) (345 mg, 1.68 mmol), bis(triphenylphosphine)palladium(II) chloride (111 mg, 0.16 mmol) and a solution of K₂CO₃ (435 mg, 3.15 mmol) in water (3 mL) under an Ar atmosphere and heating at 100 °C for 3h on oil bath. This gave after workup, purification by flash column chromatography [silica (40 g), eluting with DMA80 in DCM from 0-50%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-cyclopropylbenzofuran-5-yl)methoxy)phenyl)acetate (**88a**) (299 mg, 60 % yield) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.57 (s, 3H, D₂O exchangeable), 7.73 – 7.57 (m, 3H), 7.42 (t, *J* = 7.7 Hz, 1H), 7.31 (s, 1H), 7.28 – 7.17 (m, 2H), 7.10 (d, *J* = 8.2 Hz, 1H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.65 (s, 1H), 5.20 (s, 2H), 4.17 (s, 2H), 3.94 (q, *J* = 7.1 Hz, 2H), 3.61 (s, 2H), 2.15 – 2.03 (m, 1H), 1.07 – 0.93 (m, 5H), 0.89 – 0.81 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -118.85; MS (ES⁺): 474.3 (M+1).

Step-2: Preparation of 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-cyclopropylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**88b**)

Compound **88b** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-cyclopropylbenzofuran-5-yl)methoxy)phenyl)acetate (**88a**) (185 mg, 0.39 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (49 mg, 1.17 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-cyclopropylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**88b**) (135 mg, 78 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.66 (s, 2H, D₂O exchangeable), 7.73 – 7.59 (m, 3H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 1.4 Hz, 1H), 7.26 – 7.17 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.89 (t, *J* = 7.4, 1.1 Hz, 1H), 6.63 (s, 1H), 5.21 (s, 2H), 4.17 (s, 2H), 3.57 (s, 2H), 2.14 – 2.06 (m, 1H), 1.06 – 0.93 (m, 2H), 0.89 – 0.80 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -118.64; MS (ES⁺): 446.3 (M+1); 468.3 (M+Na); (ES⁻): 444.4 (M-1), 480.3 (M+Cl).

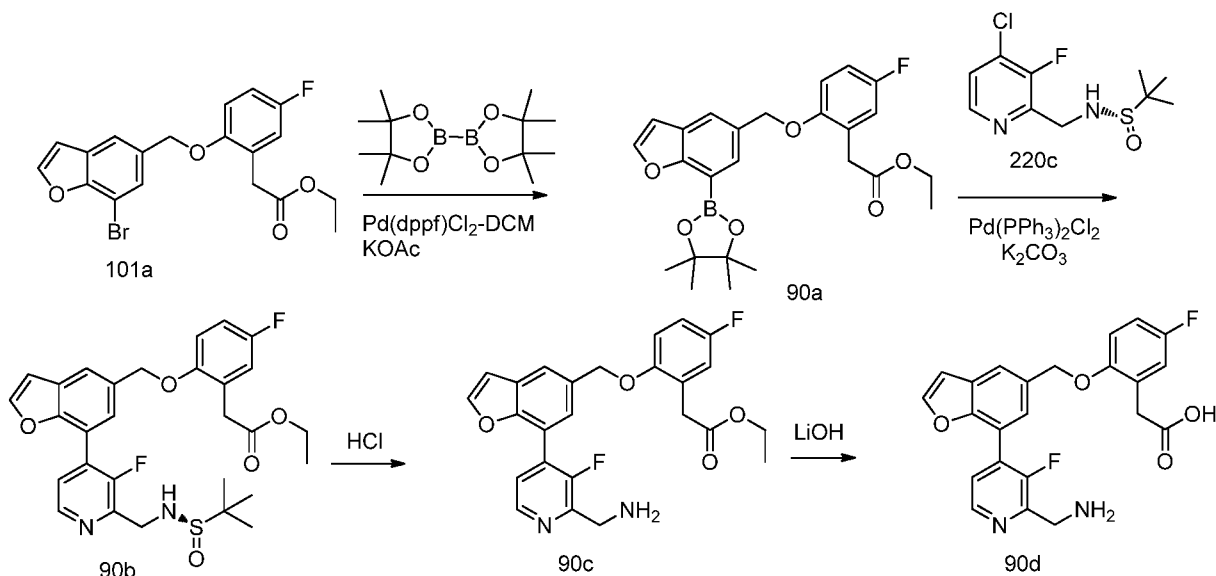
Scheme-89



Preparation of 2-(2-((7-(3-(aminomethyl)-5-methylphenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**89c**)

Compound **89c** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (327 mg, 0.75 mmol) in dioxane (15 mL) using (3-bromo-5-methylphenyl)methanamine (**89a**) (150 mg, 0.75 mmol; CAS# 1177558-42-7), bis(triphenylphosphine)palladium(II) chloride (79 mg, 0.112 mmol), a solution of K₂CO₃ (311 mg, 2.25 mmol) in water (3 mL) under an Ar atmosphere and heating at 100 °C for 13h on an oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1%) HCl] from 0-100%] ethyl 2-(2-((7-(3-(aminomethyl)-5-methylphenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**89b**) (83 mg, 26 % yield) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.46 (s, 3H, D₂O exchangeable), 8.10 (d, *J* = 2.3 Hz, 1H), 7.80 (d, *J* = 1.9 Hz, 1H), 7.72 (d, *J* = 1.7 Hz, 2H), 7.60 (d, *J* = 1.7 Hz, 1H), 7.39 (s, 1H), 7.29 – 7.18 (m, 2H), 7.15 – 7.08 (m, 1H), 7.08 – 7.03 (m, 1H), 6.96 – 6.85 (m, 1H), 5.24 (s, 2H), 4.08 (s, 2H), 3.95 (q, *J* = 7.1 Hz, 2H), 3.63 (s, 2H), 2.43 (s, 3H), 1.01 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 430.3 (M+1); and 2-(2-((7-(3-(aminomethyl)-5-methylphenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**89c**) (18 mg, 6 % yield) HCl salt as a white solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.19 (s, 1H, D₂O exchangeable), 8.25 (s, 3H, D₂O exchangeable), 8.11 – 8.07 (m, 1H), 7.82 – 7.77 (m, 1H), 7.77 – 7.71 (m, 2H), 7.65 – 7.59 (m, 1H), 7.36 (s, 1H), 7.22 (d, *J* = 7.4 Hz, 2H), 7.14 – 7.07 (m, 1H), 7.07 – 7.02 (m, 1H), 6.95 – 6.85 (m, 1H), 5.26 (s, 2H), 4.09 (s, 2H), 3.60 (s, 2H), 2.43 (s, 3H); MS (ES⁺): 402.3 (M+1); 425.3 (M+Na); (ES⁻): 400.3 (M-1); 436.3 (M+Cl).

Scheme-90



Preparation of 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)-5-fluorophenyl)acetic acid (**90d**)

Step-1: Preparation of ethyl 2-(5-fluoro-2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**90a**)

Compound **90a** was prepared according to the procedure reported in step-1 of Scheme-59 from ethyl 2-(2-((7-bromobenzofuran-5-yl)methoxy)-5-fluorophenyl)acetate (**101a**) (0.2 g, 0.49 mmol), using bis(pinacolato)diboron (0.19 g, 0.74 mmol), potassium acetate (0.10 g, 0.98 mmol) and Pd(dppf)Cl₂-CH₂Cl₂ (0.06 g, 0.07 mmol) in anhydrous dioxane (5 mL) under an Ar atmosphere and heating at 100 °C overnight. This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH=9:1 in hexane from 0-10%] ethyl 2-(5-fluoro-2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**90a**) (0.21 g, 94 % yield) as a white oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.06 (d, J = 2.2 Hz, 1H), 7.82 (d, J = 1.9 Hz, 1H), 7.64 (d, J = 1.8 Hz, 1H), 7.16 – 7.06 (m, 3H), 6.97 (d, J = 2.2 Hz, 1H), 5.15 (s, 2H), 4.01 (q, J = 7.1 Hz, 2H), 3.61 (s, 2H), 1.34 (s, 12H), 1.08 – 1.04 (m, 3H); MS (ES⁻): 453.2 (M-1).

Step-2: Preparation of (S)-ethyl 2-(2-((7-(2-((1,1-dimethylethylsulfinamido)methyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)-5-fluorophenyl)acetate (**90b**)

Compound **90b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(5-fluoro-2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**90a**) (0.21 g, 0.46 mmol) in dioxane (4 mL) using (S)-N-((4-chloro-3-fluoropyridin-2-yl)methyl)-2-methylpropane-2-sulfinamide (**220c**) (0.18 g, 0.69 mmol), bis(triphenylphosphine)palladium(II) chloride (0.05 g, 0.07 mmol) and a solution of K₂CO₃ (0.16 g, 1.16 mmol) in water (0.5 mL) under an Ar atmosphere and heating at 90 °C

for 3 h on oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with MeOH in DCM from 0-50%] (S)-ethyl 2-(2-((7-(2-((1,1-dimethylethylsulfinamido)methyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)-5-fluorophenyl)acetate (**90b**) (0.2 g, 78 % yield) as a white solid; MS (ES⁺): 557.2 (M+1); MS (ES⁻): 555.2 (M-1).

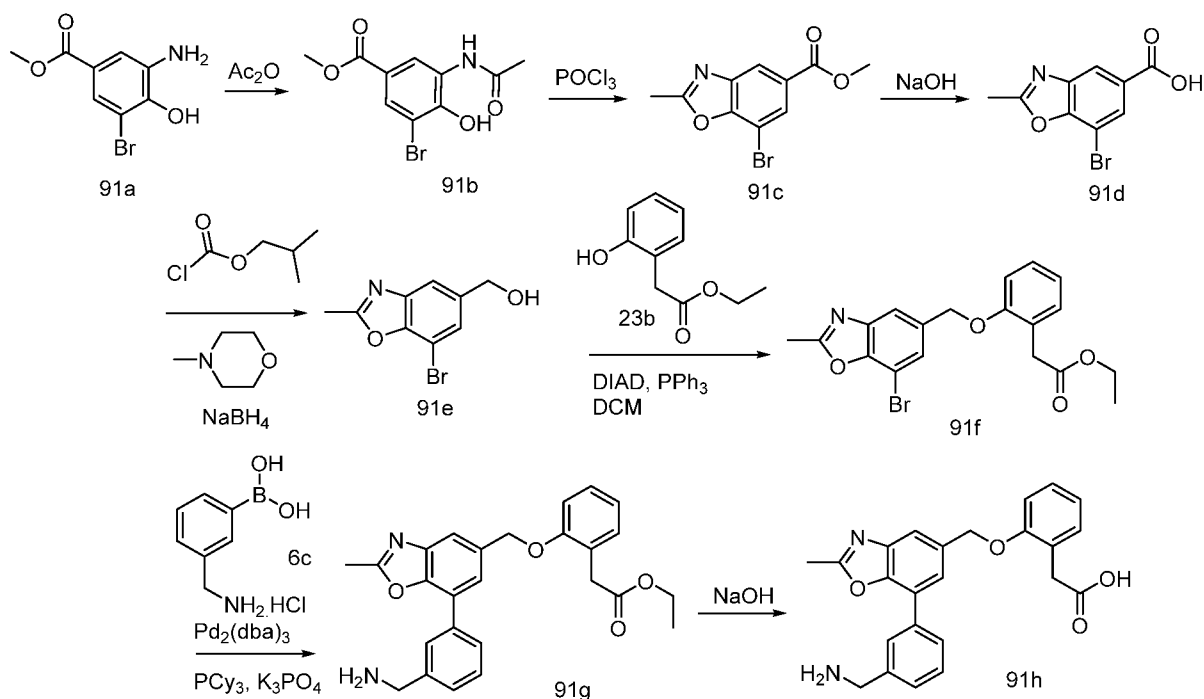
Step-3: Preparation of ethyl 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)-5-fluorophenyl)acetate (**90c**)

Compound **90c** was prepared according to the procedure reported in step-5 of Scheme-220 from (S)-ethyl 2-(2-((7-(2-((1,1-dimethylethylsulfinamido)methyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)-5-fluorophenyl)acetate (**90b**) (0.2 g, 0.36 mmol) in methanol (5 mL) using hydrochloric acid (4 M in 1,4-dioxane, 0.27 mL, 1.08 mmol). This gave after workup ethyl 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)-5-fluorophenyl)acetate (**90c**) (0.15 g, 92 % yield) as a white solid; MS (ES⁺): 453.2 (M+1); MS (ES⁻): 451.0 (M-1).

Step-4: Preparation of 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)-5-fluorophenyl)acetic acid (**90d**)

Compound **90d** was prepared according to the procedure reported in step-6 of Scheme-1 from ethyl 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)-5-fluorophenyl)acetate (**90c**) (0.19 g, 0.42 mmol) in MeOH/THF (4 mL, each) using lithium hydroxide hydrate (0.14 g, 3.36 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)benzofuran-5-yl)methoxy)-5-fluorophenyl)acetic acid (**90d**) (0.06 g, 31 % yield) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.63 (d, J = 5.0 Hz, 1H), 8.57 (s, 3H), 8.12 (d, J = 2.2 Hz, 1H), 7.90 (d, J = 1.6 Hz, 1H), 7.80 (t, J = 5.3 Hz, 1H), 7.58 (d, J = 1.4 Hz, 1H), 7.17 – 7.01 (m, 4H), 5.26 (s, 2H), 4.38 (d, J = 5.9 Hz, 2H), 3.60 (s, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -128.36, 124.02; MS (ES⁺): 425.1 (M+1); MS (ES⁻): 423.0 (M-1).

Scheme-91



Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)acetic acid (**91h**)

Step-1: Preparation of methyl 3-acetamido-5-bromo-4-hydroxybenzoate (**91b**)

To a solution of methyl 3-amino-5-bromo-4-hydroxybenzoate (**91a**) (0.3 g, 1.22 mmol; CAS# 260249-10-3) in THF (5 mL) was added acetic anhydride (0.14 mL, 1.46 mmol). The resulting mixture was stirred at RT for 3 h, diluted with water and extracted with EtOAc. The organic layer was separated washed with water, brine, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica (12 g), eluting with hexane in ethyl acetate from 0-70%] to give methyl 3-acetamido-5-bromo-4-hydroxybenzoate (**91b**) (0.12 g, 34 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.91 (s, 1H), 8.06 (d, $J = 2.1$ Hz, 1H), 7.85 (d, $J = 2.1$ Hz, 1H), 7.32 – 7.19 (m, 1H), 3.81 (s, 3H), 2.13 (s, 3H); MS (ES⁻): 286.1 & 288.2 (M-1).

Step-2: Preparation of methyl 7-bromo-2-methylbenzo[d]oxazole-5-carboxylate (**91c**)

To a 50-mL flask equipped with a condenser and an anhydrous CaCl_2 dried tube were added methyl 3-acetamido-5-bromo-4-hydroxybenzoate (**91b**) (0.28 g, 0.97 mmol), phosphoryl trichloride (1.81 mL, 19.44 mmol), and CHCl_3 (5 mL). The reaction mixture was heated at 90 °C for 40 h, cooled to room temperature, diluted with EtOAc (10 mL) and ice-water (10 mL). The reaction mixture was basified to pH 8 with aqueous NaOH and extracted with EtOAc (3 x 100 mL). The organic layers were combined, dried, filtered, and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane from 0-50%] to give methyl 7-bromo-2-

methylbenzo[d]oxazole-5-carboxylate (**91c**) (0.1 g, 38 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.17 (s, 1H), 8.09 (s, 1H), 3.89 (s, 3H), 2.69 (s, 3H); MS (ES⁺): 270.0 & 272.0 (M+1).

Step-3: Preparation of 7-bromo-2-methylbenzo[d]oxazole-5-carboxylic acid (**91d**)

Compound **91d** was prepared according to the procedure reported in step-4 of Scheme-4, from methyl 7-bromo-2-methylbenzo[d]oxazole-5-carboxylate (**91c**) (0.1 g, 0.37 mmol) in MeOH/THF (5 mL) using a solution of sodium hydroxide (1.48 mL, 3.70 mmol, 2.5 M) in water (2 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 7-bromo-2-methylbenzo[d]oxazole-5-carboxylic acid (**91d**) (0.08 g, 79 % yield) as a white solid; MS (ES⁻): 254.1 (M-1).

Step-4: Preparation of (7-bromo-2-methylbenzo[d]oxazol-5-yl)methanol (**91e**)

Compound **91e** was prepared according to the procedure reported in step-1 of Scheme-23 from 7-bromo-2-methylbenzo[d]oxazole-5-carboxylic acid (**91d**) (0.12 g, 0.46 mmol) using N-methylmorpholine (0.06 mL, 0.55 mmol) in THF (10 mL), isobutyl chloroformate (0.07 mL, 0.55 mmol) and NaBH₄ (0.05 g, 1.37 mmol) in water (0.8 mL). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-100%] (7-bromo-2-methylbenzo[d]oxazol-5-yl)methanol (**91e**) (0.08 g, 68 % yield) as a clear oil; MS (ES⁺): 242.0 & 244.1 (M+1).

Step-5: Preparation of ethyl 2-(2-((7-bromo-2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)acetate (**91f**)

Compound **91f** was prepared according to the procedure reported in step-2 of Scheme-23 from (7-bromo-2-methylbenzo[d]oxazol-5-yl)methanol (**91e**) (0.12 g, 0.50 mmol) in DCM (10 mL) using triphenylphosphine (0.17 g, 0.64 mmol) ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (0.12 g, 0.64 mmol) and di-(4-chlorobenzyl)azodicarboxylate (DIAD, 0.24 g, 0.64 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-50%] ethyl 2-(2-((7-bromo-2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)acetate (**91f**) (0.07 g, 32 % yield) as a colorless oil; MS (ES⁺): 426.1 & 428.1 (M+Na).

Step-6: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)acetate (**91g**)

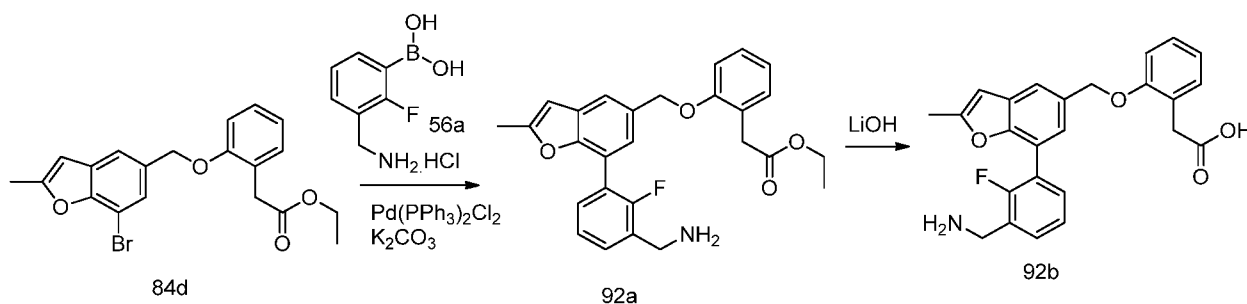
Compound **91g** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-bromo-2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)acetate (**91f**) (0.06 g, 0.15 mmol) in dioxane (4 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**)

(0.04 g, 0.22 mmol), tripotassium phosphate (3 M aqueous solution, 0.19 mL, 0.25 mmol), tricyclohexylphosphine (0.01 g, 0.05 mmol) and $\text{Pd}_2(\text{dba})_3$ (0.01 g, 0.02 mmol) under an Ar atmosphere and heating at 125 °C for 90 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)acetate (**91g**) (0.02 g, 31 % yield) as a white solid; MS (ES⁺): 431.2 (M+1).

Step-7: Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)acetic acid (**91h**)

Compound **91h** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)acetate (**91g**) (0.02 g, 0.05 mmol) in MeOH/THF (4 mL) using a solution of sodium hydroxide (0.15 mL, 0.37 mmol, 2.5 M) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)phenyl)-2-methylbenzo[d]oxazol-5-yl)methoxy)phenyl)acetic acid (**91h**) (0.01 g, 32 % yield) as a white solid; ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.37 (s, 3H), 8.00 (s, 1H), 7.94 (d, J = 7.5 Hz, 1H), 7.75 (s, 1H), 7.72 (s, 1H), 7.62 (m, 1H), 7.56 (m, 1H), 7.23 (m, 2H), 7.08 (d, J = 8.0 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 5.28 (s, 2H), 4.15 (d, J = 5.8 Hz, 2H), 3.60 (s, 2H), 2.66 (s, 3H); MS (ES⁺): 403.3 (M+1), 425.3 (M+Na); MS (ES⁻): 401.3 (M-1). HPLC purity: 87.37 %.

Scheme-92



Preparation of 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**92b**)

Step-1: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetate (**92a**)

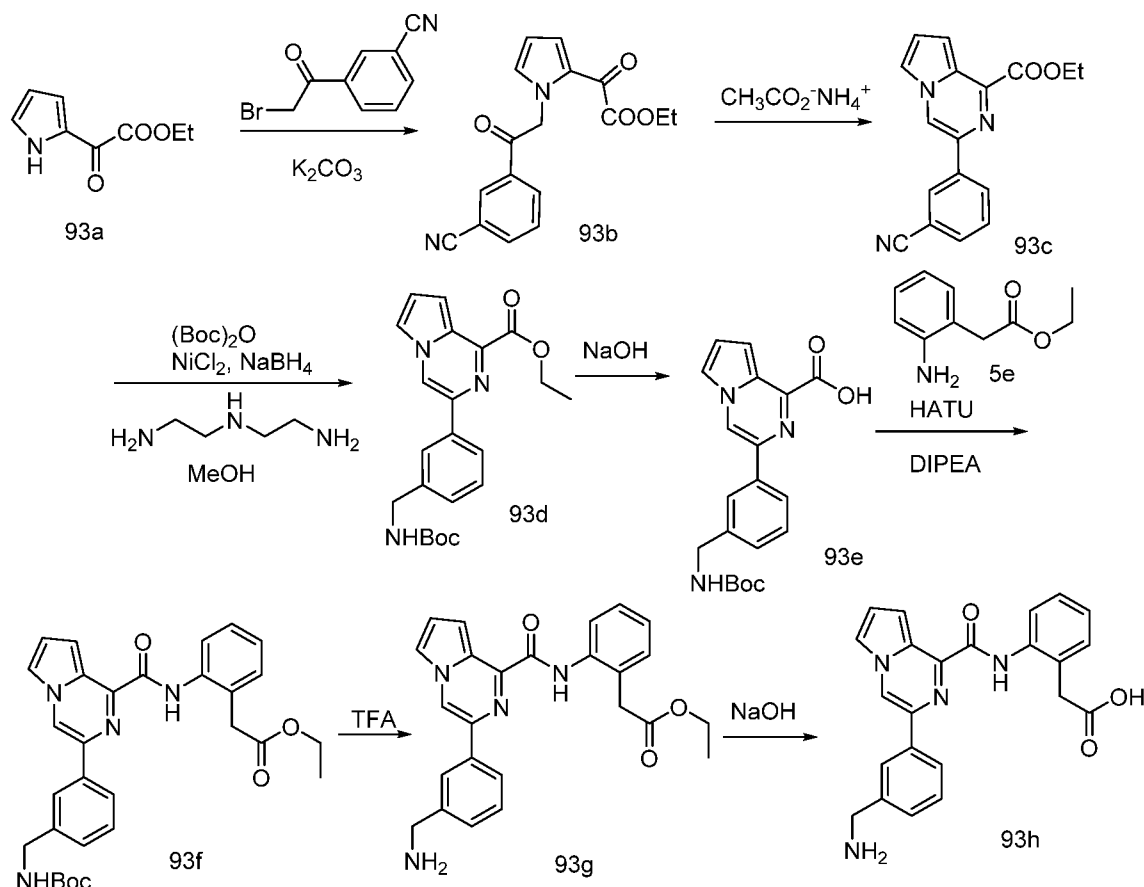
Compound **92a** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-bromo-2-methylbenzofuran-5-yl)methoxy)phenyl)acetate (**84d**) (500 mg, 1.24 mmol) in dioxane (15 mL) using 3-(aminomethyl)-2-fluorophenylboronic acid hydrochloride

(**56a**) (331 mg, 1.61 mmol), bis(triphenylphosphine)palladium(II) chloride (131 mg, 0.186 mmol), a solution of K₂CO₃ (514 mg, 3.72 mmol) in water (3 mL) and heating under an argon atmosphere at 100 °C for 3h on an oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetate (**92a**) (336 mg, 61 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.74 – 8.30 (m, 3H, D₂O exchangeable), 7.76 – 7.57 (m, 3H), 7.42 (t, *J* = 7.7 Hz, 1H), 7.31 (s, 1H), 7.29 – 7.18 (m, 2H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.67 (s, 1H), 5.20 (s, 2H), 4.16 (s, 2H), 3.94 (q, *J* = 7.1 Hz, 2H), 3.61 (s, 2H), 2.43 (s, 3H), 1.01 (t, *J* = 7.1 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -118.71; MS (ES⁺): 448.3 (M+1).

Step-2: Preparation of 2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**92b**)

Compound **92b** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetate (**92a**) (256 mg, 0.57 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (72.0 mg, 1.72 mmol) in water (1.0 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**92b**) (123 mg, 51 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.04 (s, 1H, D₂O exchangeable), 8.58 (s, 3H, D₂O exchangeable), 7.76 – 7.58 (m, 3H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.36 (s, 1H), 7.27 – 7.18 (m, 2H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.66 (t, *J* = 1.1 Hz, 1H), 5.22 (s, 2H), 4.17 (s, 2H), 3.57 (s, 2H), 2.43 (s, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -118.56; MS (ES⁺): 420.3 (M+1); (ES⁻): 418.3 (M-1), 456.3 (M+Cl); HPLC purity: 100%.

Scheme-93



Preparation of 2-(2-(3-(3-(aminomethyl)phenyl)pyrrolo[1,2-a]pyrazine-1-carboxamido)phenyl)acetic acid (**93h**)

Step-1: Preparation of ethyl 2-(1-(2-(3-cyanophenyl)-2-oxoethyl)-1H-pyrrol-2-yl)-2-oxoacetate (**93b**)

To a solution of ethyl 2-oxo-2-(1H-pyrrol-2-yl)acetate (**93a**) (1 g, 5.98 mmol; CAS# 27472-43-1), 3-(2-bromoacetyl)benzonitrile (1.608 g, 7.18 mmol) in acetonitrile (20 mL) was added potassium carbonate (1.240 g, 8.97 mmol) and the suspension was stirred at room temperature for 6 h. The reaction mixture was diluted with EtOAc (30 mL), filtered over a Celite pad, pad was washed with EtOAc (2 x 15 mL) and the filtrate was concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica gel 24g, eluting with EtOAc in hexanes 0 to 60%] to afford ethyl 2-(1-(2-(3-cyanophenyl)-2-oxoethyl)-1H-pyrrol-2-yl)-2-oxoacetate (**93b**) (900 mg, 49 % yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.19 (t, J = 1.8 Hz, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.98 - 7.91 (m, 1H), 7.58 (t, J = 7.9 Hz, 1H), 7.43 (t, J = 2.0 Hz, 1H), 7.25 (dd, J = 4.3, 1.6 Hz, 1H), 6.37 (dd, J = 4.3, 2.4 Hz, 1H), 5.93 (s, 2H), 4.30 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H).

Step-2: Preparation of ethyl 3-(3-(3-(aminomethyl)phenyl)pyrrolo[1,2-a]pyrazine-1-carboxylate (**93c**)

To a solution of ethyl 2-(1-(2-(3-cyanophenyl)-2-oxoethyl)-1H-pyrrol-2-yl)-2-oxoacetate (**93b**) (0.7 g, 2.26 mmol) in ethanol (30 mL) was added ammonium acetate (1.74 g, 22.56 mmol) and was stirred at 90 °C for 16 h. The reaction mixture was partitioned between water (100 mL) and EtOAc (80 mL) and layers were separated. The aqueous layer was extracted with EtOAc (60 mL) and the combined organics were washed with brine, dried, filtered, concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica gel 24g, eluting with EtOAc in hexane 0 to 60%] to afford ethyl 3-(3-cyanophenyl)pyrrolo[1,2-a]pyrazine-1-carboxylate (**93c**) (250 mg, 38 % yield) as a light orange solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.37 (s, 1H), 8.44 (d, *J* = 1.7 Hz, 1H), 8.38 (dt, *J* = 8.1, 1.5 Hz, 1H), 7.95 (dd, *J* = 2.6, 1.3 Hz, 1H), 7.87 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.74 (t, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 4.2 Hz, 1H), 7.14 (dd, *J* = 4.1, 2.6 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 292.2 (M+1), 314.2 (M+Na).

Step-3: Preparation of ethyl 3-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[1,2-a]pyrazine-1-carboxylate (**93d**)

Compound **93d** was prepared according to the procedure reported in step-1 of Scheme-80 from ethyl 3-(3-cyanophenyl)pyrrolo[1,2-a]pyrazine-1-carboxylate (**93c**) (210 mg, 0.721 mmol) in methanol (20 mL), THF (5 mL) using BOC-anhydride (0.251 mL, 1.08 mmol), nickel(II) chloride (9 mg, 0.072 mmol), sodium borohydride (82 mg, 2.16 mmol) and N1-(2-aminoethyl)ethane-1,2-diamine (372 mg, 3.60 mmol). This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc in hexanes 0 to 65%] ethyl 3-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[1,2-a]pyrazine-1-carboxylate (**93d**) (80 mg, 28 % yield) as a white solid.

Step-4: Preparation of 3-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[1,2-a]pyrazine-1-carboxylic acid (**93e**)

Compound **93e** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 3-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[1,2-a]pyrazine-1-carboxylate (**93d**) (75 mg, 0.19 mmol) in THF (5 mL) using an aqueous solution of NaOH (0.759 mL, 0.759 mmol, 1 M). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DCM-80 in DCM] 3-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[1,2-a]pyrazine-1-carboxylic acid (**93e**) (40 mg, 57 % yield) as a colorless solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.11 (s, 1H), 8.04 - 7.84 (m, 3H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.25 (t, *J* = 5.8 Hz, 2H), 7.06 (dd, *J* = 4.1, 2.6 Hz, 1H), 4.22 (d, *J* = 6.1 Hz, 2H), 1.40 (d, *J* = 4.9 Hz, 9H); MS (ES⁺): 390.3 (M+Na), (ES⁻): 366.3 (M-1).

Step-5: Preparation of ethyl 2-(2-(3-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[1,2-a]pyrazine-1-carboxamido)phenyl)acetate (**93f**)

Compound **93f** was prepared according to the procedure reported in step-4 of Scheme-1 from 3-(3-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[1,2-a]pyrazine-1-carboxylic acid (**93e**) (34 mg, 0.093 mmol) in DMF (2 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (25 mg, 0.14 mmol), DIPEA (0.05 mL, 0.278 mmol) and HATU (53 mg, 0.14 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with 0-60% EtOAc in hexane] ethyl 2-(2-(3-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[1,2-a]pyrazine-1-carboxamido)phenyl)acetate (**93f**) (34 mg, 70 % yield) as a semi-solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.58 (s, 1H), 9.18 (s, 1H), 8.06 (d, J = 9.8 Hz, 2H), 7.97 (dd, J = 2.6, 1.3 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.51 (d, J = 4.1 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.39 (dd, J = 5.5, 1.8 Hz, 3H), 7.31 – 7.16 (m, 2H), 7.11 (dd, J = 4.2, 2.5 Hz, 1H), 4.25 (d, J = 6.1 Hz, 2H), 3.98 (q, J = 7.2 Hz, 2H), 3.87 (s, 2H), 1.39 (s, 9H), 0.97 (t, J = 7.1 Hz, 3H); MS (ES⁺): 551.3 (M+Na).

Step-6: Preparation of ethyl 2-(2-(3-(3-(aminomethyl)phenyl)pyrrolo[1,2-a]pyrazine-1-carboxamido)phenyl)acetate (**93g**)

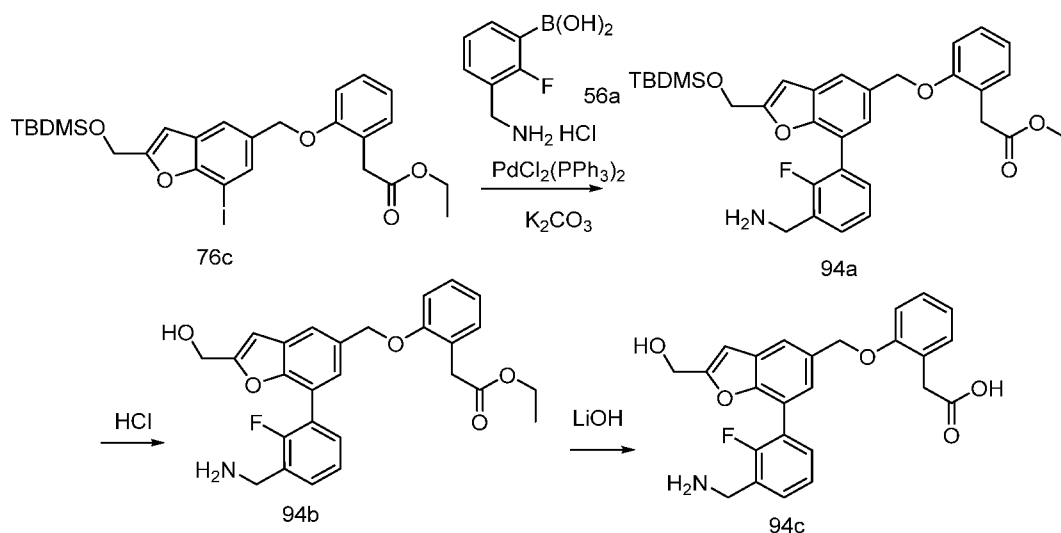
Compound **93g** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-(3-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)pyrrolo[1,2-a]pyrazine-1-carboxamido)phenyl)acetate (**93f**) (30 mg, 0.057 mmol) in DCM (2 mL) using TFA (0.044 mL, 0.568 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] ethyl 2-(2-(3-(3-(aminomethyl)phenyl)pyrrolo[1,2-a]pyrazine-1-carboxamido)phenyl)acetate (**93g**) (25 mg, 103 % yield) TFA salt as a brown syrup. This was used in the next reaction without further purification; MS (ES⁺): 429.3 (M+1), 451.3 (M+Na).

Step-7: Preparation of 2-(2-(3-(3-(aminomethyl)phenyl)pyrrolo[1,2-a]pyrazine-1-carboxamido)phenyl)acetic acid (**93h**)

Compound **93h** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-(3-(3-(aminomethyl)phenyl)pyrrolo[1,2-a]pyrazine-1-carboxamido)phenyl)acetate (**93g**) (25 mg, 0.057 mmol) in THF (5 mL) using an aqueous solution of NaOH (0.114 mL, 0.228 mmol, 2 M). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(3-(3-(aminomethyl)phenyl)pyrrolo[1,2-a]pyrazine-1-carboxamido)phenyl)acetic acid (**93h**) (14 mg, 61 % yield) hydrochloride salt as a white solid; ¹H NMR (300 MHz,

DMSO-*d*₆) δ 10.67 (s, 1H, D₂O exchangeable), 9.26 (s, 1H), 8.51 – 8.24 (m, 4H, 3H D₂O exchangeable), 8.16 (d, *J* = 7.5 Hz, 1H), 8.01 – 7.97 (m, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.63 – 7.47 (m, 4H), 7.43 – 7.34 (m, 2H), 7.27 – 7.18 (m, 1H), 7.16 – 7.10 (m, 1H), 4.15 (q, *J* = 5.9 Hz, 2H), 3.79 (s, 2H); MS (ES⁺): 401.3 (M+1), 423.3 (M+Na), (ES⁻): 399.3 (M-1); HPLC purity: 97.62 %.

Scheme-94



Preparation of 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-(hydroxymethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**94c**)

Step-1: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)benzofuran-5-yl)methoxy)phenyl)acetate (**94a**)

Compound **94a** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((2-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**76c**)

(7.2 g, 12.40 mmol) in dioxane (50 mL) using 3-(aminomethyl)-2-fluorophenylboronic acid hydrochloride (**56a**) (3.82 g, 18.60 mmol), a solution of K_2CO_3 (5.14 g, 37.2 mmol) in water (10 mL), bis(triphenylphosphine)palladium(II) chloride (1.31 g, 1.86 mmol) and heating at 100 °C for 3h on oil bath. This gave after workup, purification by flash column chromatography [silica (80 g), eluting with DMA80 in DCM from 0-50%] ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)benzofuran-5-yl)methoxy)phenyl)acetate (**94a**) (5.4 g, 75 % yield) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.64 (d, *J* = 1.7 Hz, 1H), 7.58 – 7.49 (m, 3H), 7.41 – 7.35 (m, 1H), 7.33 (s, 1H), 7.27 – 7.13 (m, 3H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.89 – 6.79 (m, 2H), 5.15 (s, 2H), 4.71 (s, 2H), 3.84 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 2H), 3.56 (s, 2H), 0.92 (t, *J* = 7.1, 2.3 Hz, 3H), 0.80 (s, 9H), 0.00 (s, 6H).

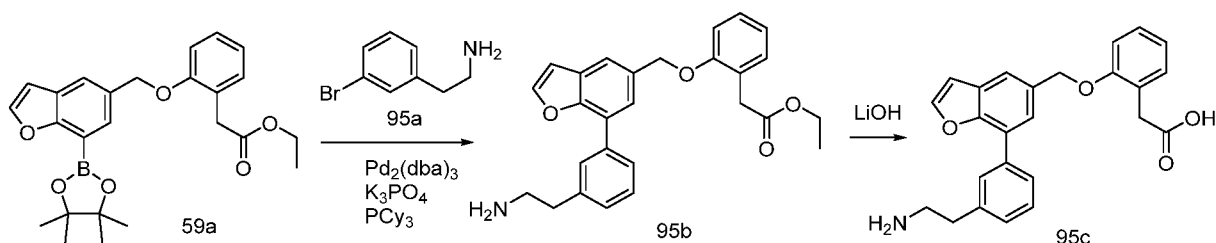
Step-2: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-(hydroxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**94b**)

To a solution of ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-((*tert*-butyldimethylsilyl)oxy)methyl)benzofuran-5-yl)methoxy)phenyl)acetate (**94a**) (700 mg, 1.21 mmol) in THF (10 mL) was added HCl (2N aqueous) (1.82 mL, 3.63 mmol). The resulting mixture was stirred at RT for 12h, concentrated in vacuum to dryness and the residue obtained. After TLC showed the reaction went completion, the organic solvent was then removed, the residue was purified by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 01-00%] to afford ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-(hydroxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**94b**) (173 mg, 31 % yield) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.62 (s, 3H, D₂O exchangeable), 7.75 – 7.69 (m, 2H), 7.69 – 7.61 (m, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.30 – 7.18 (m, 2H), 7.15 – 7.07 (m, 1H), 6.91 (t, *J* = 7.4, 1.2 Hz, 1H), 6.85 (s, 1H), 5.50 (t, *J* = 5.8 Hz, 1H, D₂O exchangeable), 5.22 (s, 2H), 4.55 (d, *J* = 4.8 Hz, 2H), 4.16 (s, 2H), 3.94 (q, *J* = 7.1 Hz, 2H), 3.62 (s, 2H), 1.01 (t, *J* = 7.1 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -118.74; MS (ES⁺): 464.3 (M+1); (ES⁻): 498.3 (M+Cl).

Step-3: Preparation of 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-(hydroxymethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**94c**)

Compound **94c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-(hydroxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**94b**) (420 mg, 0.73 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (92 mg, 2.18 mmol) in water (1.0 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-(hydroxymethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**94c**) (249 mg, 79 % yield) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.21 (s, 1H, D₂O exchangeable), 8.63 (s, 3H, D₂O exchangeable), 7.75 (d, *J* = 1.6 Hz, 1H), 7.73 – 7.62 (m, 2H), 7.46 – 7.37 (m, 2H), 7.28 – 7.17 (m, 2H), 7.09 (d, *J* = 8.1 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.84 (s, 1H), 5.24 (s, 2H), 4.55 (s, 2H), 4.16 (d, *J* = 5.7 Hz, 2H), 3.58 (s, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -118.57; MS (ES⁺): 436.3 (M+1); (ES⁻): 470.3 (M+Cl).

Scheme-95



Preparation of 2-(2-((7-(3-(2-aminoethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**95c**)

Step-1: Preparation of ethyl 2-(2-((7-(3-(2-aminoethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**95b**)

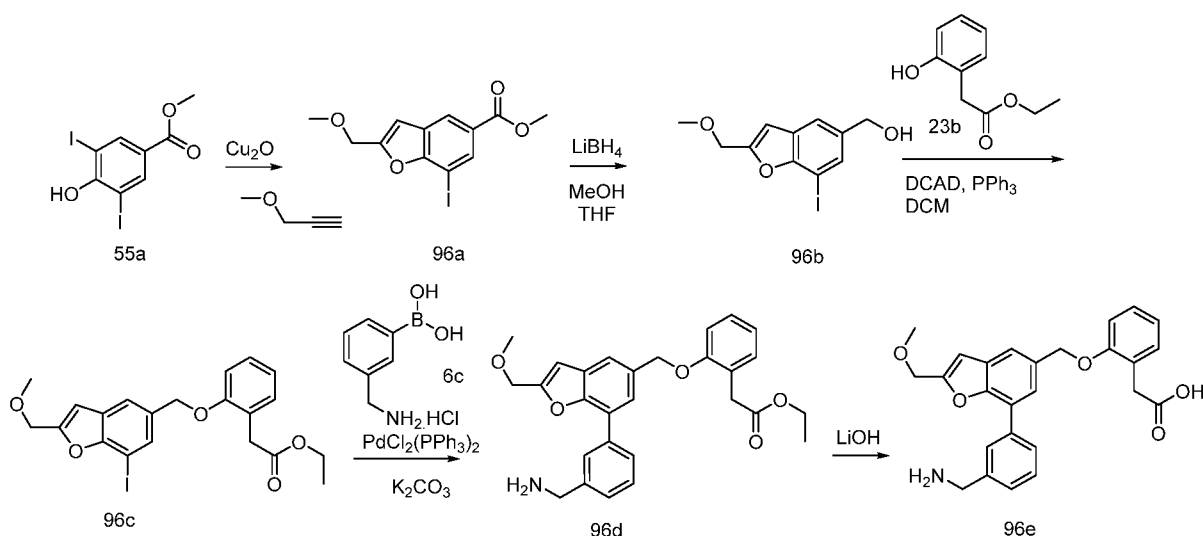
Compound **95b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (450 mg, 1.03 mmol) in dioxane (6 mL) using 3-bromophenethylamine (**95a**) (351 mg, 1.75 mmol; CAS# 58971-11-2), tripotassium phosphate (3M, 0.584 mL, 1.75 mmol), tricyclohexylphosphine (87 mg, 0.31 mmol) and $\text{Pd}_2(\text{dba})_3$ (94 mg, 0.10 mmol) under an Ar atmosphere and heating at 120 °C for 90 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-70%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(3-(2-aminoethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**95b**) (252 mg, 57 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.27 – 7.92 (m, 4H, partially D_2O exchangeable), 7.81 – 7.73 (m, 2H), 7.72 (d, $J = 1.5$ Hz, 1H), 7.60 (d, $J = 1.6$ Hz, 1H), 7.51 (t, $J = 7.6$ Hz, 1H), 7.34 (d, $J = 7.6$ Hz, 1H), 7.30 – 7.19 (m, 2H), 7.12 (d, $J = 8.1$ Hz, 1H), 7.08 – 7.02 (m, 1H), 6.91 (t, $J = 7.4$ Hz, 1H), 5.25 (s, 2H), 3.93 (q, $J = 7.1$ Hz, 2H), 3.63 (s, 2H), 3.18 – 3.05 (m, 2H), 3.05 – 2.96 (m, 2H), 0.99 (t, $J = 7.1$ Hz, 3H); MS (ES⁺): 430.3 (M+1); (ES⁻): 464.3 (M+Cl).

Step-2: Preparation of 2-(2-((7-(3-(2-aminoethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**95c**)

Compound **95c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(2-aminoethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetate (**95b**) (160 mg, 0.37 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (47 mg, 1.12 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(2-aminoethyl)phenyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**95c**) (82 mg, 55 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.18

(s, 1H, D₂O exchangeable), 8.16 – 7.96 (m, 4H, D₂O exchangeable), 7.83 – 7.72 (m, 3H), 7.64 (d, $J = 1.7$ Hz, 1H), 7.50 (t, $J = 7.6$ Hz, 1H), 7.37 – 7.29 (m, 1H), 7.28 – 7.20 (m, 2H), 7.13 – 7.06 (m, 1H), 7.04 (d, $J = 2.2$ Hz, 1H), 6.90 (t, $J = 7.4, 1.1$ Hz, 1H), 5.27 (s, 2H), 3.60 (s, 2H), 3.18 – 3.06 (m, 2H), 3.06 – 2.94 (m, 2H); MS (ES⁺): 402.3 (M+1); (ES⁻): 400.3 (M-1), 436.3 (M+Cl).

Scheme-96



Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**96e**)

Step-1: Preparation of methyl 7-iodo-2-(methoxymethyl)benzofuran-5-carboxylate (**96a**)

Compound **96a** was prepared according to the procedure reported in step-1 of Scheme-55, from methyl 4-hydroxy-3,5-diiodobenzoate (**55a**) (7 g, 17.33 mmol) in pyridine (15 mL) using methyl propargyl ether (1.22 g, 17.33 mmol) and copper(I) oxide (1.24 g, 8.66 mmol). This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-70%] methyl 7-iodo-2-(methoxymethyl)benzofuran-5-carboxylate (**96a**) (3.45 g, 58 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.27 (d, $J = 1.5$ Hz, 1H), 8.22 (d, $J = 1.5$ Hz, 1H), 7.18 (d, $J = 0.8$ Hz, 1H), 4.60 (s, 2H), 3.88 (s, 3H), 3.36 (s, 3H).

Step-2: Preparation of (7-iodo-2-(methoxymethyl)benzofuran-5-yl)methanol (**96b**)

Compound **96b** was prepared according to the procedure reported in step-2 of Scheme-76 from methyl 7-iodo-2-(methoxymethyl)benzofuran-5-carboxylate (**96a**) (3.45 g, 9.97 mmol) in THF (60 mL) using LiBH₄ (14.95 mL, 29.9 mmol, 2 M solution in THF) and MeOH (0.96 g, 29.9 mmol). This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-60%] (7-iodo-2-(methoxymethyl)benzofuran-5-yl)methanol (**96b**) (2.94 g, 93 % yield) as a white solid; ¹H

NMR (300 MHz, DMSO-*d*₆) δ 7.66 – 7.62 (m, 1H), 7.56 – 7.51 (m, 1H), 7.02 (t, *J* = 0.9 Hz, 1H), 5.26 (t, *J* = 5.8, 1.1 Hz, 1H), 4.58 – 4.50 (m, 4H), 3.33 (s, 3H).

Step-3: Preparation of ethyl 2-(2-((7-iodo-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**96c**)

Compound **96c** was prepared according to the procedure reported in step-2 of Scheme-23 from (7-iodo-2-(methoxymethyl)benzofuran-5-yl)methanol (**96b**) (2.94 g, 9.24 mmol) in DCM (180 mL) using triphenylphosphine (2.67 g, 10.17 mmol), ethyl 2-(2-hydroxyphenyl)acetate (**23b**) (1.83 g, 10.17 mmol) and di-(4-chlorobenzyl)azodicarboxylate (DCAD, 3.73 g, 10.17 mmol) in DCM (20 mL). This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-50%] ethyl 2-(2-((7-iodo-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**96c**) (3.92 g, 88 % yield) as a clear oil, which became a white solid after standing at RT. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.74 (d, *J* = 1.5 Hz, 1H), 7.67 (d, *J* = 1.5 Hz, 1H), 7.29 – 7.18 (m, 2H), 7.10 – 7.04 (m, 2H), 6.91 (t, *J* = 7.4 Hz, 1H), 5.14 (s, 2H), 4.56 (s, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.61 (s, 2H), 3.34 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H).

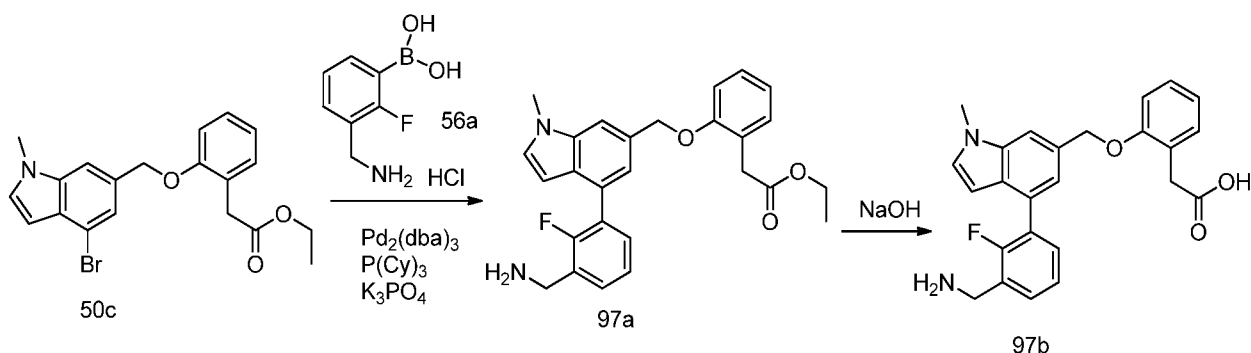
Step-4: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**96d**)

Compound **96d** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-iodo-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**96c**) (500 mg, 1.04 mmol) in dioxane (15 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (254 mg, 1.35 mmol), a solution of K₂CO₃ (432 mg, 3.12 mmol) in water (3 mL), bis(triphenylphosphine)palladium(II) chloride (110 mg, 0.16 mmol) and heating at 100 °C for 3h on oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**96d**) (262 mg, 55 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.61 (s, 3H, D₂O exchangeable), 7.98 (s, 1H), 7.95 – 7.85 (m, 1H), 7.70 (d, *J* = 1.6 Hz, 1H), 7.66 – 7.56 (m, 3H), 7.30 – 7.18 (m, 2H), 7.15 – 7.09 (m, 1H), 7.00 (s, 1H), 6.92 (t, *J* = 7.4, 1.1 Hz, 1H), 5.24 (s, 2H), 4.59 (s, 2H), 4.12 (s, 2H), 3.95 (q, *J* = 7.2 Hz, 2H), 3.57 (s, 2H), 3.33 (s, 3H), 1.00 (t, *J* = 7.1, 1.4 Hz, 3H); MS (ES⁺): 460.3 (M+1); (ES⁻): 494.3 (M+Cl).

Step-5: Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**96e**)

Compound **96e** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**96d**) (152 mg, 0.33 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (42 mg, 0.99 mmol) in water (1.0 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)phenyl)-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**96e**) (95 mg, 67 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 12.22 (s, 1H, D $_2$ O exchangeable), 8.53 (s, 3H, D $_2$ O exchangeable), 7.97 (s, 1H), 7.95 – 7.88 (m, 1H), 7.75 – 7.70 (m, 1H), 7.64 (d, J = 1.7 Hz, 1H), 7.61 – 7.53 (m, 2H), 7.27 – 7.17 (m, 2H), 7.10 (d, J = 8.1 Hz, 1H), 6.99 (s, 1H), 6.90 (t, J = 7.3 Hz, 1H), 5.26 (s, 2H), 4.58 (s, 2H), 4.13 (s, 2H), 3.60 (s, 2H), 3.33 (s, 3H); MS (ES $^+$): 432.3 (M+1); (ES $^-$): 430.3 (M-1), 466.3 (M+Cl).

Scheme-97



Preparation of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-methyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**97b**)

Step-1: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-methyl-1H-indol-6-yl)methoxy)phenyl)acetate (**97a**)

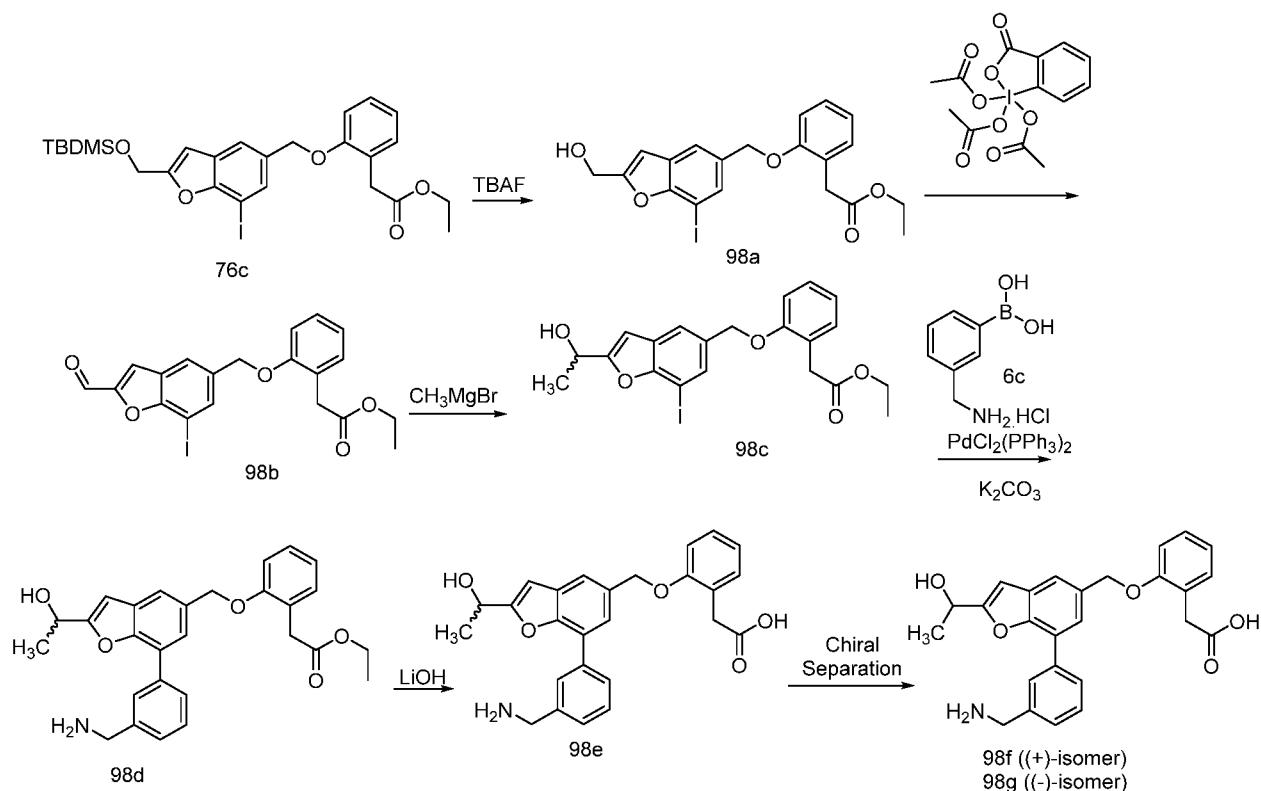
Compound **97a** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((4-bromo-1-methyl-1H-indol-6-yl)methoxy)phenyl)acetate (**50c**) (0.5 g, 1.24 mmol) in dioxane (5 mL) using 3-(aminomethyl)-2-fluorophenylboronic acid hydrochloride (**56a**) (0.38 g, 1.86 mmol), tripotassium phosphate (3 M aqueous solution, 0.70 mL, 2.11 mmol), tricyclohexylphosphine (0.11 g, 0.37 mmol) and $\text{Pd}_2(\text{dba})_3$ (0.11 g, 0.12 mmol) under an Ar atmosphere and heating at 125 °C for 90 min in a microwave. This gave after workup, purification by flash column chromatography [silica (24 g), eluting with hexane in ethyl acetate from 0-70%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-methyl-1H-indol-6-yl)methoxy)phenyl)acetate (**97a**) (0.26 g, 47 % yield) as

a white solid; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 8.44 (s, 3H), 7.68 – 7.54 (m, 3H), 7.44 – 7.34 (m, 2H), 7.29 – 7.18 (m, 2H), 7.18 – 7.10 (m, 2H), 6.90 (t, J = 7.4 Hz, 1H), 6.35 (t, J = 2.9 Hz, 1H), 5.25 (s, 2H), 4.16 (s, 2H), 3.93 (q, J = 7.0 Hz, 2H), 3.85 (s, 3H), 3.63 (s, 2H), 1.00 (t, J = 7.1 Hz, 3H); ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ -118.88; MS (ES+): 447.3 (M+1); MS (ES-): 481.3 (M+Cl). HPLC purity: 98.44%.

Step-2: Preparation of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-methyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**97b**)

Compound **97b** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-methyl-1H-indol-6-yl)methoxy)phenyl)acetate (**97a**) (0.08 g, 0.18 mmol) in MeOH/THF (4 mL) using a solution of sodium hydroxide (0.57 mL, 1.43 mmol, 2.5 M) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-methyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**97b**) (0.02 g, 21 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 12.17 (s, 1H), 8.41 (s, 4H), 7.64 (s, 1H), 7.63 – 7.54 (m, 1H), 7.45 – 7.35 (m, 2H), 7.29 – 7.15 (m, 3H), 7.11 (d, J = 8.1 Hz, 1H), 6.95 – 6.86 (m, 1H), 6.34 (t, J = 3.0 Hz, 1H), 5.27 (s, 2H), 4.17 (s, 2H), 3.84 (s, 3H), 3.60 (s, 2H); ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ -118.79; MS (ES+): 419.3 (M+1); MS (ES-): 417.4 (M-1), 453.3 (M+Cl). HPLC purity: 94.07%.

Scheme-98



Preparation of racemic 2-(2-((7-(3-(aminomethyl)phenyl)-2-(1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**98e**), (+)-isomer (**98f**) and (-)-isomer (**98g**)

Step-1: Preparation of ethyl 2-(2-((2-(hydroxymethyl)-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**98a**)

Compound **98a** was prepared according to the procedure reported in step-5 of Scheme-76 from ethyl 2-(2-((2-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**76c**) (4 g, 6.89 mmol) in THF (60 mL) using added TBAF (2.25 g, 8.61 mmol). This gave after workup, purification by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-70%] ethyl 2-(2-((2-(hydroxymethyl)-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**98a**) (2.5 g, 78 % yield) as a clear oil; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.70 (d, $J = 1.6$ Hz, 1H), 7.63 (d, $J = 1.5$ Hz, 1H), 7.29 – 7.18 (m, 2H), 7.07 (d, $J = 8.1$ Hz, 1H), 6.95 – 6.87 (m, 2H), 5.54 (t, $J = 5.9$ Hz, 1H), 5.14 (s, 2H), 4.60 (d, $J = 5.9$ Hz, 2H), 4.04 (q, $J = 7.1$ Hz, 2H), 3.61 (s, 2H), 1.09 (t, $J = 7.1$ Hz, 3H); MS (ES⁺): 489.1 (M+Na).

Step-2: Preparation of ethyl 2-(2-((2-formyl-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**98b**)

To a solution of ethyl 2-(2-((2-(hydroxymethyl)-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**98a**) (500 mg, 1.07 mmol) in DCM (20 mL) was added Dess-Martin Periodinane (546 mg, 1.29 mmol). The resulting mixture was stirred at RT for 3h,

diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried, filtered, and evaporated in vacuo. The crude product was purified by flash column chromatography [silica gel (24 g)] to afford ethyl 2-(2-((2-formyl-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**98b**) (410 mg, 82 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.88 (s, 1H), 8.12 (s, 1H), 8.02 (d, *J* = 1.6 Hz, 1H), 7.93 (d, *J* = 1.6 Hz, 1H), 7.31 – 7.18 (m, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.93 (t, *J* = 7.4, 1.1 Hz, 1H), 5.20 (s, 2H), 4.03 (q, *J* = 7.1, 1.7 Hz, 2H), 3.63 (s, 2H), 1.09 (t, *J* = 7.1, 1.7 Hz, 3H).

Step-3: Preparation of ethyl 2-(2-((2-(1-hydroxyethyl)-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**98c**)

To a solution of ethyl 2-(2-((2-formyl-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**98b**) (410 mg, 0.88 mmol) in THF (20 mL) at -78 °C was added methylmagnesium bromide (1.4M in THF) (0.63 mL, 0.88 mmol). The resulting mixture was stirred at -78 °C for 1h, quenched with saturated NH₄Cl solution and extracted with EtOAc (3x). The combined organic layers were washed with saturated aqueous sodium bicarbonate, dried, filtered and evaporated in vacuo. The crude product was purified by flash column chromatography [silica gel (24 g), eluting with EtOAc in hexane from 0-60%] to afford ethyl 2-(2-((2-(1-hydroxyethyl)-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**98c**) (290 mg, 68% yield) as a yellow semi-solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.69 (d, *J* = 1.5 Hz, 1H), 7.62 (d, *J* = 1.6 Hz, 1H), 7.29 – 7.18 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.91 (t, *J* = 7.3 Hz, 2H), 6.85 (s, 1H), 5.61 – 5.53 (m, 1H), 5.13 (s, 2H), 4.92 – 4.80 (m, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.61 (s, 2H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 503.2 (M+Na).

Step-4: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**98d**)

Compound **98d** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((2-(1-hydroxyethyl)-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**98c**) (285 mg, 0.59 mmol) in dioxane (15 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (145 mg, 0.77 mmol), a solution of K₂CO₃ (246 mg, 1.78 mmol) in water (3 mL), bis(triphenylphosphine)palladium(II) chloride (63 mg, 0.089 mmol) and heating at 100 °C for 3h on an oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**98d**) (156 mg, 57 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.51 (s, 3H, D₂O exchangeable), 8.01 (d, *J* = 2.3 Hz, 1H), 7.97 – 7.88 (m,

1H), 7.65 (d, $J = 1.7$ Hz, 1H), 7.61 – 7.52 (m, 3H), 7.31 – 7.18 (m, 2H), 7.11 (d, $J = 8.1$ Hz, 1H), 6.96 – 6.85 (m, 1H), 6.79 (s, 1H), 5.58 (s, 1H, D₂O exchangeable), 5.23 (s, 2H), 4.88 (d, $J = 6.9$ Hz, 1H), 4.13 (s, 2H), 3.95 (q, $J = 7.1$ Hz, 2H), 3.63 (s, 2H), 1.49 (d, $J = 6.5$ Hz, 3H), 1.01 (t, $J = 7.1, 1.5$ Hz, 3H); MS (ES⁺): 460.3 (M+1); (ES⁻): 494.3 (M+Cl).

Step-5: Preparation of racemic 2-(2-((7-(3-(aminomethyl)phenyl)-2-(1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**98e**)

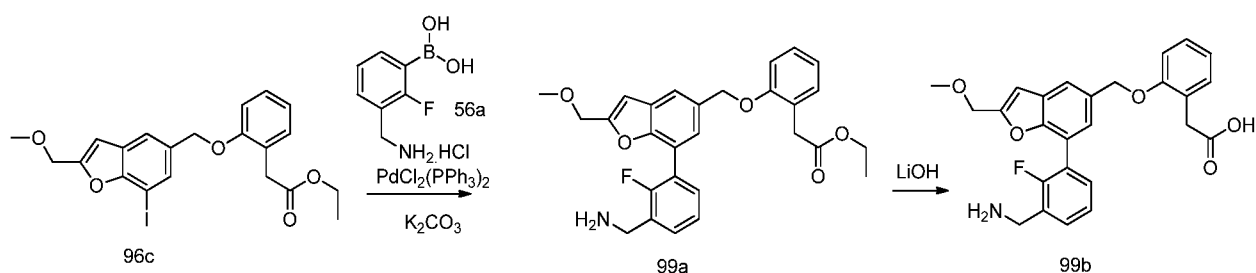
Compound **98e** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**98d**) (92 mg, 0.20 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (25 mg, 0.6 mmol) in water (1.0 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] racemic 2-(2-((7-(3-(aminomethyl)phenyl)-2-(1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**98e**) (53 mg, 61 % yield) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (s, 1H, D₂O exchangeable), 8.49 (s, 3H, D₂O exchangeable), 8.05 – 7.90 (m, 2H), 7.73 – 7.66 (m, 1H), 7.64 – 7.52 (m, 3H), 7.27 – 7.18 (m, 2H), 7.13 – 7.05 (m, 1H), 6.90 (t, $J = 7.4$ Hz, 1H), 6.78 (s, 1H), 5.26 (s, 2H), 4.88 (q, $J = 6.6$ Hz, 1H), 4.13 (d, $J = 5.9$ Hz, 2H), 3.60 (s, 2H), 1.49 (d, $J = 6.6$ Hz, 3H); MS (ES⁺): 432.3 (M+1); (ES⁻): 430.4 (M-1), 466.3 (M+Cl).

Step-6: Preparation of (+)-isomer 2-(2-((7-(3-(aminomethyl)phenyl)-2-(1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**98f**) and (-)-isomer 2-(2-((7-(3-(aminomethyl)phenyl)-2-(1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**98g**)
Racemic compound 2-(2-((7-(3-(aminomethyl)phenyl)-2-(1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**98e**) (30 mgs) was subjected to chiral separation using a chiral column (CHIRALPAK IBN), eluting with Hexane/Ethanol/TEA (85/15/0.1) to afford:

1. Peak-1 (17.2 mg) as a white wax. This sample from chiral separation was dissolved in acetonitrile and water and lyophilized to dryness to afford (+)-2-(2-((7-(3-(aminomethyl)phenyl)-2-(1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**98f**) (9 mg) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.35 – 8.28 (m, 1H), 8.12 (d, $J = 7.9$ Hz, 1H), 7.87 (d, $J = 1.7$ Hz, 1H), 7.61 (d, $J = 1.6$ Hz, 1H), 7.50 (t, $J = 7.7$ Hz, 1H), 7.36 (d, $J = 7.8$ Hz, 1H), 7.15 – 7.05 (m, 2H), 6.95 (d, $J = 8.0$ Hz, 1H), 6.85 – 6.76 (m, 2H), 5.59 (s, 1H, D₂O exchangeable), 5.25 (s, 2H), 4.88 (q, $J = 6.5$ Hz, 1H), 4.02 (s, 2H), 3.40 (s, 2H), 1.49 (d, $J = 6.5$ Hz, 3H); MS (ES⁺): 432.2 (M+1), MS (ES⁻): 430.2 (M-1); Enantiomeric purity: (%ee) = 93.7%; Optical rotation: $[\alpha]_D = (+) 28.0$ [DMSO/CH₃OH (1:1), 0.05].

2. Peak-2 (71.3 mg) as a yellow wax. This sample from chiral separation was dissolved in acetonitrile and water and lyophilized to dryness to afford (-)-2-(2-((7-(3-(aminomethyl)phenyl)-2-(1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**98g**) (26 mg); This was further purified by reverse-phase column chromatography [EZ-PREP, C-18 column, 50 g, eluting with 0.1% aq. HCl in water and acetonitrile from 0-100%] to afford (-)-2-(2-((7-(3-(aminomethyl)phenyl)-2-(1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**98g**) (2.1 mg) HCl salt as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.23 (s, 1H, D_2O exchangeable), 8.31 (bs, 3H, D_2O exchangeable), 8.00 – 7.91 (m, 2H), 7.68 (d, $J = 1.6$ Hz, 1H), 7.64 – 7.57 (m, 2H), 7.56 – 7.49 (m, 1H), 7.23 (s, 1H), 7.21 (s, 1H), 7.08 (d, $J = 8.1$ Hz, 1H), 6.90 (t, $J = 7.3$ Hz, 1H), 6.79 (d, $J = 0.9$ Hz, 1H), 5.58 (s, 1H, D_2O exchangeable), 5.25 (s, 2H), 4.95 – 4.82 (m, 1H), 4.29 – 4.05 (m, 2H), 3.59 (s, 2H), 1.49 (d, $J = 6.6$ Hz, 3H); MS (ES⁺): 432.3 (M+1), MS (ES⁻): 430.3 (M-1); Enantiomeric purity: (% ee) = 70.85; Optical rotation: $[\alpha]_D = (-) 24.0$ [$\text{DMSO}/\text{CH}_3\text{OH}$ (1:1), 0.05].

Scheme-99



Preparation of 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**99b**)

Step-1: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**99a**)

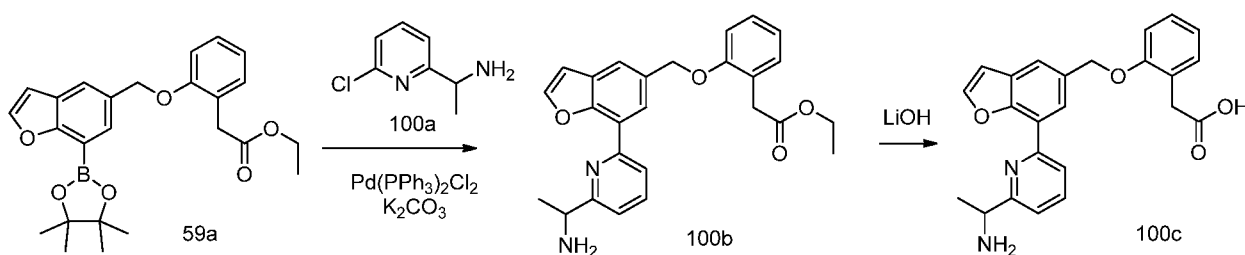
Compound **99a** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-iodo-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**96c**) (500 mg, 1.04 mmol) in dioxane (15 mL) using 3-(aminomethyl)-2-fluorophenylboronic acid hydrochloride (**56a**) (278 mg, 1.35 mmol), a solution of K_2CO_3 (432 mg, 3.12 mmol) in water (3 mL), bis(triphenylphosphine)palladium(II) chloride (110 mg, 0.16 mmol) and heating at 100°C for 3h on oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in

water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**99a**) (386 mg, 78 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.66 (s, 3H, D_2O exchangeable), 7.79 – 7.69 (m, 2H), 7.69 – 7.59 (m, 1H), 7.49 – 7.38 (m, 2H), 7.31 – 7.18 (m, 2H), 7.15 – 7.07 (m, 1H), 7.02 (s, 1H), 6.91 (t, $J = 7.4, 1.0$ Hz, 1H), 5.23 (s, 2H), 4.52 (s, 2H), 4.16 (s, 2H), 3.92 (q, $J = 7.1$ Hz, 2H), 3.62 (s, 2H), 3.28 (s, 3H), 0.99 (t, $J = 7.1$ Hz, 3H); MS (ES⁺): 478.3 (M+1); (ES⁻): 512.3 (M+Cl).

Step-2: Preparation of 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**99b**)

Compound **99b** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**99a**) (120 mg, 0.251 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (32 mg, 0.75 mmol) in water (1.0 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**99b**) (63 mg, 56 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.17 (s, 1H, D_2O exchangeable), 8.60 (s, 3H, D_2O exchangeable), 7.79 (d, $J = 1.6$ Hz, 1H), 7.75 – 7.62 (m, 2H), 7.48 – 7.39 (m, 2H), 7.28 – 7.18 (m, 2H), 7.09 (d, $J = 8.1$ Hz, 1H), 7.00 (s, 1H), 6.90 (t, $J = 7.3, 1.0$ Hz, 1H), 5.25 (s, 2H), 4.52 (s, 2H), 4.16 (s, 2H), 3.58 (s, 2H), 3.29 (s, 3H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -118.67; MS (ES⁺): 450.3 (M+1); 472.3 (M+Na); (ES⁻): 448.3 (M-1), 484.3 (M+Cl).

Scheme-100



Preparation of 2-(2-((7-(6-(1-aminoethyl)pyridin-2-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**100c**)

Step-1: Preparation of ethyl 2-(2-((7-(6-(1-aminoethyl)pyridin-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**100b**)

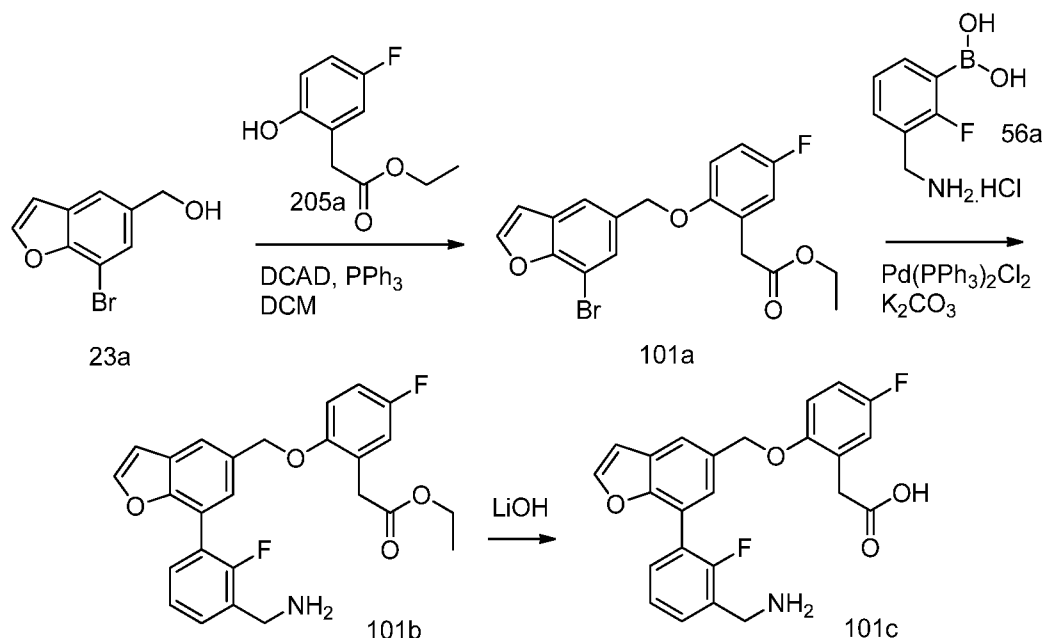
Compound **100b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-

yl)methoxy)phenyl)acetate (**59a**) (300 mg, 0.69 mmol) in dioxane (6 mL) using 1-(6-chloropyridin-2-yl)ethanamine (**100a**) (108 mg, 0.69 mmol; CAS# 1060811-97-3), potassium carbonate (190 mg, 1.38 mmol) and bis(triphenylphosphine)palladium(II) chloride (97 mg, 0.14 mmol) under an Ar atmosphere and heating at 100 °C for 90 min on an oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(6-(1-aminoethyl)pyridin-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**100b**) (82 mg, 28 % yield) as a white solid; MS (ES⁺): 431.3 (M+1).

Step-2: Preparation of 2-(2-((7-(6-(1-aminoethyl)pyridin-2-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**100c**)

Compound **100c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(6-(1-aminoethyl)pyridin-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**100b**) (82 mg, 0.19 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (24 mg, 0.57 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(6-(1-aminoethyl)pyridin-2-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**100c**) (29 mg, 38 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.68 (s, 3H, D₂O exchangeable), 8.53 (d, *J* = 1.6 Hz, 1H), 8.35 (d, *J* = 7.9 Hz, 1H), 8.16 (d, *J* = 2.2 Hz, 1H), 8.07 (t, *J* = 7.9 Hz, 1H), 7.86 (d, *J* = 1.6 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 7.4 Hz, 2H), 7.16 – 7.06 (m, 2H), 6.91 (t, *J* = 7.4 Hz, 1H), 5.32 (s, 2H), 4.70 – 4.54 (m, 1H), 3.61 (s, 2H), 1.62 (d, *J* = 6.8 Hz, 3H); MS (ES⁺): 403.3 (M+1); 425.3 (M+Na); (ES⁻): 401.3 (M-1), 437.3 (M+Cl).

Scheme-101



Preparation of 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)-5-fluorophenyl)acetic acid (**101c**)

Step-1: Preparation of ethyl 2-(2-((7-bromobenzofuran-5-yl)methoxy)-5-fluorophenyl)acetate (**101a**)

Compound **101a** was prepared according to the procedure reported in step-2 of Scheme-23 from (7-bromobenzofuran-5-yl)methanol (**23a**) (2 g, 8.81 mmol) in DCM (30 mL) using triphenylphosphine (3.00 g, 11.45 mmol), ethyl 2-(5-fluoro-2-hydroxyphenyl)acetate (**205a**) (2.27 g, 11.45 mmol) and a solution of di-(4-chlorobenzyl)azodicarboxylate (DCAD, 4.20 g, 11.45 mmol) in DCM (20 mL). This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc/MeOH (9:1) in hexanes from 0-50%] ethyl 2-(2-((7-bromobenzofuran-5-yl)methoxy)-5-fluorophenyl)acetate (**101a**) (1.04 g, 29 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.15 (d, *J* = 2.2 Hz, 1H), 7.70 (d, *J* = 1.5 Hz, 1H), 7.59 (d, *J* = 1.5 Hz, 1H), 7.20 – 7.02 (m, 4H), 5.16 (s, 2H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.64 (s, 2H), 1.08 (t, *J* = 7.1 Hz, 3H); MS (ES⁻): 406.9 (M-1).

Step-2: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)-5-fluorophenyl)acetate (**101b**)

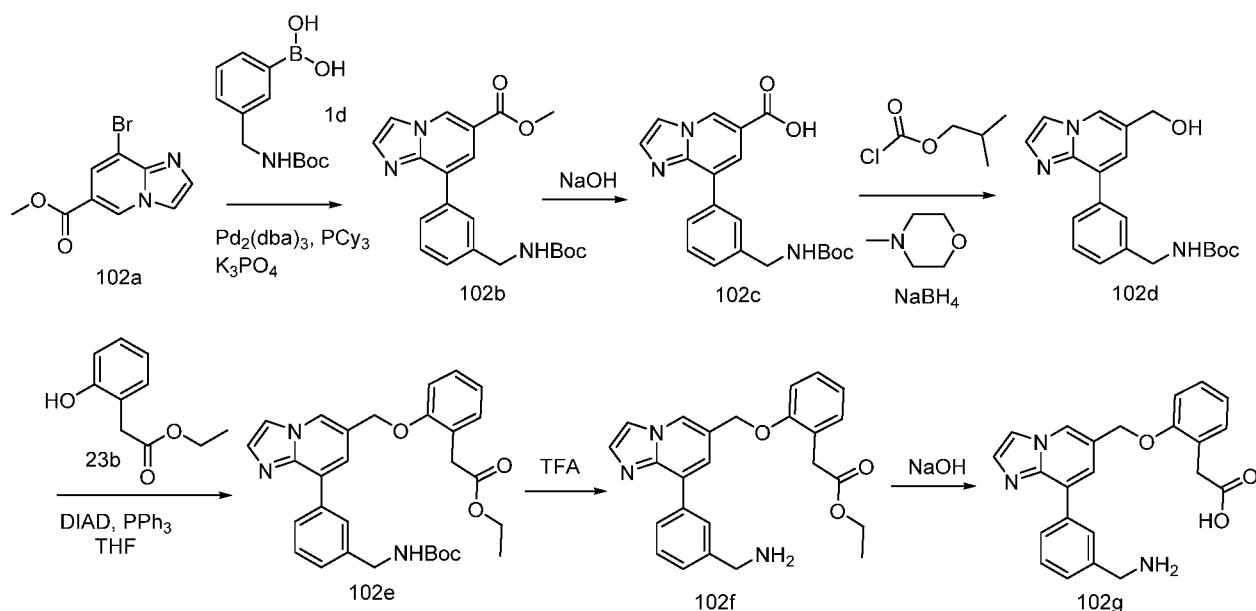
Compound **101b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-bromobenzofuran-5-yl)methoxy)-5-fluorophenyl)acetate (**101a**) (0.3 g, 0.74 mmol) in dioxane (4 mL) using (3-(aminomethyl)-2-fluorophenyl)boronic acid hydrochloride (**56a**) (0.23 g, 1.11 mmol), a solution of K₂CO₃ (0.20 g, 1.47 mmol) in water (0.5 mL), Pd(PPh₃)₂Cl₂ (0.08 g, 0.11 mmol) and heating under an Ar atmosphere at 90 °C for 3 h. This gave after workup, purification by flash column chromatography [silica (12 g),

eluting with MeOH in DCM from 0-50%] ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)-5-fluorophenyl)acetate (**101b**) (0.21 g, 63 % yield) as a white solid; this was then purified by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] to furnish compound **101b** HCl salt as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.51 (s, 3H), 8.06 (d, J = 2.2 Hz, 1H), 7.78 (d, J = 1.6 Hz, 1H), 7.74 – 7.62 (m, 2H), 7.47 – 7.39 (m, 2H), 7.17 – 7.04 (m, 4H), 5.22 (s, 2H), 4.17 (s, 2H), 3.93 (q, J = 7.1 Hz, 2H), 3.64 (s, 2H), 1.00 (t, J = 7.1 Hz, 3H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -118.53, 124.00; MS (ES+): 452.9 (M+1); MS (ES-): 450.9 (M-1).

Step-3: Preparation of 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)-5-fluorophenyl)acetic acid (**101c**)

Compound **101c** was prepared according to the procedure reported in step-6 of Scheme-1 from ethyl 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)-5-fluorophenyl)acetate (**101b**) (0.16 g, 0.35 mmol) in THF/methanol (6 mL each) using a solution of lithium hydroxide hydrate (0.12 g, 2.84 mmol) in water (1 mL). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)-2-fluorophenyl)benzofuran-5-yl)methoxy)-5-fluorophenyl)acetic acid (**101c**) (0.08 g, 53 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.54 (s, 3H), 8.06 (d, J = 2.2 Hz, 1H), 7.81 (d, J = 1.6 Hz, 1H), 7.68 (td, J = 7.1, 5.1 Hz, 2H), 7.48 – 7.38 (m, 2H), 7.12 (dd, J = 7.6, 2.2 Hz, 1H), 7.11 – 7.07 (m, 2H), 7.06 (d, J = 2.2 Hz, 1H), 5.24 (s, 2H), 4.17 (s, 2H), 3.60 (s, 2H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -118.40, 124.07; MS (ES+): 424.9 (M+1); MS (ES-): 422.9 (M-1).

Scheme-102



Preparation of 2-(2-((8-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridin-6-yl)methoxy)phenyl)acetic acid (**102g**)

Step-1: Preparation of methyl 8-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)imidazo[1,2-a]pyridine-6-carboxylate (**102b**)

Compound **102b** was prepared according to the procedure reported in step-3 of Scheme-1 from methyl 8-bromoimidazo[1,2-a]pyridine-6-carboxylate (**102a**) (1.00 g, 3.92 mmol; CAS#1234616-08-0) in dioxane (20 mL) using 3-(((*tert*-butoxycarbonyl)amino)methyl)phenylboronic acid (**1d**) (0.984 g, 3.92 mmol), tripotassium phosphate (2.222 mL, 6.66 mmol; 3 M solution) in water (1 mL), tricyclohexylphosphine (0.220 g, 0.784 mmol) and $\text{Pd}_2(\text{dba})_3$ (0.197 g, 0.216 mmol) under a nitrogen atmosphere and heating at 90 °C for 12 h on an oil bath. This gave after workup, purification by flash column chromatography [silica (40 g), eluting with EtOAc/methanol (9:1) in hexane from 0-100%] methyl 8-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)imidazo[1,2-a]pyridine-6-carboxylate (**102b**) (1.289 g, 86 % yield) as a pale yellow solid; ^1H NMR (300 MHz, DMSO- d_6) δ 9.38 (d, J = 1.6 Hz, 1H), 8.24 - 8.21 (m, 1H), 8.05 (d, J = 7.7 Hz, 1H), 7.91 (s, 1H), 7.81 - 7.68 (m, 2H), 7.59 - 7.41 (m, 2H), 7.32 (d, J = 7.6 Hz, 1H), 4.30 - 4.13 (m, 2H), 3.92 (s, 3H), 1.41 (s, 9H); MS (ES $^+$): 382.3 (M+1).

Step-2: Preparation of 8-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)imidazo[1,2-a]pyridine-6-carboxylic acid (**102c**)

Compound **102c** was prepared according to the procedure reported in step-4 of Scheme-4, from methyl 8-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)imidazo[1,2-a]pyridine-6-carboxylate (**102b**) (1.25 g, 3.28 mmol) in THF (10 mL) and methanol (20 mL) using sodium

hydroxide (2 M aq.) (6.55 mL, 13.11 mmol). This gave after workup 8-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)imidazo[1,2-a]pyridine-6-carboxylic acid (**102c**) (1.06 g, 88 % yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.50 (s, 1H), 9.36 (d, J = 1.6 Hz, 1H), 8.27 (s, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.93 - 7.77 (m, 3H), 7.57 - 7.43 (m, 2H), 7.34 (d, J = 7.6 Hz, 1H), 4.23 (d, J = 6.1 Hz, 2H), 1.40 (s, 9H).

Step-3: Preparation of *tert*-butyl 3-(6-(hydroxymethyl)imidazo[1,2-a]pyridin-8-yl)benzylcarbamate (**102d**)

Compound **102d** was prepared according to the procedure reported in step-1 of Scheme-23 from 8-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)imidazo[1,2-a]pyridine-6-carboxylic acid (**102c**) (0.60 g, 1.633 mmol) using N-methylmorpholine (0.215 mL, 1.960 mmol) in THF (20 mL), isobutyl chloroformate (0.257 mL, 1.960 mmol) and NaBH₄ (0.185 g, 4.90 mmol) in water (3 mL). This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc/MeOH (9:1) in hexanes from 0-40%] *tert*-butyl 3-(6-(hydroxymethyl)imidazo[1,2-a]pyridin-8-yl)benzylcarbamate (**102d**) (0.443 g, 77 % yield) as a pale-yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.52 - 8.44 (m, 1H), 8.08 - 7.99 (m, 2H), 7.95 (s, 1H), 7.59 (d, J = 1.2 Hz, 1H), 7.53 - 7.37 (m, 3H), 7.28 (d, J = 7.6 Hz, 1H), 5.40 (t, J = 5.6 Hz, 1H), 4.57 (d, J = 5.6, 1.1 Hz, 2H), 4.21 (d, J = 6.2 Hz, 2H), 1.40 (s, 9H); MS (ES⁺): 354.3 (M+1), 376.3 (M+Na); MS (ES⁻): 352.3 (M-1).

Step-4: Preparation of ethyl 2-(2-((8-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)imidazo[1,2-a]pyridin-6-yl)methoxy)phenyl)acetate (**102e**)

Compound **102e** was prepared according to the procedure reported in step-2 of Scheme-23 from *tert*-butyl 3-(6-(hydroxymethyl)imidazo[1,2-a]pyridin-8-yl)benzylcarbamate (**102d**) (0.300 g, 0.849 mmol) in THF (25 mL) using triphenylphosphine (0.289 g, 1.104 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (0.199 g, 1.104 mmol) and DIAD (0.215 mL, 1.104 mmol). This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-100%] ethyl 2-(2-((8-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)imidazo[1,2-a]pyridin-6-yl)methoxy)phenyl)acetate (**102e**) (0.328 g, 75 % yield) as a pale-yellow solid; MS (ES⁺): 516.4 (M+1), 538.3 (M+Na); MS (ES⁻): 514.5 (M-1), 550.4 (M+Cl).

Step-5: Preparation of ethyl 2-(2-((8-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridin-6-yl)methoxy)phenyl)acetate (**102f**)

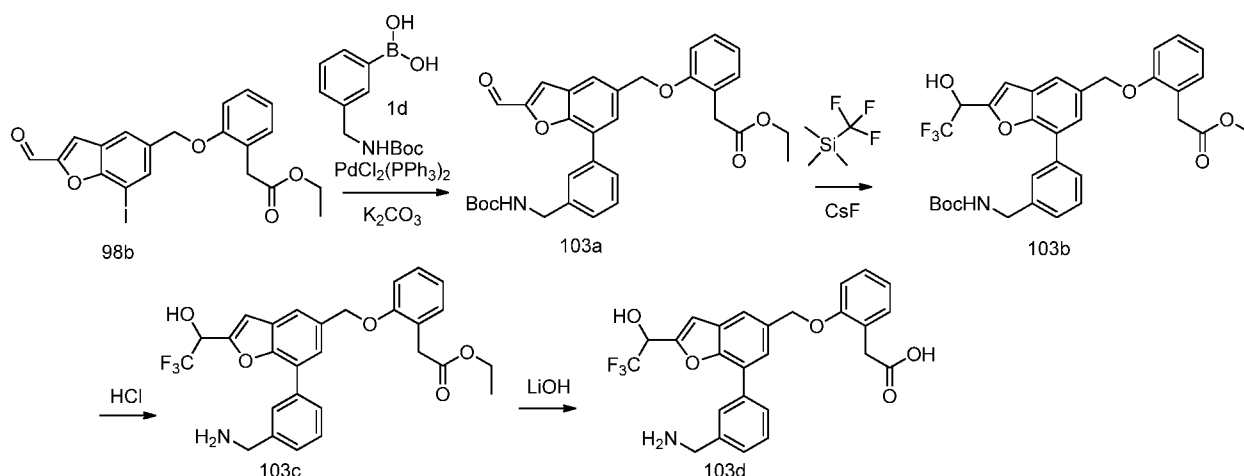
Compound **102f** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-((8-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)imidazo[1,2-a]pyridin-6-

yl)methoxy)phenyl)acetate (**102e**) (0.318 g, 0.617 mmol) in DCM (10 mL) using TFA (0.713 mL, 9.25 mmol). This gave after workup and purification by reverse phase column [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((8-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridin-6-yl)methoxy)phenyl)acetate (**102f**) (0.172 g, 67 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.01 (s, 1H), 8.65 (s, 3H), 8.53 - 8.45 (m, 1H), 8.18 (s, 1H), 8.09 - 7.97 (m, 2H), 7.89 - 7.76 (m, 1H), 7.73 - 7.64 (m, 2H), 7.35 - 7.22 (m, 2H), 7.18 (d, *J* = 8.1 Hz, 1H), 6.97 (td, *J* = 7.4, 1.1 Hz, 1H), 5.32 (s, 2H), 4.24 - 4.07 (m, 2H), 3.90 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 2H), 0.97 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 416.3 (M+1); MS (ES⁻): 450.3 (M+Cl).

Step-6: Preparation of 2-(2-((8-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridin-6-yl)methoxy)phenyl)acetic acid (**102g**)

Compound **102g** was prepared according to the procedure reported in step-4 of Scheme-4 from ethyl 2-(2-((8-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridin-6-yl)methoxy)phenyl)acetate (**102f**) (0.055 g, 0.132 mmol) in THF (4 mL) and methanol (8 mL) using sodium hydroxide (0.265 mL, 0.530 mmol, 2 M aqueous). This gave after workup and purification by reverse phase column [C18 (30 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((8-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridin-6-yl)methoxy)phenyl)acetic acid (**102g**) (0.023 g, 45 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.30 (s, 1H, D₂O exchangeable), 9.01 (s, 1H), 8.66 (s, 3H, D₂O exchangeable), 8.55 - 8.44 (m, 1H), 8.17 (s, 1H), 8.04 (d, *J* = 6.1 Hz, 2H), 7.89 - 7.77 (m, 1H), 7.72 - 7.62 (m, 2H), 7.34 - 7.21 (m, 2H), 7.15 (d, *J* = 8.1 Hz, 1H), 6.96 (t, *J* = 7.4 Hz, 1H), 5.34 (s, 2H), 4.15 (q, *J* = 5.9 Hz, 2H), 3.64 (s, 2H); MS (ES⁺): 388.3 (M+1); MS (ES⁻): 386.3 (M-1), 422.3 (M+Cl), 773.5 (2M-1); HPLC purity: 98.95%

Scheme-103



Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-(2,2,2-trifluoro-1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**103d**)

Step-1: Preparation of ethyl 2-(2-((7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-formylbenzofuran-5-yl)methoxy)phenyl)acetate (**103a**)

Compound **103a** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((2-formyl-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**98b**) (2.2 g, 4.74 mmol) in dioxane (15 mL) using (3-((*tert*-butoxycarbonyl)amino)methyl)phenylboronic acid (**1d**) (1.79 g, 7.11 mmol), a solution of K₂CO₃ (1.965 g, 14.22 mmol) in water (3 mL), bis(triphenylphosphine)palladium(II) chloride (0.50 g, 0.71 mmol) and heating at 100 °C for 3h on an oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] ethyl 2-(2-((7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-formylbenzofuran-5-yl)methoxy)phenyl)acetate (**103a**) (1.52 g, 59% yield) as a brown semi-solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.90 (s, 1H), 8.07 (d, *J* = 1.3 Hz, 1H), 7.93 (d, *J* = 1.6 Hz, 1H), 7.81 – 7.71 (m, 3H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.49 – 7.39 (m, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.30 – 7.20 (m, 2H), 7.12 (d, *J* = 8.2 Hz, 1H), 6.92 (t, *J* = 7.4 Hz, 1H), 5.28 (s, 2H), 4.24 (d, *J* = 6.2 Hz, 2H), 3.92 (q, *J* = 7.1 Hz, 2H), 3.64 (s, 2H), 1.38 (s, 9H), 0.97 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 566.3 (M+Na); (ES⁻) 542.5 (M-1).

Step-2: Preparation of ethyl 2-(2-((7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-(2,2,2-trifluoro-1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**103b**)

Trimethyl(trifluoromethyl)silane (CAS#: 81290-20-2) (283 mg, 1.99 mmol) and CsF (233 mg, 1.53 mmol) were added to a solution of ethyl 2-(2-((7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-formylbenzofuran-5-yl)methoxy)phenyl)acetate (**103a**) (833 mg, 1.53 mmol) in anhydrous THF (20 mL) at room temperature under Ar and the mixture was sonicated for 20 min to initiate the reaction. The mixture was stirred at room temp for 12 h, after which aqueous HCl (1 M, 15 mL) was added and the mixture stirred for a further 15 min. The mixture was extracted with EtOAc, washed with saturated NaHCO₃, brine, dried and evaporated in vacuo. The residue obtained was purified by flash column chromatography [silica (24 g), eluting with (EtOAc/hexane 7:3)] to afford ethyl 2-(2-((7-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-(2,2,2-trifluoro-1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**103b**) (312 mg, 33 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.81 – 7.69 (m, 3H), 7.60 (d, *J* = 1.6 Hz, 1H), 7.55 – 7.41 (m, 2H), 7.36 – 7.18 (m, 4H), 7.17 – 7.07 (m, 2H), 6.91 (t, *J* = 7.4, 1.1 Hz, 1H), 5.56 – 5.42 (m, 1H), 5.24 (s,

2H), 4.23 (d, $J = 6.1$ Hz, 2H), 3.91 (q, $J = 7.1$ Hz, 2H), 3.62 (s, 2H), 1.39 (s, 9H), 0.96 (t, $J = 7.1$ Hz, 3H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -75.90; MS (ES+): 636.3 (M+Na).

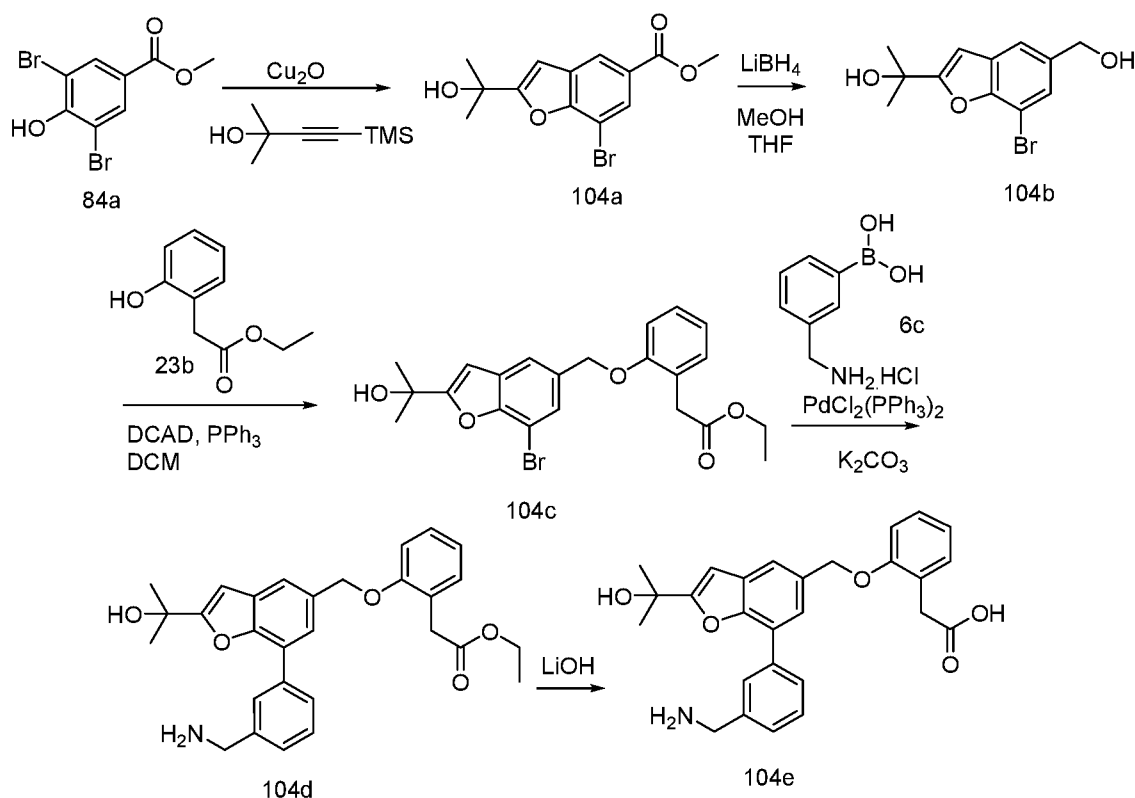
Step-3: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(2,2,2-trifluoro-1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**103c**)

Compound **103c** was prepared according to the procedure reported in step-2 of Scheme-94, from ethyl 2-(2-((7-(3-(((tert-butoxycarbonyl)amino)methyl)phenyl)-2-(2,2,2-trifluoro-1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**103b**) (300 mg, 0.49 mmol) in THF (10 mL) using hydrochloric acid (2.45 mL, 4.89 mmol) and heating at 60 °C for 2 h. This gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with DMA80 in DCM from 0-60%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(2,2,2-trifluoro-1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**103c**) (109 mg, 43 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.38 (s, 3H, D₂O exchangeable), 7.98 (s, 1H), 7.94 (d, $J = 7.4$ Hz, 1H), 7.75 (d, $J = 1.6$ Hz, 1H), 7.67 (d, $J = 1.6$ Hz, 1H), 7.65 – 7.52 (m, 2H), 7.34 – 7.27 (m, 1H), 7.27 – 7.19 (m, 2H), 7.16 (s, 1H), 7.11 (d, $J = 8.3$ Hz, 1H), 6.91 (t, $J = 7.3$ Hz, 1H), 5.53 (p, $J = 6.9$ Hz, 1H), 5.24 (s, 2H), 4.12 (s, 2H), 3.92 (q, $J = 7.1$ Hz, 2H), 3.63 (s, 2H), 0.97 (t, $J = 7.1$ Hz, 3H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -75.83; MS (ES+): 514.3 (M+1); (ES-): 512.3 (M+1); 548.3 (M+Cl).

Step-4: Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-(2,2,2-trifluoro-1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**103d**)

Compound **103d** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(2,2,2-trifluoro-1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**103c**) (78 mg, 0.15 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (19 mg, 0.46 mmol) in water (1.0 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)phenyl)-2-(2,2,2-trifluoro-1-hydroxyethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**103d**) (39 mg, 53 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 12.20 (s, 1H, D₂O exchangeable), 8.41 (s, 2H, D₂O exchangeable), 8.03 – 7.92 (m, 2H), 7.78 (d, $J = 1.5$ Hz, 1H), 7.71 (d, $J = 1.6$ Hz, 1H), 7.65 – 7.53 (m, 2H), 7.31 (d, $J = 6.5$ Hz, 1H), 7.28 – 7.19 (m, 2H), 7.15 (s, 1H), 7.09 (d, $J = 8.1$ Hz, 1H), 6.91 (t, $J = 7.3$ Hz, 1H), 5.60 – 5.47 (m, 1H), 5.27 (s, 2H), 4.13 (s, 2H), 3.60 (s, 2H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -75.81; MS (ES+): 486.3 (M+1); (ES-): 484.3 (M-1), 520.3 (M+Cl).

Scheme-104



Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-(2-hydroxypropan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**104e**)

Step-1: Preparation of methyl 7-bromo-2-(2-hydroxypropan-2-yl)benzofuran-5-carboxylate (**104a**)

Compound **104a** was prepared according to the procedure reported in step-1 of Scheme-55, from methyl 3,5-dibromo-4-hydroxybenzoate (**84a**) (7 g, 22.59 mmol) in pyridine (20 mL) using 2-methyl-4-(trimethylsilyl)but-3-yn-2-ol (3.53 g, 22.59 mmol; CAS#: 5272-33-3) and copper(I) oxide (3.23 g, 22.59 mmol). This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-70%] methyl 7-bromo-2-(2-hydroxypropan-2-yl)benzofuran-5-carboxylate (**104a**) (5 g, 71% yield) as a yellow oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.25 (d, *J* = 1.6 Hz, 1H), 8.01 (d, *J* = 1.6 Hz, 1H), 6.95 (d, *J* = 0.9 Hz, 1H), 5.56 (s, 1H, D₂O exchangeable), 3.89 (s, 3H), 1.55 (s, 6H).

Step-2: Preparation of 2-(7-bromo-5-(hydroxymethyl)benzofuran-2-yl)propan-2-ol (**104b**)

Compound **104b** was prepared according to the procedure reported in step-2 of Scheme-76 from methyl 7-bromo-2-(2-hydroxypropan-2-yl)benzofuran-5-carboxylate (**104a**) (4 g, 12.77 mmol) in THF (60 mL) using LiBH₄ (19.16 mL, 38.3 mmol, 2 M solution in THF) and MeOH (1.23 g, 38.3 mmol). This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-60%] 2-(7-bromo-5-

(hydroxymethyl)benzofuran-2-yl)propan-2-ol (**104b**) (2.86 g, 79 % yield) as a clear oil; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 7.50 (d, $J = 1.2$ Hz, 1H), 7.42 (d, $J = 1.4$ Hz, 1H), 6.77 (d, $J = 1.1$ Hz, 1H), 5.44 (s, 1H, D_2O exchangeable), 5.28 (t, $J = 5.8$, 1.1 Hz, 1H, D_2O exchangeable), 4.55 (d, $J = 5.8$ Hz, 2H), 1.53 (s, 6H).

Step-3: Preparation of ethyl 2-(2-((7-bromo-2-(2-hydroxypropan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**104c**)

Compound **104c** was prepared according to the procedure reported in step-2 of Scheme-23 from 2-(7-bromo-5-(hydroxymethyl)benzofuran-2-yl)propan-2-ol (**104b**) (2.82 g, 9.89 mmol) in DCM (180 mL) using triphenylphosphine (2.85 g, 10.88 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (1.87 g, 10.38 mmol) and di-(4-chlorobenzyl)azodicarboxylate (DCAD, 3.99 g, 10.88 mmol) in DCM (20 mL). This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-50%] ethyl 2-(2-((7-bromo-2-(2-hydroxypropan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**104c**) (1.8 g, 41 % yield) as a clear oil, which became a white solid on standing; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 7.63 (d, $J = 1.4$ Hz, 1H), 7.53 (d, $J = 1.4$ Hz, 1H), 7.28 – 7.18 (m, 2H), 7.06 (d, $J = 8.1$ Hz, 1H), 6.91 (t, $J = 7.4$ Hz, 1H), 6.80 (s, 1H), 5.47 (d, $J = 1.1$ Hz, 1H), 5.16 (s, 2H), 4.03 (q, $J = 7.1$ Hz, 3H), 1.53 (s, 6H), 1.09 (t, $J = 7.1$ Hz, 3H).

Step-4: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(2-hydroxypropan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**104d**)

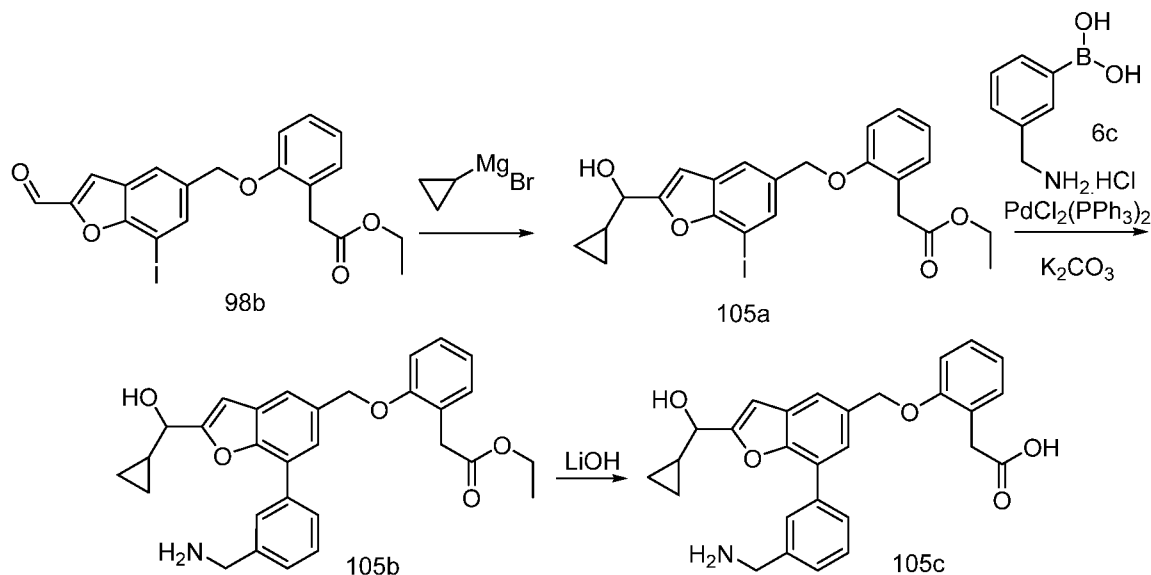
Compound **104d** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-bromo-2-(2-hydroxypropan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**104c**) (700 mg, 1.57 mmol) in dioxane (25 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (381 mg, 2.03 mmol), a solution of K_2CO_3 (649 mg, 4.69 mmol) in water (3 mL), bis(triphenylphosphine)palladium(II) chloride (165 mg, 0.24 mmol) and heating at 100 °C for 3h on oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(2-hydroxypropan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**104d**) (585 mg, 79 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 8.46 (s, 3H, D_2O exchangeable), 8.01 – 7.93 (m, 2H), 7.64 (d, $J = 1.6$ Hz, 1H), 7.62 – 7.53 (m, 3H), 7.29 – 7.19 (m, 2H), 7.11 (d, $J = 8.0$ Hz, 1H), 6.91 (t, $J = 7.2$ Hz, 1H), 6.76 (s, 1H), 5.48 (s, 1H, D_2O exchangeable), 5.23 (s, 2H), 4.13 (d, $J = 5.7$ Hz, 2H), 3.94 (q, $J = 7.1$ Hz, 2H),

3.63 (s, 2H), 1.55 (s, 6H), 1.00 (t, $J = 7.1$ Hz, 3H); MS (ES⁺): 474.3 (M+1); (ES⁻): 508.3 (M+Cl)

Step-5: Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-(2-hydroxypropan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**104e**)

Compound **104e** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(2-hydroxypropan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**104d**) (70 mg, 0.15 mmol) in MeOH/THF (5 mL) using a solution of lithium hydroxide monohydrate (12.41 mg, 0.30 mmol) in water (1.0 mL). This gave after workup and purification by flash column chromatography [silica (4g), eluting with DMA80 in DCM from 0-80%] 2-(2-((7-(3-(aminomethyl)phenyl)-2-(2-hydroxypropan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**104e**) (20 mg, 30 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.35 (s, 1H), 8.15 (d, $J = 8.0$ Hz, 1H), 7.89 (s, 1H), 7.60 (s, 1H), 7.50 (t, $J = 7.7$ Hz, 1H), 7.35 (d, $J = 7.5$ Hz, 1H), 7.15 – 7.03 (m, 2H), 6.93 (d, $J = 8.1$ Hz, 1H), 6.88 – 6.67 (m, 2H), 5.50 (s, 1H, D₂O exchangeable), 5.25 (s, 2H), 4.01 (s, 2H), 3.39 (s, 2H), 1.55 (s, 6H); ¹H NMR (300 MHz, Methanol-*d*₄) δ 8.25 – 8.13 (m, 2H), 7.89 (s, 1H), 7.55 – 7.40 (m, 2H), 7.29 (d, $J = 7.6$ Hz, 1H), 7.16 (t, $J = 7.8$ Hz, 2H), 6.96 (d, $J = 8.1$ Hz, 1H), 6.87 (t, $J = 7.4$ Hz, 1H), 6.70 (s, 1H), 5.21 (s, 2H), 4.09 (s, 2H), 3.59 (s, 2H), 1.64 (s, 6H); MS (ES⁺): 446.3 (M+1); (ES⁻): 444.4 (M-1), 480.3 (M+Cl).

Scheme-105



Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-

(cyclopropyl(hydroxy)methyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**105c**)

Step-1: Preparation of ethyl 2-(2-((2-(cyclopropyl(hydroxy)methyl)-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**105a**)

Compound **105a** was prepared according to the procedure reported in step-3 of Scheme-98, from ethyl 2-(2-((2-formyl-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**98b**) (500 mg, 1.08 mmol) in THF (20 mL) using cyclopropyl magnesium bromide (1.0 M in THF, 1.185 mL, 1.185 mmol) at -78 °C. This gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with EtOAc in hexane from 0-60%] ethyl 2-(2-((2-(cyclopropyl(hydroxy)methyl)-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**105a**) (227 mg, 42 % yield) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.69 (s, 1H), 7.63 (s, 1H), 7.29 – 7.16 (m, 2H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.97 – 6.80 (m, 2H), 5.64 (d, *J* = 5.5 Hz, 1H), 5.14 (s, 2H), 4.16 (t, *J* = 6.6 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 2H), 3.61 (s, 2H), 1.34 – 1.18 (m, 1H), 1.09 (t, *J* = 7.0 Hz, 3H), 0.59 – 0.28 (m, 4H).

Step-2: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(cyclopropyl(hydroxy)methyl)benzofuran-5-yl)methoxy)phenyl)acetate (**105b**)

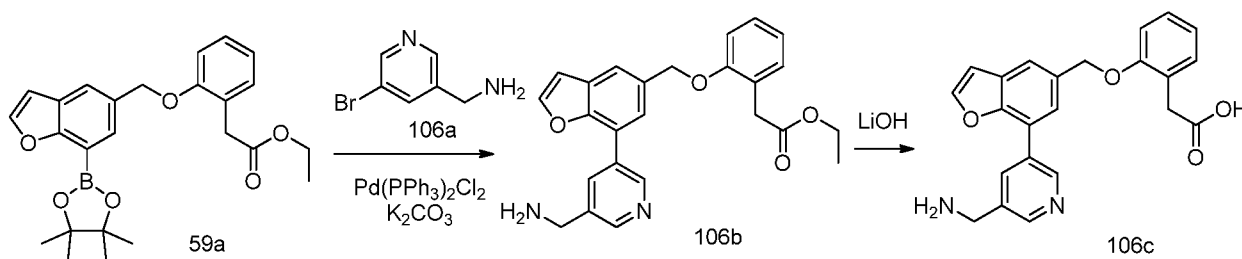
Compound **105b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((2-(cyclopropyl(hydroxy)methyl)-7-iodobenzofuran-5-yl)methoxy)phenyl)acetate (**105a**) (227 mg, 0.45 mmol) in dioxane (15 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (109 mg, 0.58 mmol), a solution of K₂CO₃ (186 mg, 1.35 mmol) in water (3 mL), bis(triphenylphosphine)palladium(II) chloride (47 mg, 0.067 mmol) and heating at 100 °C for 3h on an oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(cyclopropyl(hydroxy)methyl)benzofuran-5-yl)methoxy)phenyl)acetate (**105b**) (150 mg, 69 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.86 (s, 1H), 7.77 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.62 (d, *J* = 1.5 Hz, 1H), 7.55 (d, *J* = 1.6 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.30 – 7.19 (m, 2H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.94 – 6.86 (m, 1H), 6.81 (s, 1H), 5.55 (s, 1H), 5.23 (s, 2H), 4.16 (d, *J* = 7.6 Hz, 1H, D₂O exchangeable), 3.94 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 2H), 3.63 (s, 2H), 1.32 – 1.16 (m, 1H), 1.00 (t, *J* = 7.1 Hz, 3H), 0.58 – 0.48 (m, 2H), 0.48 – 0.37 (m, 2H); MS (ES⁺): 486.3 (M+1); (ES⁻): 484.3 (M-1), 520.4 (M+Cl).

Step-3: Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-(cyclopropyl(hydroxy)methyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**105c**)

Compound **105c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-(cyclopropyl(hydroxy)methyl)benzofuran-5-yl)methoxy)phenyl)acetate (**105b**) (96 mg, 0.20 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (25 mg, 0.6 mmol) in water (1.0 mL). This gave

after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)phenyl)-2-(cyclopropyl(hydroxy)methyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**105c**) (50 mg, 55% yield) HCl salt as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.34 (s, 1H), 8.15 (d, $J = 7.8$ Hz, 1H), 7.89 (s, 1H), 7.62 (s, 1H), 7.49 (t, $J = 7.7$ Hz, 1H), 7.35 (d, $J = 7.6$ Hz, 1H), 7.13-7.05 (m, 2H), 6.94 (d, $J = 8.1$ Hz, 1H), 6.87 – 6.77 (m, 2H), 5.26 (s, 2H), 4.17 (d, $J = 7.6$ Hz, 2H), 4.01 (s, 2H), 3.40 (s, 2H), 1.33 – 1.21 (m, 1H), 0.59 – 0.48 (m, 2H), 0.48 – 0.33 (m, 2H); MS (ES⁺): 458.3 (M+1); 480.3 (M+Na); (ES⁻): 456.4 (M-1), 492.3 (M+Cl).

Scheme-106



Preparation of 2-(2-((7-(5-(aminomethyl)pyridin-3-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**106c**)

Step-1: Preparation of ethyl 2-(2-((7-(5-(aminomethyl)pyridin-3-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**106b**)

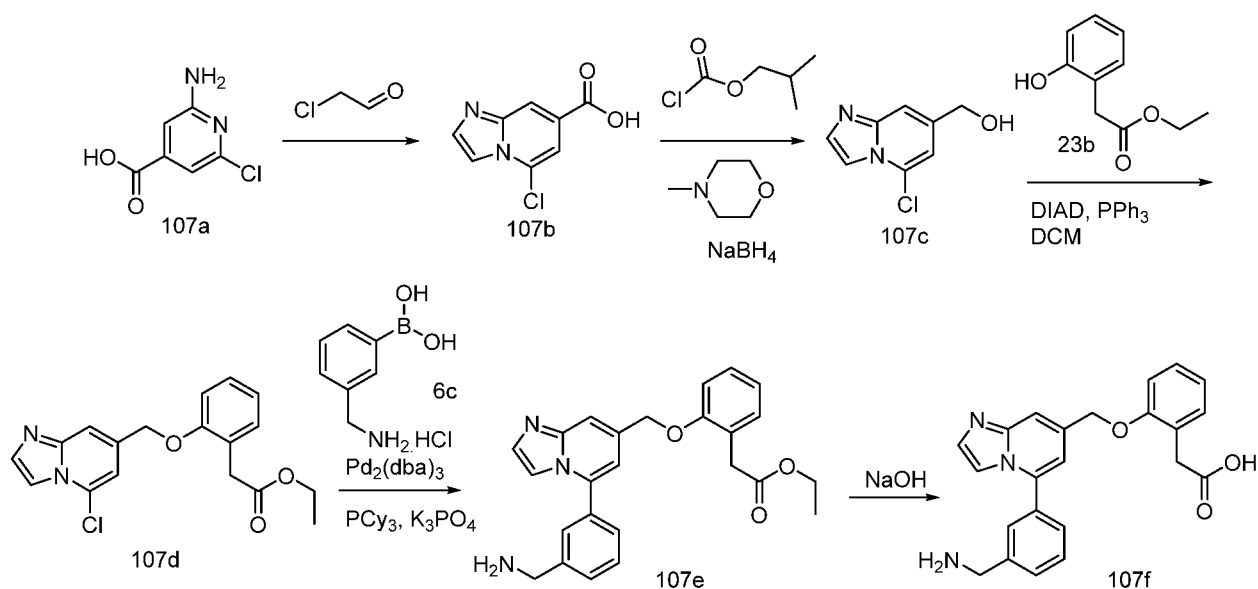
Compound **106b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (382 mg, 0.88 mmol) in dioxane (10 mL) using (5-bromopyridin-3-yl)methanamine (**106a**) (246 mg, 1.31 mmol), bis(triphenylphosphine)palladium(II) chloride (92 mg, 0.13 mmol) and a solution of K_2CO_3 (363 mg, 2.63 mmol) in water (1 mL) under an Ar atmosphere and heating at 95 °C for 2 h on oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-70%] ethyl 2-(2-((7-(5-(aminomethyl)pyridin-3-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**106b**) (112 mg, 31% yield) as a white solid; MS (ES⁺): 417.3 (M+1).

Step-2: Preparation of 2-(2-((7-(5-(aminomethyl)pyridin-3-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**106c**)

Compound **106c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(5-(aminomethyl)pyridin-3-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**106b**) (112 mg, 0.27 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (34 mg, 0.81 mmol) in water (1 mL). This gave after workup and purification

by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(5-(aminomethyl)pyridin-3-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**106c**) (55 mg, 53 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 9.26 (d, J = 1.8 Hz, 1H), 8.72 (s, 1H), 8.58 (d, J = 1.7 Hz, 1H), 8.15 (t, J = 1.7 Hz, 1H), 7.90 (s, 1H), 7.76 (d, J = 1.5 Hz, 1H), 7.16 – 7.06 (m, 3H), 6.98 (d, J = 8.1 Hz, 1H), 6.86 – 6.77 (m, 1H), 5.29 (s, 2H), 4.07 (s, 2H), 3.43 (s, 2H); MS (ES $^{+}$): 389.3 (M+1); 411.2 (M+Na); (ES $^{-}$): 387.3 (M-1), 423.3 (M+Cl).

Scheme-107



Preparation of 2-(2-((5-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridin-7-yl)methoxy)phenyl)acetic acid (**107f**)

Step-1: Preparation of 5-chloroimidazo[1,2-a]pyridine-7-carboxylic acid (**107b**)

To a solution of 2-amino-6-chloroisonicotinic acid (**107a**) (0.5 g, 2.90 mmol; CAS# 6313-55-9) in EtOH (20 mL) was added 2-chloroacetaldehyde (1.47 mL, 11.59 mmol) and heated at reflux overnight. The reaction mixture was cooled to RT diluted with EtOAc, washed with water, brine, dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-100%] to afford 5-chloroimidazo[1,2-a]pyridine-7-carboxylic acid (**107b**) (0.45 g, 79 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.03 (s, 1H), 7.95 (s, 1H), 7.77 (d, J = 1.3 Hz, 1H), 7.50 (d, J = 1.2 Hz, 1H); MS (ES $^{+}$): 197.0 & 199.1 (M+1); MS (ES $^{-}$): 195.1 & 197.1 (M-1).

Step-2: Preparation of (5-chloroimidazo[1,2-a]pyridin-7-yl)methanol (**107c**)

Compound **107c** was prepared according to the procedure reported in step-1 of Scheme-23 from 5-chloroimidazo[1,2-a]pyridine-7-carboxylic acid (**107b**) (0.6 g, 3.05 mmol) using N-methylmorpholine (0.40 mL, 3.66 mmol) in THF (50 mL), isobutyl chloroformate (0.48 mL, 3.66 mmol) and NaBH₄ (0.35 g, 9.16 mmol) in water (0.8 mL). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] (5-chloroimidazo[1,2-a]pyridin-7-yl)methanol (**107c**) (0.3 g, 54 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.96 (s, 1H), 7.67 (s, 1H), 7.51 (s, 1H), 7.12 (s, 1H), 5.51 (t, J = 5.8 Hz, 1H), 4.55 (dd, J = 5.8, 1.1 Hz, 2H); MS (ES⁺): 183.1 (M+1).

Step-3: Preparation of ethyl 2-(2-((5-chloroimidazo[1,2-a]pyridin-7-yl)methoxy)phenyl)acetate (**107d**)

Compound **107d** was prepared according to the procedure reported in step-2 of Scheme-23 from (5-chloroimidazo[1,2-a]pyridin-7-yl)methanol (**107c**) (0.15 g, 0.82 mmol) in DCM (10 mL) using triphenylphosphine (0.28 g, 1.07 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (0.19 g, 1.07 mmol) and di-(4-chlorobenzyl)azodicarboxylate (DIAD, 0.39 g, 1.07 mmol). This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-60%] ethyl 2-(2-((5-chloroimidazo[1,2-a]pyridin-7-yl)methoxy)phenyl)acetate (**107d**) (0.2 g, 71 % yield) as a colorless oil; MS (ES⁻): 343.2 (M-1).

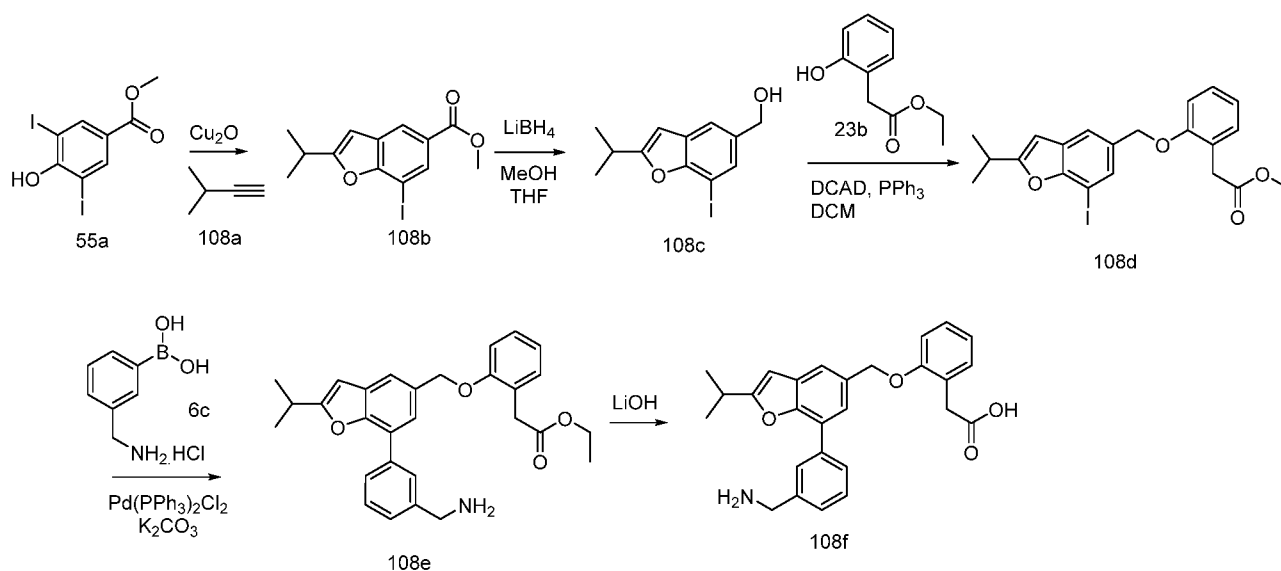
Step-4: Preparation of ethyl 2-(2-((5-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridin-7-yl)methoxy)phenyl)acetate (**107e**)

Compound **107e** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((5-chloroimidazo[1,2-a]pyridin-7-yl)methoxy)phenyl)acetate (**107d**) (0.15 g, 0.44 mmol) in dioxane (4 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (0.12 g, 0.65 mmol), tripotassium phosphate (3 M aqueous solution, 0.25 mL, 0.74 mmol), tricyclohexylphosphine (0.04 g, 0.13 mmol) and Pd₂(dba)₃ (0.04 g, 0.04 mmol) under an Ar atmosphere and heating at 125 °C for 120 min in a microwave. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] ethyl 2-(2-((5-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridin-7-yl)methoxy)phenyl)acetate (**107e**) (0.08 g, 44 % yield) as a white solid; MS (ES⁺): 416.3 (M+1).

Step-5: Preparation of 2-(2-((5-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridin-7-yl)methoxy)phenyl)acetic acid (**107f**)

Compound **107f** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-((5-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridin-7-yl)methoxy)phenyl)acetate (**107e**) 0.07 g, 0.17 mmol) in MeOH/THF (4 mL) using a solution of sodium hydroxide (0.61 mL, 1.52 mmol, 2.5 M) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((5-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridin-7-yl)methoxy)phenyl)acetic acid (**107f**) (0.01 g, 9 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 11.89 (s, 1H), 8.55 (s, 3H), 7.67 (dt, J = 14.6, 6.9 Hz, 2H), 7.56 (t, J = 2.9 Hz, 1H), 7.44 (dt, J = 15.3, 7.7 Hz, 1H), 7.34 (s, 1H), 7.21 (d, J = 7.3 Hz, 2H), 7.09 (d, J = 8.4 Hz, 1H), 6.90 (t, J = 7.3 Hz, 1H), 6.45 (q, J = 2.7 Hz, 1H), 5.29 (s, 2H), 4.16 (q, J = 5.9 Hz, 2H), 3.60 (s, 2H); MS (ES $^+$): 388.3 (M+1); MS (ES $^-$): 386.3 (M-1), 422.3 (M+Cl). HPLC purity: 95.72%.

Scheme-108



Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-isopropylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**108f**)

Step-1: Preparation of methyl 7-iodo-2-isopropylbenzofuran-5-carboxylate (**108b**)

Compound **108b** was prepared according to the procedure reported in step-1 of Scheme-55, from methyl 4-hydroxy-3,5-diiodobenzoate (**55a**) (10 g, 24.76 mmol) in pyridine (10 mL) using 3-methylbut-1-yn-3-ol (**108a**) (1.69 g, 24.76 mmol; CAS#: 598-23-2) and copper(I) oxide (1.77 g, 12.38 mmol). This gave after workup and purification by flash column chromatography [silica (80 g), eluting with EtOAc in hexane from 0-70%] methyl 7-iodo-2-isopropylbenzofuran-5-carboxylate (**108b**) (5.77 g, 68 % yield) as a white solid; ^1H NMR

(300 MHz, DMSO-*d*₆) δ 8.18 (d, *J* = 1.6 Hz, 1H), 8.15 (d, *J* = 1.6 Hz, 1H), 6.86 (d, *J* = 1.1 Hz, 1H), 3.87 (s, 3H), 3.20 – 3.07 (m, 1H), 1.32 (d, *J* = 6.9 Hz, 6H).

Step-2: Preparation of (7-iodo-2-isopropylbenzofuran-5-yl)methanol (**108c**)

Compound **108c** was prepared according to the procedure reported in step-2 of Scheme-76 from methyl 7-iodo-2-isopropylbenzofuran-5-carboxylate (**108b**) (4.77 g, 13.86 mmol) in THF (200 mL) using LiBH₄ (13.86 mL, 27.7 mmol, 2 M solution in THF) and MeOH (1.12 mL, 27.7 mmol). This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc in hexane from 0-60%] (7-iodo-2-isopropylbenzofuran-5-yl)methanol (**108c**) (2.7 g, 62 % yield) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.56 (d, *J* = 1.5 Hz, 1H), 7.46 (d, *J* = 1.5 Hz, 1H), 6.69 (d, *J* = 1.1 Hz, 1H), 5.27 (t, *J* = 5.8 Hz, 1H), 4.52 (d, *J* = 5.8 Hz, 2H), 3.16 – 3.00 (m, 1H), 1.30 (d, *J* = 6.9 Hz, 6H).

Step-3: Preparation of ethyl 2-(2-((7-iodo-2-isopropylbenzofuran-5-yl)methoxy)phenyl)acetate (**108d**)

Compound **108d** was prepared according to the procedure reported in step-2 of Scheme-23 from (7-iodo-2-isopropylbenzofuran-5-yl)methanol (**108c**) (2.7 g, 8.54 mmol) in DCM (50 mL) using triphenylphosphine (2.46 g, 9.39 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (1.69 g, 9.39 mmol) and di-(4-chlorobenzyl)azodicarboxylate (DCAD, 3.45 g, 9.39 mmol) in DCM (20 mL). This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-50%] ethyl 2-(2-((7-iodo-2-isopropylbenzofuran-5-yl)methoxy)phenyl)acetate (**108d**) (2.8 g, 69 % yield) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.65 (d, *J* = 1.5 Hz, 1H), 7.58 (d, *J* = 1.5 Hz, 1H), 7.28 – 7.17 (m, 2H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.73 (d, *J* = 1.0 Hz, 1H), 5.13 (s, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.61 (s, 2H), 3.18 – 2.99 (m, 1H), 1.29 (s, 7H), 1.09 (t, *J* = 7.1 Hz, 3H).

Step-4: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-isopropylbenzofuran-5-yl)methoxy)phenyl)acetate (**108e**)

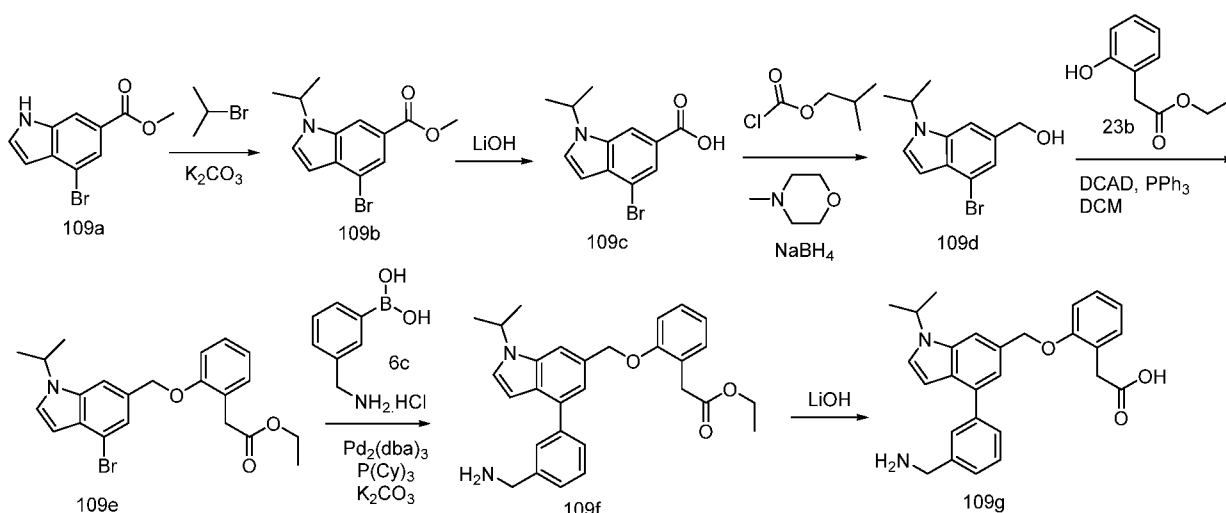
Compound **108e** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-iodo-2-isopropylbenzofuran-5-yl)methoxy)phenyl)acetate (**108d**) (850 mg, 1.78 mmol) in dioxane (20 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (433 mg, 2.31 mmol), a solution of K₂CO₃ (737 mg, 5.33 mmol) in water (5 mL), bis(triphenylphosphine)palladium(II) chloride (187 mg, 0.27 mmol) and heating at 100 °C for 3h on oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] followed by purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from

0-100%] ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-isopropylbenzofuran-5-yl)methoxy)phenyl)acetate (**108e**) (468 mg, 58 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.44 (s, 3H, D $_2$ O exchangeable), 7.97 (d, J = 2.3 Hz, 1H), 7.93 (dt, J = 7.4, 1.7 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.59 – 7.56 (m, 1H), 7.54 (d, J = 1.7 Hz, 1H), 7.29 – 7.19 (m, 2H), 7.10 (d, J = 8.1 Hz, 1H), 6.91 (td, J = 7.4, 1.0 Hz, 1H), 6.67 (d, J = 1.0 Hz, 1H), 5.22 (s, 2H), 4.13 (s, 2H), 3.94 (q, J = 7.1 Hz, 2H), 3.63 (s, 2H), 3.18 – 3.04 (m, 1H), 1.32 (d, J = 6.9 Hz, 6H), 1.00 (t, J = 7.1 Hz, 3H); MS (ES $^+$): 458.3 (M+1); (ES $^-$): 492.3 (M+Cl).

Step-5: Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)-2-isopropylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**108f**)

Compound **108f** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(aminomethyl)phenyl)-2-isopropylbenzofuran-5-yl)methoxy)phenyl)acetate (**108e**) (225 mg, 0.49 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (62 mg, 1.48 mmol) in water (1.0 mL). This gave after workup 2-(2-((7-(3-(aminomethyl)phenyl)-2-isopropylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**108f**) (165 mg, 78 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 9.16 (s, 3H, D $_2$ O exchangeable), 8.01 (d, J = 1.9 Hz, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.64 – 7.62 (m, 1H), 7.62 – 7.55 (m, 2H), 7.55 – 7.49 (m, 1H), 7.23 – 7.16 (m, 2H), 7.06 (d, J = 8.3 Hz, 1H), 6.89 (t, J = 7.3 Hz, 1H), 6.66 (d, J = 1.0 Hz, 1H), 5.24 (s, 2H), 4.12 (s, 2H), 3.57 (s, 2H), 3.19 – 3.06 (m, 1H), 1.33 (d, J = 6.9 Hz, 6H); MS (ES $^+$): 430.3 (M+1); (ES $^-$): 428.4 (M+1); 464.4 (M+Cl).

Scheme-109



Preparation of 2-(2-((4-(3-(aminomethyl)phenyl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**109g**)

Step-1: Preparation of methyl 4-bromo-1-isopropyl-1H-indole-6-carboxylate (**109b**)

To a solution of methyl 4-bromo-1H-indole-6-carboxylate (**109a**) (1.5 g, 5.90 mmol; CAS# 882679-96-1) in DMF (10 mL) was added 2-bromopropane (1.3 mL, 14.76 mmol), potassium carbonate (2.86 g, 20.66 mmol) and heated at 60 °C for 3 days. The reaction mixture was diluted with EtOAc (100 mL), washed with water (3x), brine, dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica (12 g), eluting with EtOAc in hexane from 0-60%] to afford methyl 4-bromo-1-isopropyl-1H-indole-6-carboxylate (**109b**) (0.85 g, 49 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.20 (s, 1H), 7.90 (d, J = 3.2 Hz, 1H), 7.79 (s, 1H), 6.54 (d, J = 3.2 Hz, 1H), 4.92 (m, 1H), 3.88 (s, 3H), 1.47 (d, J = 6.6 Hz, 6H); MS (ES⁺): 297.4 (M+1).

Step-2: Preparation of 4-bromo-1-isopropyl-1H-indole-6-carboxylic acid (**109c**)

Compound **109c** was prepared according to the procedure reported in step-6 of Scheme-1, from methyl 4-bromo-1-isopropyl-1H-indole-6-carboxylate (**109b**) (0.8 g, 2.70 mmol) in THF/MeOH (20 mL) using a solution of lithium hydroxide hydrate (0.68 g, 16.21 mmol) in water (3 mL). This gave after workup 4-bromo-1-isopropyl-1H-indole-6-carboxylic acid (**109c**) (0.7 g, 92 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.96 (s, 1H), 8.17 (s, 1H), 7.88 (d, J = 3.3 Hz, 1H), 7.77 (s, 1H), 6.52 (d, J = 3.2 Hz, 1H), 4.90 (m, 1H), 1.47 (d, J = 6.6 Hz, 6H); MS (ES⁻): 282.2 (M-1).

Step-3: Preparation of (4-bromo-1-isopropyl-1H-indol-6-yl)methanol (**109d**)

Compound **109d** was prepared according to the procedure reported in step-1 of Scheme-23 from 4-bromo-1-isopropyl-1H-indole-6-carboxylic acid (**109c**) (0.75 g, 2.66 mmol) using N-methylmorpholine (0.35 mL, 3.19 mmol) in THF (100 mL), isobutyl chloroformate (0.42 mL, 3.19 mmol) and NaBH₄ (0.30 g, 7.97 mmol) in water (0.8 mL). This gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc/MeOH=9:1 in hexane from 0-100%] (4-bromo-1-isopropyl-1H-indol-6-yl)methanol (**109d**) (0.65 g, 91 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.58 (d, J = 3.3 Hz, 1H), 7.47 (s, 1H), 7.21 (s, 1H), 6.37 (d, J = 3.3 Hz, 1H), 5.24 (t, J = 5.8 Hz, 1H), 4.73 (m, 1H), 4.58 (d, J = 5.8 Hz, 2H), 1.45 (d, J = 6.7 Hz, 6H).

Step-4: Preparation of ethyl 2-(2-((4-bromo-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetate (**109e**)

Compound **109e** was prepared according to the procedure reported in step-2 of Scheme-23 from (4-bromo-1-isopropyl-1H-indol-6-yl)methanol (**109d**) (0.65 g, 2.42 mmol) in DCM (10 mL) using triphenylphosphine (0.83 g, 3.15 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (0.57 g, 3.15 mmol) and di-(4-chlorobenzyl)azodicarboxylate (DCAD, 1.16 g, 3.15 mmol).

This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane from 0-60%] ethyl 2-(2-((4-bromo-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetate (**109e**)

(0.12 g, 12 % yield) as a colorless oil; MS (ES⁻): 428.3 & 430.2 (M-1).

Step-5: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)phenyl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetate (**109f**)

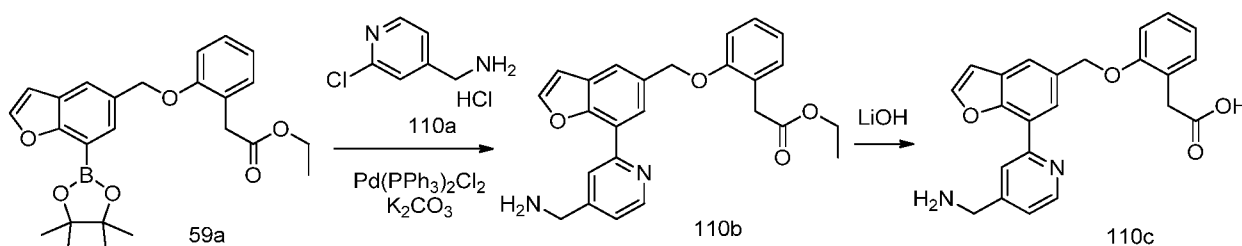
Compound **109f** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((4-bromo-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetate (**109e**) (0.3 g, 0.70 mmol) in dioxane (15 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (0.2 g, 1.05 mmol), K₂CO₃ (0.29 g, 2.09 mmol) in water (2 mL) and bis(triphenylphosphine)Palladium(II) chloride (0.07 g, 0.11 mmol) under an Ar atmosphere and heating at 100 °C for 4 h in an oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with MeOH in DCM from 0-20%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((4-(3-(aminomethyl)phenyl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetate (**109f**) (0.25 g, 79 % yield) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.29 (s, 3H), 7.80 (d, J = 1.7 Hz, 1H), 7.67 (dt, J = 7.7, 1.4 Hz, 1H), 7.64 (s, 1H), 7.61 (d, J = 3.3 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.27 – 7.20 (m, 2H), 7.19 (d, J = 1.2 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 6.90 (td, J = 7.4, 1.1 Hz, 1H), 6.67 (d, J = 3.3 Hz, 1H), 5.25 (s, 2H), 4.81 (p, J = 6.7 Hz, 1H), 4.13 (s, 2H), 3.92 (q, J = 7.1 Hz, 2H), 3.63 (s, 2H), 1.50 (d, J = 6.6 Hz, 6H), 0.98 (t, J = 7.1 Hz, 3H); MS (ES⁺): 457.5 (M+1); MS (ES⁻): 491.6 (M+Cl). HPLC purity: 97.55 %.

Step-6: Preparation of 2-(2-((4-(3-(aminomethyl)phenyl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**109g**)

Compound **109g** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((4-(3-(aminomethyl)phenyl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetate (**109f**) (0.04 g, 0.09 mmol) in THF/MeOH (4 mL) using a solution of lithium hydroxide hydrate (0.02 g, 0.53 mmol) in water (1 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((4-(3-(aminomethyl)phenyl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**109g**) (0.02 g, 56 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.21 (s, 1H), 8.33 (s, 4H), 7.80 (s, 1H), 7.68 (m, 2H), 7.61 (d, J = 3.3 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.25 – 7.20 (m, 3H), 7.11 (m,

1H), 6.94 – 6.86 (m, 1H), 6.67 (d, $J = 3.3$ Hz, 1H), 5.27 (s, 2H), 4.81 (p, $J = 6.8$ Hz, 1H), 4.13 (s, 2H), 3.60 (s, 2H), 1.49 (d, $J = 6.6$ Hz, 6H); MS (ES⁻): 427.5 (M-1).

Scheme-110



Preparation of 2-(2-((7-(4-(aminomethyl)pyridin-2-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**110c**)

Step-1: Preparation of ethyl 2-(2-((7-(4-(aminomethyl)pyridin-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**110b**)

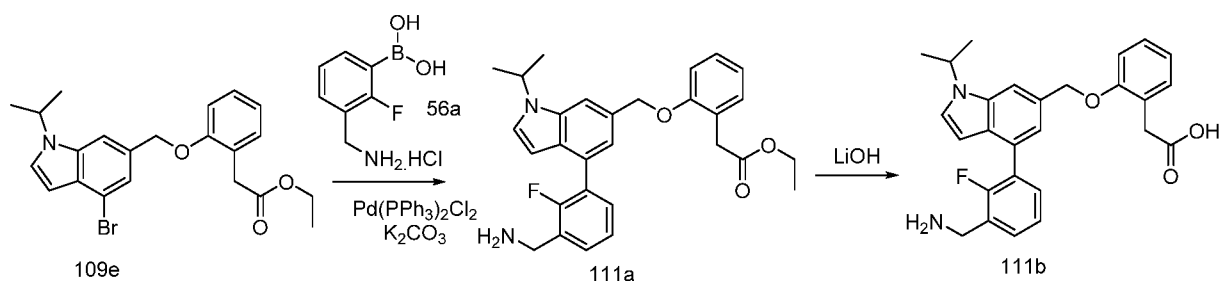
Compound **110b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**59a**) (330 mg, 0.76 mmol) in dioxane (10 mL) using (2-chloropyridin-4-yl)methanamine hydrochloride (**110a**) (203 mg, 1.14 mmol), bis(triphenylphosphine)palladium(II) chloride (80 mg, 0.11 mmol) and a solution of K₂CO₃ (314 mg, 2.27 mmol) in water (1 mL) under an Ar atmosphere and heating at 100 °C for 3 h on oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-70%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(4-(aminomethyl)pyridin-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**110b**) (220 mg, 70 % yield) HCl salt as an off white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.82 (d, $J = 5.1$ Hz, 1H), 8.73 (s, 3H, D₂O exchangeable), 8.41 (s, 1H), 8.18 (d, $J = 2.2$ Hz, 1H), 8.14 (d, $J = 1.7$ Hz, 1H), 7.84 (d, $J = 1.6$ Hz, 1H), 7.63 (dd, $J = 5.2, 1.5$ Hz, 1H), 7.32 – 7.18 (m, 2H), 7.17 – 7.10 (m, 2H), 6.92 (td, $J = 7.4, 1.1$ Hz, 1H), 5.27 (s, 2H), 4.23 (q, $J = 6.0$ Hz, 2H), 3.97 (q, $J = 7.1$ Hz, 2H), 3.62 (s, 2H), 1.00 (t, $J = 7.1$ Hz, 3H); MS (ES⁺): 417.3 (M+1); (ES⁻): 451.4 (M+Cl).

Step-2: Preparation of 2-(2-((7-(4-(aminomethyl)pyridin-2-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**110c**)

Compound **110c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(4-(aminomethyl)pyridin-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**110b**) (133 mg, 0.32 mmol) in MeOH/THF (20 mL) using a solution of lithium hydroxide monohydrate (27 mg, 0.64 mmol) in water (2 mL). This gave after workup and purification

by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(4-(aminomethyl)pyridin-2-yl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**110c**) (72 mg, 58% yield) HCl salt as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.83 (d, $J = 5.1$ Hz, 1H), 8.68 (s, 3H, D_2O exchangeable), 8.39 (d, $J = 1.5$ Hz, 1H), 8.17 (d, $J = 2.2$ Hz, 1H), 8.14 (d, $J = 1.7$ Hz, 1H), 7.87 (d, $J = 1.6$ Hz, 1H), 7.63 (dd, $J = 5.3, 1.5$ Hz, 1H), 7.26 – 7.19 (m, 2H), 7.14 – 7.06 (m, 2H), 6.90 (t, $J = 7.4$ Hz, 1H), 5.30 (s, 2H), 4.23 (q, $J = 5.9$ Hz, 2H), 3.59 (s, 2H); MS (ES⁺): 389.3 (M+1); (ES⁻): 387.3 (M-1); 423.3 (M+Cl).

Scheme-111



Preparation of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**111b**)

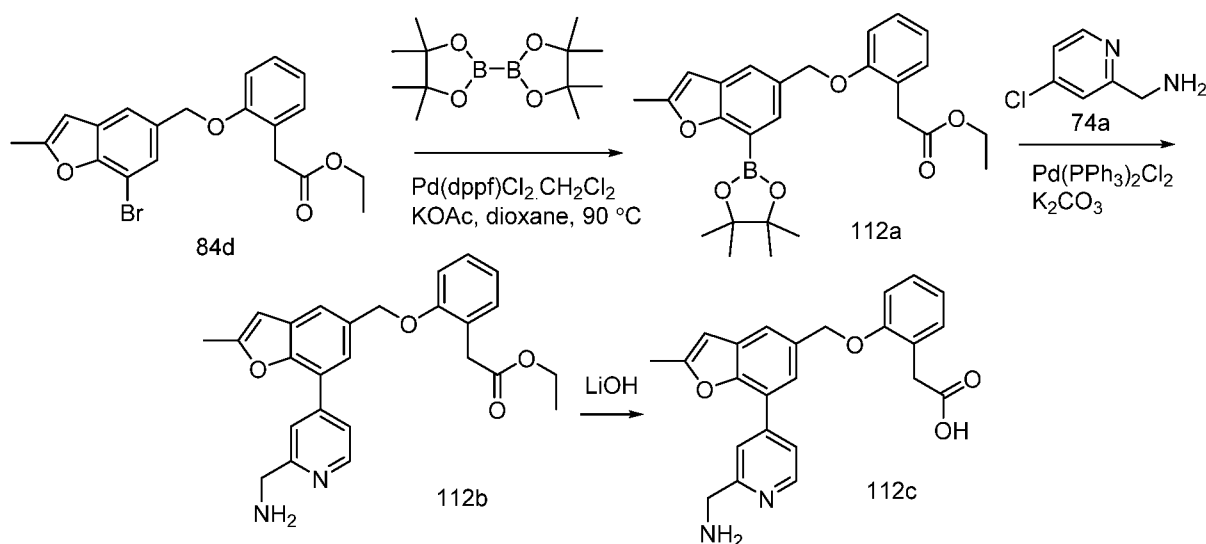
Step-1: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetate (**111a**)

Compound **111a** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((4-bromo-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetate (**109e**) (0.4 g, 0.93 mmol) in dioxane (15 mL) using 3-(aminomethyl)-2-fluorophenylboronic acid hydrochloride (**56a**) (0.29 g, 1.39 mmol), K_2CO_3 (0.39 g, 2.79 mmol) in water (2 mL) and bis(triphenylphosphine)Palladium(II) chloride (0.10 g, 0.14 mmol) under an Ar atmosphere and heating at 100 °C for 2 h in an oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with MeOH in DCM from 0-20%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetate (**111a**) (0.31 g, 70 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.44 (s, 4H), 7.68 (s, 1H), 7.62 – 7.55 (m, 3H), 7.39 (t, $J = 7.6$ Hz, 1H), 7.29 – 7.17 (m, 2H), 7.16 – 7.10 (m, 2H), 6.90 (td, $J = 7.4, 1.1$ Hz, 1H), 6.38 (t, $J = 3.0$ Hz, 1H), 5.24 (s, 2H), 4.81 (m, 1H), 4.16 (s, 2H), 3.91 (q, $J = 7.1$ Hz, 2H), 3.62 (s, 2H), 1.49 (d, $J = 6.6$ Hz, 6H), 0.98 (t, $J = 7.1$ Hz, 3H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -118.90; MS (ES⁺): 475.4 (M+1); MS (ES⁻): 509.5 (M+Cl). HPLC purity: 91.15 %.

Step-2: Preparation of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**111b**)

Compound **111b** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetate (**111a**) (0.15 g, 0.32 mmol) in THF/MeOH (8 mL) using a solution of lithium hydroxide hydrate (0.066 g, 1.58 mmol) in water (2 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**111b**) (0.03 g, 23 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 12.20 (s, 1H), 8.46 (s, 4H), 7.71 (s, 1H), 7.66 – 7.56 (m, 3H), 7.38 (t, J = 7.6 Hz, 1H), 7.25 – 7.19 (m, 2H), 7.17 – 7.08 (m, 2H), 6.90 (t, J = 7.4 Hz, 1H), 6.37 (t, J = 3.0 Hz, 1H), 5.26 (s, 2H), 4.82 (m, 1H), 4.16 (d, J = 5.7 Hz, 2H), 3.59 (s, 2H), 1.49 (d, J = 6.6 Hz, 6H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -118.84; MS (ES $^+$): 447.3 (M+1); MS (ES $^-$): 445.4 (M-1), 481.4 (M+Cl). HPLC purity: 90.91 %.

Scheme-112



Preparation of 2-(2-((7-(2-(aminomethyl)pyridin-4-yl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**112c**)

Step-1: Preparation of ethyl 2-(2-((2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**112a**)

Compound **112a** was prepared according to the procedure reported in step-1 of Scheme-59 from ethyl 2-(2-((7-bromo-2-methylbenzofuran-5-yl)methoxy)phenyl)acetate (**84d**) (5 g, 12.40 mmol), using bis(pinacolato)diboron (4.72 g, 18.60 mmol, CAS#: 73183-34-3), potassium acetate (3.65 g, 37.2 mmol) and $\text{Pd(dppf)Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (1.01 g, 1.240 mmol) in

anhydrous dioxane (100 mL) under an Ar atmosphere and heating at 90 °C overnight. This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-40%] ethyl 2-(2-((2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**112a**) (5.2 g, 93 % yield) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.69 (d, *J* = 1.8 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.29 – 7.17 (m, 2H), 7.09 (d, *J* = 8.1 Hz, 1H), 6.96 – 6.85 (m, 1H), 6.58 (d, *J* = 1.3 Hz, 1H), 5.13 (s, 2H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.59 (s, 2H), 2.47 (s, 3H), 1.33 (s, 12H), 1.06 (t, *J* = 7.1 Hz, 3H).

Step-2: Preparation of ethyl 2-(2-((7-(2-(aminomethyl)pyridin-4-yl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetate (**112b**)

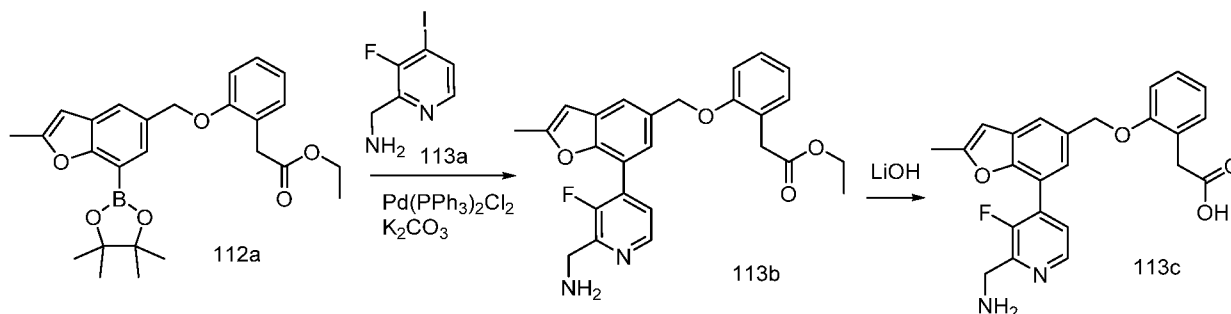
Compound **112b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**112a**) (1.5 g, 3.33 mmol) in dioxane (30 mL) using (4-chloropyridin-2-yl)methanamine (**74a**) (0.71 g, 5.00 mmol), bis(triphenylphosphine)palladium(II) chloride (0.35 g, 0.500 mmol) and a solution of K₂CO₃ (1.38 g, 9.99 mmol) in water (5 mL) under an Ar atmosphere and heating at 100 °C for 2 h on oil bath. This gave after workup, purification by flash column chromatography [silica (40 g), eluting with DMA80 in DCM from 0-70%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(2-(aminomethyl)pyridin-4-yl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetate (**112b**) (616 mg, 43 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.77 (d, *J* = 5.2 Hz, 1H), 8.59 (s, 3H, D₂O exchangeable), 8.09 – 8.03 (m, 1H), 7.96 (dd, *J* = 5.3, 1.7 Hz, 1H), 7.72 – 7.65 (m, 2H), 7.30 – 7.19 (m, 2H), 7.14 – 7.08 (m, 1H), 6.92 (td, *J* = 7.4, 1.1 Hz, 1H), 6.73 (d, *J* = 1.3 Hz, 1H), 5.24 (s, 2H), 4.36 – 4.23 (m, 2H), 3.95 (q, *J* = 7.1 Hz, 2H), 3.64 (s, 2H), 2.52 (s, 3H), 1.00 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 431.3 (M+1); (ES⁻): 465.4 (M+Cl)

Step-3: Preparation of 2-(2-((7-(2-(aminomethyl)pyridin-4-yl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**112c**)

Compound **112c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(2-(aminomethyl)pyridin-4-yl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetate (**112b**) (332 mg, 0.77 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (65 mg, 1.54 mmol) in water (2 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(2-(aminomethyl)pyridin-4-yl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**112c**) (278 mg, 90 % yield) HCl salt as

a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.73 (d, $J = 5.2$ Hz, 1H), 8.13 (s, 1H), 8.01 (dd, $J = 5.4, 1.6$ Hz, 1H), 7.78 (d, $J = 1.6$ Hz, 1H), 7.71 (d, $J = 1.5$ Hz, 1H), 7.26 – 7.16 (m, 2H), 7.04 (d, $J = 8.4$ Hz, 1H), 6.88 (t, $J = 7.4$ Hz, 1H), 6.72 (s, 1H), 5.25 (s, 2H), 4.25 (s, 2H), 3.54 (s, 2H), 2.52 (s, 3H); MS (ES⁺): 403.3 (M+1); (ES⁻): 401.3 (M-1), 437.3 (M+Cl).

Scheme-113



Preparation of 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**113c**)

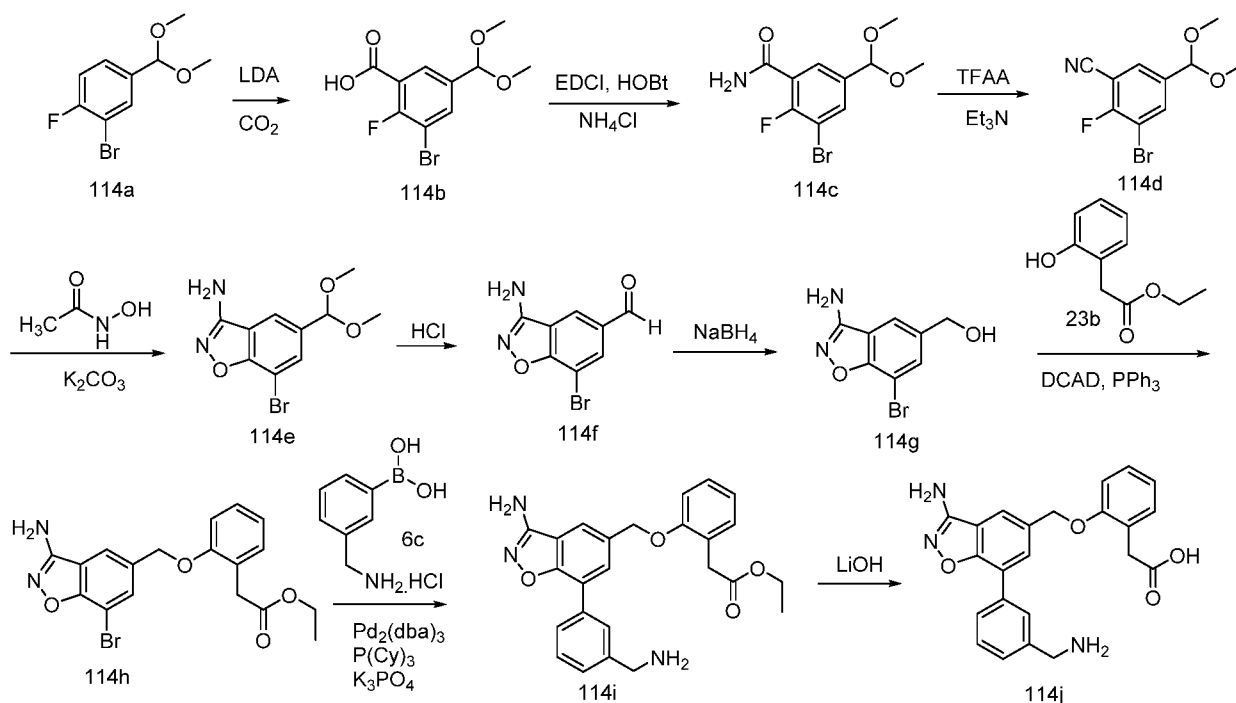
Step-1: Preparation of ethyl 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetate (**113b**)

Compound **113b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**112a**) (500 mg, 1.11 mmol) in dioxane (8 mL) using (3-fluoro-4-iodopyridin-2-yl)methanamine (**113a**) (200 mg, 0.79 mmol; CAS# 1805589-86-9), bis(triphenylphosphine)palladium(II) chloride (83 mg, 0.12 mmol) and a solution of K_2CO_3 (329 mg, 2.38 mmol) in water (2 mL) under an Ar atmosphere and heating at 100 °C for 1 h on oil bath. This gave after workup, purification by flash column chromatography [silica (40 g), eluting with DMA80 in DCM from 0-70%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetate (**113b**) (170 mg, 48 % yield) HCl salt as a white solid.; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.63 (d, $J = 5.0$ Hz, 1H), 8.58 (s, 3H, D_2O exchangeable), 7.78 (t, $J = 5.3$ Hz, 1H), 7.74 (d, $J = 1.6$ Hz, 1H), 7.44 (s, 1H), 7.29 – 7.18 (m, 2H), 7.11 (d, $J = 8.0$ Hz, 1H), 6.91 (td, $J = 7.3, 1.0$ Hz, 1H), 6.73 (d, $J = 1.3$ Hz, 1H), 5.22 (s, 2H), 4.37 (s, 2H), 3.93 (q, $J = 7.1$ Hz, 2H), 3.62 (s, 2H), 2.45 (s, 4H), 1.00 (t, $J = 7.1$ Hz, 3H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -128.74; MS (ES⁺): 449.3 (M+1); (ES⁻): 483.3 (M+Cl).

Step-2: Preparation of 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**113c**)

Compound **113c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetate (**113b**) (112 mg, 0.25 mmol) in MeOH/THF (10 mL) using a solution of lithium hydroxide monohydrate (21 mg, 0.50 mmol) in water (2 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)-2-methylbenzofuran-5-yl)methoxy)phenyl)acetic acid (**113c**) (67 mg, 64 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 12.28 (s, 1H, D $_2$ O exchangeable), 8.69 – 8.54 (m, 4H, partially D $_2$ O exchangeable), 7.82 – 7.74 (m, 2H), 7.49 (s, 1H), 7.28 – 7.19 (m, 2H), 7.09 (d, J = 8.1 Hz, 1H), 6.91 (td, J = 7.4, 1.1 Hz, 1H), 6.72 (d, J = 1.3 Hz, 1H), 5.25 (s, 2H), 4.45 – 4.28 (m, 2H), 3.58 (s, 2H), 2.45 (s, 4H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -128.55; MS (ES $^+$): 421.3 (M+1); (ES $^-$): 455.3 (M+Cl).

Scheme-114



Preparation of 2-(2-((3-amino-7-(3-(aminomethyl)phenyl)benzo[d]isoxazol-5-yl)methoxy)phenyl)acetic acid (**114j**)

Step-1: Preparation of 3-bromo-5-(dimethoxymethyl)-2-fluorobenzoic acid (**114b**)

To a solution of lithium diisopropylamide (7.23 mL, 14.45 mmol) in THF (30 mL) cooled to -78 °C was added a solution of 2-bromo-4-(dimethoxymethyl)-1-fluorobenzene (**114a**) (3 g, 12.04 mmol; CAS # 81358-65-8) in THF (10 mL) and stirred at -78 °C for 25 min. The reaction mixture was quenched with dry ice and stirred at -78 °C for 1 h and allowed to warm

to RT over a period of 0.5 h. The reaction mixture was diluted with water (50 mL), ethyl acetate (100 mL) and acidified with 4 N HCl to pH 4. The aqueous layer was separated and extracted with ethyl acetate (75 mL). The organic layers were combined washed with brine (75 mL), dried, filtered and concentrated in vacuum to afford 3-bromo-5-(dimethoxymethyl)-2-fluorobenzoic acid (**114b**) (2.56 g, 73% yield) as a yellow solid which was used as such for next step; MS (ES⁻): 291.1 & 293.1 (M-1).

Step-2: Preparation of 3-bromo-5-(dimethoxymethyl)-2-fluorobenzamide (114c**)**

To a suspension of 3-bromo-5-(dimethoxymethyl)-2-fluorobenzoic acid (**114b**) (2.4 g, 8.19 mmol), ammonium chloride (1.314 g, 24.57 mmol), and 1H-benzo[d][1,2,3]triazol-1-ol (0.111 g, 0.819 mmol) in DMF (35 mL) was added N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (2.355 g, 12.28 mmol), N-ethyl-N-isopropylpropan-2-amine (2.85 mL, 16.38 mmol) and stirred at RT for 15 h. The reaction mixture was diluted with ethyl acetate (150 mL), washed with water (2 x 75 mL), brine (75 mL), dried, filtered and concentrated in vacuum. The residue obtained purified by flash column chromatography [silica gel eluting with hexanes/ethyl acetate (1:0 to 1:1)] to afford 3-bromo-5-(dimethoxymethyl)-2-fluorobenzamide (**114c**) (435 mg, 18% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.89 (s, 1H), 7.78 – 7.70 (m, 2H), 7.60 (dd, *J* = 6.2, 2.1 Hz, 1H), 5.42 (s, 1H), 3.27 (d, *J* = 0.7 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -108.83; MS (ES⁻): 326.1 & 328.1 (M+Cl).

Step-3: Preparation of 3-bromo-5-(dimethoxymethyl)-2-fluorobenzonitrile (114d**)**

To a solution of 3-bromo-5-(dimethoxymethyl)-2-fluorobenzamide (**114c**) (418 mg, 1.431 mmol) and triethylamine (0.598 mL, 4.29 mmol) in DCM (20 mL) cooled to 0 °C was added dropwise 2,2,2-trifluoroacetic anhydride (0.298 mL, 2.147 mmol) and stirred at 0 °C for 2 h. The reaction mixture was diluted with dichloromethane (75 mL), washed with 1 N NaHCO₃ (50 mL), brine (50 mL), dried, filtered and concentrated in vacuum. The residue obtained purified by flash column chromatography [silica gel eluting with hexanes/ethyl acetate (1:0 to 3:1)] to afford 3-bromo-5-(dimethoxymethyl)-2-fluorobenzonitrile (**114d**) (366 mg, 93%) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.01 (dd, *J* = 6.7, 2.0 Hz, 1H), 7.90 (dd, *J* = 5.8, 2.0 Hz, 1H), 5.43 (s, 1H), 3.28 (s, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -103.08.

Step-4: Preparation of 7-bromo-5-(dimethoxymethyl)benzo[d]isoxazol-3-amine (114e**)**

To a solution of 3-bromo-5-(dimethoxymethyl)-2-fluorobenzonitrile (**114d**) (350 mg, 1.277 mmol) in DMF (12 mL) was added N-hydroxyacetamide (288 mg, 3.83 mmol), potassium carbonate (529 mg, 3.83 mmol) and heated at 90 °C for 5 h. The reaction mixture was cooled

to RT, diluted with ethyl acetate (100 mL) and washed with water (50 mL). The aqueous phase was extracted with ethyl acetate (50 mL). The organic layers were combined washed with brine, dried, filtered and concentrated in vacuum. The residue obtained purified by flash column chromatography [silica gel eluting with hexanes/ethyl acetate (1:0 to 2:1)] to afford 7-bromo-5-(dimethoxymethyl)benzo[d]isoxazol-3-amine (**114e**) (162 mg, 44%) as an off-white solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.95 (d, *J* = 1.3 Hz, 1H), 7.72 (d, *J* = 1.3 Hz, 1H), 6.65 (s, 2H), 5.51 (s, 1H), 3.26 (s, 6H); MS (ES⁻): 321.1 (M + Cl).

Step-5: Preparation of 3-amino-7-bromobenzo[d]isoxazole-5-carbaldehyde (**114f**)

To a solution of 7-bromo-5-(dimethoxymethyl)benzo[d]isoxazol-3-amine (**114e**) (155 mg, 0.540 mmol) in THF (4 mL) was added conc. hydrogen chloride (0.112 mL, 1.350 mmol) and stirred at RT for 6 h. Additional conc. HCl (0.25 mL) was added and the reaction was continued stirring at RT for 24 h. The reaction mixture was diluted with ethyl acetate (100 mL) washed with 1 N NaHCO₃ (40 mL), brine (40 mL), dried, filtered and concentrated in vacuum to afford 3-amino-7-bromobenzo[d]isoxazole-5-carbaldehyde (**114f**) (137 mg) as an off-white solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.99 (s, 1H), 8.49 (d, *J* = 1.3 Hz, 1H), 8.32 (d, *J* = 1.3 Hz, 1H), 6.90 (s, 2H); MS (ES⁻): 239.1 (M-1).

Step-6: Preparation of (3-amino-7-bromobenzo[d]isoxazol-5-yl)methanol (**114g**)

To a solution of 3-amino-7-bromobenzo[d]isoxazole-5-carbaldehyde (**114f**) (135 mg, 0.560 mmol) in THF (15 mL) cooled to 0 °C was added sodium borohydride (42.4 mg, 1.120 mmol) and stirred at RT for 21 h. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (40 mL), brine (40 mL), dried, filtered and concentrated in vacuum. The residue obtained purified by flash column chromatography [silica gel eluting with hexanes/ethyl acetate (1:0 to 0:1)] to afford (3-amino-7-bromobenzo[d]isoxazol-5-yl)methanol (**114g**) (101 mg, 78% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.81 (s, 1H), 7.69 (s, 1H), 6.57 (s, 2H), 5.42 (t, *J* = 5.6 Hz, 1H), 4.57 (d, *J* = 5.4 Hz, 2H); MS (ES⁻): 241.2 (M-1).

Step-7: Preparation of ethyl 2-(2-((3-amino-7-bromobenzo[d]isoxazol-5-yl)methoxy)phenyl)acetate (**114h**)

Compound **114h** was prepared according to the procedure reported in step-2 of Scheme-23 (3-amino-7-bromobenzo[d]isoxazol-5-yl)methanol (**114g**) (95 mg, 0.39 mmol) in DCM (5 mL) using triphenylphosphine (154 mg, 0.59 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (176 mg, 0.98 mmol) and di-(4-chlorobenzyl)azodicarboxylate (DCAD, 215 mg, 0.59 mmol). This gave after workup and purification by flash column chromatography [silica (12 g),

eluting with hexanes/ethyl acetate (1:0 to 2:1)] ethyl 2-(2-((3-amino-7-bromobenzo[d]isoxazol-5-yl)methoxy)phenyl)acetate (**114h**) (189 mg) as a white solid; MS (ES⁻): 439.2 (M+Cl).

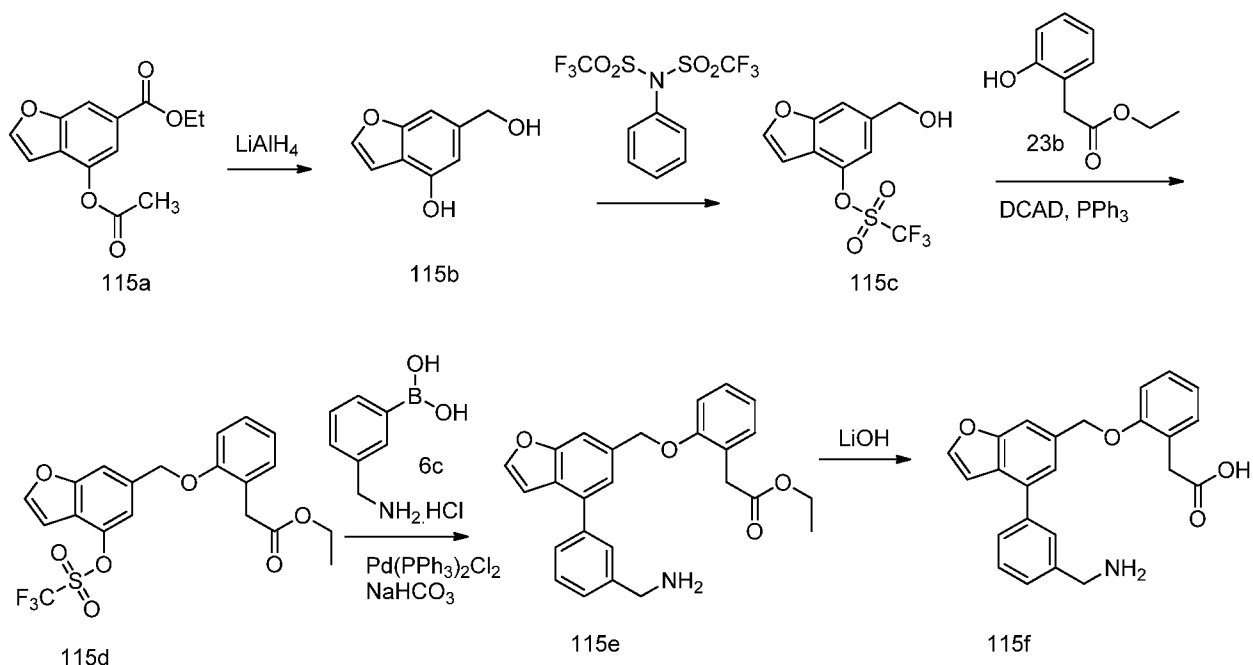
Step-8: Preparation of ethyl 2-(2-((3-amino-7-(3-(aminomethyl)phenyl)benzo[d]isoxazol-5-yl)methoxy)phenyl)acetate (**114i**)

Compound **114i** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((3-amino-7-bromobenzo[d]isoxazol-5-yl)methoxy)phenyl)acetate (**114h**) (100 mg, 0.25 mmol) in dioxane (3 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (69 mg, 0.37 mmol), tricyclohexylphosphine (41.5 mg, 0.148 mmol), a solution of tripotassium phosphate (0.14 mL, 0.42 mmol, 3 M), water (0.1 mL) and Pd₂(dba)₃ (68 mg, 0.074 mmol) and heating under an Ar atmosphere in a microwave at 125 °C for 2 h. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with dichloromethane/methanol (1:0 to 9:1)] ethyl 2-(2-((3-amino-7-(3-(aminomethyl)phenyl)benzo[d]isoxazol-5-yl)methoxy)phenyl)acetate (**114i**) (5 mg, 5 % yield) as a white solid; MS (ES⁺): 432.3 (M+1) & 454.3 (M+Na).

Step-9: Preparation of 2-(2-((3-amino-7-(3-(aminomethyl)phenyl)benzo[d]isoxazol-5-yl)methoxy)phenyl)acetic acid (**114j**)

Compound **114j** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((3-amino-7-(3-(aminomethyl)phenyl)benzo[d]isoxazol-5-yl)methoxy)phenyl)acetate (**114i**) (5 mg, 0.012 mmol) in THF (3 mL) and MeOH (3 mL) using a solution of lithium hydroxide hydrate (5 mg, 0.12 mmol) in water (3 mL). This gave after workup and purification by flash column chromatography [silica gel, eluting with dichloromethane/DMA 80 (1:0 to 1:2)] 2-(2-((3-amino-7-(3-(aminomethyl)phenyl)benzo[d]isoxazol-5-yl)methoxy)phenyl)acetic acid (**114j**) (3 mg, 64%) as a white solid; ¹H NMR (300 MHz, Methanol-*d*₄) δ 8.26 (s, 1H), 8.19 (s, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.76 (s, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.24 – 7.14 (m, 2H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.90 (t, *J* = 7.3 Hz, 1H), 5.27 (s, 2H), 4.21 (s, 2H), 3.61 (s, 2H); MS (ES⁺): 404.2 (M+1); HPLC purity: 91.21%.

Scheme-115



Preparation of 2-(2-((4-(3-(aminomethyl)phenyl)benzofuran-6-yl)methoxy)phenyl)acetic acid (**115f**)

Step-1: Preparation of 6-(hydroxymethyl)benzofuran-4-ol (**115b**)

To a solution of ethyl 4-acetoxybenzofuran-6-carboxylate (**115a**) (2 g, 8.06 mmol; prepared according to the procedure reported by Yang, Xinye et al; in WO2017036404 (A1)-2017-03-09) in THF (30 mL) cooled to 0 °C was added lithium aluminum hydride (0.612 g, 16.11 mmol) and stirred at RT for 24 h. The reaction mixture was quenched carefully with 20% aqueous Na₂SO₄ (20 mL), water (100 mL) and extracted with ethyl acetate (150 and 100 mL). The combined organic layer was washed with water (100 mL), brine (100 mL), dried, filtered and concentrated in vacuum. The residue obtained purified by flash column chromatography [silica gel eluting with hexanes/ethyl acetate (1:0 to 1:1)] to afford 6-(hydroxymethyl)benzofuran-4-ol (**115b**) (883 mg, 67% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.85 (s, 1H), 7.76 (d, *J* = 2.2 Hz, 1H), 6.96 (p, *J* = 0.9 Hz, 1H), 6.89 (dd, *J* = 2.2, 1.0 Hz, 1H), 6.60 – 6.58 (m, 1H), 5.17 (bs, 1H), 4.49 (bs, 2H); MS (ES⁻): 163.1 (M-1).

Step-2: Preparation of 6-(hydroxymethyl)benzofuran-4-yl trifluoromethanesulfonate (**115c**)

To a solution of 6-(hydroxymethyl)benzofuran-4-ol (**115b**) (860 mg, 5.24 mmol) in DMF (20 mL) was added 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (1910 mg, 5.24 mmol), triethylamine (1.460 mL, 10.48 mmol) and stirred at RT for 14 h. The reaction mixture was diluted with ethyl acetate (150 mL), washed with water (2 x 60 mL), brine (60 mL), dried, filtered and concentrated in vacuum. The residue obtained purified by flash column chromatography [silica gel eluting with hexanes/ethyl acetate (1:0 to 3:1)] to

afford 6-(hydroxymethyl)benzofuran-4-yl trifluoromethanesulfonate (**115c**) (1.239 g, 80% yield) as a light brown oil. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.16 (d, *J* = 2.3 Hz, 1H), 7.71 (p, *J* = 0.9 Hz, 1H), 7.36 (bs, 1H), 7.02 (dd, *J* = 2.3, 0.9 Hz, 1H), 5.58 – 5.47 (m, 1H), 4.68 – 4.62 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -72.88; MS (ES⁻): 331.1 (M+Cl).

Step-3: Preparation of ethyl 2-(2-((4-(((trifluoromethyl)sulfonyl)oxy)benzofuran-6-yl)methoxy)phenyl)acetate (**115d**)

Compound **115d** was prepared according to the procedure reported in step-2 of Scheme-23 from 6-(hydroxymethyl)benzofuran-4-yl trifluoromethanesulfonate (**115c**) (1.18 g, 3.98 mmol) in DCM (30 mL) using triphenylphosphine (1.567 g, 5.98 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (1.077 g, 5.98 mmol) and di-(4-chlorobenzyl)azodicarboxylate (DCAD, 2.194 g, 5.98 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with hexanes/ethyl acetate (1:0 to 5:1)] ethyl 2-(2-((4-(((trifluoromethyl)sulfonyl)oxy)benzofuran-6-yl)methoxy)phenyl)acetate (**115d**) (1.624 g, 89% yield) as a light brown gum; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.23 (d, *J* = 2.3 Hz, 1H), 7.86 (s, 1H), 7.50 (s, 1H), 7.24 (d, *J* = 7.6 Hz, 2H), 7.10 – 7.01 (m, 2H), 6.96 – 6.89 (m, 1H), 5.29 (s, 2H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.66 (s, 2H), 1.07 (t, *J* = 7.1 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -72.74; (ES⁺): 481.2 (M+Na).

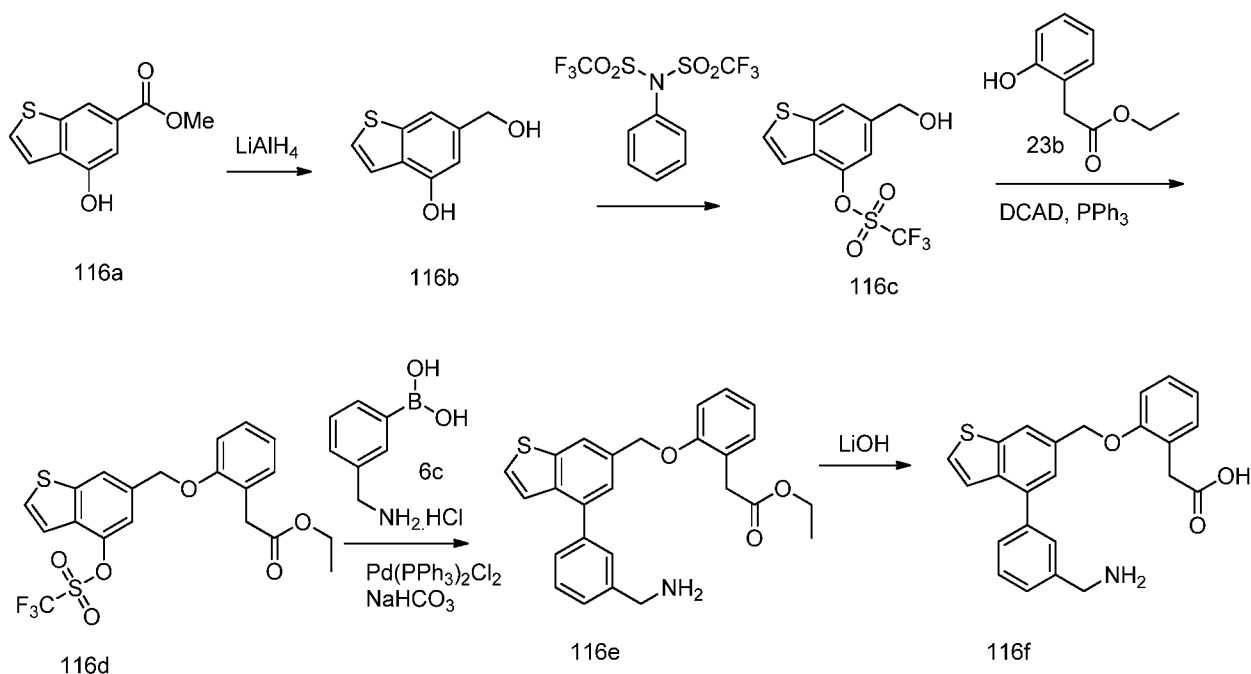
Step-4: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)phenyl)benzofuran-6-yl)methoxy)phenyl)acetate (**115e**)

Compound **115e** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((4-(((trifluoromethyl)sulfonyl)oxy)benzofuran-6-yl)methoxy)phenyl)acetate (**115d**) (500 mg, 1.091 mmol) in dioxane (10 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (307 mg, 1.636 mmol), a solution of sodium bicarbonate (275 mg, 3.27 mmol) in water (1 mL), Pd(PPh₃)₂Cl₂ (230 mg, 0.327 mmol) and heating under an Ar atmosphere at 100 °C for 3 h. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with dichloromethane/methanol (1:0 to 9:1)] ethyl 2-(2-((4-(3-(aminomethyl)phenyl)benzofuran-6-yl)methoxy)phenyl)acetate (**115e**) (295 mg, 65% yield) as a brown gum; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.10 (d, *J* = 2.2 Hz, 1H), 7.66 (s, 2H), 7.56 – 7.33 (m, 4H), 7.30 – 7.18 (m, 2H), 7.13 – 7.06 (m, 2H), 6.91 (t, *J* = 7.4 Hz, 1H), 5.28 (s, 2H), 3.95 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 2H), 3.65 (s, 2H), 1.02 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 416.3 (M+1).

Step-5: Preparation of 2-(2-((4-(3-(aminomethyl)phenyl)benzofuran-6-yl)methoxy)phenyl)acetic acid (**115f**)

Compound **115f** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((4-(3-(aminomethyl)phenyl)benzofuran-6-yl)methoxy)phenyl)acetate (**115e**) (200 mg, 0.48 mmol) in THF (10 mL) and MeOH (10 mL) using a solution of lithium hydroxide hydrate (124 mg, 2.89 mmol) in water (10 mL). This gave after workup and purification by flash column chromatography [silica gel, eluting with dichloromethane/methanol (1:0 to 9:1)] 2-(2-((4-(3-(aminomethyl)phenyl)benzofuran-6-yl)methoxy)phenyl)acetic acid (**115f**) (125 mg, yield: 67%) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.17 (s, 1H), 8.09 (d, $J = 2.2$ Hz, 1H), 7.75 – 7.67 (m, 3H), 7.48 (t, $J = 7.6$ Hz, 1H), 7.36 (d, $J = 7.6$ Hz, 1H), 7.15 – 7.14 (m, 1H), 7.12 – 7.05 (m, 2H), 6.96 (d, $J = 8.0$ Hz, 1H), 6.83 – 6.77 (m, 1H), 5.28 (s, 2H), 4.00 (s, 2H), 3.39 (s, 2H); MS (ES $^+$): 388.3 (M+1), 410.3 (M+Na); MS (ES $^-$): 386.3 (M-1), 422.2 (M + Cl); HPLC purity: 99.26%.

Scheme-116



Preparation of 2-(2-((4-(3-(aminomethyl)phenyl)benzo[b]thiophen-6-yl)methoxy)phenyl)acetic acid (**116f**)

Step-1: Preparation of 6-(hydroxymethyl)benzo[b]thiophen-4-ol (**116b**)

Compound **116b** was prepared according to the procedure reported in step-1 of Scheme-115 from methyl 4-hydroxybenzo[b]thiophene-6-carboxylate (**116a**) (950 mg, 4.56 mmol; CAS# 314725-14-9) in THF (15 mL) using lithium aluminum hydride (260 mg, 6.84 mmol). This gave after workup and purification by flash column chromatography [silica gel, eluting with hexanes/ethyl acetate (1:0 to 1:1)] 6-(hydroxymethyl)benzo[b]thiophen-4-ol (**116b**) (545 mg, 66% yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 9.92 (s, 1H), 7.50 (d, $J = 5.5$

Hz, 1H), 7.40 (dd, $J = 5.5, 0.8$ Hz, 1H), 7.33 – 7.30 (m, 1H), 6.72 – 6.70 (m, 1H), 5.20 (t, $J = 5.8$ Hz, 1H), 4.53 – 4.49 (m, 2H); MS (ES⁺): 181.05 (M+1), 203.05 (M+Na); MS (ES⁻): 179.10 (M-1).

Step-2: Preparation of 6-(hydroxymethyl)benzo[b]thiophen-4-yl trifluoromethanesulfonate (116c)

Compound **116c** was prepared according to the procedure reported in step-2 of Scheme-116 from

6-(hydroxymethyl)benzo[b]thiophen-4-ol (**116b**) (535 mg, 2.97 mmol) in DMF (12 mL) using 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (1082 mg, 2.97 mmol) and triethylamine (0.828 mL, 5.94 mmol). This gave after workup and purification by flash column chromatography [silica gel, eluting with hexanes/ethyl acetate (1:0 to 3:1)] 6-(hydroxymethyl)benzo[b]thiophen-4-yl trifluoromethanesulfonate (**116c**) (720 mg, 78% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.09 (m, 1H), 7.99 (d, $J = 5.6$ Hz, 1H), 7.45 (d, $J = 1.1$ Hz, 1H), 7.41 (dd, $J = 5.6, 0.8$ Hz, 1H), 5.54 (t, $J = 5.8$ Hz, 1H), 4.67 (d, $J = 5.7$ Hz, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -73.06; MS (ES⁺): MS (ES⁻): 311.10 (M-1).

Step-3: Preparation of ethyl 2-(2-((4-(((trifluoromethyl)sulfonyl)oxy)benzo[b]thiophen-6-yl)methoxy)phenyl)acetate (116d)

Compound **116d** was prepared according to the procedure reported in step-2 of Scheme-23 from 6-(hydroxymethyl)benzo[b]thiophen-4-yl trifluoromethanesulfonate (**116c**) (110 mg, 0.352 mmol) in DCM (4 mL) using triphenylphosphine (139 mg, 0.53 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (95 mg, 0.53 mmol) and di-(4-chlorobenzyl)azodicarboxylate (DCAD, 194 mg, 0.53 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with hexanes/ethyl acetate (1:0 to 1:1)] ethyl 2-(2-((4-(((trifluoromethyl)sulfonyl)oxy)benzo[b]thiophen-6-yl)methoxy)phenyl)acetate (**116d**) (115 mg, 69% yield) as a colorless oil. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.23 (s, 1H), 8.06 (d, $J = 5.6$ Hz, 1H), 7.58 (s, 1H), 7.46 (d, $J = 5.6$ Hz, 1H), 7.31 – 7.19 (m, 2H), 7.08 (d, $J = 8.1$ Hz, 1H), 6.93 (t, $J = 7.4$ Hz, 1H), 5.30 (s, 2H), 4.00 (q, $J = 7.1$ Hz, 2H), 3.66 (s, 2H), 1.06 (t, $J = 7.1$ Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -72.96; MS (ES⁺): 497.1 (M+Na); MS (ES⁻): 473.1 (M-1).

Step-4: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)phenyl)benzo[b]thiophen-6-yl)methoxy)phenyl)acetate (116e)

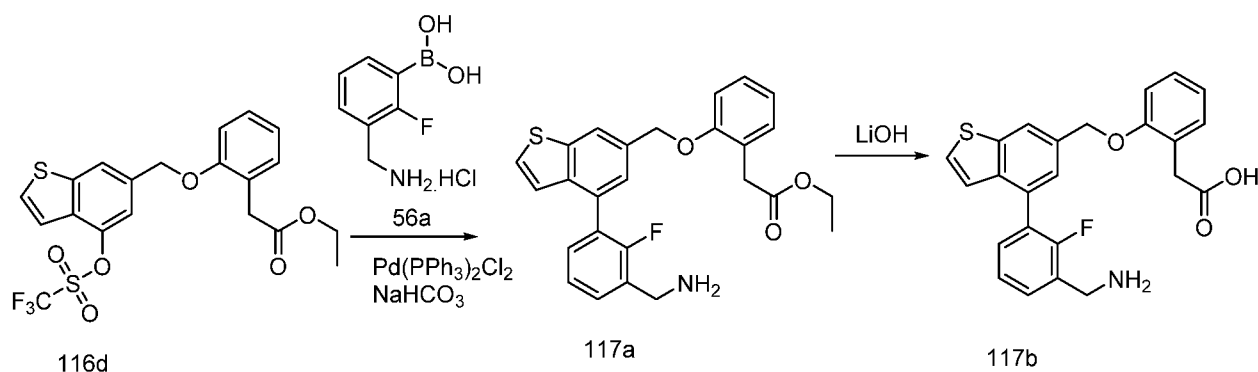
Compound **116e** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((4-(((trifluoromethyl)sulfonyl)oxy)benzo[b]thiophen-6-

yl)methoxy)phenyl)acetate (**116d**) (172 mg, 0.363 mmol) in dioxane (4 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (102 mg, 0.544 mmol), a solution of sodium bicarbonate (91 mg, 1.088 mmol) in water (1 mL), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (76 mg, 0.109 mmol) and heating under an Ar atmosphere at 95 °C for 3 h. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with dichloromethane/methanol (1:0 to 9:1)] ethyl 2-(2-((4-(3-(aminomethyl)phenyl)benzo[b]thiophen-6-yl)methoxy)phenyl)acetate (**116e**) (38 mg, 24% yield) as a colorless gum; MS (ES⁺): 432.2 (M+1).

Step-5: Preparation of 2-(2-((4-(3-(aminomethyl)phenyl)benzo[b]thiophen-6-yl)methoxy)phenyl)acetic acid (**116f**)

Compound **116f** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((4-(3-(aminomethyl)phenyl)benzo[b]thiophen-6-yl)methoxy)phenyl)acetate (**116e**) (35 mg, 0.081 mmol) in THF (4 mL) and MeOH (4 mL) using a solution of lithium hydroxide hydrate (21 mg, 0.49 mmol) in water (4 mL). This gave after workup 2-(2-((4-(3-(aminomethyl)phenyl)benzo[b]thiophen-6-yl)methoxy)phenyl)acetic acid (**116f**) (24 mg, 74% yield) as an off-white solid ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.07 (s, 1H), 7.92 (s, 1H), 7.80 (d, *J* = 5.5 Hz, 1H), 7.67 – 7.63 (m, 1H), 7.61 (d, *J* = 1.4 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.16 – 7.09 (m, 2H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.83 (t, *J* = 7.3 Hz, 1H), 5.28 (s, 2H), 4.06 (s, 2H), 3.45 (s, 2H); MS (ES⁺): 404.3 (M+1), 426.3 (M+Na); MS (ES⁻): 402.3 (M-1); HPLC purity: 90.05%.

Scheme-117



Preparation of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)benzo[b]thiophen-6-yl)methoxy)phenyl)acetic acid (**117b**)

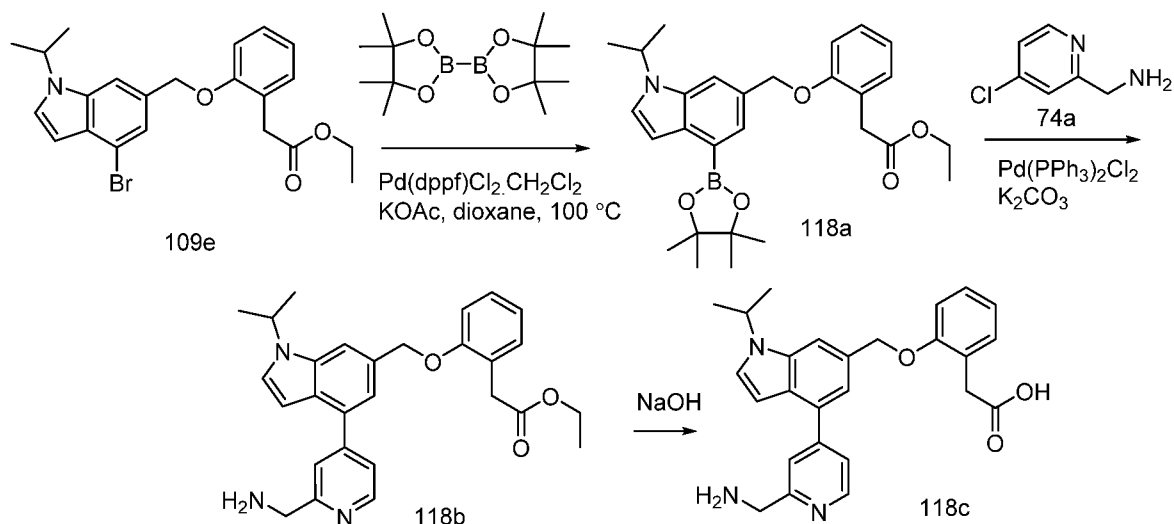
Step-1: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)benzo[b]thiophen-6-yl)methoxy)phenyl)acetate (**117a**)

Compound **117a** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((4-(((trifluoromethyl)sulfonyl)oxy)benzo[b]thiophen-6-yl)methoxy)phenyl)acetate (**116d**) (300 mg, 0.632 mmol) in dioxane (8 mL) using (3-(aminomethyl)-2-fluorophenyl)boronic acid hydrochloride (**56a**) (195 mg, 0.95 mmol), a solution of sodium bicarbonate (159 mg, 1.9 mmol) in water (0.8 mL), Pd(PPh₃)₂Cl₂ (133 mg, 0.19 mmol) and heating under an nitrogen atmosphere at 100 °C for 3 h. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with dichloromethane/methanol (1:0 to 19:1)] ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)benzo[b]thiophen-6-yl)methoxy)phenyl)acetate (**117a**) (225 mg, 79% yield) as a brown gum; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.11 – 8.08 (m, 1H), 7.80 (d, *J* = 5.6 Hz, 1H), 7.59 (td, *J* = 7.0, 2.5 Hz, 1H), 7.41 – 7.39 (m, 1H), 7.38 – 7.19 (m, 4H), 7.18 – 7.08 (m, 2H), 6.91 (td, *J* = 7.4, 1.1 Hz, 1H), 5.27 (s, 2H), 3.91 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 2H), 3.64 (s, 2H), 1.00 (t, *J* = 7.1 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -122.29; MS (ES⁺): 450.20 (M+1).

Step-2: Preparation of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)benzo[b]thiophen-6-yl)methoxy)phenyl)acetic acid (**117b**)

Compound **117b** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)benzo[b]thiophen-6-yl)methoxy)phenyl)acetate (**117a**) (200 mg, 0.445 mmol) in THF (10 mL) and MeOH (10 mL) using a solution of lithium hydroxide hydrate (114 mg, 2.67 mmol) in water (10 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)benzo[b]thiophen-6-yl)methoxy)phenyl)acetic acid (**117b**) (91 mg, 43% yield) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.61 (s, 3H), 8.17 (s, 1H), 7.83 (d, *J* = 5.5 Hz, 1H), 7.69 (td, *J* = 7.3, 1.9 Hz, 1H), 7.56 (td, *J* = 7.4, 1.8 Hz, 1H), 7.47 – 7.36 (m, 2H), 7.29 – 7.18 (m, 3H), 7.08 (d, *J* = 8.1 Hz, 1H), 6.91 (t, *J* = 7.3 Hz, 1H), 5.31 (s, 2H), 4.16 (s, 2H), 3.60 (s, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -118.48; MS (ES⁺): 422.1 (M+1); HPLC purity: 99.60%; Analysis calculated for C₂₄H₂₀FNO₃S•1.0 HCl•1.0 H₂O: C, 60.56; H, 4.87; N, 2.94; Cl, 7.45; Found: C, 60.69; H, 4.66; N, 2.95; Cl, 7.22.

Scheme-118



Preparation of 2-(2-((4-(2-(aminomethyl)pyridin-4-yl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**118c**)

Step-1: Preparation of ethyl 2-(2-((1-isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-6-yl)methoxy)phenyl)acetate (**118a**)

Compound **118a** was prepared according to the procedure reported in step-1 of Scheme-59 from ethyl 2-(2-((4-bromo-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetate (**109e**) (0.9 g, 2.09 mmol), using bis(pinacolato)diboron (0.80 g, 3.14 mmol, CAS#: 73183-34-3), potassium acetate (0.62 g, 6.27 mmol) and Pd(dppf)Cl₂-CH₂Cl₂ (0.26 g, 0.31 mmol) in anhydrous dioxane (30 mL) under an Ar atmosphere and heating at 100 °C overnight. This gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH 9:1 in hexane from 0-10%] ethyl 2-(2-((1-isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-6-yl)methoxy)phenyl)acetate (**118a**) (0.6 g, 60 % yield) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.70 (s, 1H), 7.53 (d, *J* = 3.2 Hz, 1H), 7.46 (d, *J* = 1.3 Hz, 1H), 7.29 – 7.17 (m, 2H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.89 (t, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 3.3 Hz, 1H), 5.18 (s, 2H), 4.76 (p, *J* = 6.7 Hz, 1H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.60 (s, 2H), 1.44 (d, *J* = 6.6 Hz, 6H), 1.32 (d, *J* = 2.0 Hz, 12H), 1.04 (t, *J* = 7.1 Hz, 3H); MS (ES⁺) 479.4 (M+1).

Step-2: Preparation of ethyl 2-(2-((4-(2-(aminomethyl)pyridin-4-yl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetate (**118b**)

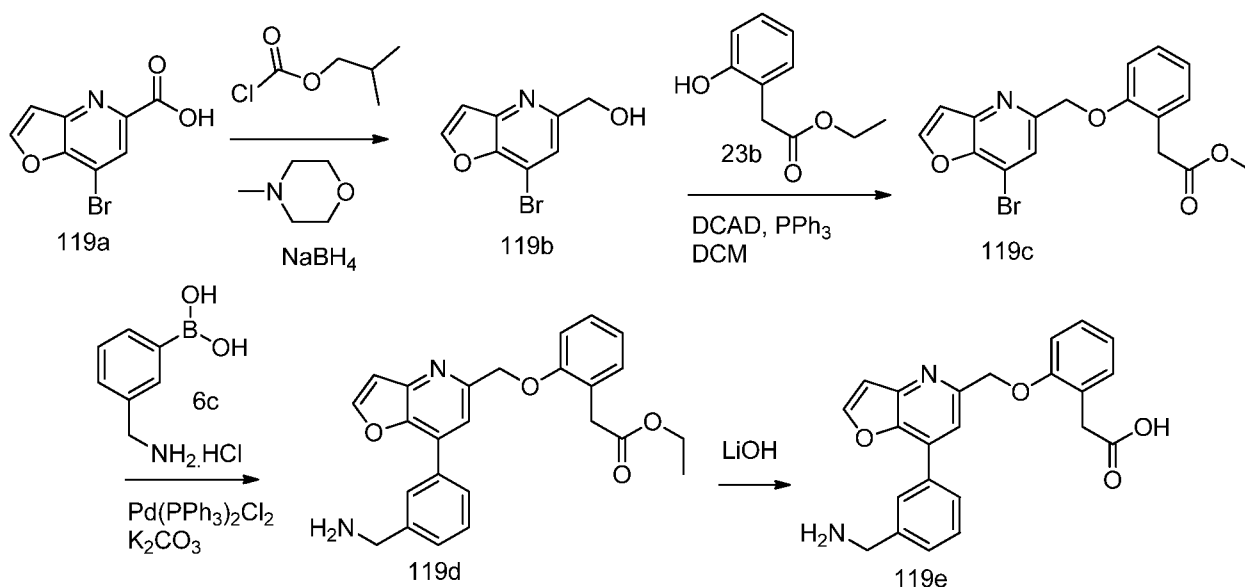
Compound **118b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((1-isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-6-yl)methoxy)phenyl)acetate (**118a**) (0.6 g, 1.26 mmol) in dioxane (10 mL) using (4-chloropyridin-2-yl)methanamine (**74a**) (0.216 mL, 1.885 mmol), bis(triphenylphosphine)palladium(II) chloride (0.13 g, 0.19 mmol) and a solution of K₂CO₃

(0.43 g, 3.14 mmol) in water (1 mL) under an Ar atmosphere and heating at 100 °C for 2 h on oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with MeOH in DCM from 0-50%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((4-(2-(aminomethyl)pyridin-4-yl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetate (**118b**) (0.3 g, 52 % yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.72 (d, J = 5.2 Hz, 1H), 8.38 (s, 3H), 7.83 (s, 1H), 7.75 (s, 1H), 7.72 (d, J = 5.2 Hz, 1H), 7.69 (d, J = 3.3 Hz, 1H), 7.33 (s, 1H), 7.28 – 7.20 (m, 2H), 7.13 (d, J = 8.2 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 6.73 (d, J = 3.3 Hz, 1H), 5.27 (s, 2H), 4.92 – 4.77 (m, 1H), 4.30 (q, J = 6.0 Hz, 2H), 3.92 (q, J = 7.1 Hz, 2H), 3.64 (s, 2H), 1.50 (d, J = 6.7 Hz, 6H), 0.97 (t, J = 7.1 Hz, 3H); MS (ES⁺): 458.5 (M+1); MS (ES⁻): 492.5 (M+Cl). HPLC purity: 96.70 %.

Step-3: Preparation of 2-(2-((4-(2-(aminomethyl)pyridin-4-yl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**118c**)

Compound **118c** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-((4-(2-(aminomethyl)pyridin-4-yl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetate (**118b**) (0.15 g, 0.33 mmol) in MeOH/THF (6 mL) using a solution of sodium hydroxide (0.07 g, 1.64 mmol) in water (2 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((4-(2-(aminomethyl)pyridin-4-yl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**118c**) (0.04 g, 27 % yield) as a yellow solid; ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.72 (d, J = 5.2 Hz, 1H), 8.44 (s, 3H), 7.86 (d, J = 1.6 Hz, 1H), 7.78 (s, 1H), 7.74 (dd, J = 5.2, 1.7 Hz, 1H), 7.68 (d, J = 3.3 Hz, 1H), 7.37 (d, J = 1.2 Hz, 1H), 7.27 – 7.21 (m, 2H), 7.12 (d, J = 8.1 Hz, 1H), 6.90 (td, J = 7.3, 1.0 Hz, 1H), 6.74 (d, J = 3.2 Hz, 1H), 5.29 (s, 2H), 4.84 (p, J = 6.6 Hz, 1H), 4.30 (s, 2H), 3.61 (s, 2H), 1.50 (d, J = 6.6 Hz, 6H).; MS (ES⁺): 430.5 (M+1); MS (ES⁻): 428.5 (M-1), 464.5 (M+Cl). HPLC purity: 96.70 %.

Scheme-119



Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)furo[3,2-b]pyridin-5-yl)methoxy)phenyl)acetic acid (**119e**)

Step-1: Preparation of (7-bromofuro[3,2-b]pyridin-5-yl)methanol (**119b**)

Compound **119b** was prepared according to the procedure reported in step-1 of Scheme-23 from 7-bromofuro[3,2-b]pyridine-5-carboxylic acid (**119a**) (800 mg, 3.31 mmol, purchased from PharmaBlock, PB95208) using N-methylmorpholine (0.44 mL, 3.97 mmol) in THF (10 mL), isobutyl chloroformate (0.52 mL, 3.97 mmol) and NaBH₄ (375 mg, 9.92 mmol) in water (5 mL). This gave after workup (7-bromofuro[3,2-b]pyridin-5-yl)methanol (**119b**) (580 mg, 77 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.41 (d, *J* = 2.3 Hz, 1H), 7.66 (s, 1H), 7.20 (d, *J* = 2.3 Hz, 1H), 5.59 (t, *J* = 6.0 Hz, 1H, D₂O exchangeable), 4.64 (d, *J* = 6.0 Hz, 2H); MS (ES⁻): 226.0, 227.0 (M-1).

Step-2: Preparation of ethyl 2-(2-((7-bromofuro[3,2-b]pyridin-5-yl)methoxy)phenyl)acetate (**119c**)

Compound **119c** was prepared according to the procedure reported in step-2 of Scheme-23 from (7-bromofuro[3,2-b]pyridin-5-yl)methanol (**119b**) (380 mg, 1.67 mmol) in DCM (15 mL) using triphenylphosphine (481 mg, 1.83 mmol), ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (330 mg, 1.83 mmol) and di-(4-chlorobenzyl)azodicarboxylate (DCAD, 673 mg, 1.83 mmol) in DCM (20 mL). This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-50%] ethyl 2-(2-((7-bromofuro[3,2-b]pyridin-5-yl)methoxy)phenyl)acetate (**119c**) (450 mg, 69% yield) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.48 (d, *J* = 2.3 Hz, 1H), 7.70 (s, 1H), 7.28 (d, *J* = 2.2 Hz, 1H), 7.25

(d, $J = 7.3$ Hz, 2H), 7.07 (d, $J = 8.4$ Hz, 1H), 6.94 (t, $J = 7.4$ Hz, 1H), 5.26 (s, 2H), 4.05 (q, $J = 7.1$ Hz, 2H), 3.68 (s, 2H), 1.11 (t, $J = 7.1$ Hz, 3H); MS (ES⁺): 412.1, 414.1 (M+Na).

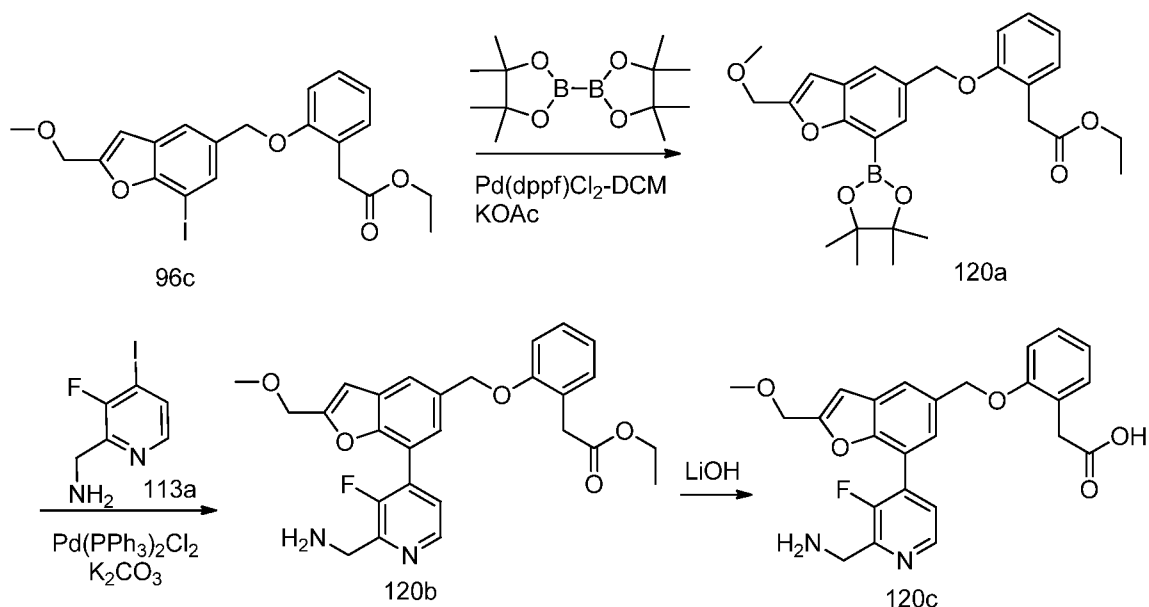
Step-3: Preparation of ethyl 2-(2-((7-(3-(aminomethyl)phenyl)furo[3,2-b]pyridin-5-yl)methoxy)phenyl)acetate (**119d**)

Compound **119d** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((7-bromofuro[3,2-b]pyridin-5-yl)methoxy)phenyl)acetate (**119c**) (110 mg, 0.28 mmol) in dioxane (5 mL) using 3-(aminomethyl)phenylboronic acid hydrochloride (**6c**) (79 mg, 0.42 mmol), bis(triphenylphosphine)palladium(II) chloride (39.6 mg, 0.056 mmol) and K₂CO₃ (117 mg, 0.85 mmol) in water (1 mL) under an Ar atmosphere and heating at 100 °C for 3 h on an oil bath. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM from 0-50%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(3-(aminomethyl)phenyl)furo[3,2-b]pyridin-5-yl)methoxy)phenyl)acetate (**119d**) (95 mg, 81 % yield) HCl salt as an off white solid; ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.45 (d, $J = 2.3$ Hz, 1H), 8.37 (s, 3H, D₂O exchangeable), 8.13 (s, 1H), 8.06 – 8.00 (m, 1H), 7.73 (s, 1H), 7.68 – 7.63 (m, 2H), 7.27 – 7.21 (m, 3H), 7.10 (d, $J = 8.1$ Hz, 1H), 6.92 (td, $J = 7.4, 1.1$ Hz, 1H), 5.31 (s, 2H), 4.15 (q, $J = 5.8$ Hz, 2H), 3.93 (q, $J = 7.1$ Hz, 2H), 3.69 (s, 2H), 0.96 (t, $J = 7.1$ Hz, 3H); MS (ES⁺): 417.2 (M+1); (ES⁻): 415.3 (M-1); 451.2 (M+Cl).

Step-4: Preparation of 2-(2-((7-(3-(aminomethyl)phenyl)furo[3,2-b]pyridin-5-yl)methoxy)phenyl)acetic acid (**119e**)

Compound **119e** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(3-(aminomethyl)phenyl)furo[3,2-b]pyridin-5-yl)methoxy)phenyl)acetate (**119d**) (60 mg, 0.14 mmol) in MeOH/THF (6 mL) using a solution of lithium hydroxide monohydrate (15 mg, 0.36 mmol) in water (1.0 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(3-(aminomethyl)phenyl)furo[3,2-b]pyridin-5-yl)methoxy)phenyl)acetic acid (**119e**) (36 mg, 64% yield) HCl salt as a white solid; ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.52 – 8.34 (m, 4H, partially D₂O exchangeable), 8.14 (s, 1H), 8.06 (dt, $J = 6.6, 2.0$ Hz, 1H), 7.79 (s, 1H), 7.69 – 7.62 (m, 2H), 7.27 – 7.20 (m, 3H), 7.08 (d, $J = 8.1$ Hz, 1H), 6.92 (td, $J = 7.4, 1.0$ Hz, 1H), 5.34 (s, 2H), 4.16 (q, $J = 5.9$ Hz, 2H), 3.66 (s, 2H); MS (ES⁺): 389.4 (M+1); (ES⁻): 387.4 (M-1); 423.4 (M+Cl).

Scheme-120



Preparation of 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**120c**)

Step-1: Preparation of ethyl 2-(2-((2-(methoxymethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**120a**)

Compound **120a** was prepared according to the procedure reported in step-1 of Scheme-59 from ethyl 2-(2-((7-iodo-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**96c**) (3 g, 6.25 mmol), using bis(pinacolato)diboron (2.38 g, 9.37 mmol), potassium acetate (1.84 g, 18.74 mmol) and Pd(dppf)Cl₂-CH₂Cl₂ (0.77 g, 0.94 mmol) in anhydrous dioxane (30 mL) under an Ar atmosphere and heating at 100 °C overnight. This gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane from 0-40%] ethyl 2-(2-((2-(methoxymethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**120a**) (1.8 g, 60 % yield) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.96 (s, 1H), 7.80 (d, *J* = 1.8 Hz, 1H), 7.65 (d, *J* = 1.8 Hz, 1H), 7.29 – 7.18 (m, 2H), 7.09 (d, *J* = 7.8 Hz, 1H), 6.92 – 6.90 (m, 1H), 5.16 (s, 2H), 4.55 (s, 2H), 4.04 – 3.98 (m, 2H), 3.59 (s, 2H), 3.33 (s, 3H), 1.34 (s, 12H), 1.05 – 1.01 (m, 3H); MS (ES⁺): 503.4 (M+Na).

Step-2: Preparation of ethyl 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**120b**)

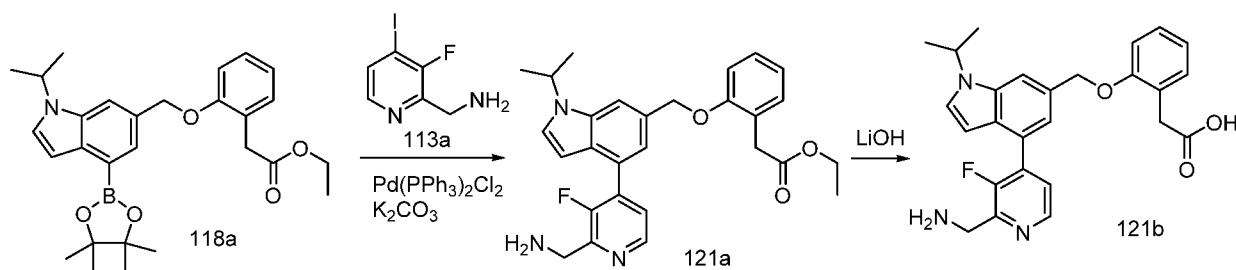
Compound **120b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((2-(methoxymethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-5-yl)methoxy)phenyl)acetate (**120a**) (1334 mg, 2.78 mmol) in dioxane (10

mL) using (3-fluoro-4-iodopyridin-2-yl)methanamine (**113a**) 500 mg, 1.99 mmol), bis(triphenylphosphine)palladium(II) chloride (209 mg, 0.30 mmol) and a solution of K₂CO₃ (823 mg, 5.95 mmol) in water (3 mL) under an Ar atmosphere and heating at 100 °C for 3 h on oil bath. This gave after workup, purification by flash column chromatography [silica (80 g), eluting with DMA80 in DCM from 0-70%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**120b**) (455 mg, 48 % yield) as an off white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.65 (d, *J* = 4.9 Hz, 1H), 8.56 (s, 3H, D₂O exchangeable), 7.86 (d, *J* = 1.6 Hz, 1H), 7.79 (t, *J* = 5.3 Hz, 1H), 7.54 (d, *J* = 1.5 Hz, 1H), 7.31 – 7.19 (m, 2H), 7.15 – 7.09 (m, 1H), 7.07 (s, 1H), 6.92 (td, *J* = 7.4, 1.1 Hz, 1H), 5.25 (s, 2H), 4.54 (s, 2H), 4.38 (d, *J* = 6.1 Hz, 2H), 3.93 (q, *J* = 7.1 Hz, 2H), 3.63 (s, 2H), 3.30 (s, 3H), 0.99 (t, *J* = 7.1 Hz, 3H); ¹⁹F NMR (339 MHz, DMSO) δ -128.76; MS (ES⁺): 479.2 (M+1); 501.2 (M+Na); (ES⁻): 477.3 (M-1).

Step-3: Preparation of 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**120c**)

Compound **120c** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetate (**120b**) (255 mg, 0.53 mmol) in MeOH/THF (8 mL) using a solution of lithium hydroxide monohydrate (56 mg, 1.33 mmol) in water (1.0 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((7-(2-(aminomethyl)-3-fluoropyridin-4-yl)-2-(methoxymethyl)benzofuran-5-yl)methoxy)phenyl)acetic acid (**120c**) (140 mg, 58 % yield) as a white solid; ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.17 (s, 1H, D₂O exchangeable), 8.63 (dd, *J* = 4.9, 1.3 Hz, 1H), 8.49 (s, 3H, D₂O exchangeable), 7.88 (d, *J* = 1.7 Hz, 1H), 7.79 (t, *J* = 5.3 Hz, 1H), 7.57 (s, 1H), 7.27 – 7.18 (m, 2H), 7.09 (d, *J* = 8.1 Hz, 1H), 7.04 (d, *J* = 1.4 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 5.27 (s, 2H), 4.53 (s, 2H), 4.37 (d, *J* = 5.9 Hz, 2H), 3.58 (s, 2H), 3.29 (s, 3H); ¹⁹F NMR (339 MHz, DMSO) δ -128.57; MS (ES⁺): 451.2 (M+1); (ES⁻): 449.3 (M-1).

Scheme-121



Preparation of 2-(2-((4-(2-(aminomethyl)-3-fluoropyridin-4-yl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**121b**)

Step-1: Preparation of ethyl 2-(2-((4-(2-(aminomethyl)-3-fluoropyridin-4-yl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetate (**121a**)

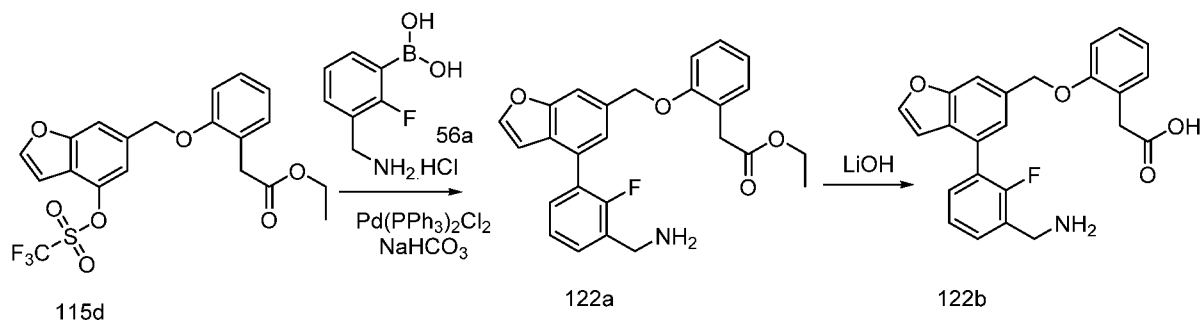
Compound **121a** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((1-isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-6-yl)methoxy)phenyl)acetate (**118a**) (0.85 g, 1.79 mmol) in dioxane (10 mL) using (3-fluoro-4-iodopyridin-2-yl)methanamine (**113a**) (0.3 g, 1.19 mmol), bis(triphenylphosphine)palladium(II) chloride (0.13 g, 0.18 mmol) and a solution of K_2CO_3 (0.41 g, 2.98 mmol) in water (1.0 mL) under an Ar atmosphere and heating at 100 °C for 2 h on oil bath. This gave after workup, purification by flash column chromatography [silica (24 g), eluting with MeOH in DCM from 0-50%] followed by purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((4-(2-(aminomethyl)-3-fluoropyridin-4-yl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetate (**121a**) (0.1 g, 18 % yield) as a yellow solid; MS (ES⁺): 475.5 (M+1); MS (ES⁻): 474.5 (M-1).

Step-2: Preparation 2-(2-((4-(2-(aminomethyl)-3-fluoropyridin-4-yl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**121b**)

Compound **121b** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((4-(2-(aminomethyl)-3-fluoropyridin-4-yl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetate (**121a**) (0.1 g, 0.210 mmol) in MeOH/THF (4 mL) using a solution of lithium hydroxide monohydrate (44 mg, 1.05 mmol) in water (1.0 mL). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((4-(2-(aminomethyl)-3-fluoropyridin-4-yl)-1-isopropyl-1H-indol-6-yl)methoxy)phenyl)acetic acid (**121b**) (0.04 g, 43 % yield) as a yellow solid; ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.57 (d, J = 4.9 Hz, 1H), 8.52 – 8.46 (bs, 3H), 7.81 (s, 1H), 7.69 (t, J = 5.3 Hz, 1H), 7.65 (d, J = 3.3 Hz, 1H), 7.27 (s, 1H), 7.26 – 7.20 (m, 2H), 7.12 (d, J = 8.1 Hz, 1H), 6.90 (td, J = 7.3, 1.1 Hz, 1H), 6.40 (t, J = 3.0 Hz, 1H), 5.28 (s,

2H), 4.84 (p, $J = 6.7$ Hz, 1H), 4.36 (m, 2H), 3.59 (s, 2H), 1.49 (d, $J = 6.6$ Hz, 6H); ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ -129.76; MS (ES⁺): 448.5 (M+1); MS (ES⁻): 446.5 (M-1), 482.5 (M+Cl). HPLC purity: 95.70 %.

Scheme-122



Preparation of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)benzofuran-6-yl)methoxy)phenyl)acetic acid (**122b**)

Step-1: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)benzofuran-6-yl)methoxy)phenyl)acetate (**122a**)

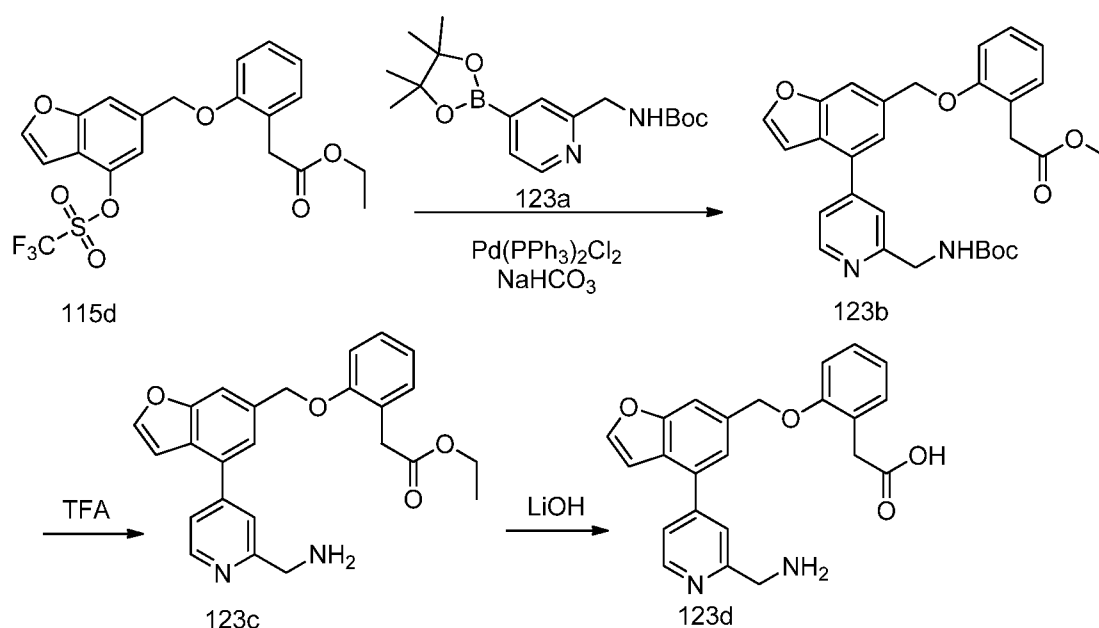
Compound **122a** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((4-(((trifluoromethyl)sulfonyl)oxy)benzofuran-6-yl)methoxy)phenyl)acetate (**115d**) (500 mg, 1.091 mmol) in dioxane (10 mL) using (3-(aminomethyl)-2-fluorophenyl)boronic acid hydrochloride (**56a**) (336 mg, 1.636 mmol), a solution of sodium bicarbonate (275 mg, 3.27 mmol) in water (1 mL) and bis(triphenylphosphine)palladium(II) chloride (230 mg, 0.327 mmol) and heating under an nitrogen atmosphere at 95 °C for 3 h. This gave after workup, purification by flash column chromatography [silica (12 g), eluting with dichloromethane/methanol (1:0 to 9:1)] ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)benzofuran-6-yl)methoxy)phenyl)acetate (**122a**) (147 mg) as a yellow gum (147 mg, 31%). MS (ES⁺): 434.4 (M + 1).

Step-2: Preparation of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)benzofuran-6-yl)methoxy)phenyl)acetic acid (**122b**)

Compound **122b** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)benzofuran-6-yl)methoxy)phenyl)acetate (**122a**) (147 mg, 0.339 mmol) in THF (7 mL) and MeOH (7 mL) using a solution of lithium hydroxide hydrate (87 mg, 2.04 mmol) in water (7 mL). This gave after workup and purification by flash column chromatography [silica gel, eluting with dichloromethane/methanol (1:0 to 9:1)] 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)benzofuran-6-yl)methoxy)phenyl)acetic acid (**122b**)

(44 mg, 32% yield) as a white solid ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.06 (d, $J = 2.2$ Hz, 1H), 7.72 (s, 1H), 7.55 (t, $J = 7.2$ Hz, 1H), 7.48 (s, 1H), 7.47 – 7.43 (m, 1H), 7.32 (t, $J = 7.6$ Hz, 1H), 7.25 – 7.18 (m, 2H), 7.06 (d, $J = 8.3$ Hz, 1H), 6.92 – 6.86 (m, 1H), 6.86 – 6.82 (m, 1H), 5.30 (s, 2H), 3.89 (s, 2H), 3.56 (s, 2H); MS (ES⁺): 406.4 (M+1), 428.4 (M+Na); MS (ES⁻): 404.5 (M-1); HPLC purity: 96.40%.

Scheme-123



Preparation of 2-(2-((4-(2-(aminomethyl)pyridin-4-yl)benzofuran-6-yl)methoxy)phenyl)acetic acid (**123d**)

Step-1: Preparation of ethyl 2-(2-((4-(2-((tert-butoxycarbonyl)amino)methyl)pyridin-4-yl)benzofuran-6-yl)methoxy)phenyl)acetate (**123b**)

Compound **123b** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((4-((trifluoromethyl)sulfonyl)oxy)benzofuran-6-yl)methoxy)phenyl)acetate (**115d**) (500 mg, 1.09 mmol) in dioxane (10 mL) using tert-butyl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)methylcarbamate (**123a**) (547 mg, 1.64 mmol; CAS# 1425334-54-8), a solution of sodium bicarbonate (275 mg, 3.27 mmol) in water (1 mL) and bis(triphenylphosphine)palladium(II) chloride (230 mg, 0.327 mmol) and heating under an nitrogen atmosphere at 95 °C for 3 h. This gave after workup, purification by flash column chromatography [silica (24 g), eluting with hexanes/ethyl acetate (1:0 to 1:1)] ethyl 2-(2-((4-(2-((tert-butoxycarbonyl)amino)methyl)pyridin-4-yl)benzofuran-6-yl)methoxy)phenyl)acetate (**123b**) (177 mg, 31%) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.62 (dd, $J = 5.0, 0.9$ Hz, 1H), 8.18 (d, $J = 2.3$ Hz, 1H), 7.79 – 7.77 (m, 1H), 7.59 – 7.49 (m, 4H), 7.31 – 7.19 (m, 2H), 7.15 – 7.06 (m, 2H), 6.92 (td, $J = 7.4, 1.1$ Hz, 1H),

5.29 (s, 2H), 4.32 (d, $J = 6.1$ Hz, 2H), 3.93 (q, $J = 7.1$ Hz, 2H), 3.65 (s, 2H), 1.40 (s, 9H), 0.99 (t, $J = 7.1$ Hz, 3H); MS (ES⁺): 539.5 (M + Na); MS (ES⁻): 515.5 (M-1).

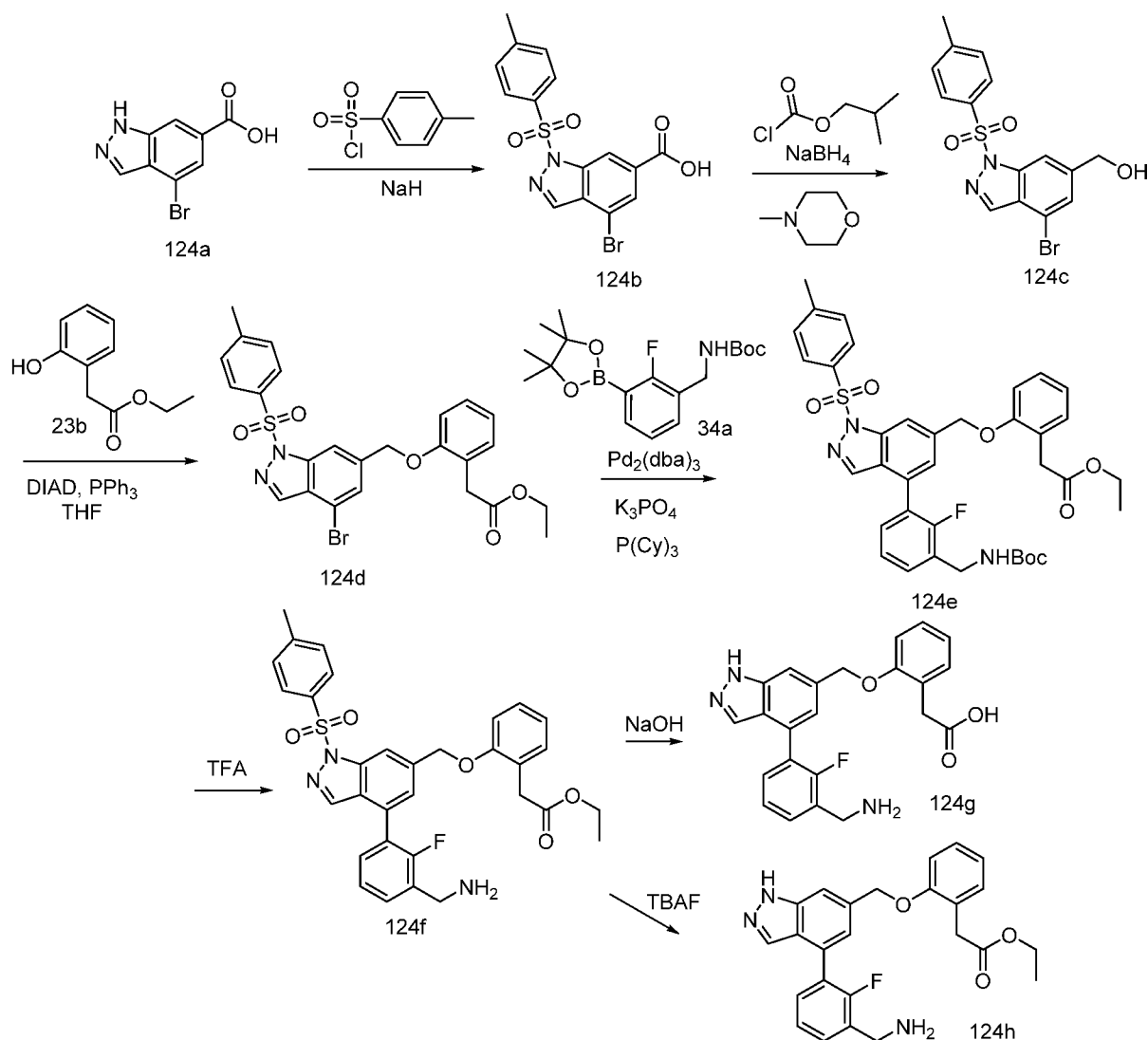
Step-2: Preparation of ethyl 2-(2-((4-(2-(aminomethyl)pyridin-4-yl)benzofuran-6-yl)methoxy)phenyl)acetate (**123c**)

Compound **123c** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-((4-(2-(((*tert*-butoxycarbonyl)amino)methyl)pyridin-4-yl)benzofuran-6-yl)methoxy)phenyl)acetate (**123b**) (160 mg, 0.31 mmol) in DCM (10 mL) using TFA (0.24 mL, 3.10 mmol). This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DCM/methanol (1:0 to 9:1)] ethyl 2-(2-((4-(2-(aminomethyl)pyridin-4-yl)benzofuran-6-yl)methoxy)phenyl)acetate (**123c**) (136 mg, 83% yield) as a light brown gum. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.76 (d, $J = 5.1$ Hz, 1H), 8.36 (s, 3H), 8.21 (d, $J = 2.3$ Hz, 1H), 7.82 (d, $J = 5.8$ Hz, 2H), 7.74 (dd, $J = 5.2, 1.7$ Hz, 1H), 7.61 (d, $J = 1.3$ Hz, 1H), 7.33 – 7.18 (m, 3H), 7.10 (d, $J = 8.1$ Hz, 1H), 6.95 – 6.88 (m, 1H), 5.30 (s, 2H), 4.33 (s, 2H), 3.96 (q, $J = 7.1$ Hz, 2H), 3.66 (s, 2H), 1.02 (t, $J = 7.1$ Hz, 3H); MS (ES⁺): 417.4 (M+1).

Step-3: Preparation of 2-(2-((4-(2-(aminomethyl)pyridin-4-yl)benzofuran-6-yl)methoxy)phenyl)acetic acid (**123d**)

Compound **123d** was prepared according to the procedure reported in step-6 of Scheme-1, from ethyl 2-(2-((4-(2-(aminomethyl)pyridin-4-yl)benzofuran-6-yl)methoxy)phenyl)acetate (**123c**) (100 mg, 0.19 mmol) in THF (6 mL) and MeOH (6 mL) using a solution of lithium hydroxide hydrate (62 mg, 1.44 mmol) in water (7 mL). This gave after workup and purification by flash column chromatography [silica gel, eluting with dichloromethane/methanol (1:0 to 9:1)] 2-(2-((4-(2-(aminomethyl)pyridin-4-yl)benzofuran-6-yl)methoxy)phenyl)acetic acid (**123d**) (25 mg, 33% yield) as an off-white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.62 (d, $J = 5.2$ Hz, 1H), 8.16 (d, $J = 2.3$ Hz, 1H), 8.15 (s, 1H), 7.81 (d, $J = 13.5$ Hz, 2H), 7.72 (dd, $J = 5.1, 1.7$ Hz, 1H), 7.26 – 7.25 (m, 1H), 7.15 – 7.10 (m, 2H), 6.99 (d, $J = 8.1$ Hz, 1H), 6.83 (t, $J = 7.3$ Hz, 1H), 5.31 (s, 2H), 4.09 (s, 2H), 3.45 (s, 2H); MS (ES⁺): 389.4 (M+1); MS (ES⁻): 387.3 (M-1), 423.3 (M+Cl).

Scheme-124



Preparation of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1H-indazol-6-yl)methoxy)phenyl)acetic acid (**124g**) and ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1H-indazol-6-yl)methoxy)phenyl)acetate (**124h**)

Step-1: Preparation of 4-bromo-1-tosyl-1H-indazole-6-carboxylic acid (**124b**)

Compound **124b** was prepared according to the procedure reported in step-1 of Scheme-40 from 4-bromo-1H-indazole-6-carboxylic acid (**124a**) (1.00 g, 4.15 mmol; CAS# 885523-43-3) in DMF (25 mL) using NaH (60% in mineral oil, 0.332 g, 8.30 mmol), tosyl-Cl (0.870 g, 4.56 mmol). This gave after workup 4-bromo-1-tosyl-1H-indazole-6-carboxylic acid (**124b**) (1.292 g, 79 % yield) as a white solid; MS (ES⁺): 395.0, 397.0 (M+2).

Step-2: Preparation of (4-bromo-1-tosyl-1H-indazol-6-yl)methanol (**124c**)

Compound **124c** was prepared according to the procedure reported in step-1 of Scheme-23 from 4-bromo-1-tosyl-1H-indazole-6-carboxylic acid (**124b**) (1.28 g, 3.24 mmol) using N-methylmorpholine (0.427 mL, 3.89 mmol) in THF (30 mL), isobutyl chloroformate (0.51 mL,

3.89 mmol) and NaBH₄ (0.368 g, 9.72 mmol) in water (3 mL). This gave after workup and purification by flash column chromatography [silica gel 24 g, eluting with ethyl acetate in hexanes from 0-100%] (4-bromo-1-*tosyl*-1H-indazol-6-yl)methanol (**124c**) (0.438 g, 36 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.49 (d, J = 0.9 Hz, 1H), 8.16 - 8.09 (m, 1H), 7.88 - 7.77 (m, 2H), 7.59 (d, J = 1.0 Hz, 1H), 7.49 - 7.36 (m, 2H), 5.64 (t, J = 5.8 Hz, 1H), 4.71 (d, J = 5.8 Hz, 2H), 2.34 (s, 3H); MS (ES⁺): 403.1, 405.1 (M+Na); MS (ES⁻): 479.1, 481.1 (M+Cl), 415.1, 417.1 (M+Cl).

Step-3: Preparation of ethyl 2-(2-((4-bromo-1-*tosyl*-1H-indazol-6-yl)methoxy)phenyl)acetate (**124d**)

Compound **124d** was prepared according to the procedure reported in step-2 of Scheme-23 from (4-bromo-1-*tosyl*-1H-indazol-6-yl)methanol (**124c**) (0.422 g, 1.107 mmol) in THF (25 mL) using triphenylphosphine (0.377 g, 1.439 mmol) ethyl 2-(2-hydroxyphenyl) acetate (**23b**) (0.259 g, 1.439 mmol) and DIAD (0.280 mL, 1.439 mmol). This gave after workup and purification by flash column chromatography [silica gel 25 g, eluting with ethyl acetate in hexanes from 0-100%] ethyl 2-(2-((4-bromo-1-*tosyl*-1H-indazol-6-yl)methoxy)phenyl)acetate (**124d**) (0.406 g, 68 % yield) as a pale-yellow solid; MS (ES⁺): 543.1, 545.1 (M+2).

Step-4: Preparation of ethyl 2-(2-((4-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)-1-*tosyl*-1H-indazol-6-yl)methoxy)phenyl)acetate (**124e**)

Compound **124e** was prepared according to the procedure reported in step-3 of Scheme-1 from ethyl 2-(2-((4-bromo-1-*tosyl*-1H-indazol-6-yl)methoxy)phenyl)acetate (**124d**) (400 mg, 0.74 mmol) in dioxane (6 mL) using *tert*-butyl 2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzylcarbamate (**34a**) (0.388 g, 1.104 mmol), tripotassium phosphate (1.3 M solution, 0.736 mL, 2.208 mmol), tricyclohexylphosphine (0.062 g, 0.221 mmol) and Pd₂(dba)₃ (0.067 g, 0.074 mmol) under an Ar atmosphere and heating at 125 °C for 45 min in a microwave. This gave after workup, purification by flash column chromatography [silica gel, 25g, eluting with methanol in DCM from 0-100%] ethyl 2-(2-((4-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)-1-*tosyl*-1H-indazol-6-yl)methoxy)phenyl)acetate (**124e**) (0.175 g, 35 % yield) as a yellow solid; MS (ES⁺): 710.3 (M+Na); MS (ES⁻): 722.2 (M+Cl).

Step-5: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-*tosyl*-1H-indazol-6-yl)methoxy)phenyl)acetate (**124f**)

Compound **124f** was prepared according to the procedure reported in step-5 of Scheme-1 from ethyl 2-(2-((4-(3-(((*tert*-butoxycarbonyl)amino)methyl)-2-fluorophenyl)-1-*tosyl*-1H-indazol-6-yl)methoxy)phenyl)acetate (**124e**) (0.17 g, 0.247 mmol) in DCM (10 mL) using

TFA (0.29 mL, 3.71 mmol). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-*tosyl*-1H-indazol-6-yl)methoxy)phenyl)acetate (**124f**) (0.061 g, 42 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.52 (d, J = 3.4 Hz, 1H), 8.43 - 8.10 (m, 3H), 7.84 (d, J = 8.3 Hz, 2H), 7.71 - 7.57 (m, 2H), 7.53 (s, 1H), 7.45 (d, J = 7.7 Hz, 1H), 7.39 (d, J = 8.3 Hz, 2H), 7.32 - 7.21 (m, 2H), 7.12 (d, J = 8.0 Hz, 1H), 6.96 (t, J = 7.4 Hz, 1H), 5.42 (s, 2H), 4.14 (s, 2H), 3.91 (q, J = 7.1 Hz, 2H), 3.69 (s, 2H), 2.34 (s, 3H), 0.94 (t, J = 7.1 Hz, 3H); MS (ES $^{+}$): 588.3 (M+1); MS (ES $^{-}$): 622.4 (M+Cl).

Step-6: Preparation of 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1H-indazol-6-yl)methoxy)phenyl)acetic acid (**124g**)

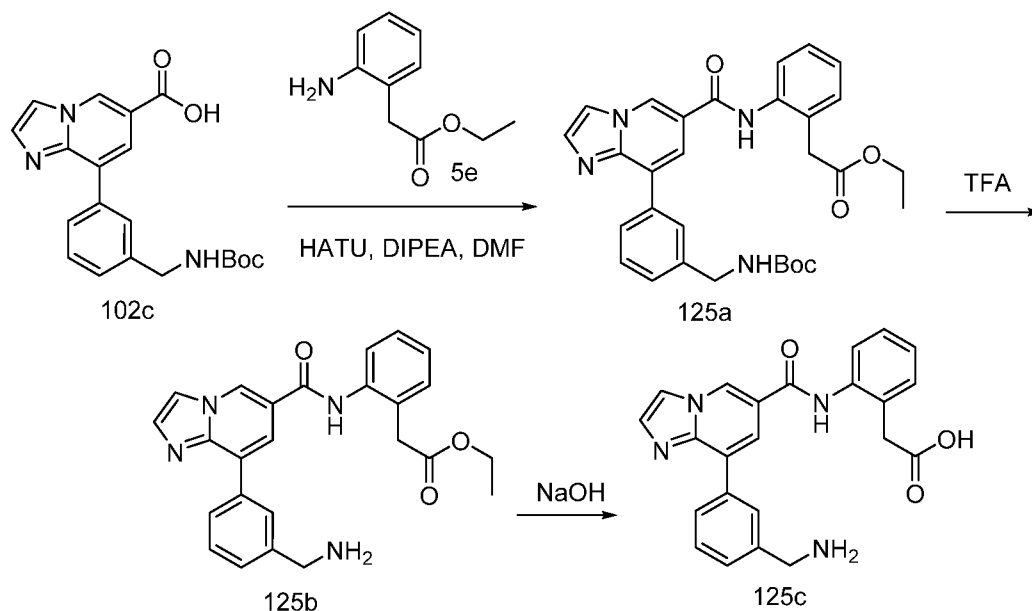
Compound **124g** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-*tosyl*-1H-indazol-6-yl)methoxy)phenyl)acetate (**124f**) (0.058 g, 0.099 mmol) in THF (3 mL) and methanol (6 mL) using a solution of sodium hydroxide (2 M aqueous, 0.493 mL, 0.987 mmol). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1H-indazol-6-yl)methoxy)phenyl)acetic acid (**124g**) (0.027 g, 68 % yield) HCl salt as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 13.30 (s, 1H), 8.39 (s, 3H), 8.05 (d, J = 3.1 Hz, 1H), 7.70 (s, 1H), 7.69 - 7.61 (m, 2H), 7.43 (t, J = 7.7 Hz, 1H), 7.28 (s, 1H), 7.25 - 7.19 (m, 2H), 7.09 (d, J = 8.2 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 5.33 (s, 2H), 4.25 - 4.13 (m, 2H), 3.60 (s, 2H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -118.45; MS (ES $^{+}$): 406.3 (M+1), 811.4 (2M+1); MS (ES $^{-}$): 404.4 (M-1), 440.3 (M+Cl), 809.5 (2M-1); HPLC purity: 92.19%.

Step-7: Preparation of ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1H-indazol-6-yl)methoxy)phenyl)acetate (**124h**)

Compound **124h** was prepared according to the procedure reported in step-1 of Scheme-58, from ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1-*tosyl*-1H-indazol-6-yl)methoxy)phenyl)acetate (**124f**) in THF (20 mL) using tetrabutylammonium fluoride (1.415 g, 5.41 mmol). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-((4-(3-(aminomethyl)-2-fluorophenyl)-1H-indazol-6-yl)methoxy)phenyl)acetate (**124h**) (0.014 g, 6 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 13.32 (s, 1H, D $_2$ O exchangeable), 8.38 (s, 4H, D $_2$ O exchangeable, 3H), 8.06 (d, J = 3.0 Hz, 1H), 7.71 - 7.61 (m, 3H), 7.44 (t, J = 7.6 Hz, 1H), 7.28 - 7.20 (m, 3H), 7.12 (d, J = 8.2 Hz, 1H), 6.92 (t, J = 7.3

Hz, 1H), 5.30 (s, 2H), 4.31 – 4.10 (m, 2H), 3.93 (q, $J = 7.1$ Hz, 2H), 3.64 (s, 2H), 0.98 (t, $J = 7.1$ Hz, 2H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -118.55; MS (ES $^{+}$): 434.4 (M+1); 456.3 (M+Na); MS (ES $^{-}$): 468.4 (M+Cl); 901.6 (2M+Cl).

Scheme-125



Preparation of 2-(2-(8-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridine-6-carboxamido)phenyl)acetic acid (**125c**)

Step-1: Preparation of ethyl 2-(2-(8-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)imidazo[1,2-a]pyridine-6-carboxamido)phenyl)acetate (**125a**)

Compound **125a** was prepared according to the procedure reported in step-4 of Scheme-1 from 8-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)imidazo[1,2-a]pyridine-6-carboxylic acid (**102c**) (0.350 g, 0.953 mmol) in DMF (10 mL) using ethyl 2-(2-aminophenyl)acetate (**5e**) (0.205 g, 1.143 mmol), DIPEA (0.830 mL, 4.76 mmol) and HATU (0.543 g, 1.429 mmol). This gave after workup and purification by flash column chromatography (Silica gel, 24 g eluting with methanol in DCM from 0-20%) ethyl 2-(2-(8-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)imidazo[1,2-a]pyridine-6-carboxamido)phenyl)acetate (**125a**) (0.388 g, 77 % yield) as a yellow syrup; MS (ES $^{-}$): 527.4 (M-1).

Step-2: Preparation of ethyl 2-(2-(8-(3-(aminomethyl)phenyl)imidazo[1,2-a]pyridine-6-carboxamido)phenyl)acetate (**125b**)

Compound **125b** was prepared according to the procedure reported in step-5 of Scheme-1 from

ethyl 2-(2-(8-(3-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)imidazo[1,2-*a*]pyridine-6-carboxamido)phenyl)acetate (**125a**) (0.371 g, 0.702 mmol) in DCM (10 mL) using TFA (0.811 mL, 10.53 mmol). This gave after workup and purification by reverse phase column chromatography [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] ethyl 2-(2-(8-(3-(aminomethyl)phenyl)imidazo[1,2-*a*]pyridine-6-carboxamido)phenyl)acetate (**125b**) (0.138 g, 46 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.67 (s, 1H), 9.54 (s, 1H), 8.63 (s, 3H), 8.57 - 8.50 (m, 2H), 8.25 - 8.12 (m, 2H), 8.07 - 7.92 (m, 1H), 7.76 - 7.61 (m, 2H), 7.43 - 7.27 (m, 4H), 4.25 - 4.12 (m, 2H), 3.96 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 2H), 1.01 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 429.4 (M+1); MS (ES⁻): 463.3 (M+Cl).

Step-3: Preparation of 2-(2-(8-(3-(aminomethyl)phenyl)imidazo[1,2-*a*]pyridine-6-carboxamido)phenyl)acetic acid (**125c**)

Compound **125c** was prepared according to the procedure reported in step-4 of Scheme-4, from ethyl 2-(2-(8-(3-(aminomethyl)phenyl)imidazo[1,2-*a*]pyridine-6-carboxamido)phenyl)acetate (**125b**) (0.065 g, 0.152 mmol) in THF (3 mL) and methanol (6 mL) using a solution of sodium hydroxide (2 M aqueous, 0.379 mL, 0.758 mmol). This gave after workup and purification by reverse phase column [C18 (50 g), eluting with ACN in water (containing 0.1% HCl) from 0-100%] 2-(2-(8-(3-(aminomethyl)phenyl)imidazo[1,2-*a*]pyridine-6-carboxamido)phenyl)acetic acid (**125c**) (0.027 g, 44 % yield) HCl salt as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.3 (bs, 1H, D₂O exchangeable), 10.61 (s, 1H, D₂O exchangeable), 9.52 (s, 1H), 8.61 (s, 3H, D₂O exchangeable), 8.52 (s, 1H), 8.48 (s, 1H), 8.17 (s, 1H), 8.14 (s, 1H), 8.01 (s, 1H), 7.75 - 7.62 (m, 2H), 7.48 - 7.22 (m, 4H), 4.24 - 4.13 (m, 2H), 3.72 (s, 2H); MS (ES⁺): 401.3 (M+1); 801.5 (2M+1); MS (ES⁻): 399.3 (M-1); 799.5 (2M-1); HPLC purity: 98.60%.

Scheme-126

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 4
CONTENANT LES PAGES 1 À 333

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 4
CONTAINING PAGES 1 TO 333

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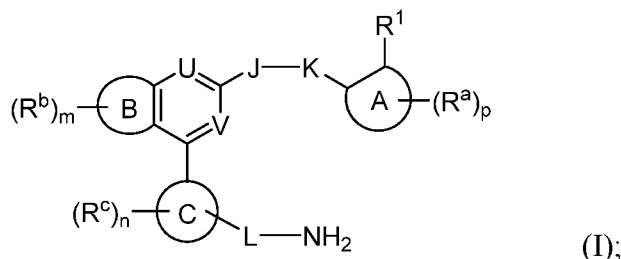
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NOTE POUR LE TOME / VOLUME NOTE:

CLAIMS

What is claimed is:

1. A compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof:



wherein:

ring $\textcircled{\text{A}}$ is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

ring $\textcircled{\text{B}}$ is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

ring $\textcircled{\text{C}}$ is aryl or heteroaryl;

R^{a} , independently for each occurrence, is halogen, cyano, hydroxy, $-\text{NH}_2$, $-\text{NH}(\text{Ac})$, $-\text{NH}(\text{alkyl})$, $-\text{NH}(\text{cycloalkyl})$, $-\text{NH}(\text{heterocycloalkyl})$, $-\text{NH}(\text{aryl})$, $-\text{NH}(\text{heteroaryl})$, $-\text{N}(\text{alkyl})_2$, $-\text{NHC}(\text{O})(\text{alkyl})$, $-\text{CH}(\text{alkyl})\text{NH}_2$, $-\text{CH}(\text{hydroxyalkyl})\text{NH}_2$, $-\text{CH}(\text{haloalkyl})\text{NH}_2$, $-\text{CH}(\text{cycloalkyl})\text{NH}_2$, $-\text{CH}(\text{heterocycloalkyl})\text{NH}_2$, $-\text{CH}(\text{aryl})\text{NH}_2$, $-\text{CH}(\text{heteroaryl})\text{NH}_2$, $-\text{CH}_2\text{NHC}(\text{O})(\text{alkyl})$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})(\text{alkyl})$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2(\text{cycloalkyl})$, $-\text{SO}_2(\text{heterocycloalkyl})$, $-\text{SO}_2(\text{alkyl})$, $-\text{SO}_2(\text{aryl})$, or $-\text{SO}_2(\text{heteroaryl})$; or is selected from the group consisting of substituted or unsubstituted aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl;

R^{b} , independently for each occurrence, is halogen, cyano, $-\text{CH}_2(\text{OCH}_2\text{CH}_2)_q\text{OCH}_3$, $-\text{alkylene}-(\text{branched or unbranched polyethylene glycol})$, $-\text{alkylene-O}-(\text{branched or unbranched polyethylene glycol})$, or $-\text{NR}^{\text{j}}\text{R}^{\text{k}}$; or is selected from the group consisting of substituted or unsubstituted alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, (hydroxy)haloalkyl, hydroxy(cycloalkyl)alkyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, arylalkyl, heteroarylalkyl,

(heteroarylalkoxy)alkyl, (arylalkoxy)alkyl, (aryloxy)alkyl, ((cycloalkyl)alkoxy)alkyl, ((heterocycloalkyl)alkoxy)alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -alkylene-NR^jR^k, tosyl, -SO₂(alkyl), -SO₂(cycloalkyl), -CO(alkyl), -CO(aryl), -CO(heteroaryl), -CO(cycloalkyl), -CO(heterocycloalkyl), -CONH(alkyl), -CONH(arylalkyl), -CONH(heteroarylalkyl), -CON(alkyl)₂, -CONH(heterocycloalkyl), and -CONH(cycloalkyl);

R^c, independently for each occurrence, is selected from the group consisting of halogen, -OH, -NR^jR^k, alkoxy, alkyl, cycloalkyl, and heterocycloalkyl;

R¹ is selected from the group consisting of -NH₂, -COOH, -CH₂COOH, -CH(NH(CO)(alkyl))COOH, -CH(NH(CO)(arylalkyl))COOH, -CH(NH(CO)(cycloalkyl))COOH, -CH(NH(CO)(aryl substituted cycloalkyl))COOH, -CH(NH(CO)(heteroaryl substituted cycloalkyl))COOH, -CH(S(alkyl))COOH, -CO(NH)CH₂(substituted or unsubstituted aryl), -CO(NH)CH₂(substituted or unsubstituted heteroaryl), -CO(NH)(substituted or unsubstituted aryl), -CO(NH)(substituted or unsubstituted heteroaryl), and -CH₂(tetrazolyl);

n is 0, 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

p is 0, 1, 2, 3, or 4;

q is an integer from 1-20;

J is -C(O)-, -NH-, -CH₂-, -O-, -S-, -S(O)-, -SO₂-, -N(alkyl)-, -CH(alkyl)-, -CH(cycloalkyl)-, -N((C(O)O)arylalkyl)-, -N((C(O)O)heteroarylalkyl)-, or -N(C(O)arylalkyl)-;

K is -C(O)-, -NH-, -CH₂-, -O-, -S-, -S(O)-, -SO₂-, -N(alkyl)-, -CH(alkyl)-, -CH(cycloalkyl)-, -N((C(O)O)arylalkyl)-, -N((C(O)O)heteroarylalkyl)-, or -N(C(O)arylalkyl)-;

wherein at least one of J and K is -C(O)-, -CH₂-, or -CH(alkyl)-;

L is selected from the group consisting of a bond, -CH₂-, -CH₂CH₂-, -CHR²-, -CF₂-, -CFR²-, -C(O)-, -C(=NR^L)-, -C(=CHR^L)-, -S(O)₂-, and -S(O)-; wherein R^L is H or alkyl;

or wherein R^L and an occurrence of R^c taken together with the intervening atoms form a substituted or unsubstituted heteroaryl ring;

R² is alkyl, cycloalkyl, hydroxyalkyl, or haloalkyl;

R^j and R^k are each independently H or are selected from the group consisting of substituted or unsubstituted alkyl, aminoalkyl, (heterocycloalkyl)alkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, -CO(aryl), -CO(arylalkyl), -CO(heteroarylalkyl), and -CO((heterocycloalkyl)alkyl);

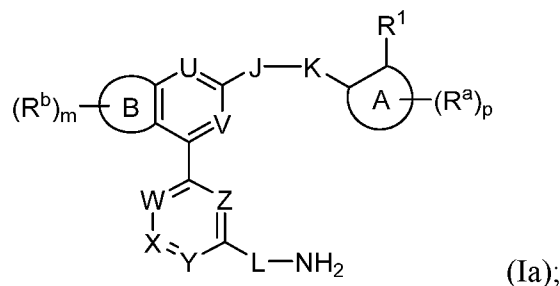
U is N or CR^3 ;

R^3 is H, halogen, alkyl, cycloalkyl, aryl, heteroaryl, alkoxy, haloalkyl, -CN, -CONH₂, -CO₂H, -CH₂CO₂H, -NH₂, hydroxyalkyl, aminoalkyl, -OH, -NH(alkyl), -N(alkyl)₂, thioalkyl, or -S(alkyl);

V is N, CH, C(halogen), or C(alkyl); and

the stereochemical configuration at any chiral center is *R*, *S*, or a mixture of *R* and *S*.

2. The compound of formula (I), having the structure of formula (Ia):



wherein:

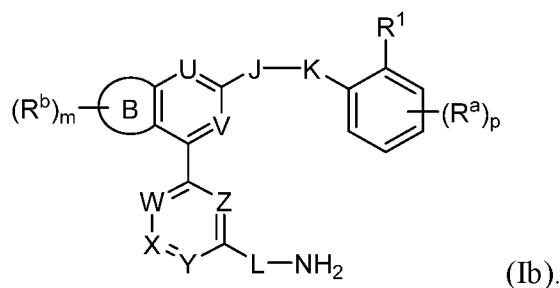
W is N, CH, or CR^c ;

X is N, CH, or CR^c ;

Y is N, CH, or CR^c ; and

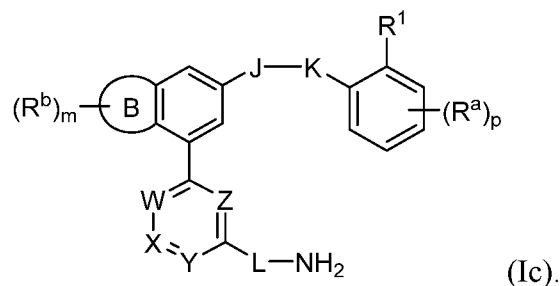
Z is N, CH, or CR^c .

3. The compound of claim 1 or 2, wherein ring $\textcircled{A}$ is naphthyl, indenyl, cyclopentyl, pyrrolidinyl, phenyl, benzofuranyl, thiophenyl, or pyridinyl.
4. The compound of claim 3, wherein ring $\textcircled{A}$ is phenyl, thiophenyl, or pyridinyl.
5. The compound of any one of claims 1-4, having the structure of formula (Ib):

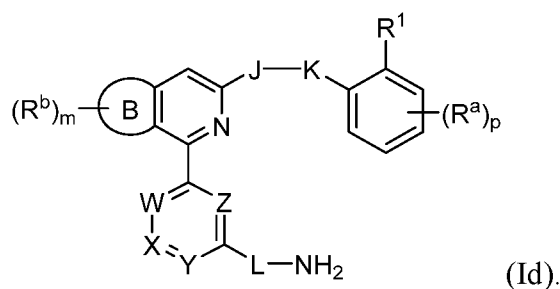


6. The compound of any one of claims 1-5, wherein p is 1.
7. The compound of claim 6, wherein R^a is halogen, cyano, hydroxy, -NH₂, -NH(Ac), -NH(alkyl), -N(alkyl)₂, -NHC(O)(alkyl), -CH₂NHC(O)(alkyl), -C(O)NH₂, or -C(O)(alkyl); or is selected from the group consisting of substituted or unsubstituted aryl, heteroaryl, cycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl.
8. The compound of claim 6, wherein R^a is halogen, cyano, -NH₂, -NH(Ac), -C(O)CH₃, -C(O)NH₂, or hydroxymethyl; or substituted or unsubstituted aryl, heteroaryl, cycloalkyl, alkoxy, alkyl, or aminoalkyl.
9. The compound of claim 6, wherein R^a is halogen, -NH(Ac), or -C(O)CH₃; or substituted or unsubstituted aryl, heteroaryl, cycloalkyl, alkoxy, alkyl, or aminoalkyl.
10. The compound of claim 7, wherein R^a is alkyl, cycloalkyl, or halogen.
11. The compound of any one of claims 1-5, wherein p is 0.
12. The compound of any one of claims 1-11, wherein R¹ is -CH₂COOH.
13. The compound of any one of claims 1-11, wherein R¹ is -CO(NH)CH₂(substituted or unsubstituted aryl).
14. The compound of any one of claims 1-13, wherein -J-K- is selected from the group consisting of -C(O)-NH-, -NH-C(O)-, and -CH₂O-.

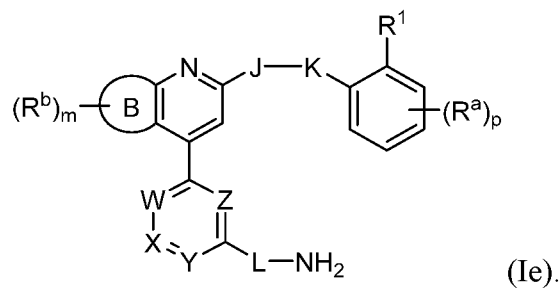
15. The compound of any one of claims 1-14, wherein $-J-K-$ is $-\text{CH}_2\text{O}-$.
16. The compound of any one of claims 1-15, wherein U is CH.
17. The compound of any one of claims 1-16, wherein V is CH.
18. The compound of any one of claims 1-15, having the structure of formula (Ic):



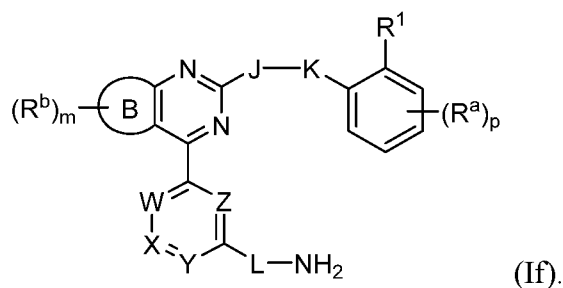
19. The compound of any one of claims 1-15, having the structure of formula (Id):



20. The compound of any one of claims 1-15, having the structure of formula (Ie):



21. The compound of any one of claims 1-15, having the structure of formula (If):



22. The compound of any one of claims 1-21, wherein ring $\textcircled{\text{B}}$ is heteroaryl.
23. The compound of claim 22, wherein ring $\textcircled{\text{B}}$ is furyl, oxazolyl, isoxazolyl, thiophenyl, pyrrolyl, pyrazolyl, or imidazolyl.
24. The compound of claim 23, wherein ring $\textcircled{\text{B}}$ is furyl, thiophenyl, or pyrrolyl.
25. The compound of claim 24, wherein ring $\textcircled{\text{B}}$ is furyl.
26. The compound of any one of claims 1-25, wherein m is 0.
27. The compound of any one of claims 1-25, wherein m is 1.
28. The compound of claim 25, wherein R^b , independently for each occurrence, is halogen, cyano, $-\text{CH}_2(\text{OCH}_2\text{CH}_2)_q\text{OCH}_3$, or $-\text{NR}^j\text{R}^k$; or is selected from the group consisting of substituted or unsubstituted alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, (hydroxy)haloalkyl, hydroxy(cycloalkyl)alkyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, arylalkyl, heteroarylalkyl, (heteroarylalkoxy)alkyl, (arylalkoxy)alkyl, (aryloxy)alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -alkylene- NR^jR^k , tosyl, $-\text{SO}_2(\text{alkyl})$, $-\text{SO}_2(\text{cycloalkyl})$, $-\text{CO}(\text{alkyl})$, $-\text{CO}(\text{cycloalkyl})$, -CONH(alkyl), -CONH(arylalkyl), -CON(alkyl)₂, and -CONH(cycloalkyl).

29. The compound of claim 27, wherein R^b is halogen; or is selected from the group consisting of substituted or unsubstituted alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, and (cycloalkyl)alkyl.
30. The compound of claim 27, wherein R^b is substituted or unsubstituted -alkylene- NR^jR^k .
31. The compound of any one of claims 1-25, wherein m is 2.
32. The compound of claim 31, wherein each R^b is alkyl.
33. The compound of any one of claims 1-32, wherein each of W, X, Y, and Z is CH.
34. The compound of any one of claims 1-32, wherein at least one of W, X, Y, and Z is CR^c .
35. The compound of claim 34, wherein Z is CR^c .
36. The compound of claim 34 or 35, wherein Y is CR^c .
37. The compound of any one of claims 34-36, wherein R^c is selected from the group consisting of halogen, -OH, $-NR^jR^k$, alkoxy, and alkyl.
38. The compound of any one of claims 34-36, wherein R^c is halogen, e.g., fluoride.
39. The compound of any one of claims 1-32 and 34, wherein at least one of W, X, Y, and Z is N.
40. The compound of claim 39, wherein Z is N.
41. The compound of claim 39, wherein Y is N.
42. The compound of any one of claims 1-41, wherein L is $-CH_2-$.

43. The compound of claim 1, wherein:

ring $\textcircled{\text{A}}$ is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

ring $\textcircled{\text{B}}$ is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

ring $\textcircled{\text{C}}$ is aryl or heteroaryl;

R^a , independently for each occurrence, is selected from the group consisting of halogen, cyano, hydroxy, $-\text{NH}_2$, $-\text{NH}(\text{Ac})$, $-\text{NH}(\text{alkyl})$, $-\text{N}(\text{alkyl})_2$, $-\text{NHC}(\text{O})(\text{alkyl})$, $-\text{CH}_2\text{NHC}(\text{O})(\text{alkyl})$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})(\text{alkyl})$, optionally substituted aryl, optionally substituted heteroaryl, cycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl;

R^b , independently for each occurrence, is selected from the group consisting of halogen, cyano, $-\text{NR}^j\text{R}^k$, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, (hydroxy)haloalkyl, hydroxy(cycloalkyl)alkyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-\text{alkylene}-\text{NR}^j\text{R}^k$, tosyl, $-\text{SO}_2(\text{alkyl})$, $-\text{SO}_2(\text{cycloalkyl})$, $-\text{CO}(\text{alkyl})$, $-\text{CO}(\text{cycloalkyl})$, $-\text{CONH}(\text{alkyl})$, $-\text{CON}(\text{alkyl})_2$, and $-\text{CONH}(\text{cycloalkyl})$;

R^c , independently for each occurrence, is selected from the group consisting of halogen, $-\text{OH}$, $-\text{NR}^j\text{R}^k$, alkoxy, and alkyl;

R^1 is selected from the group consisting of $-\text{NH}_2$, $-\text{CH}_2\text{COOH}$, $-\text{CH}(\text{NH}(\text{CO})(\text{alkyl}))\text{COOH}$, $-\text{CH}(\text{NH}(\text{CO})(\text{arylalkyl}))\text{COOH}$, $-\text{CH}(\text{NH}(\text{CO})(\text{cycloalkyl}))\text{COOH}$, $-\text{CH}(\text{NH}(\text{CO})(\text{aryl substituted cycloalkyl}))\text{COOH}$, $-\text{CO}(\text{NH})\text{CH}_2\text{aryl}$, $-\text{CO}(\text{NH})\text{CH}_2\text{heteroaryl}$, $-\text{CO}(\text{NH})\text{aryl}$, and $-\text{CO}(\text{NH})\text{heteroaryl}$;

n is 0, 1, or 2;

m is 0, 1, or 2;

p is 0, 1, or 2;

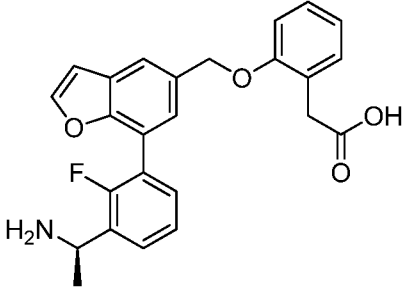
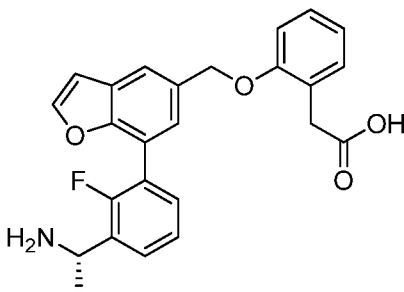
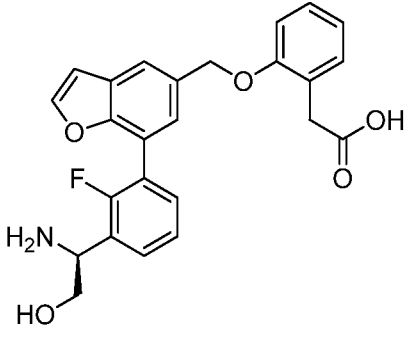
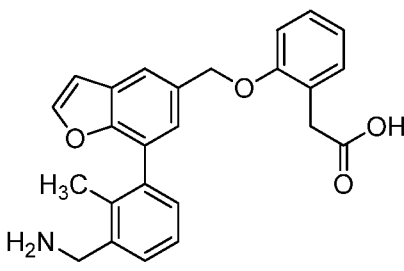
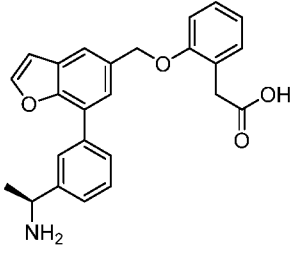
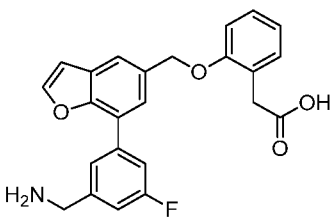
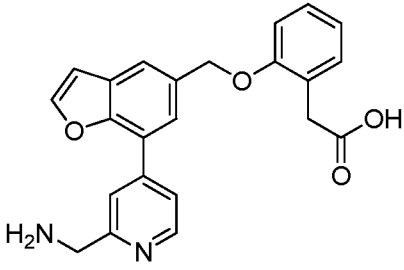
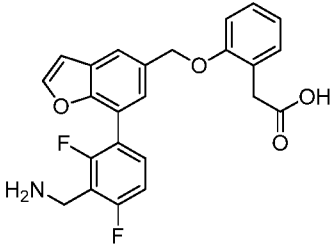
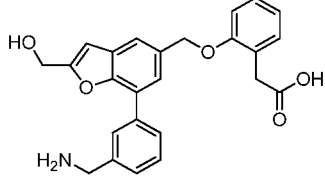
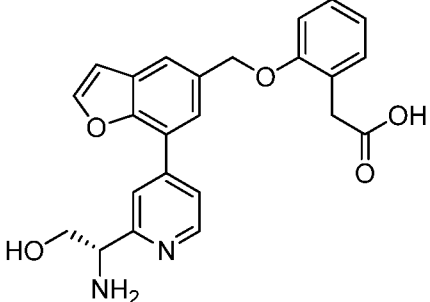
J is $-\text{C}(\text{O})-$, $-\text{NH}-$, $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{N}(\text{alkyl})-$, or $-\text{CH}(\text{alkyl})-$;

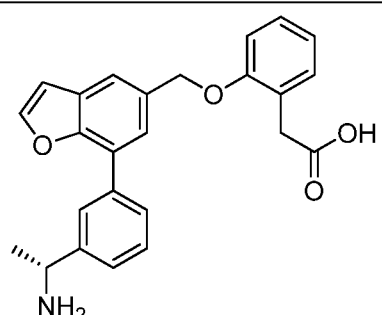
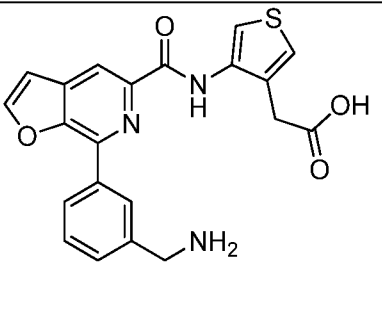
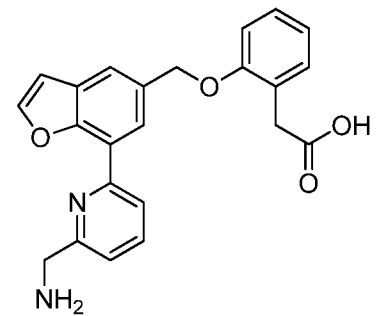
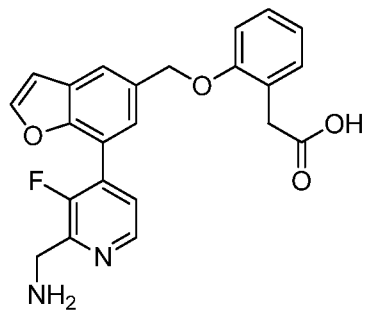
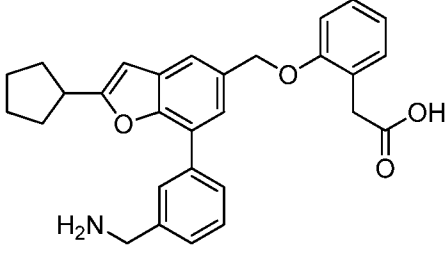
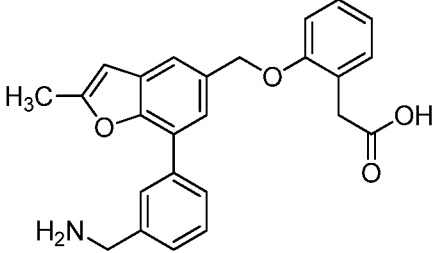
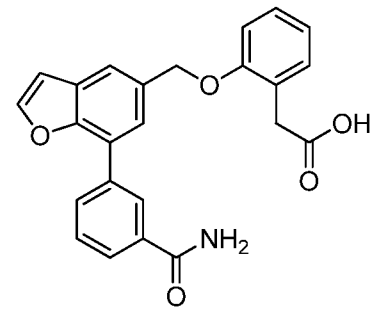
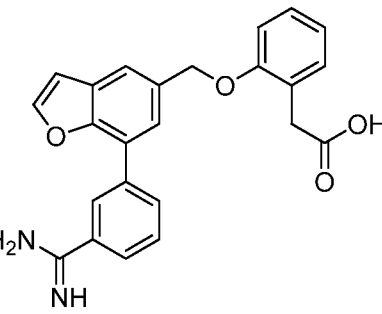
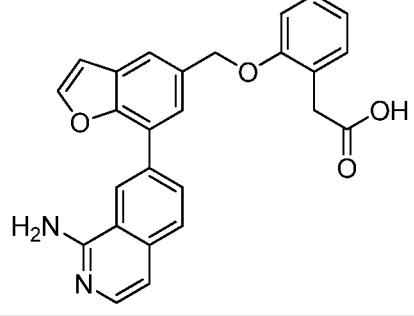
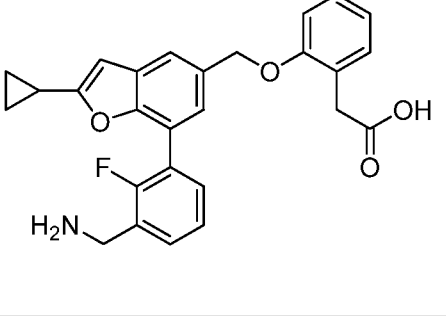
K is $-\text{C}(\text{O})-$, $-\text{NH}-$, $-\text{O}-$, $-\text{CH}_2-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{N}(\text{alkyl})-$, or $-\text{CH}(\text{alkyl})-$;

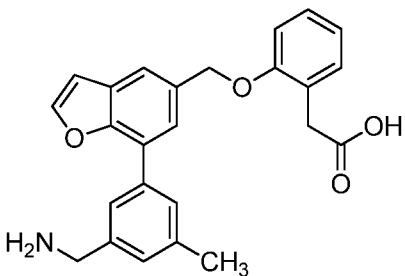
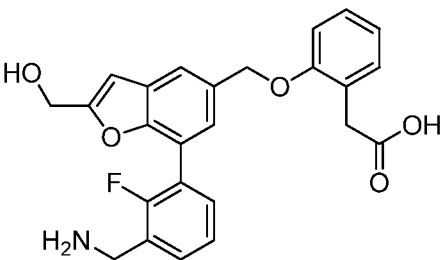
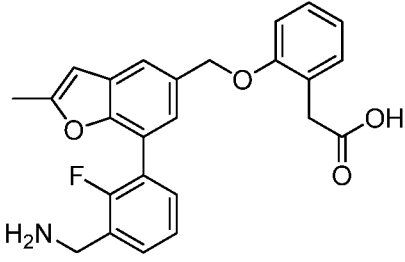
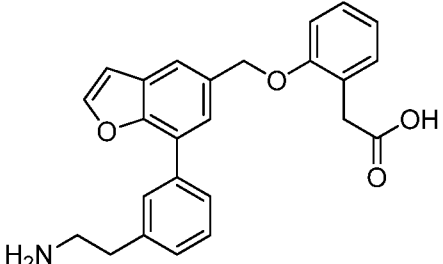
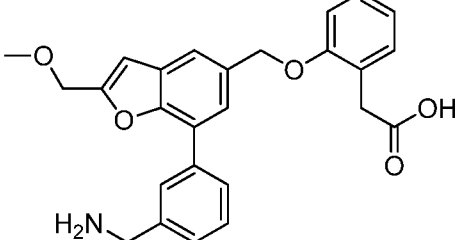
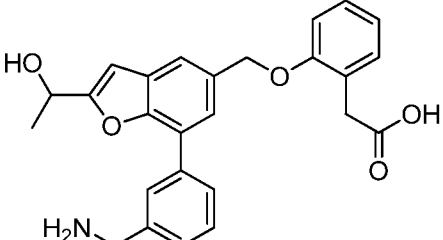
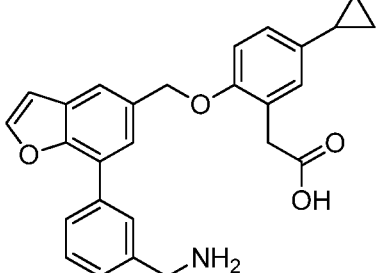
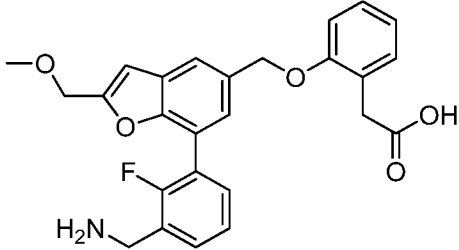
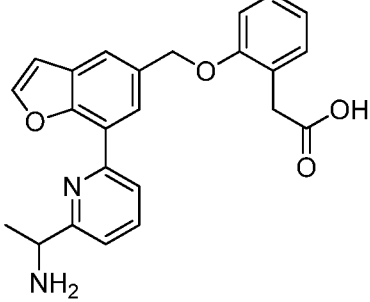
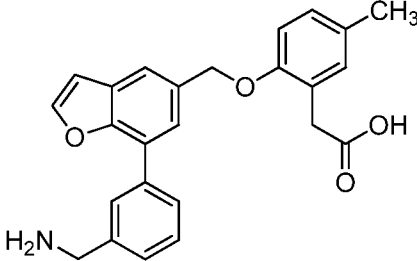
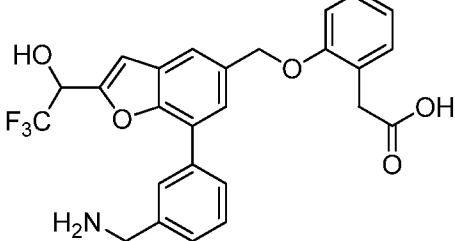
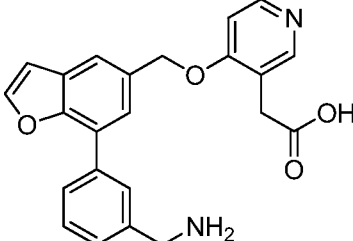
wherein at least one of J and K is $-\text{C}(\text{O})-$, $-\text{CH}_2-$, or $-\text{CH}(\text{alkyl})-$;

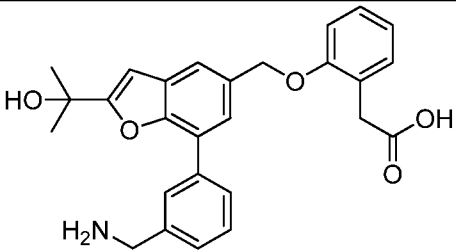
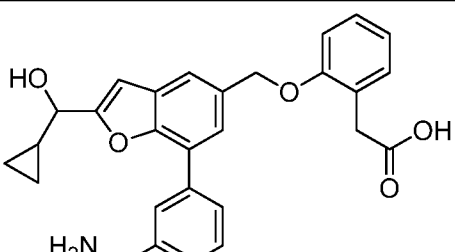
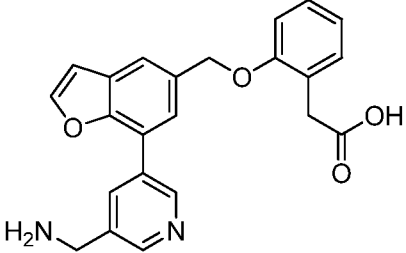
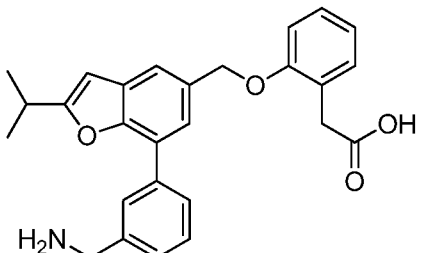
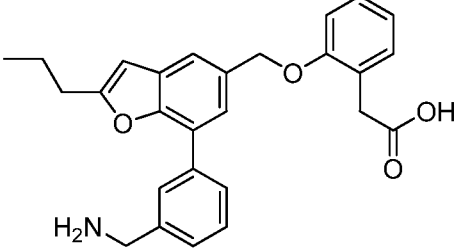
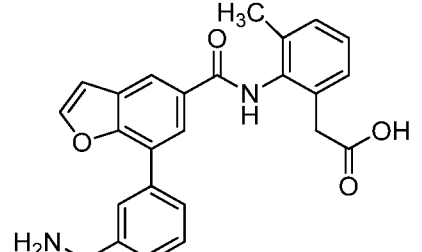
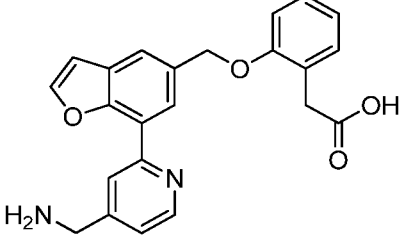
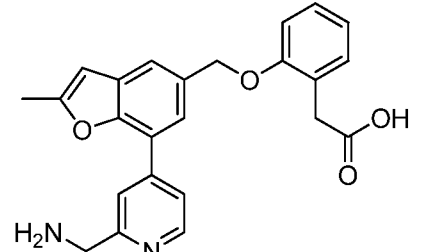
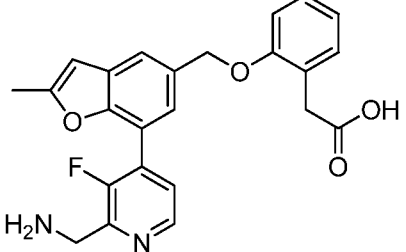
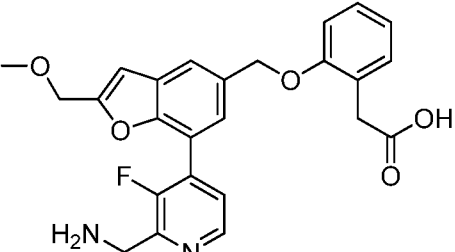
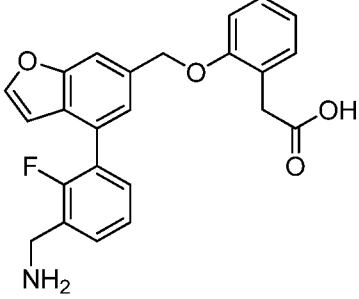
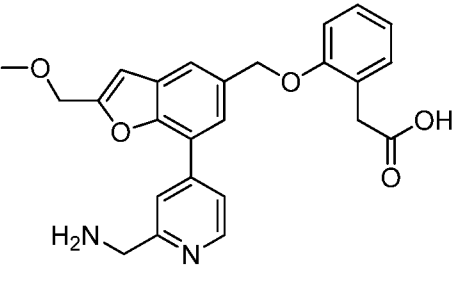
L is selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CHR}^2-$, $-\text{CF}_2-$, $-\text{CFR}^2-$, $-\text{C}(\text{O})-$, $-\text{C}(=\text{NR}^L)-$, and $-\text{C}(=\text{CHR}^L)-$; wherein R^L is H or alkyl;
 or wherein R^L and an occurrence of R^c taken together with the intervening atoms form a substituted or unsubstituted heteroaryl ring;
 R^2 is alkyl, hydroxyalkyl, or haloalkyl;
 R^j and R^k are each independently selected from the group consisting of H, alkyl, aminoalkyl, (heterocycloalkyl)alkyl, and heterocycloalkyl;
 U is N or CR^3 ;
 R^3 is H, halogen, alkyl, alkoxy, or haloalkyl; and
 V is N or CH.

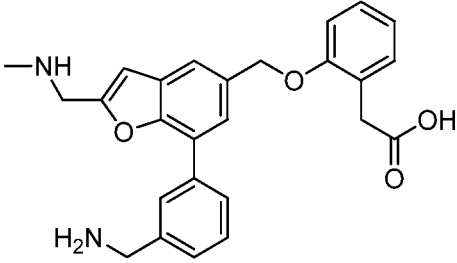
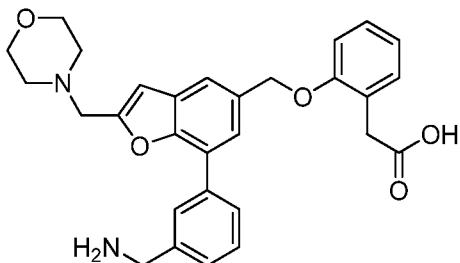
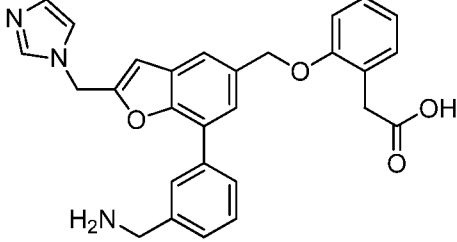
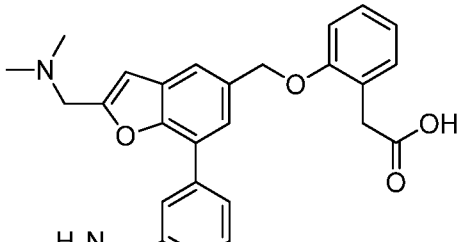
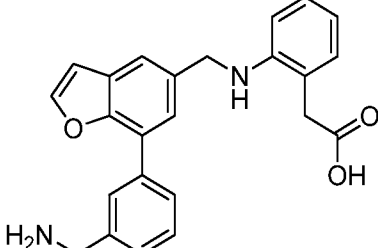
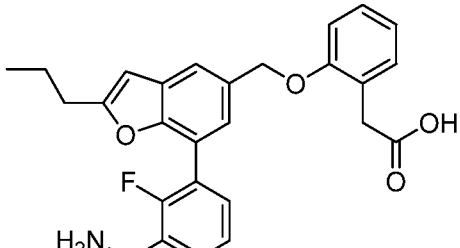
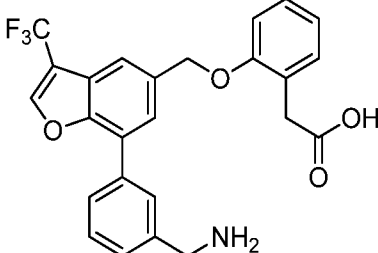
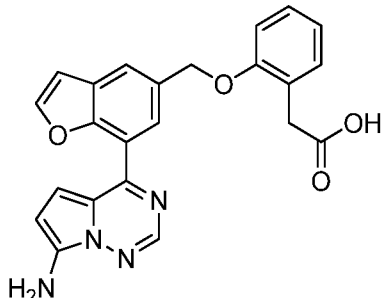
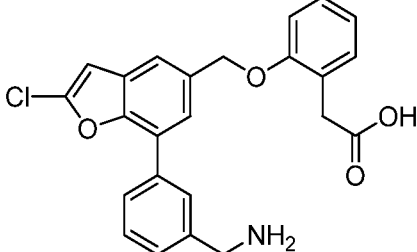
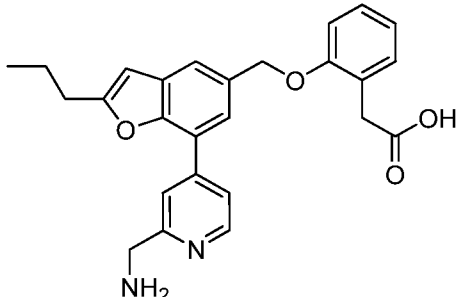
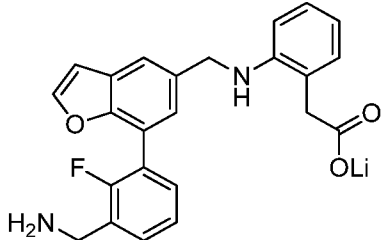
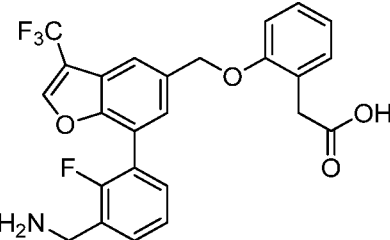
44. The compound of claim 1, selected from the following table:

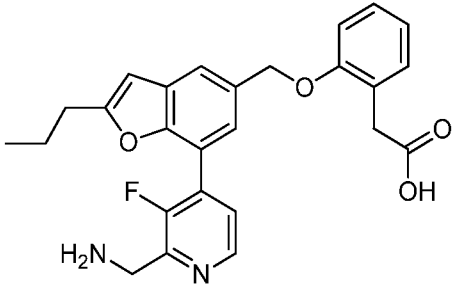
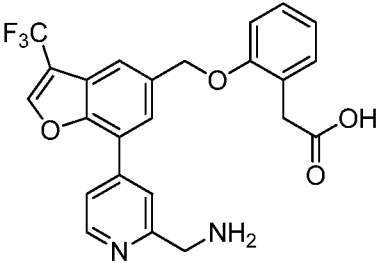
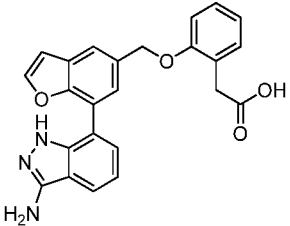
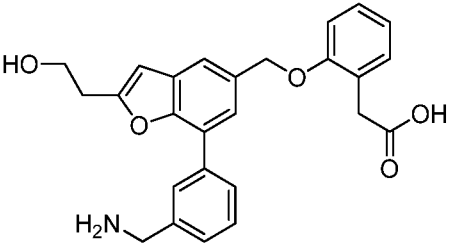
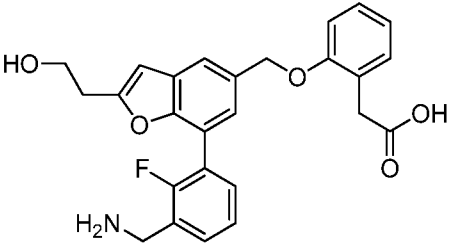
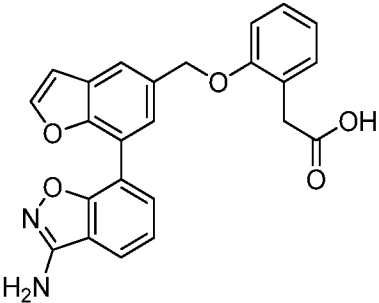
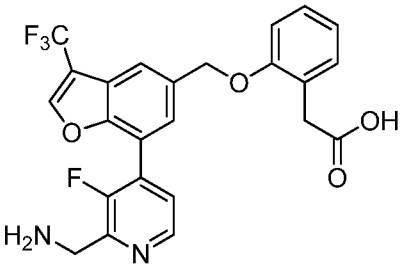
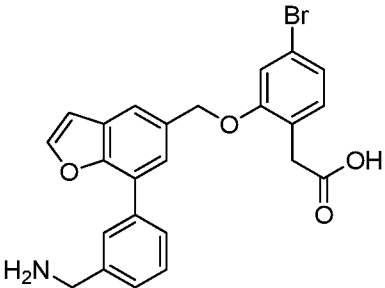
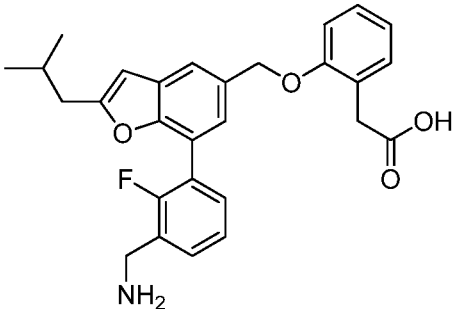
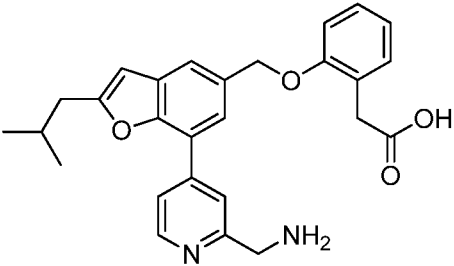
	
	
	
	
	

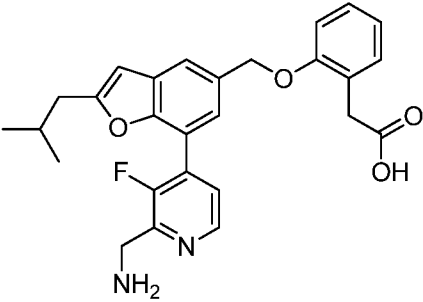
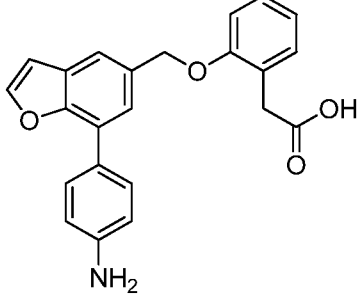
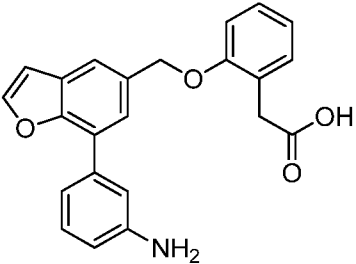
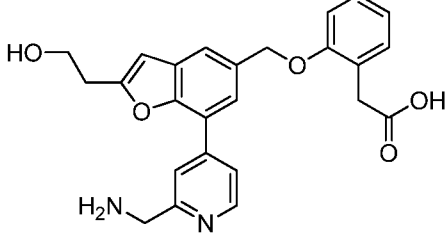
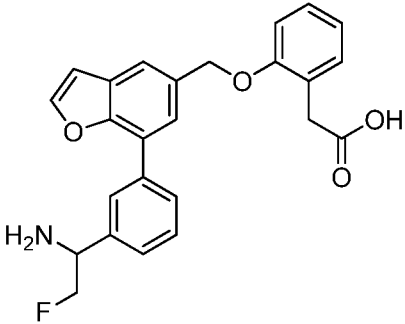
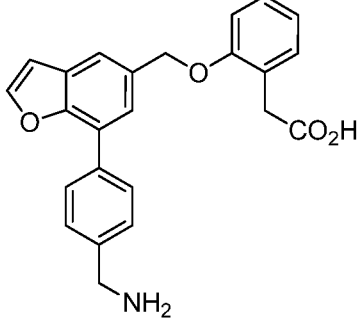
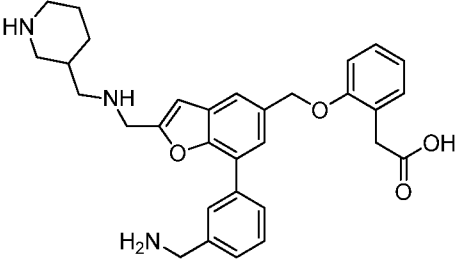
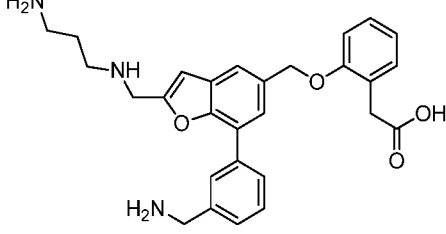
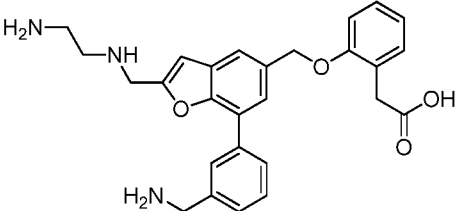
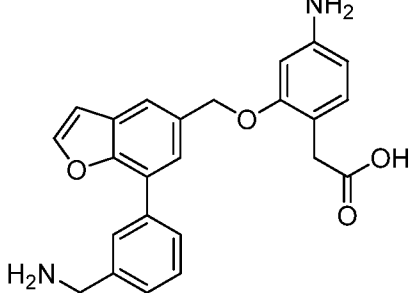
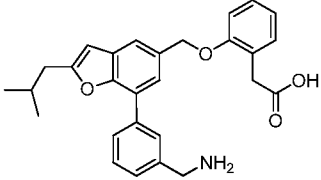
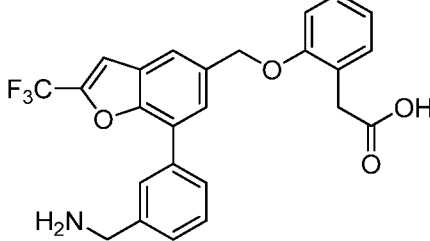
	
	
	
	
	

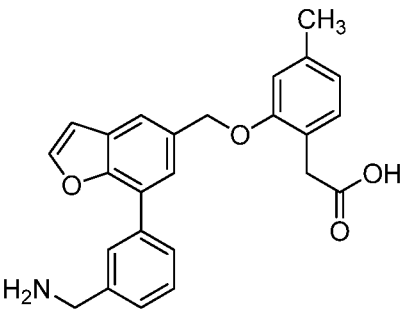
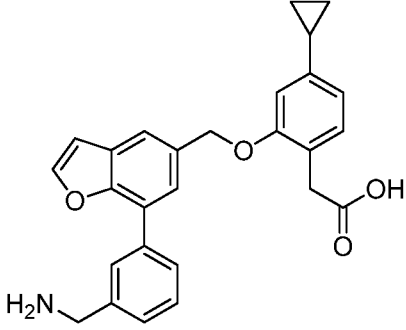
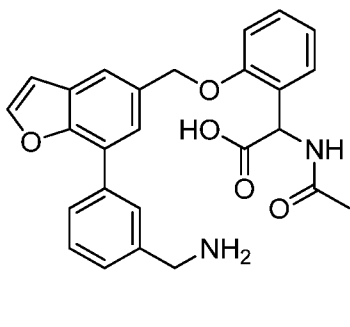
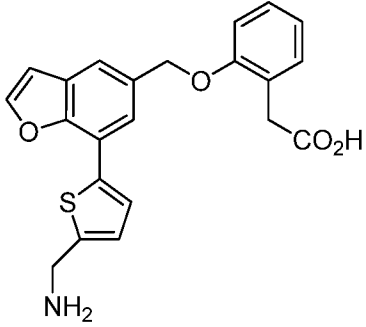
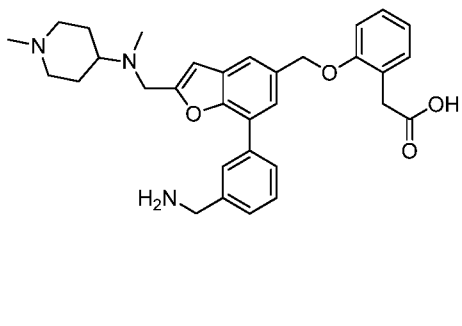
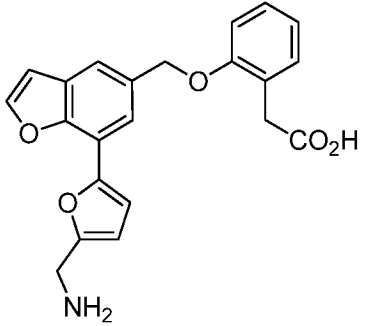
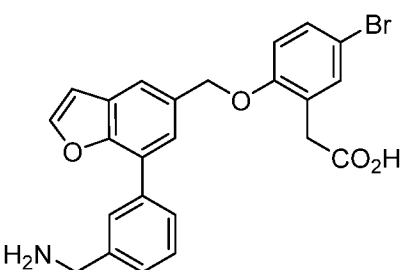
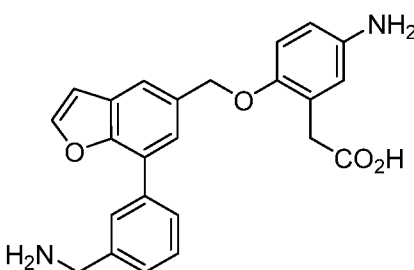
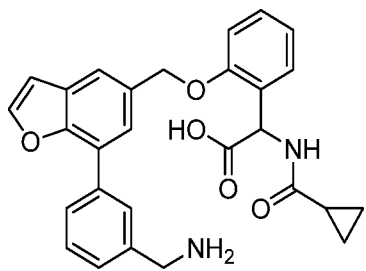
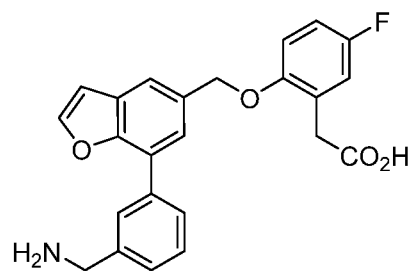
	
	
	
	
	
	

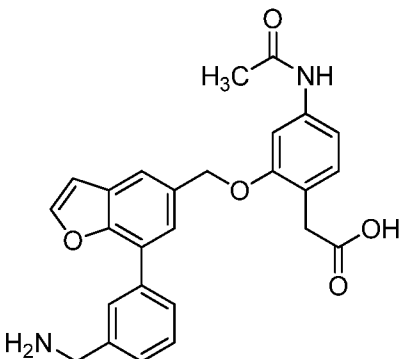
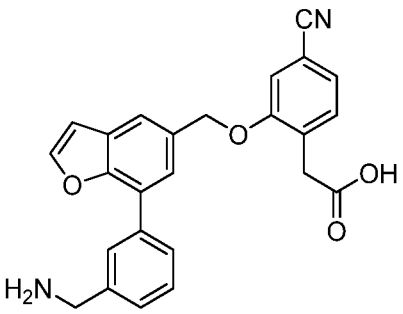
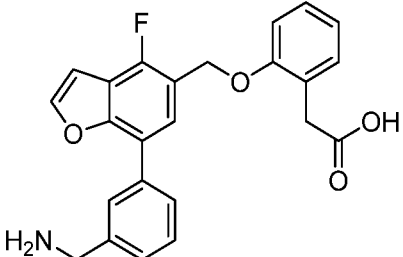
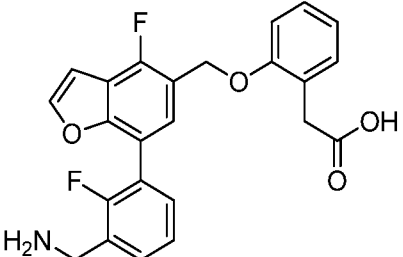
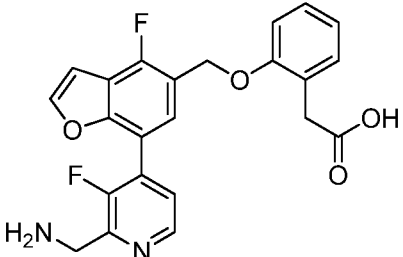
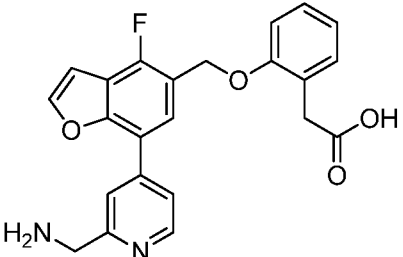
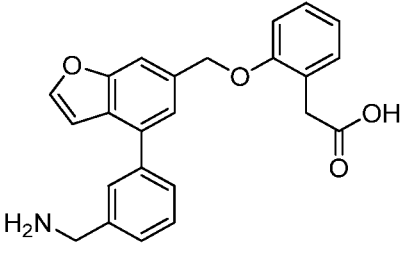
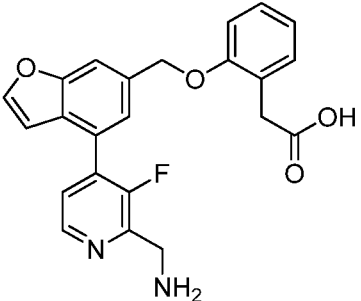
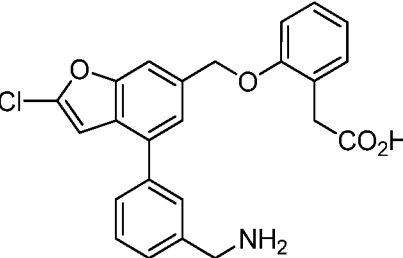
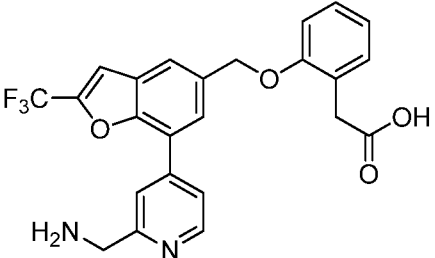
	
	
	
	
	
	

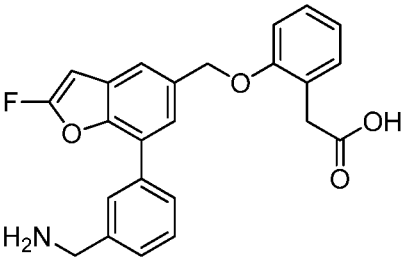
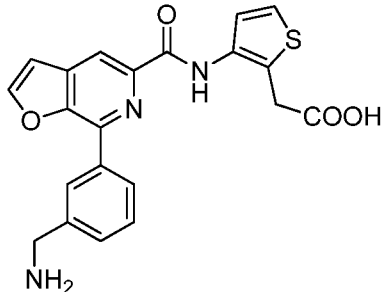
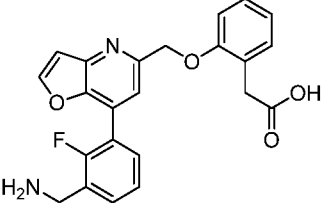
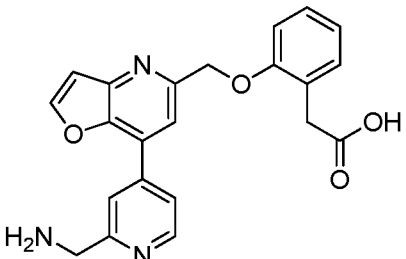
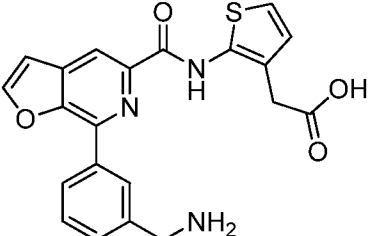
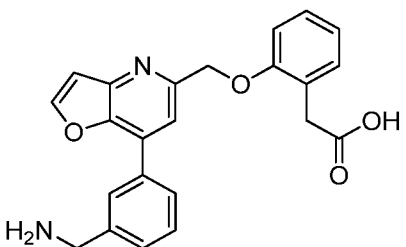
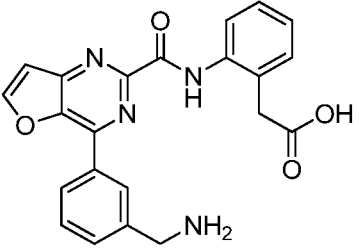
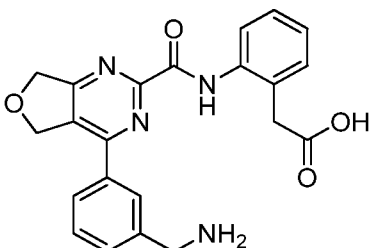
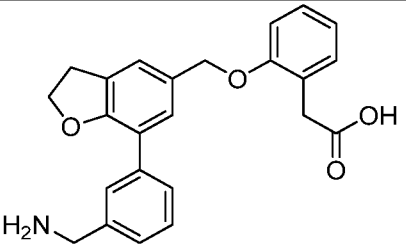
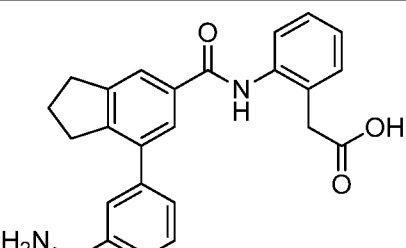
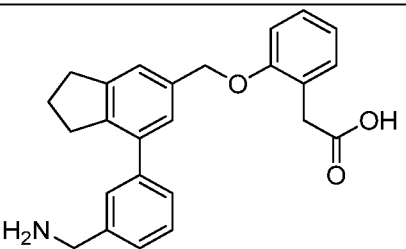
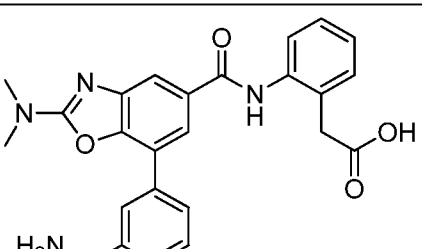
	
	
	
	
	
	

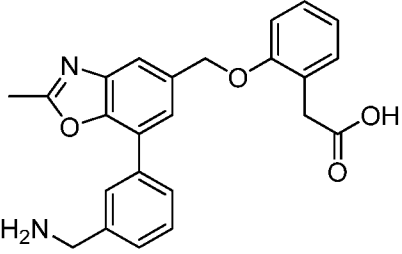
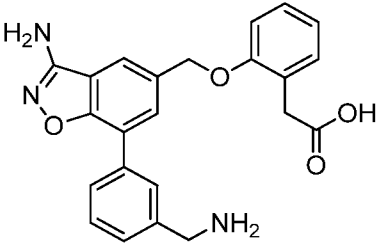
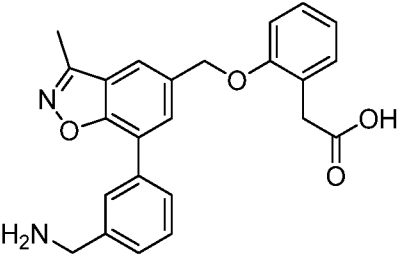
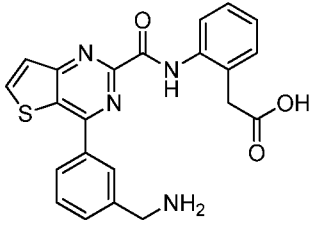
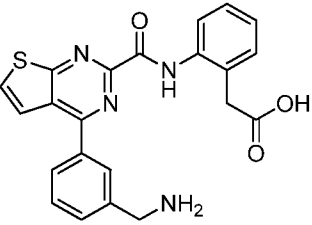
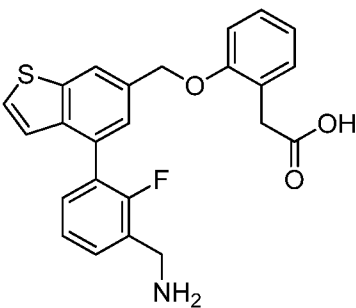
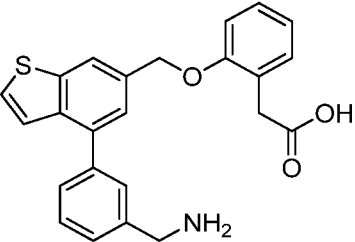
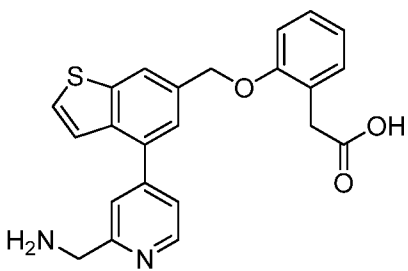
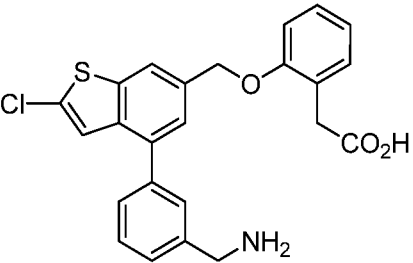
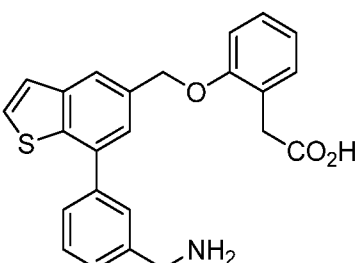
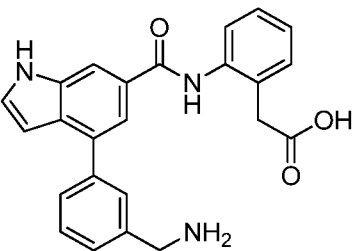
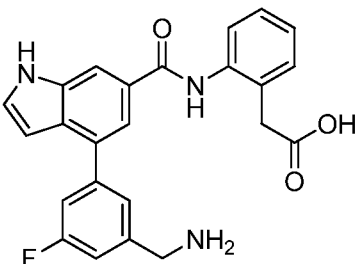
	
	
	
	
	

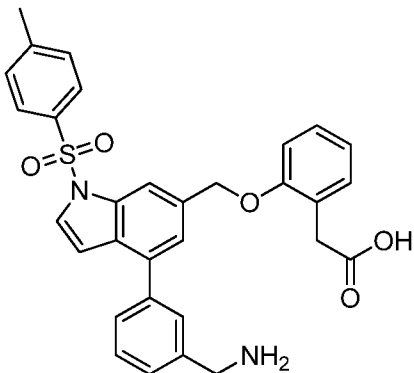
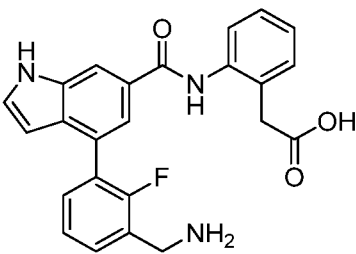
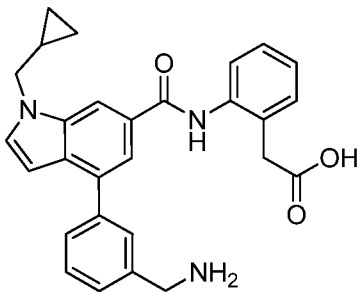
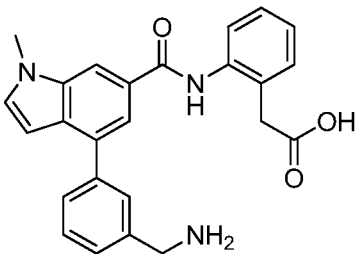
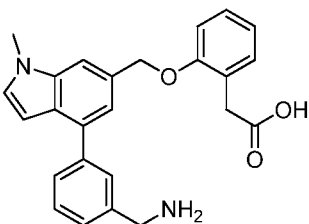
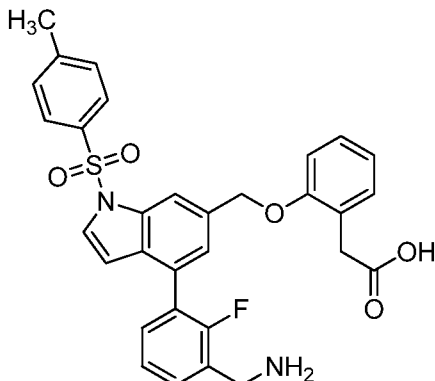
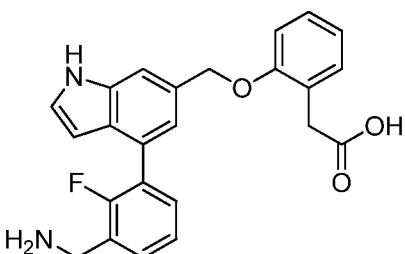
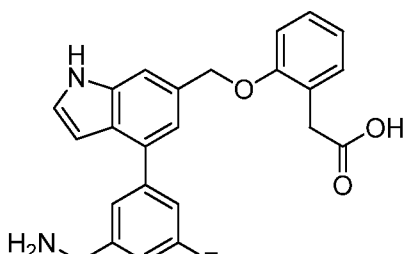
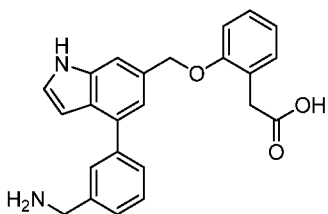
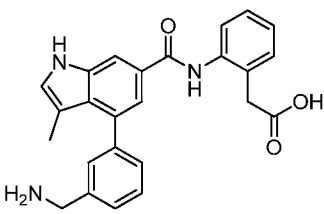
	
	
	
	
	
	

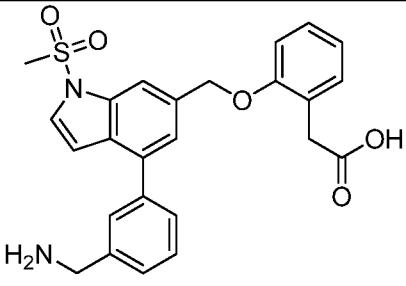
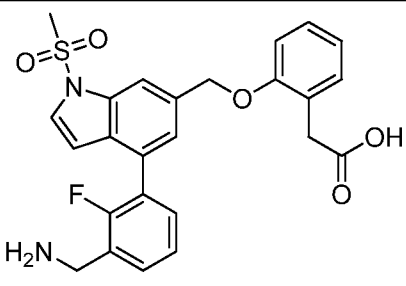
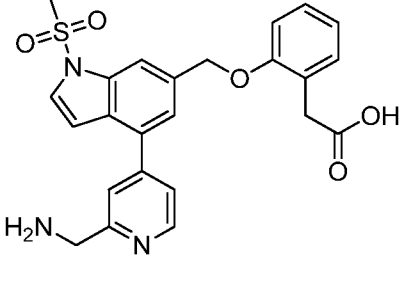
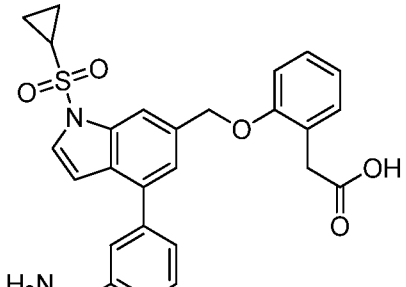
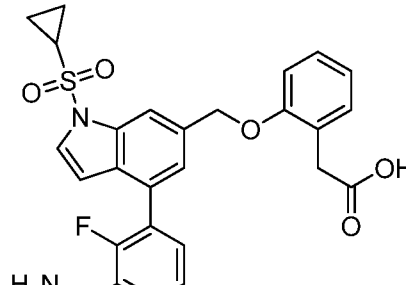
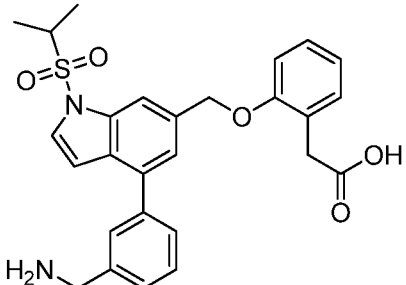
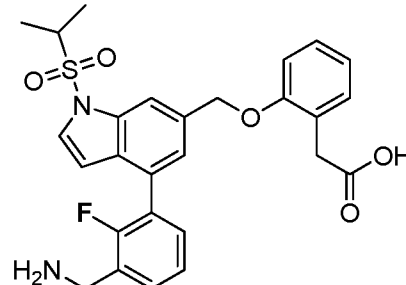
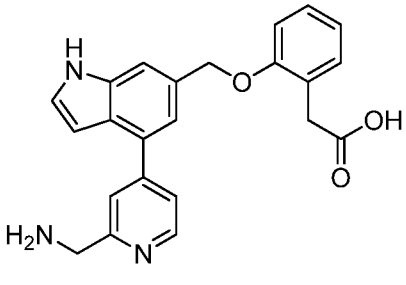
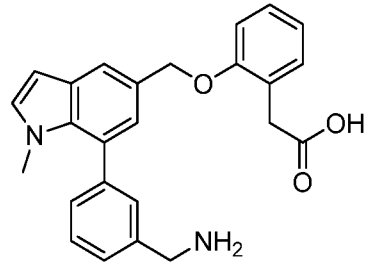
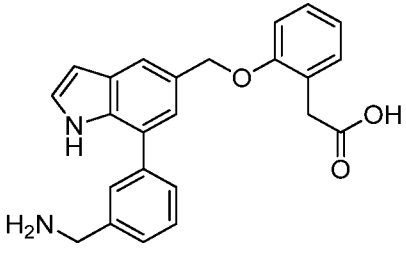
	
	
	
	
	

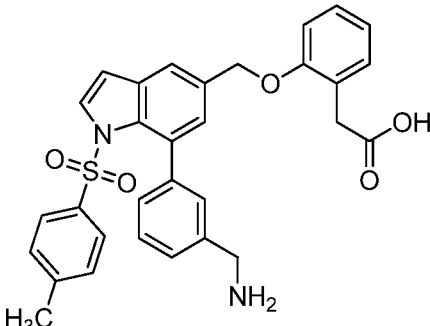
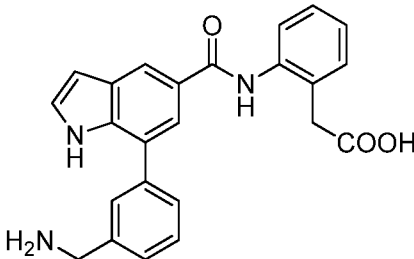
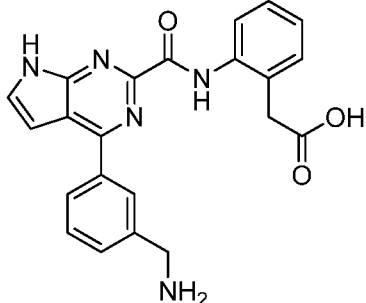
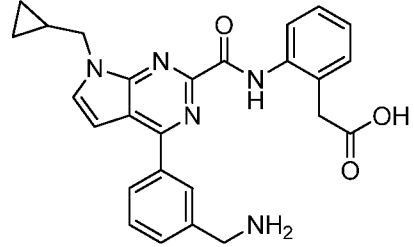
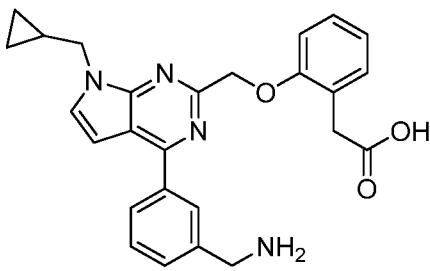
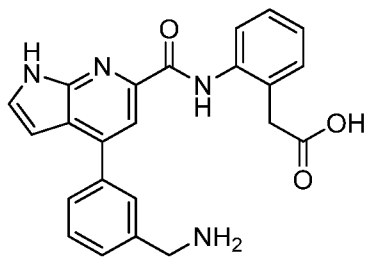
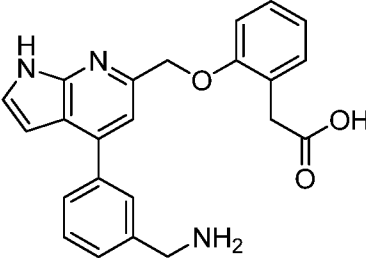
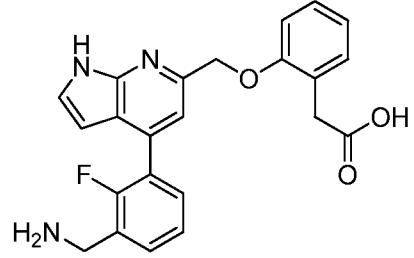
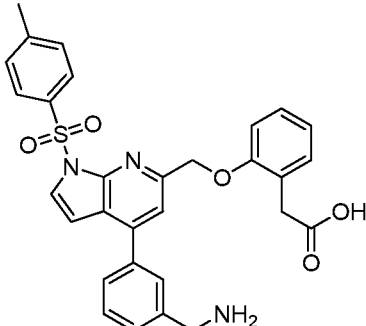
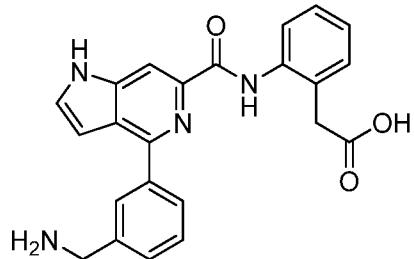
	
	
	
	
	

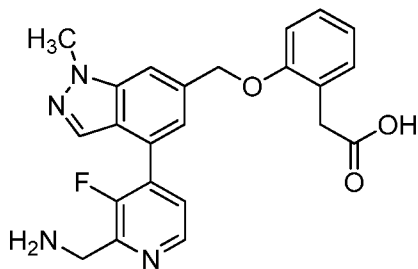
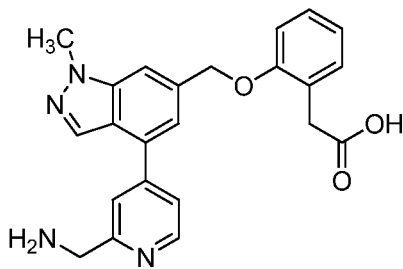
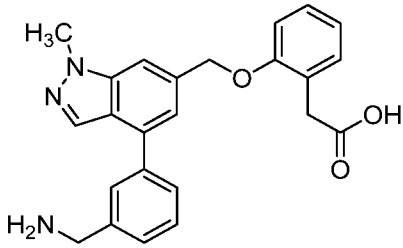
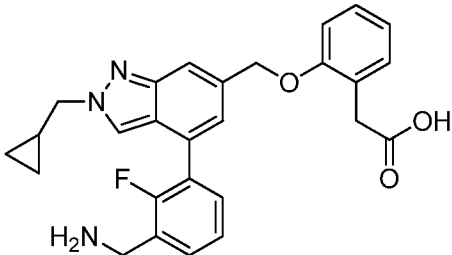
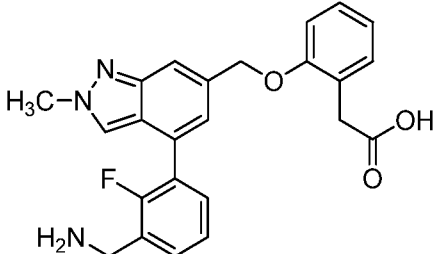
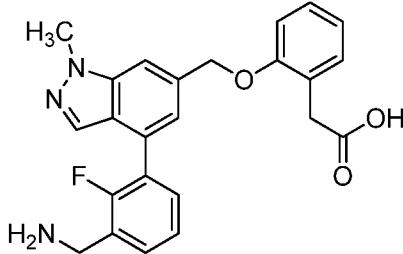
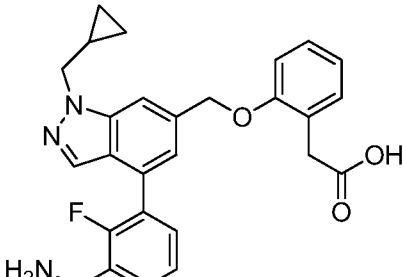
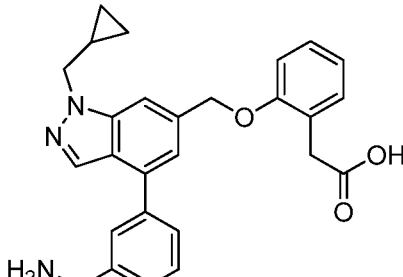
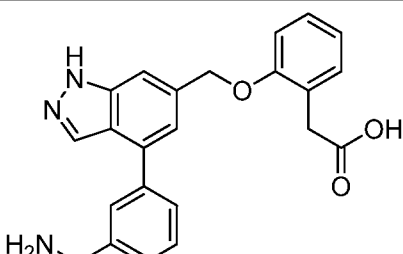
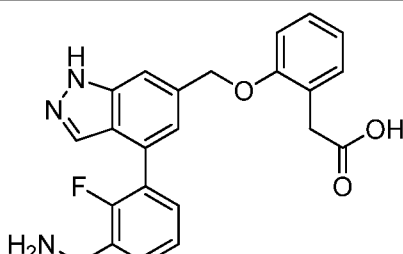
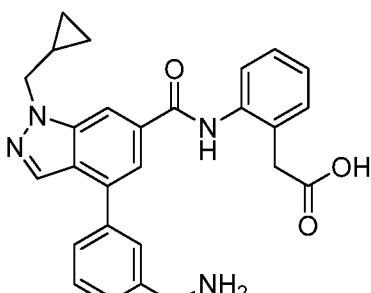
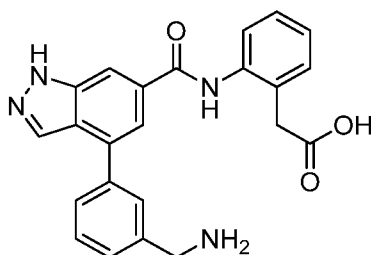
	
	
	
	
	
	

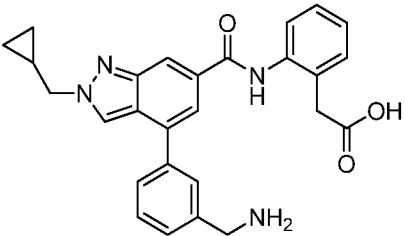
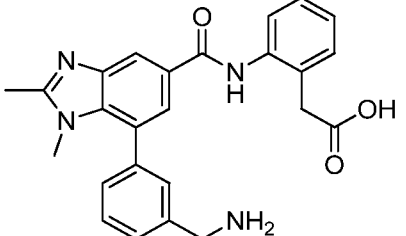
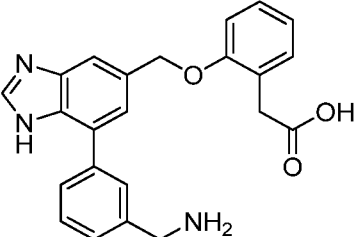
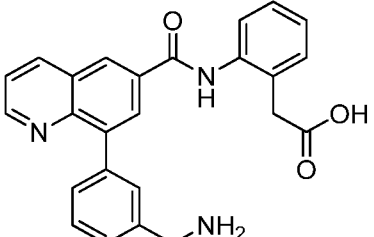
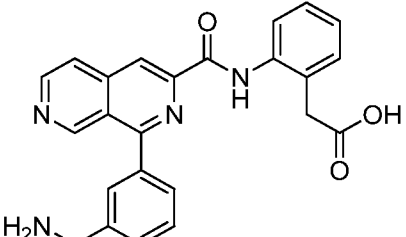
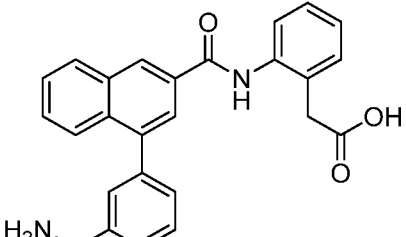
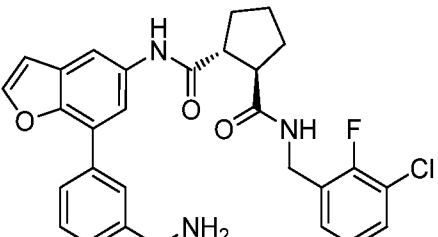
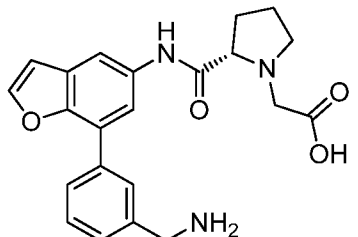
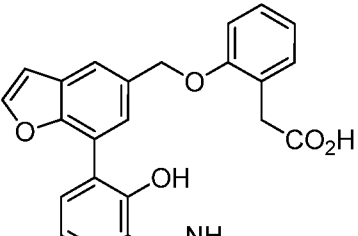
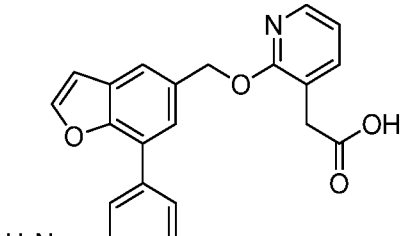
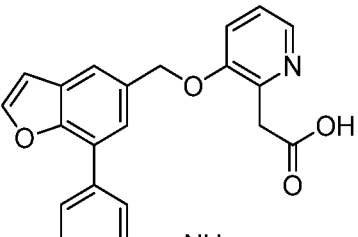
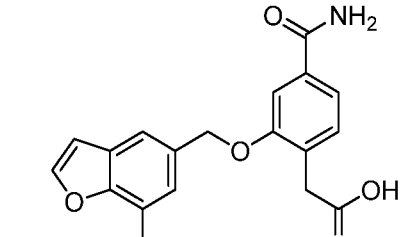
	
	
	
	
	
	

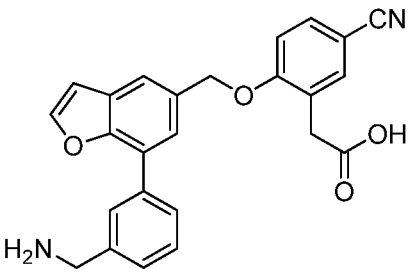
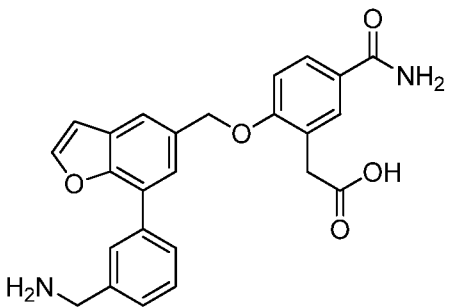
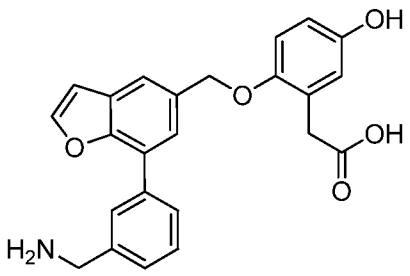
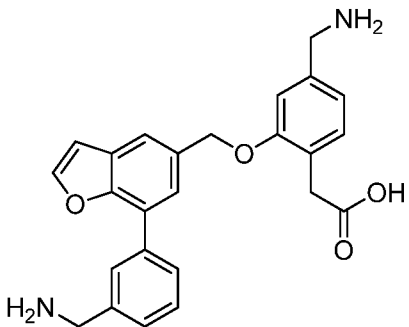
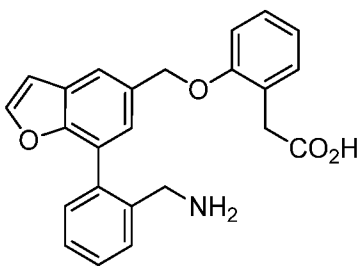
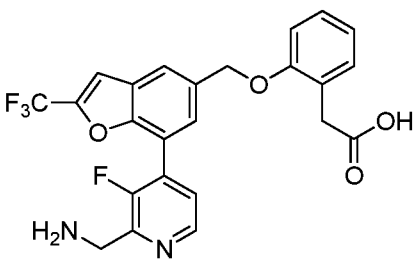
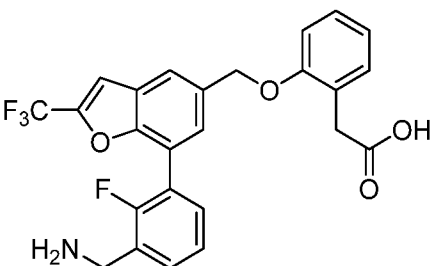
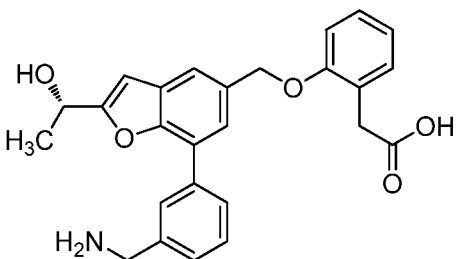
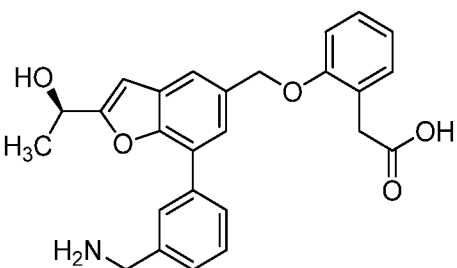
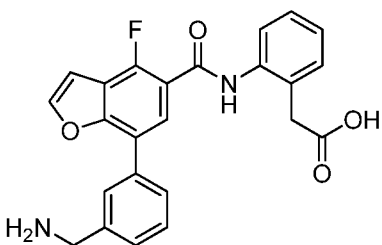
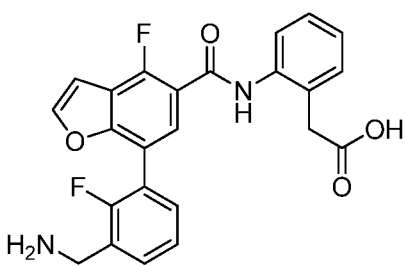
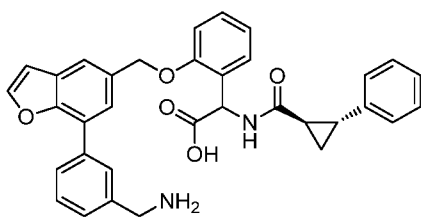
	
	
	
	
	

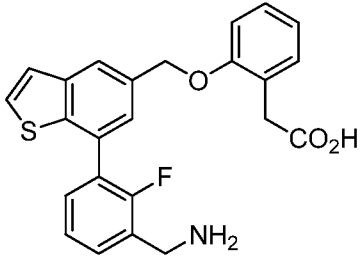
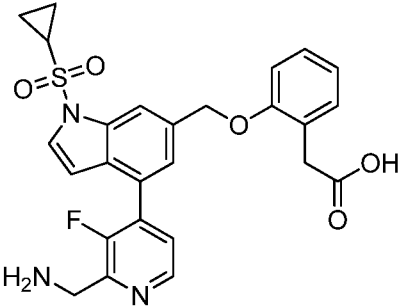
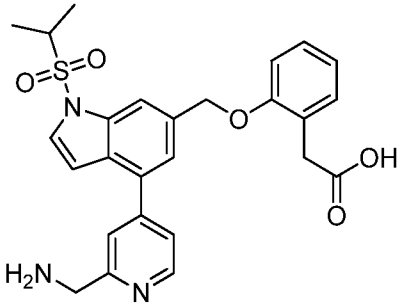
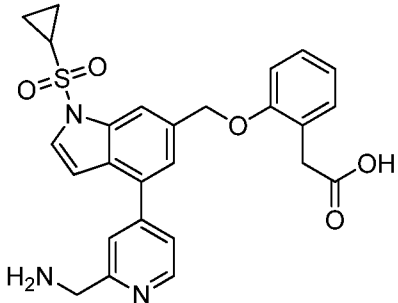
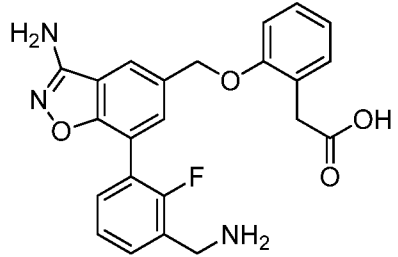
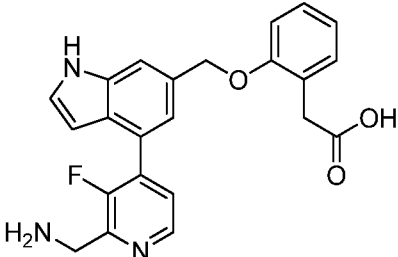
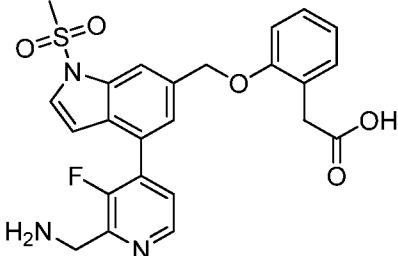
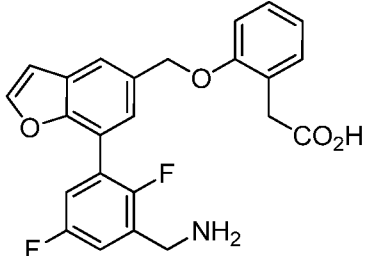
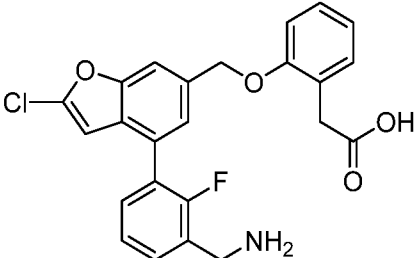
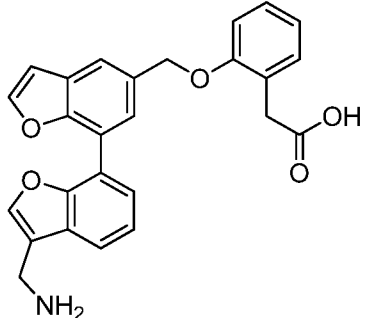
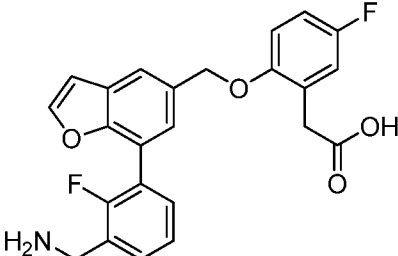
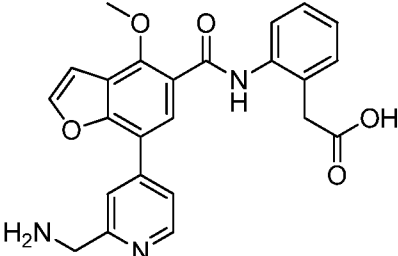
	
	
	
	
	

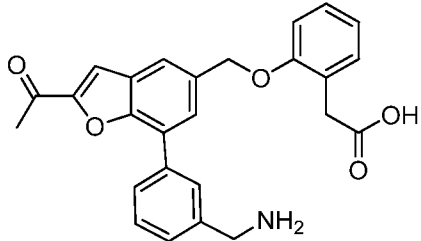
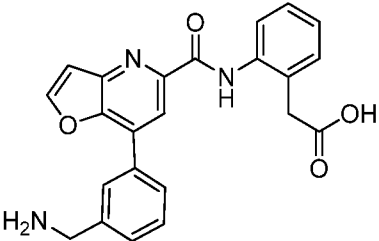
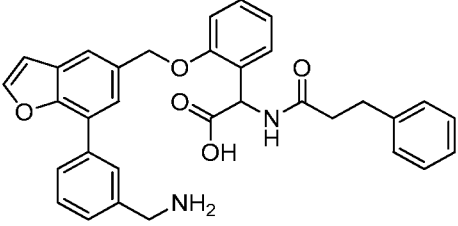
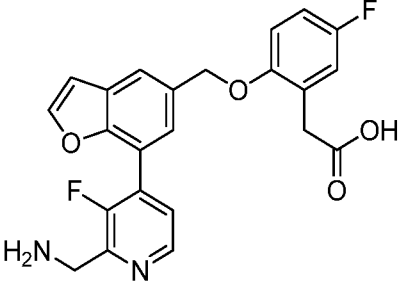
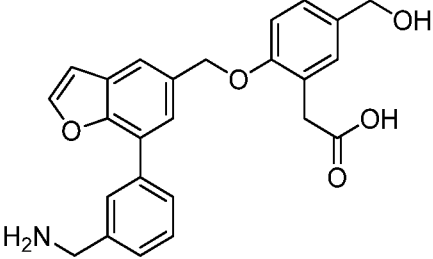
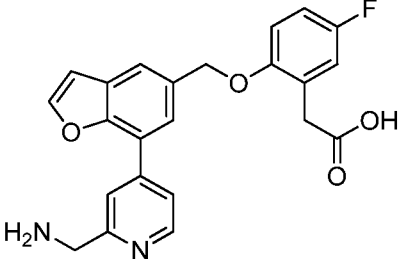
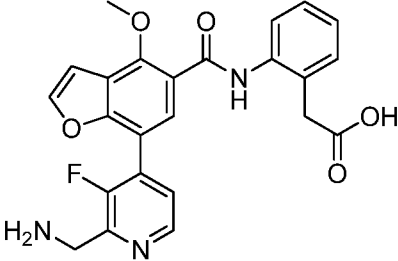
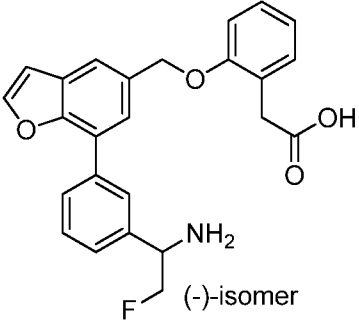
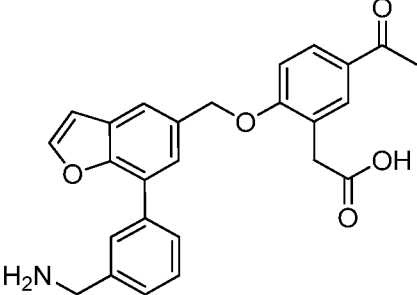
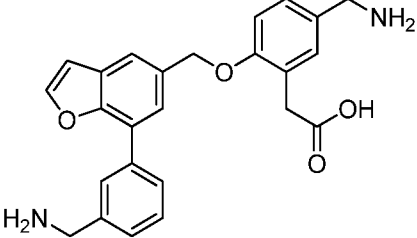
	
	
	
	
	

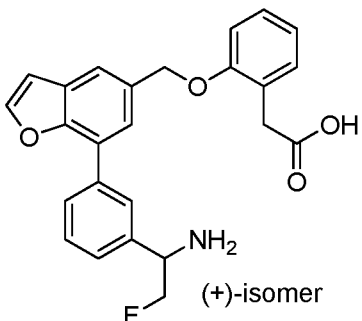
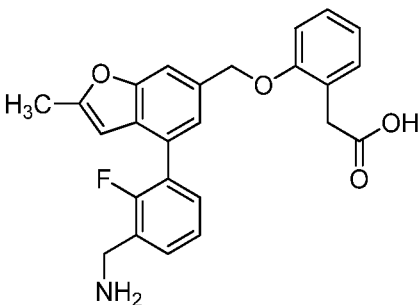
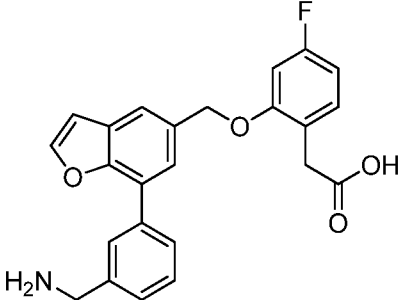
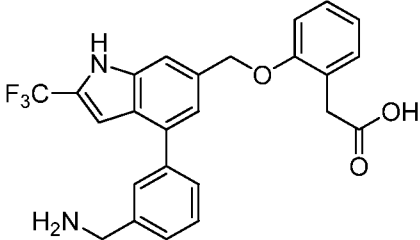
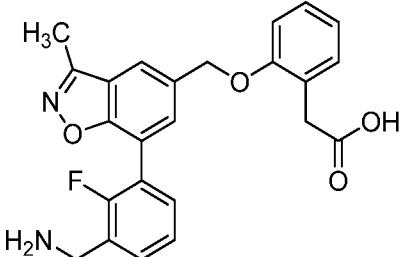
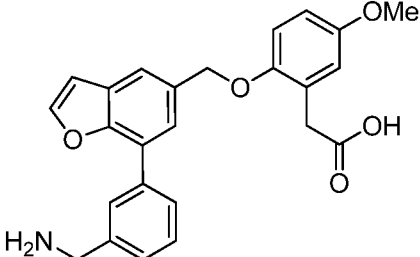
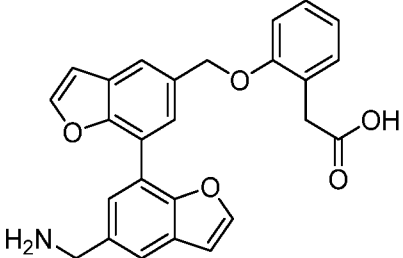
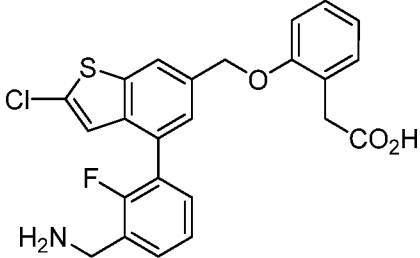
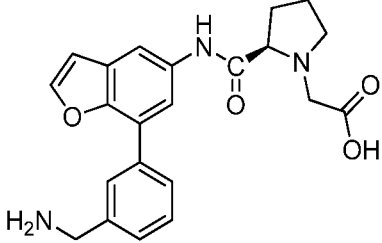
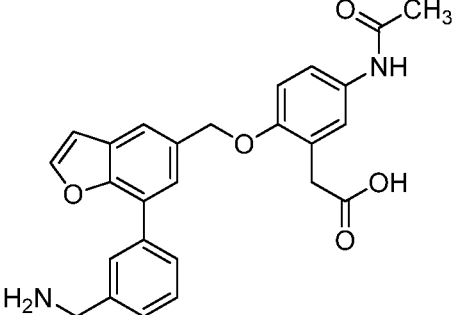
	
	
	
	
	
	

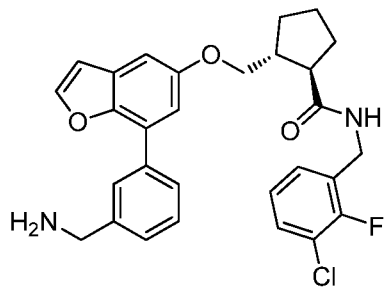
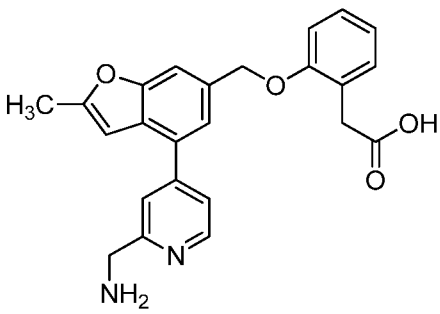
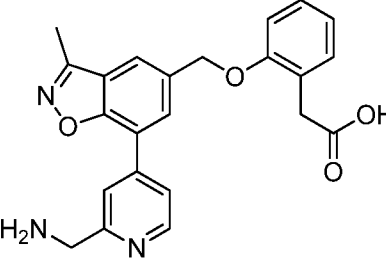
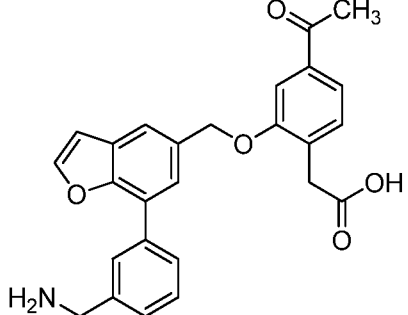
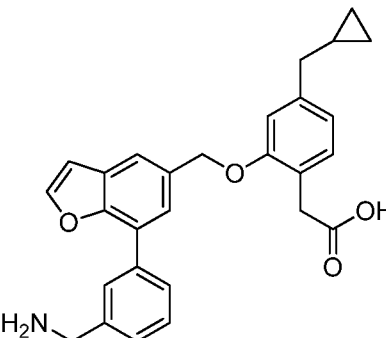
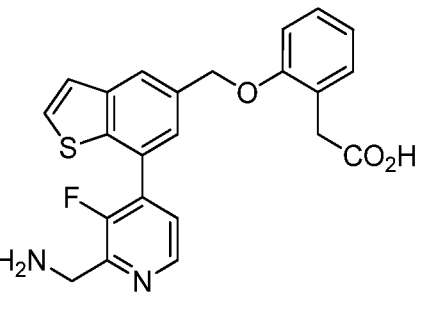
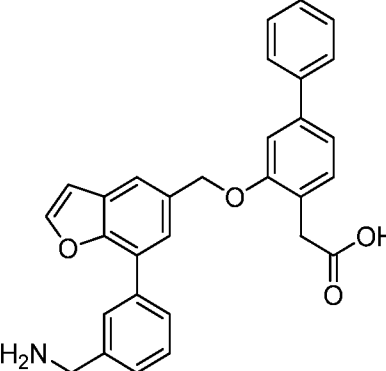
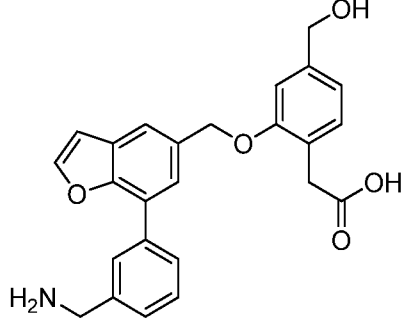
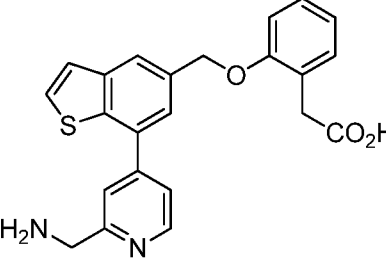
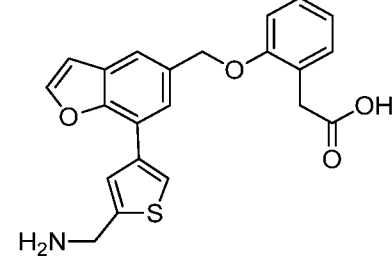
	
	
	
	
	
	

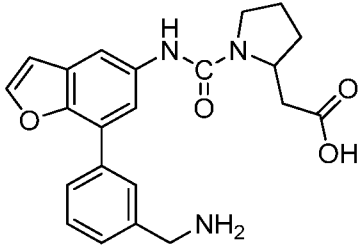
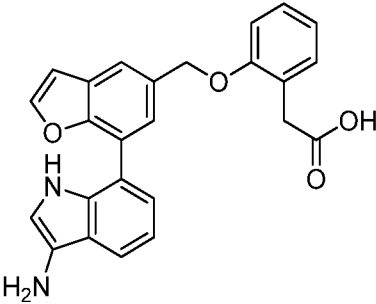
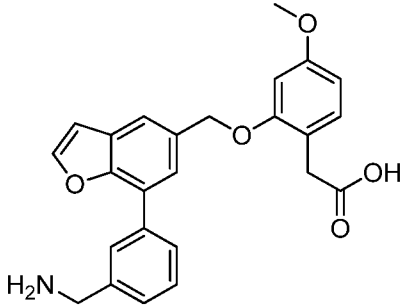
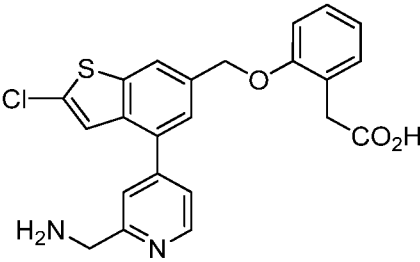
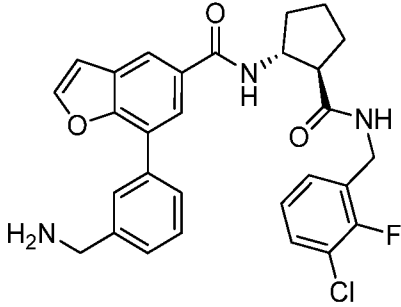
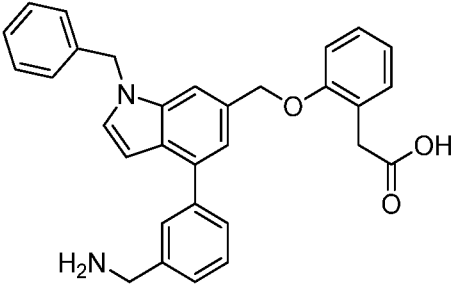
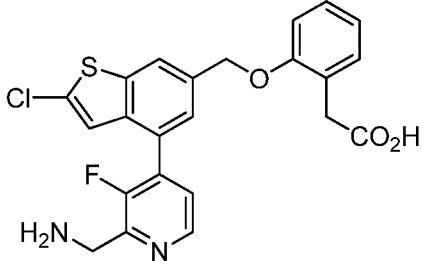
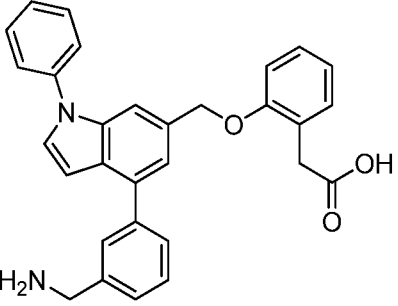
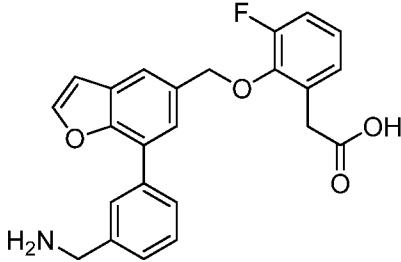
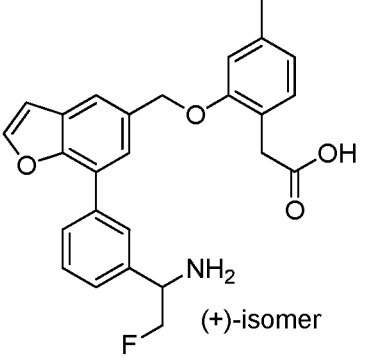
	
	
	
	
	
	

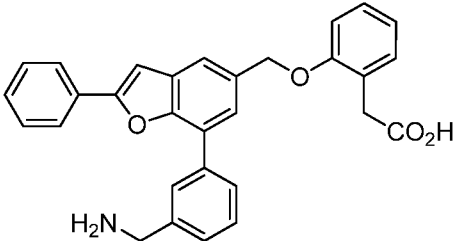
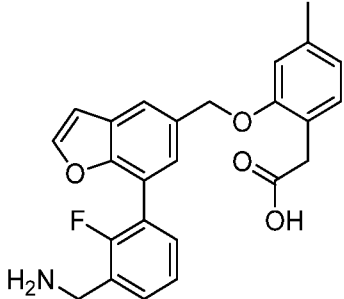
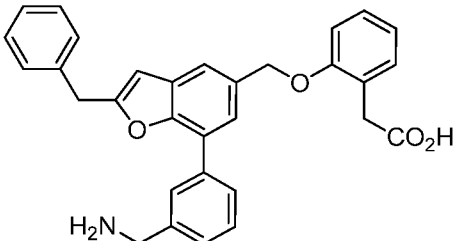
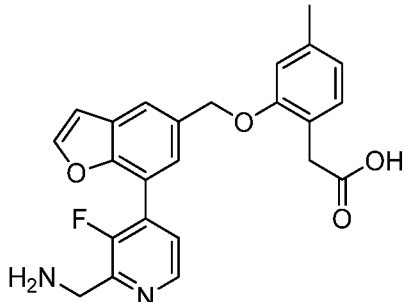
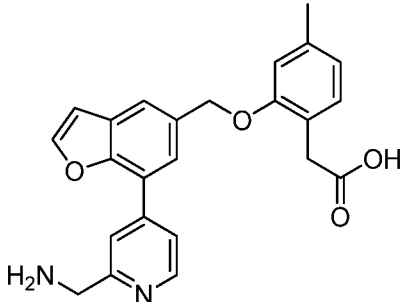
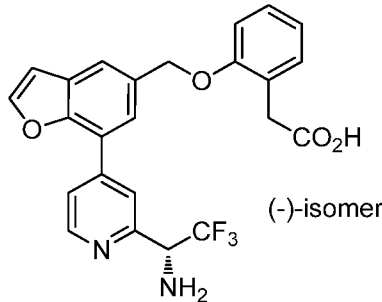
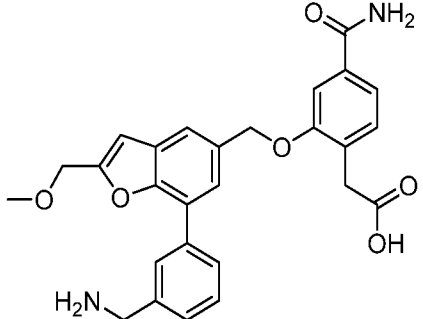
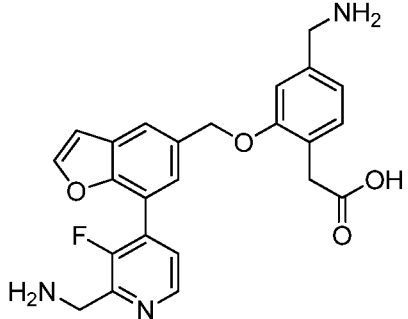
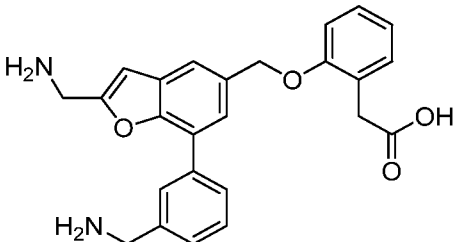
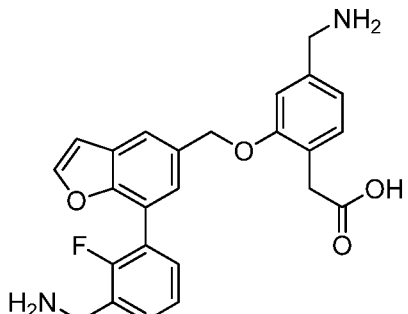
	
	
	
	
	
	

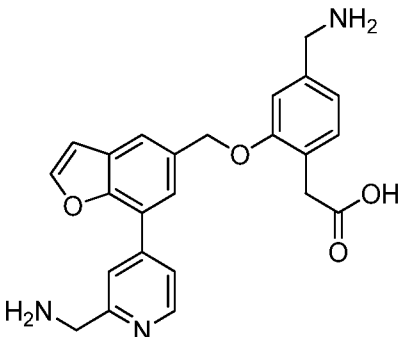
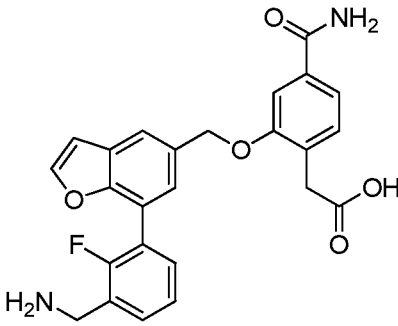
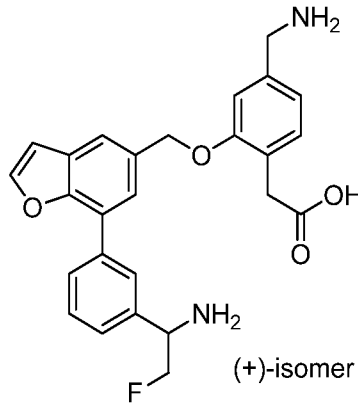
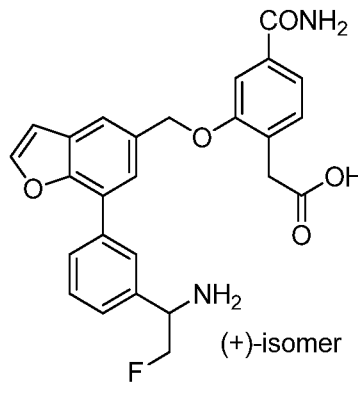
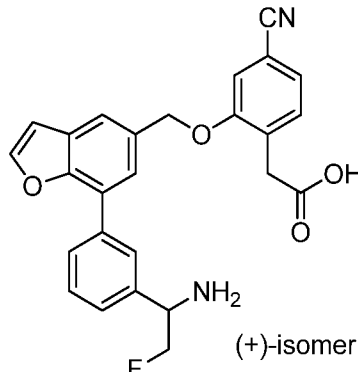
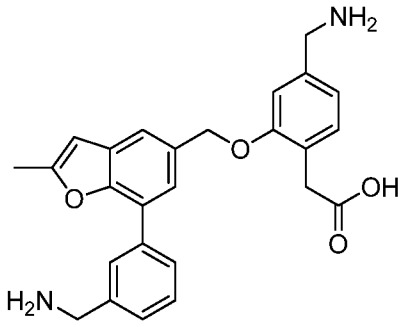
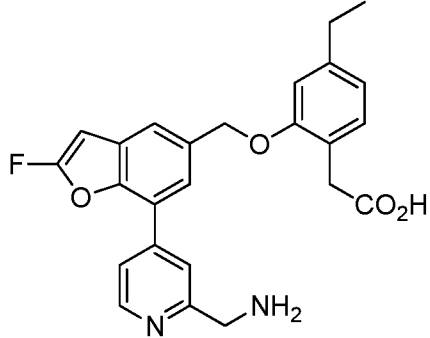
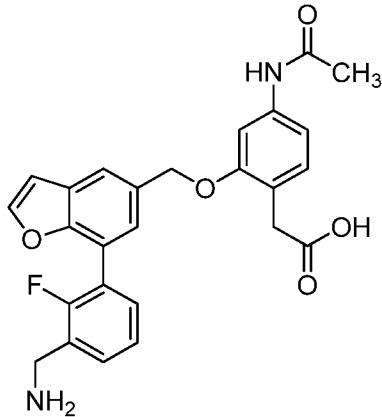
	
	
	
	
	

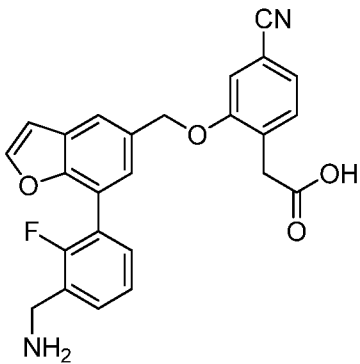
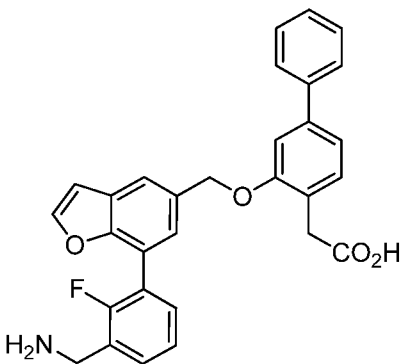
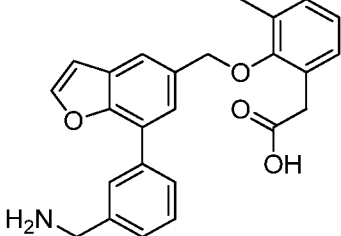
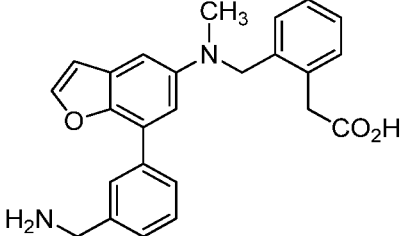
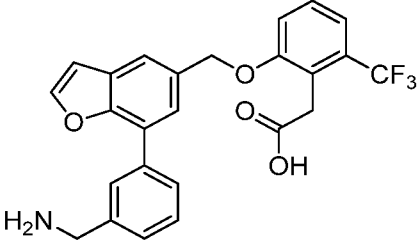
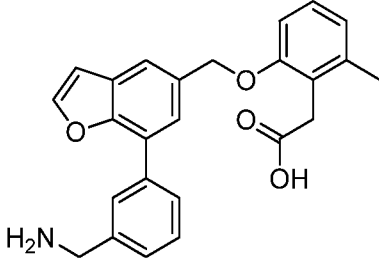
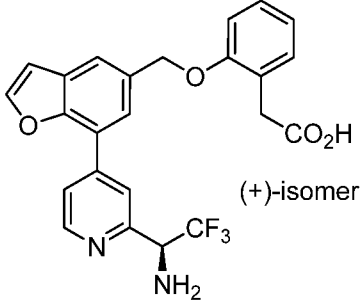
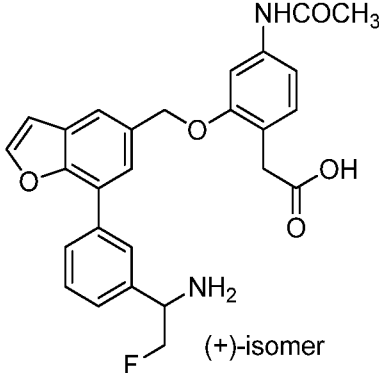
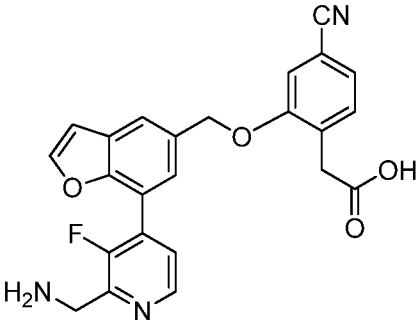
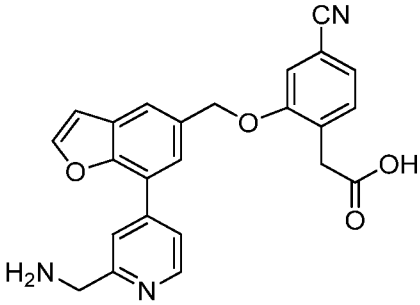
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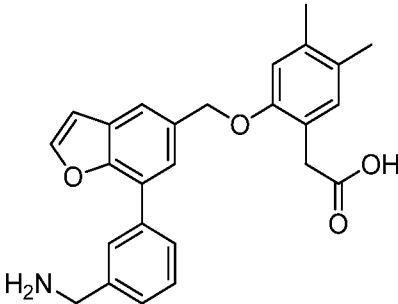
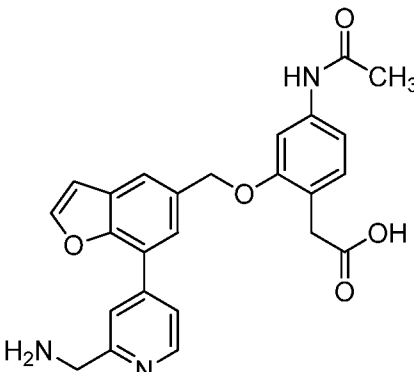
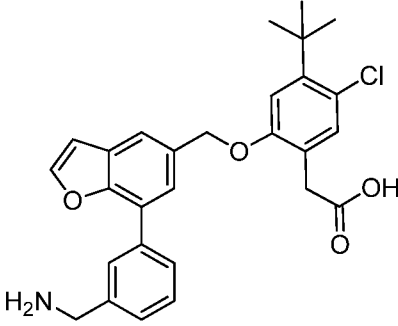
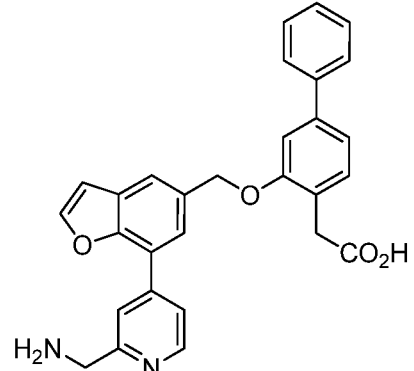
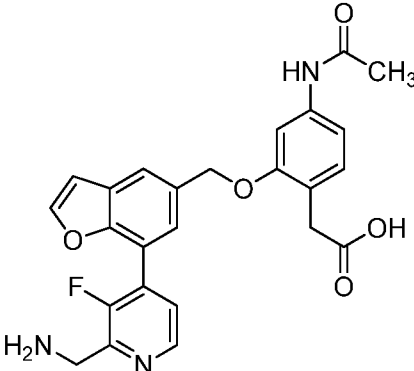
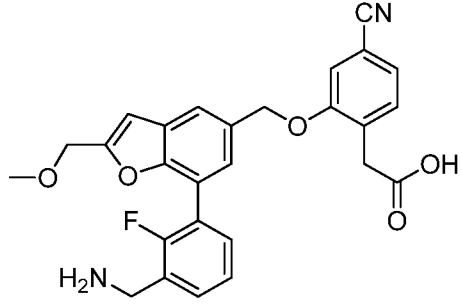
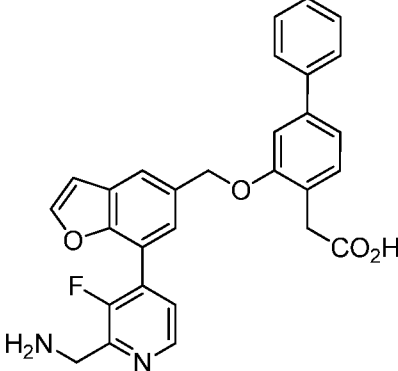
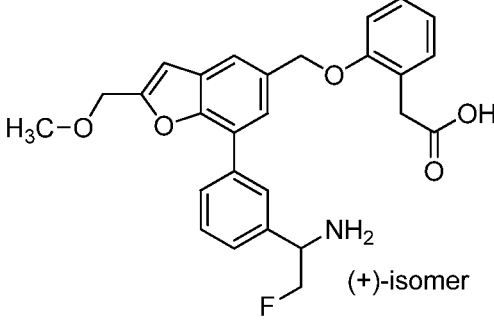
	
	
	
	
	

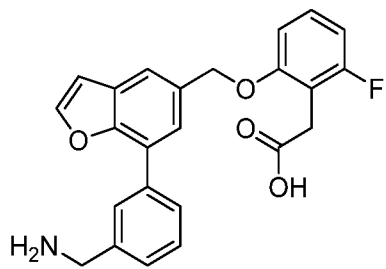
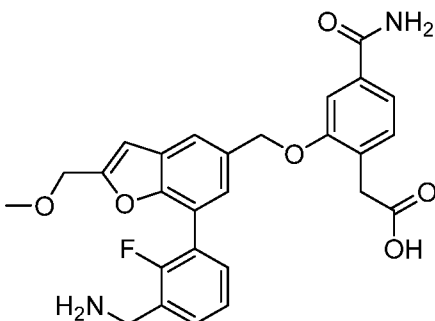
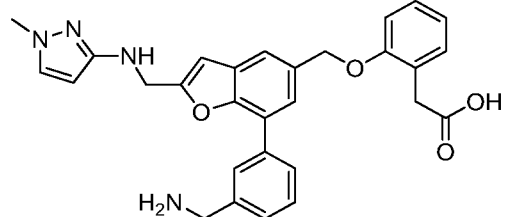
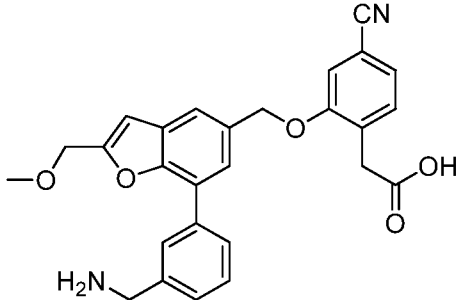
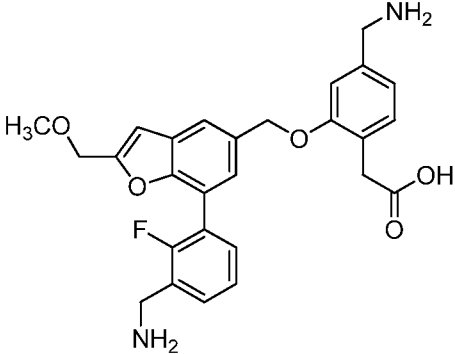
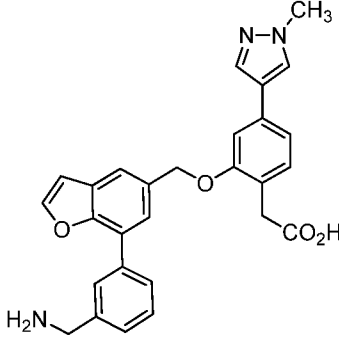
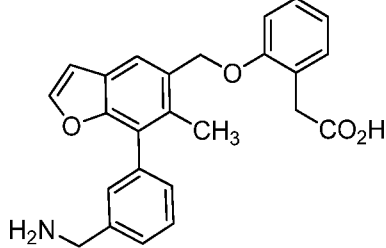
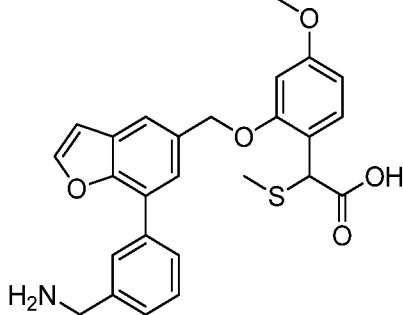
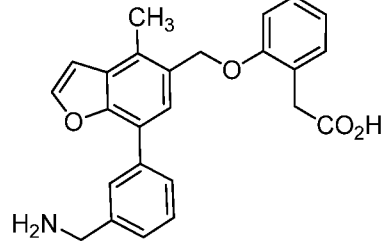
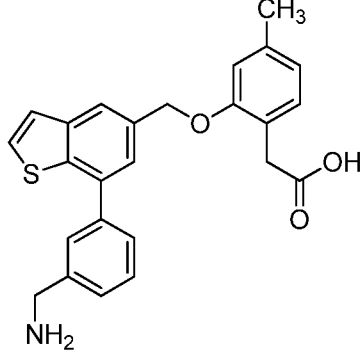
	
	
	
	
	

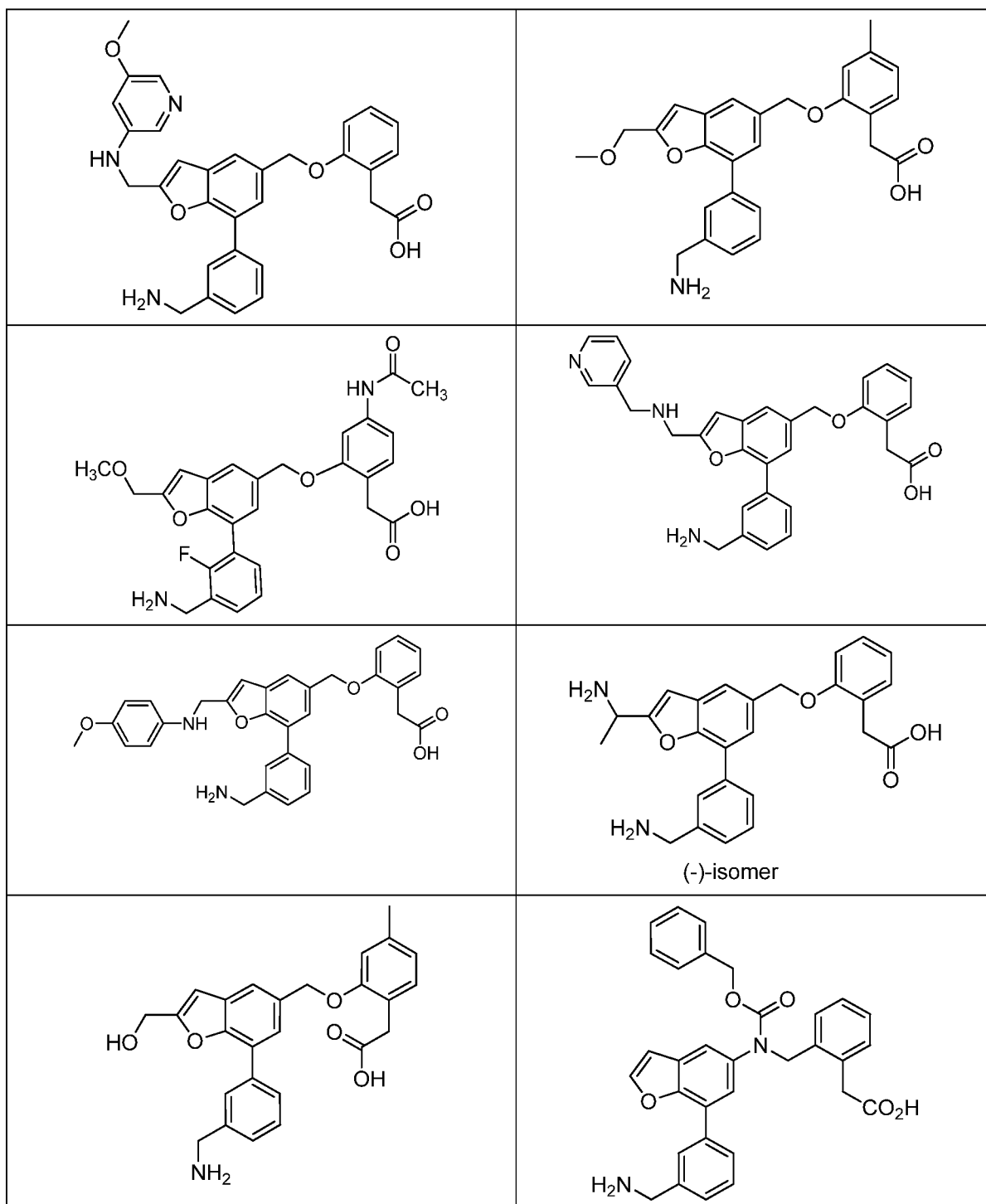
	
	
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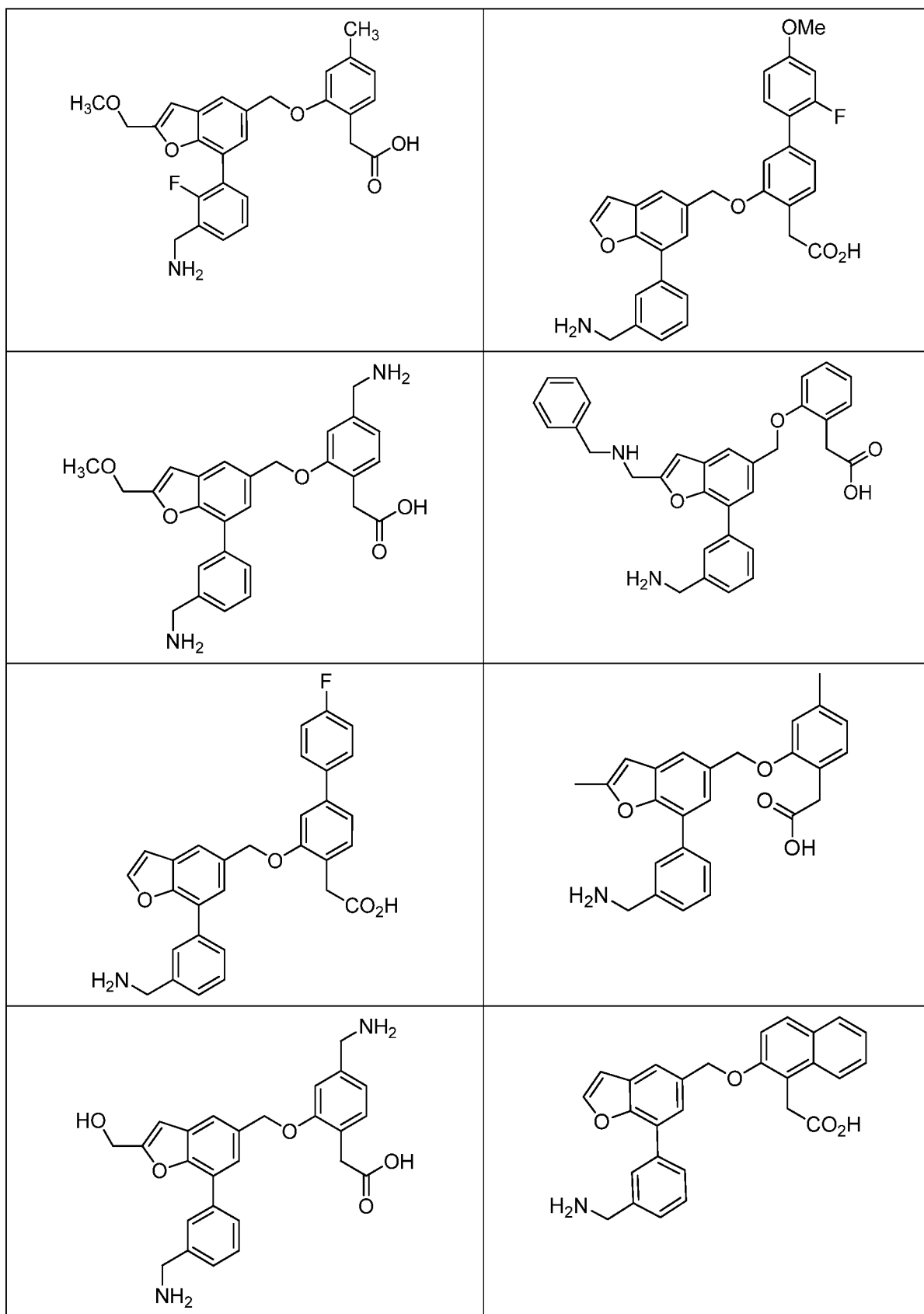
	
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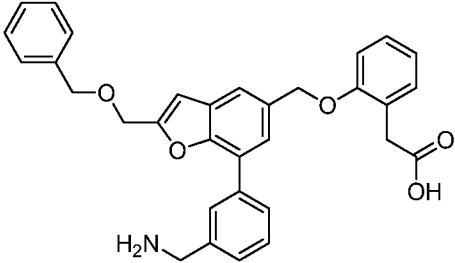
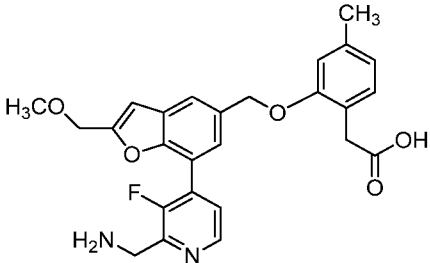
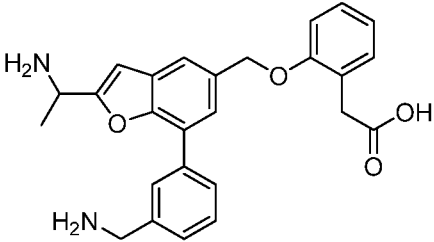
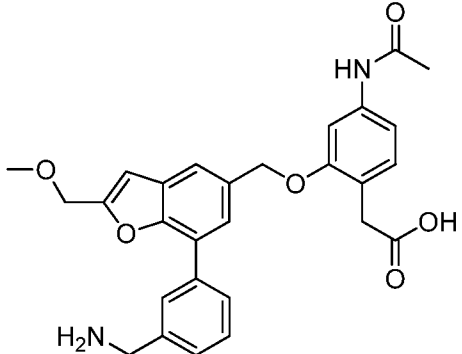
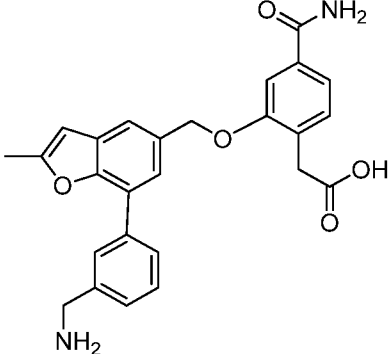
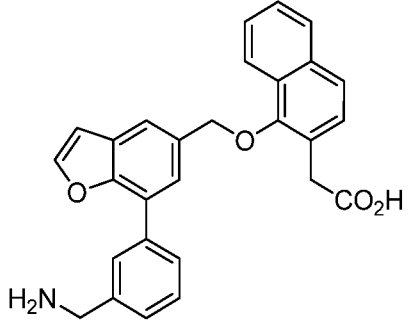
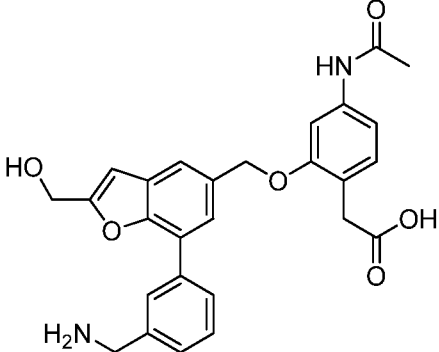
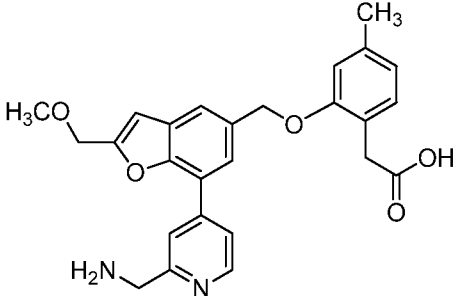
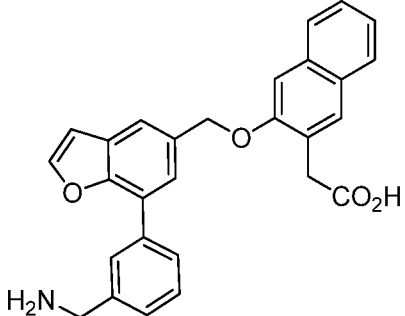
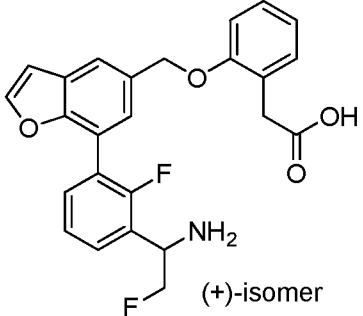
	
	
	
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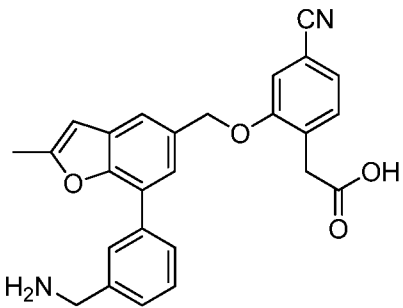
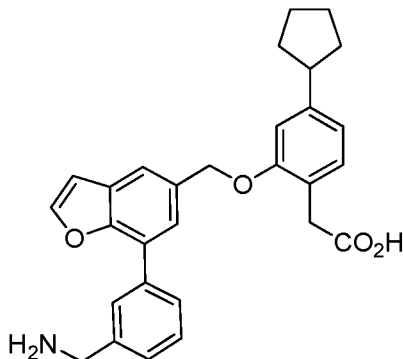
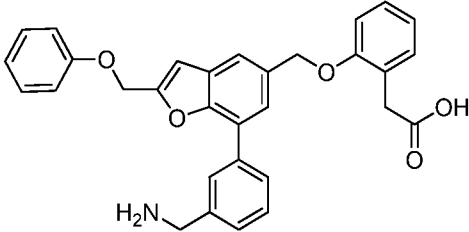
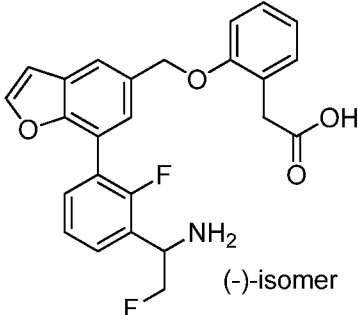
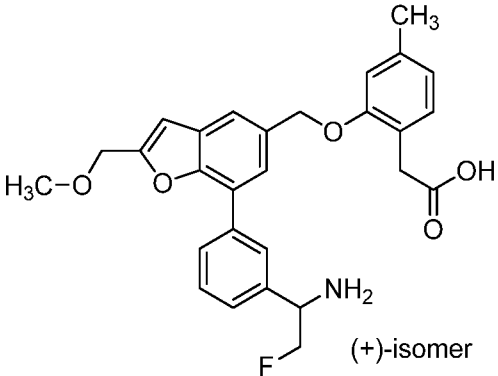
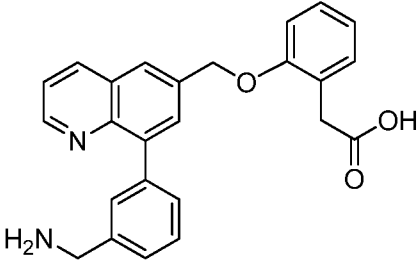
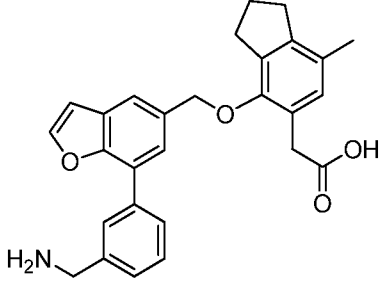
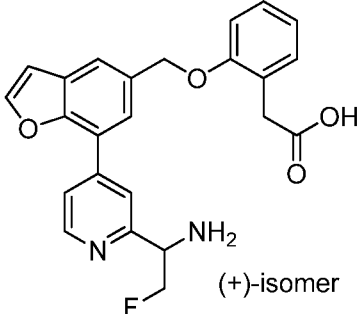
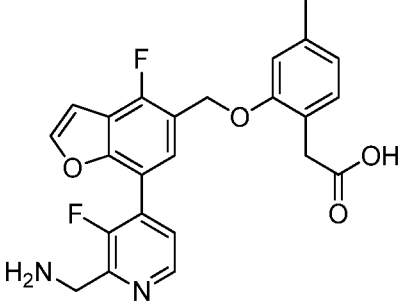
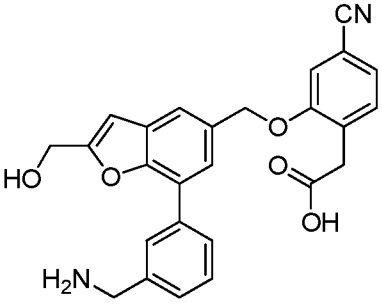
	
	
	
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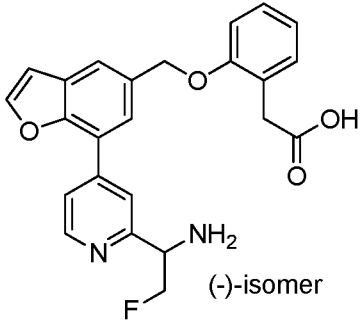
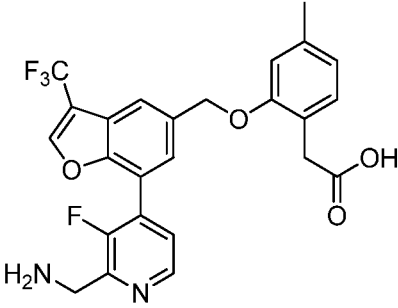
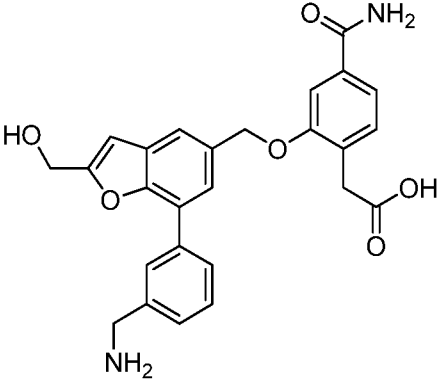
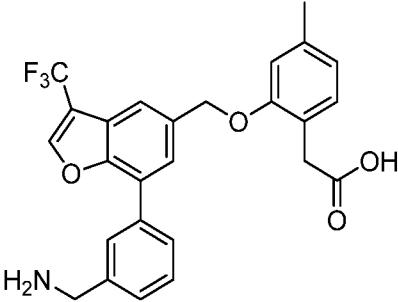
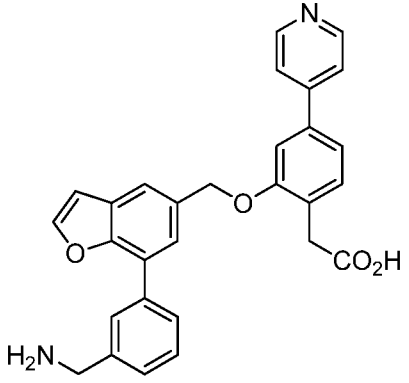
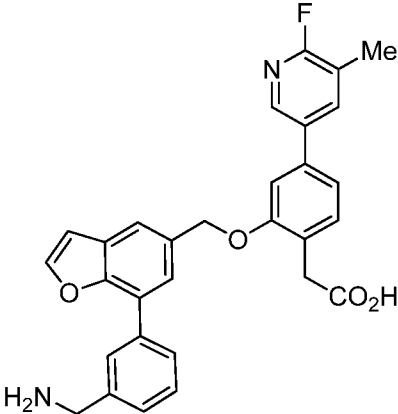
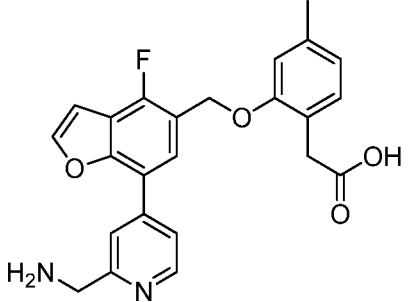
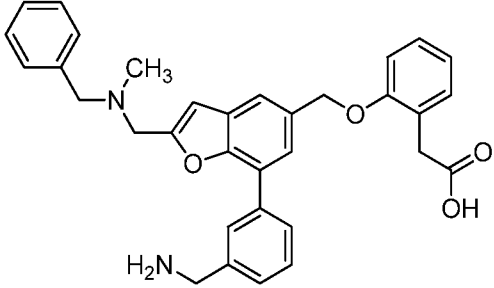
	
	
	
	
	

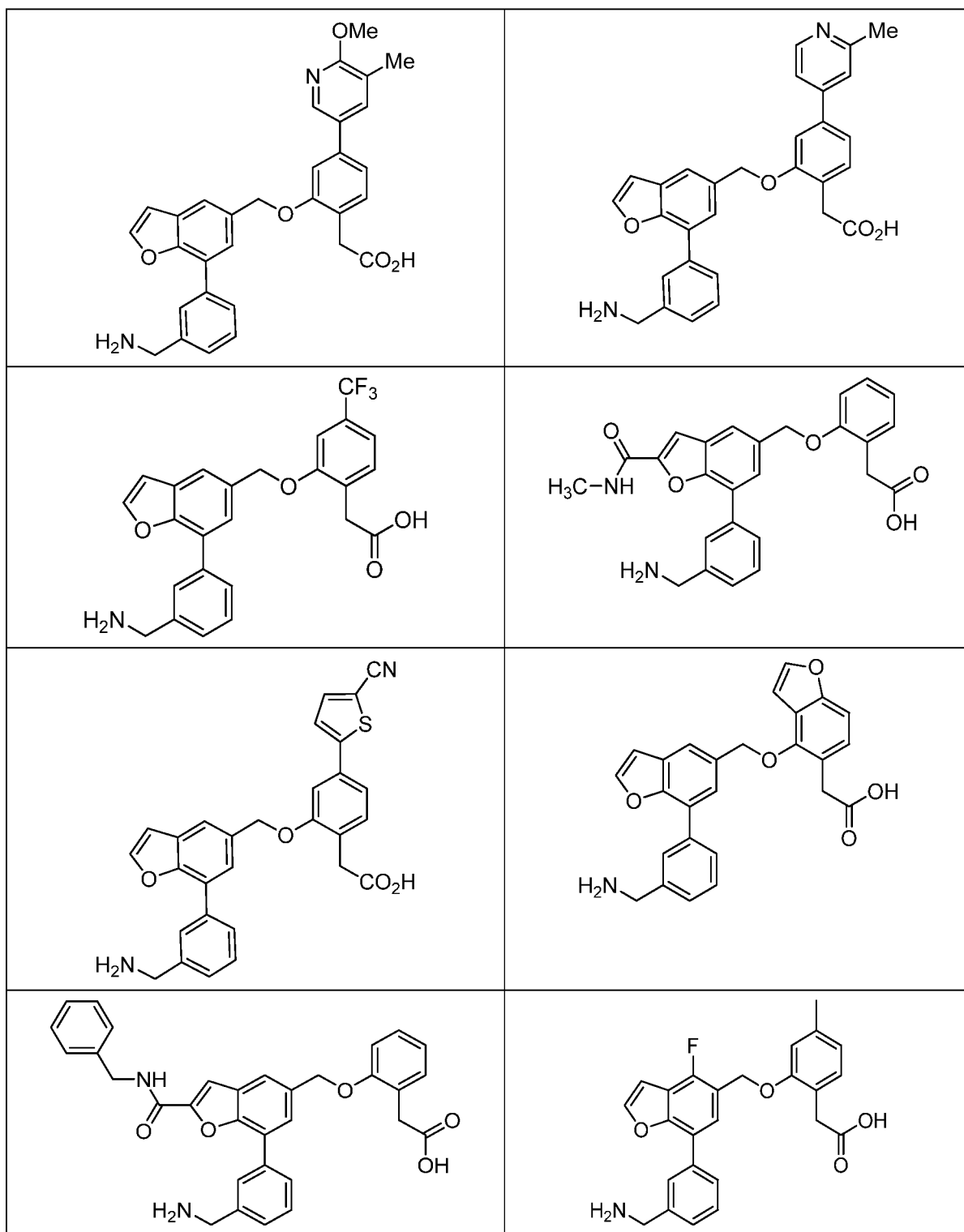


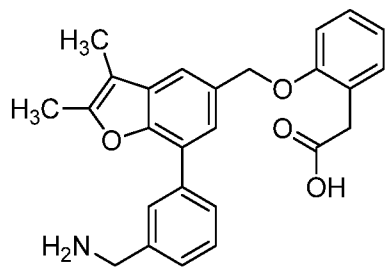
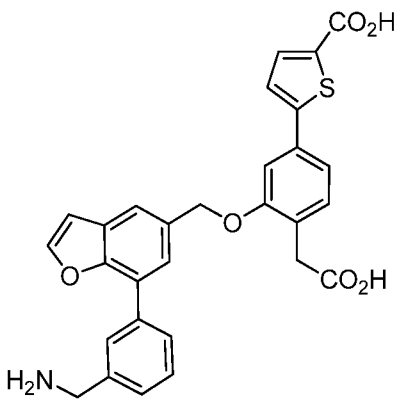
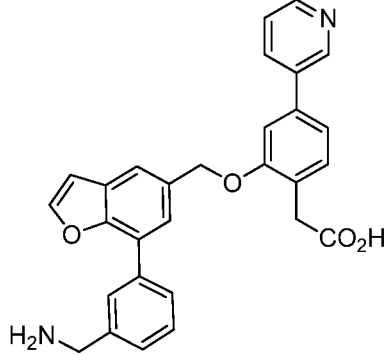
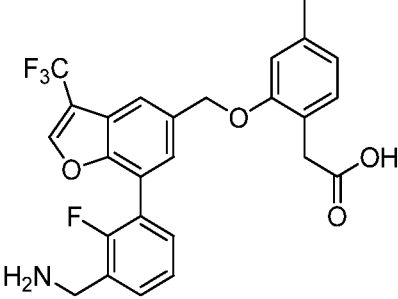
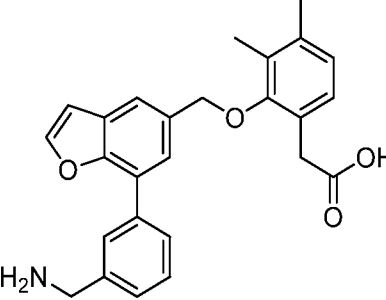
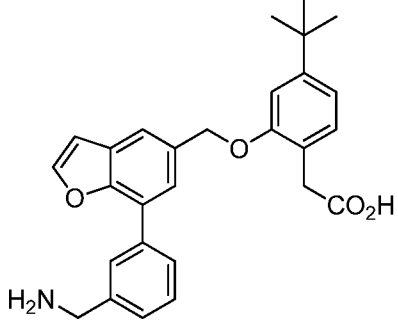
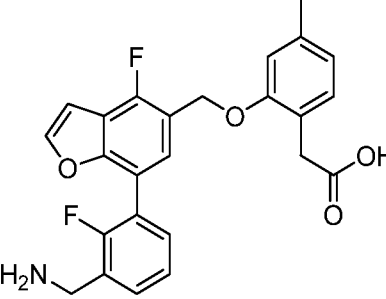
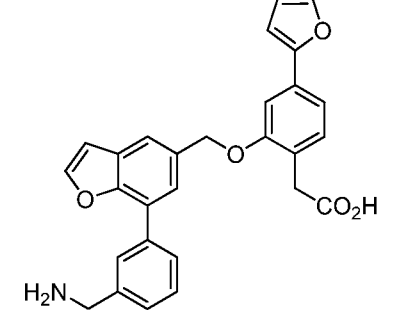
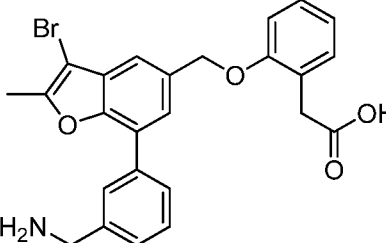
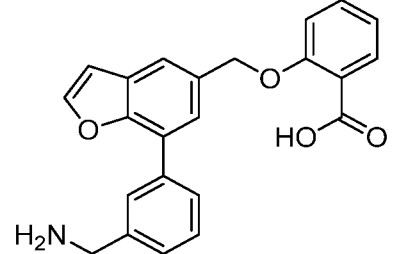


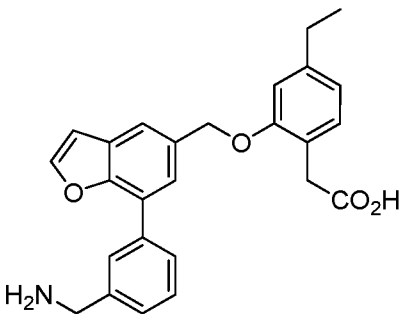
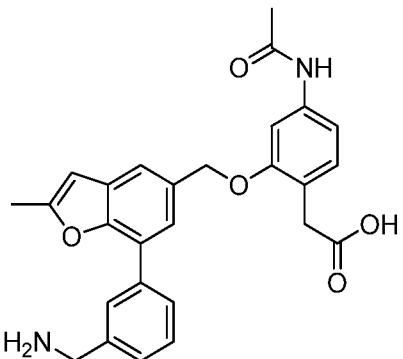
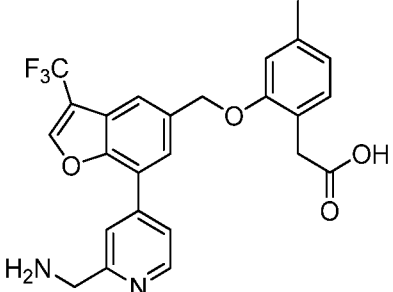
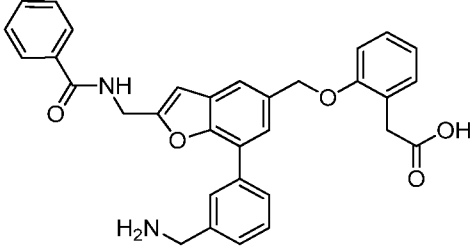
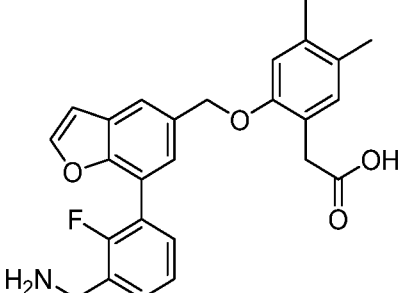
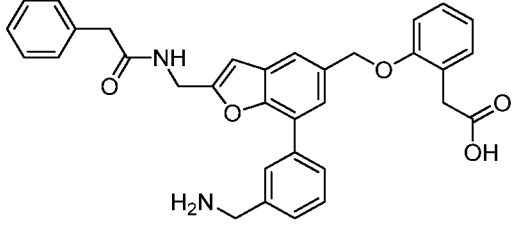
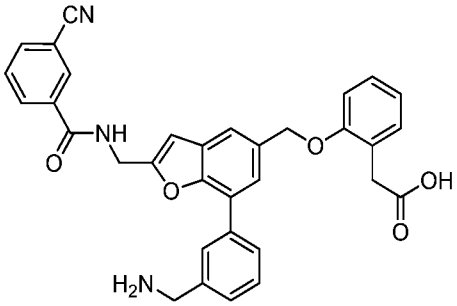
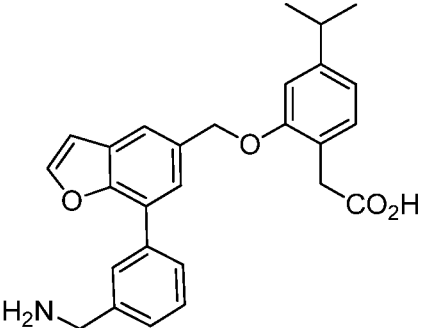
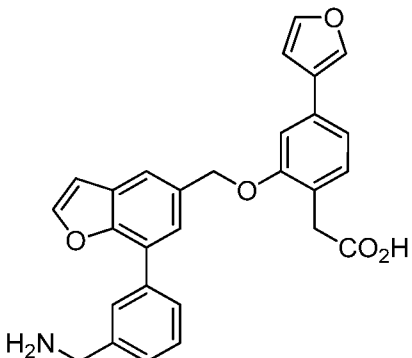
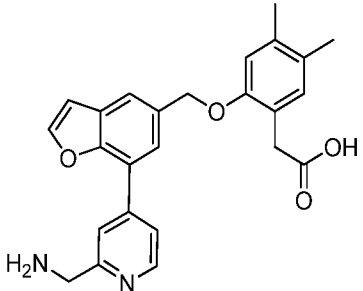
	
	
	
	
	

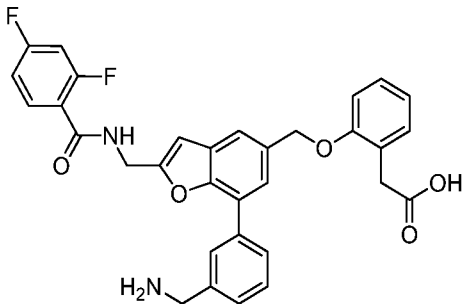
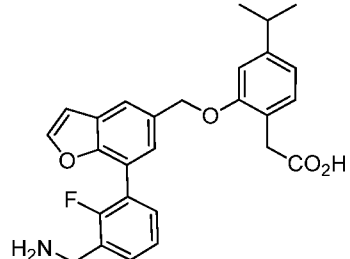
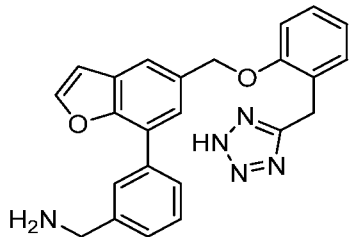
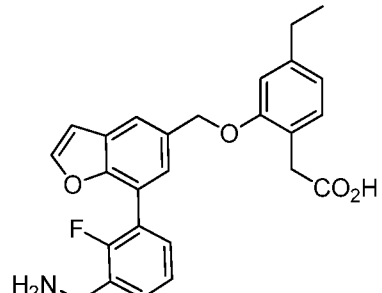
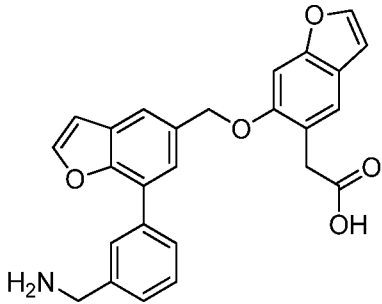
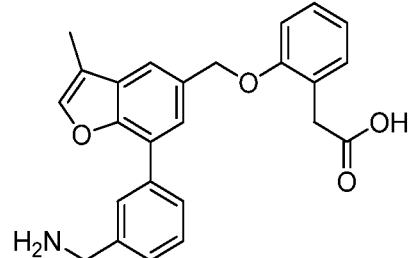
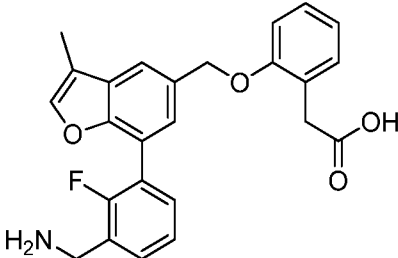
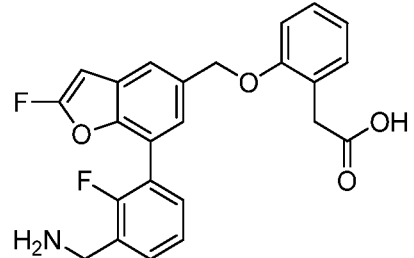
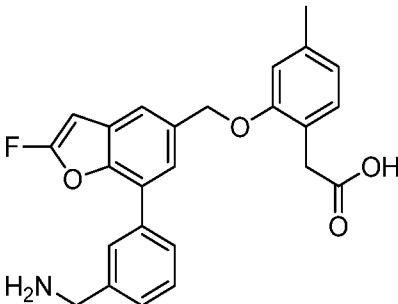
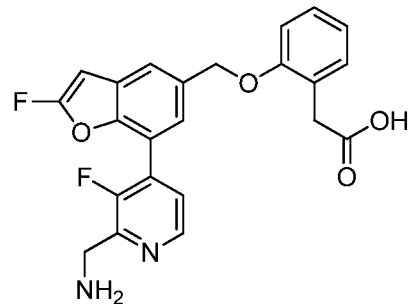
	
	
	
	
	

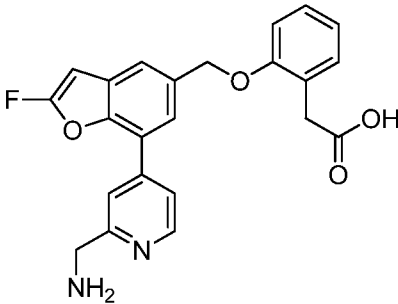
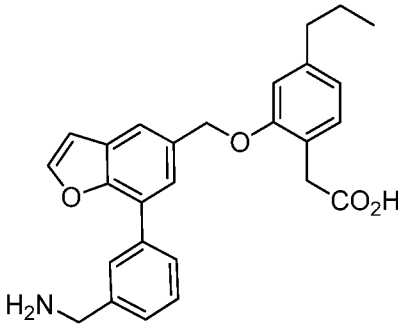
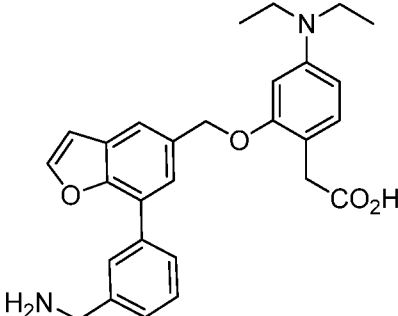
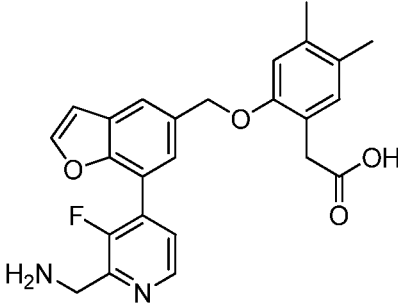
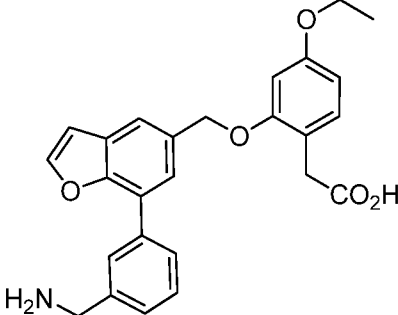
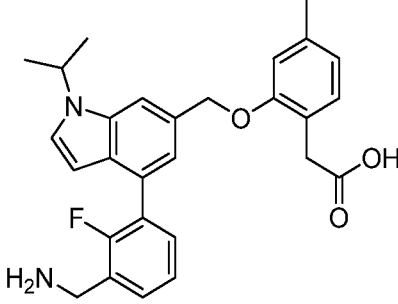
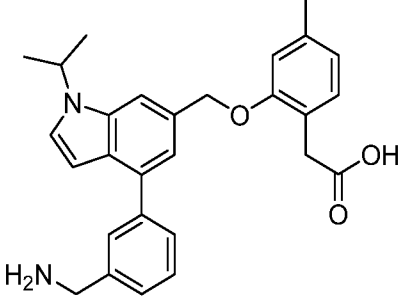
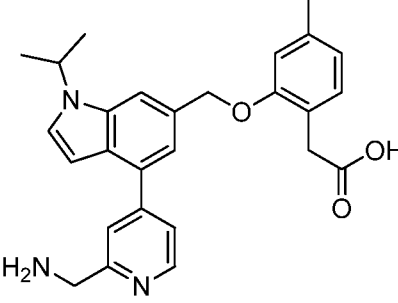
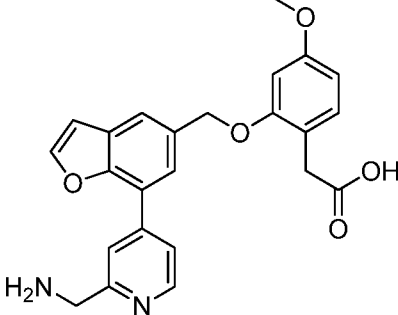
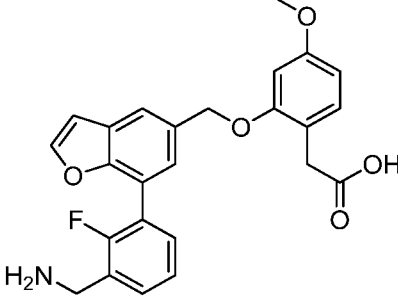
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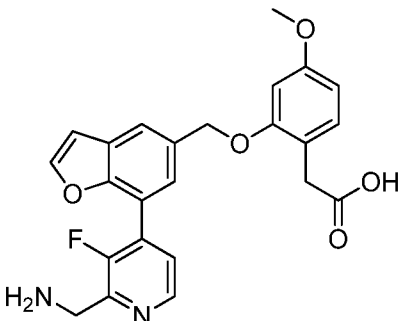
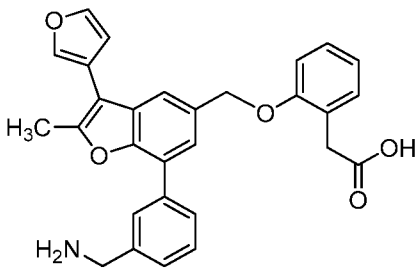
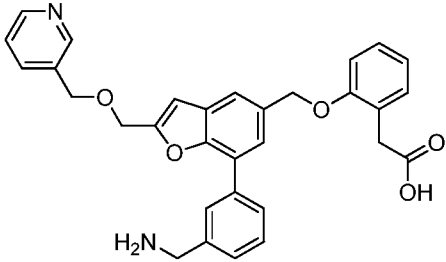
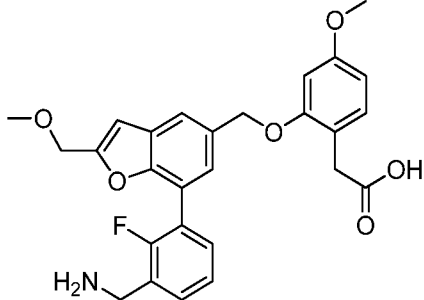
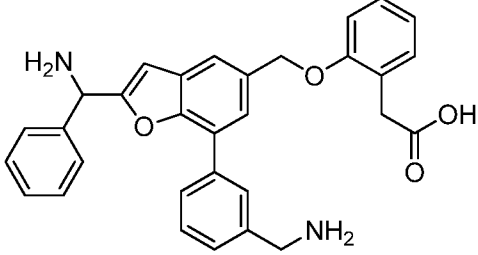
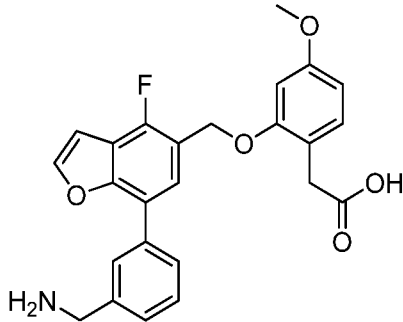
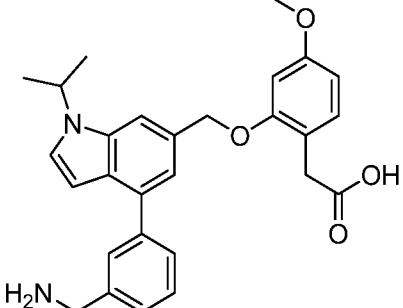
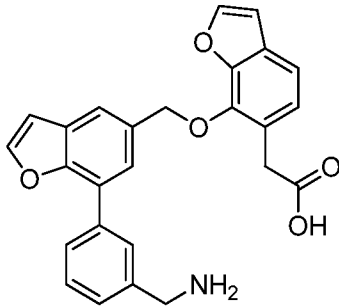
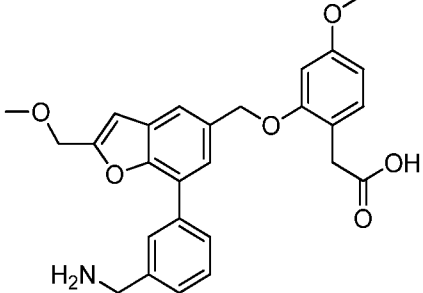
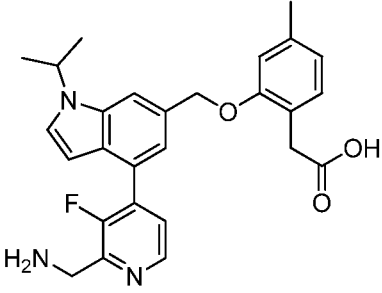


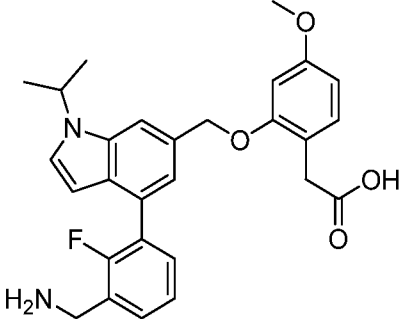
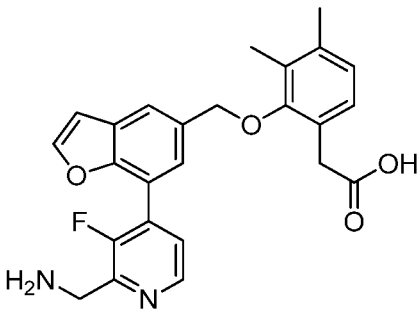
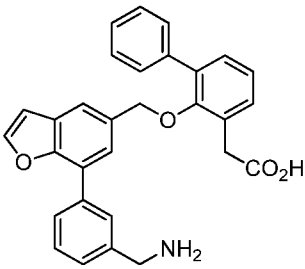
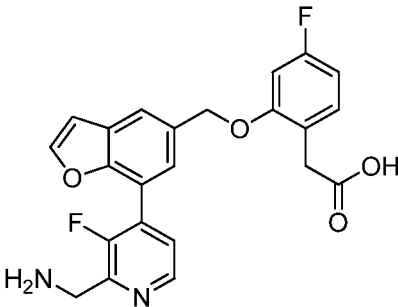
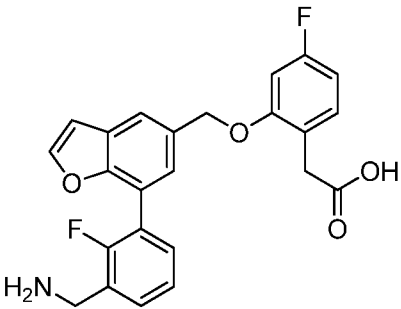
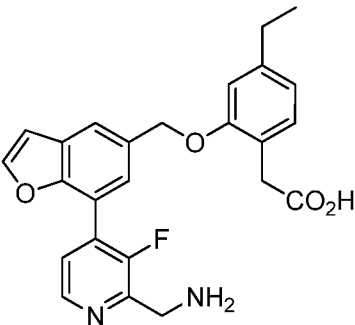
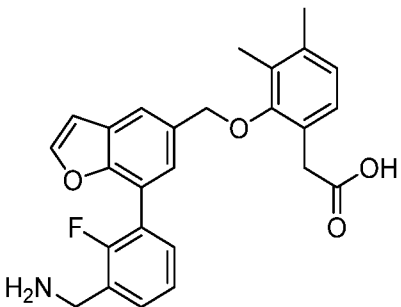
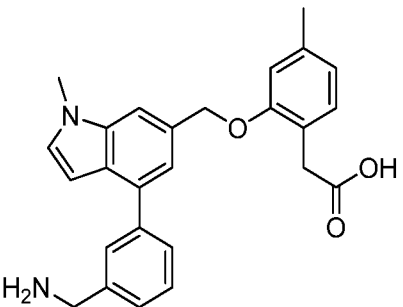
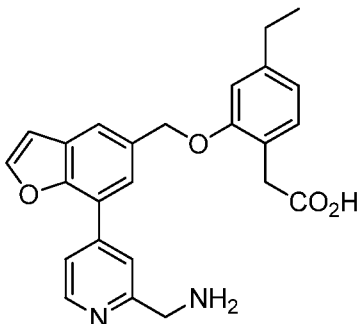
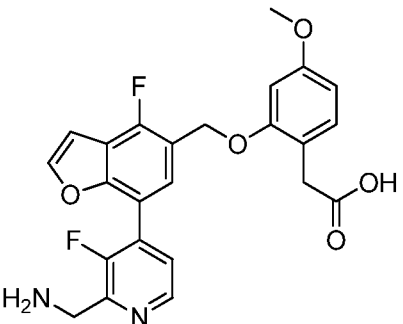
	
	
	
	
	

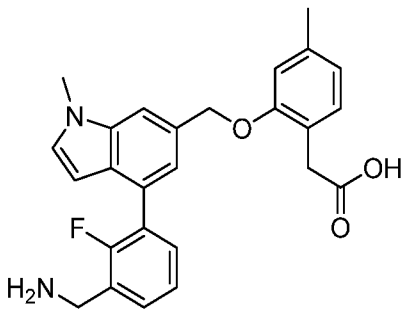
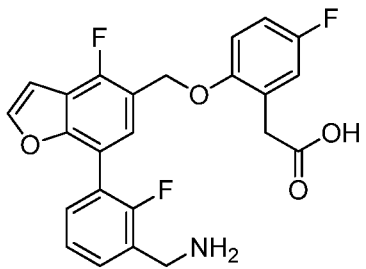
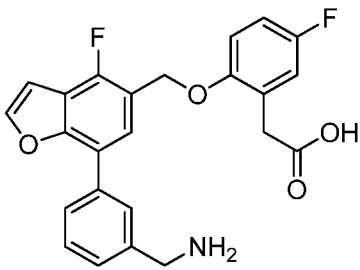
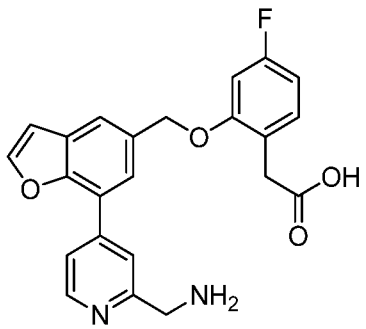
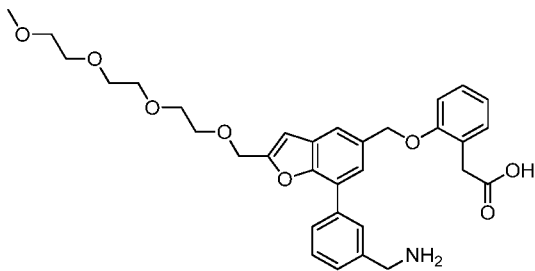
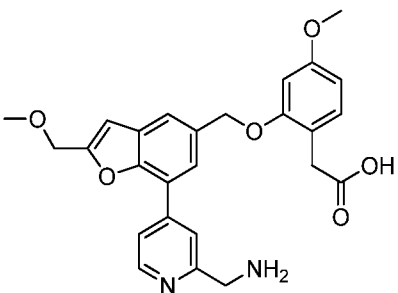
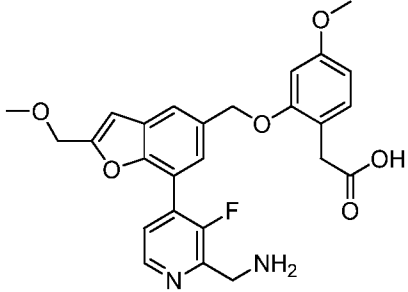
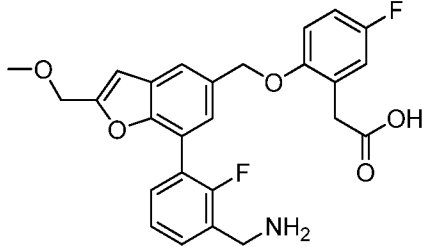
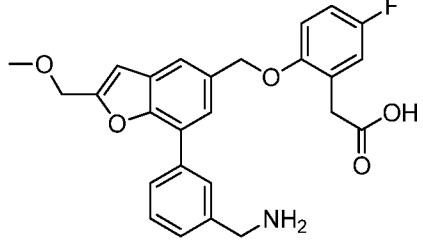
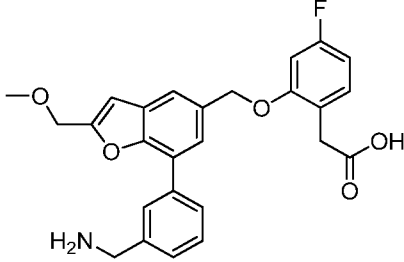
	
	
	
	
	

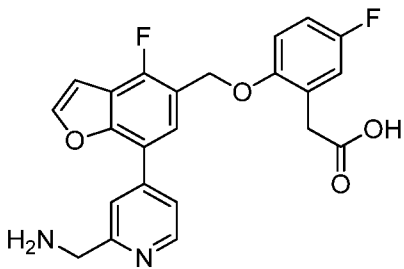
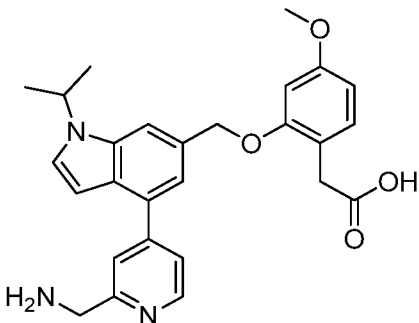
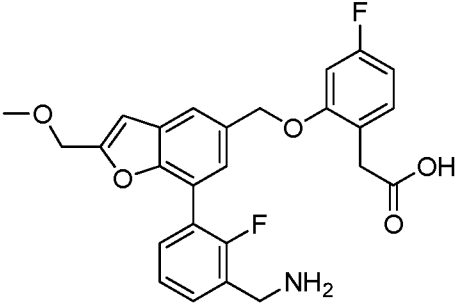
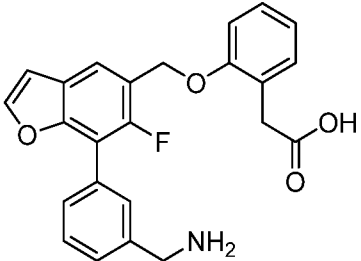
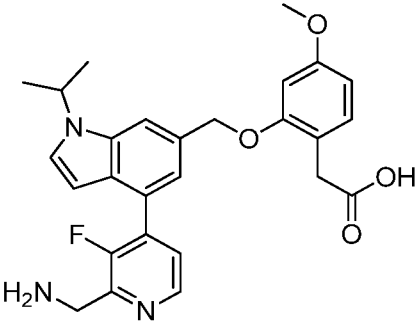
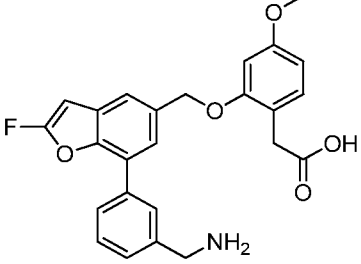
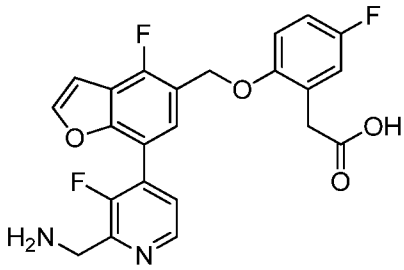
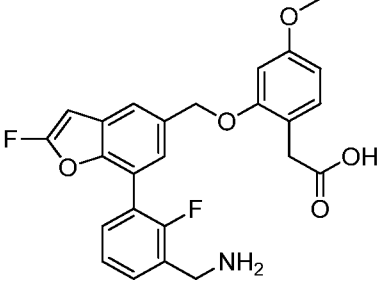
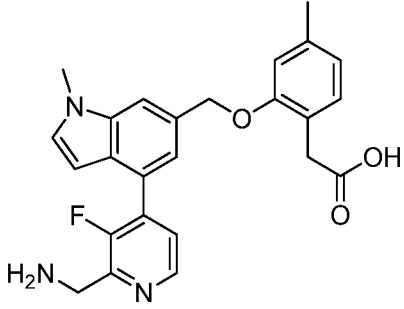
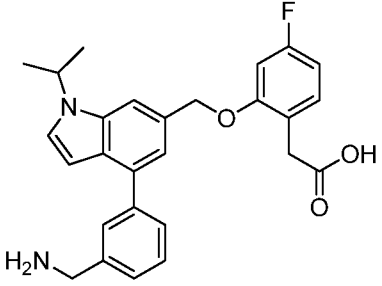
	
	
	
	
	

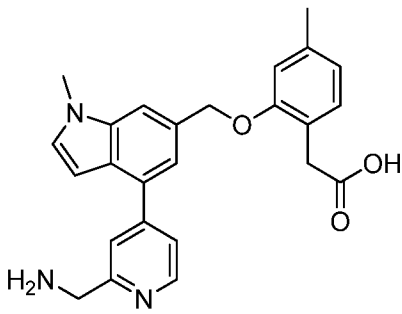
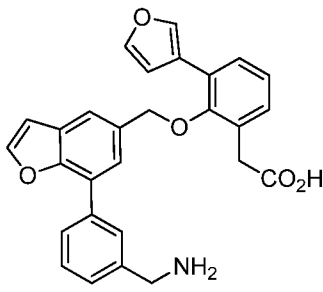
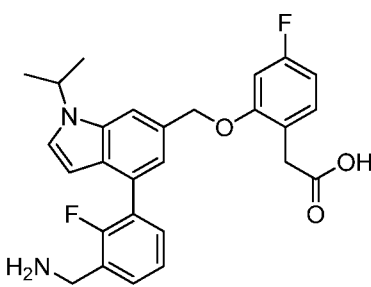
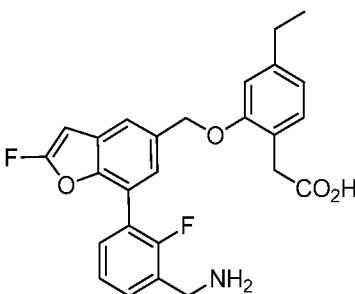
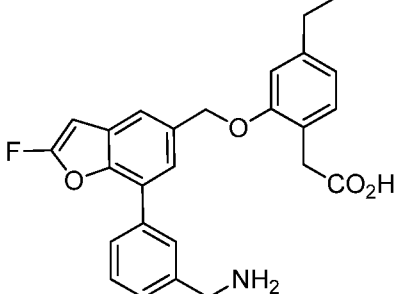
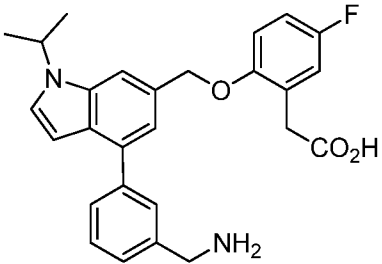
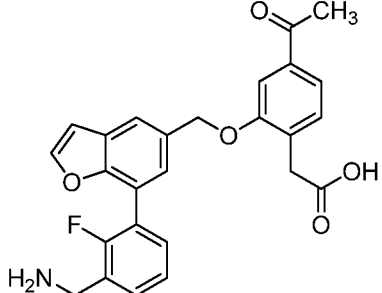
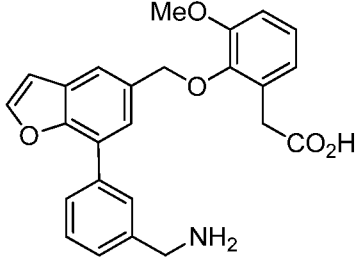
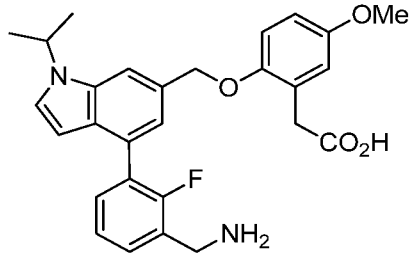
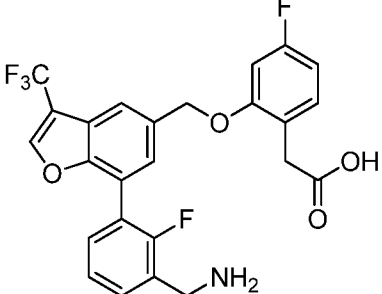
	
	
	
	
	

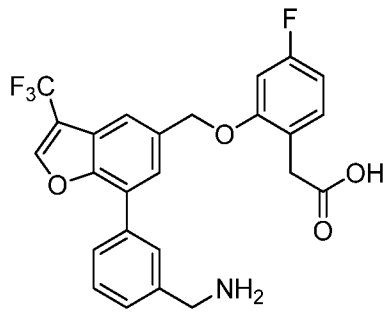
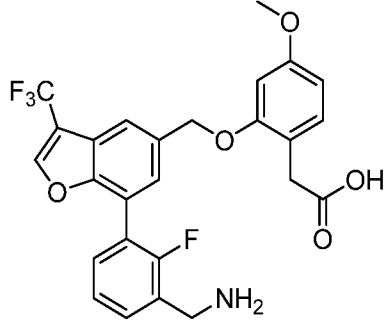
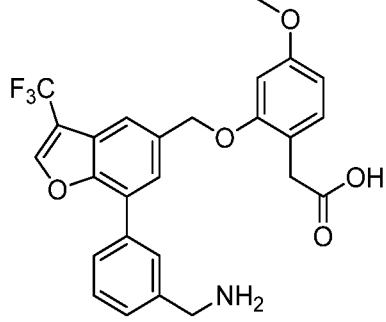
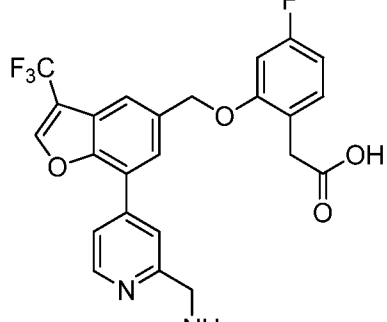
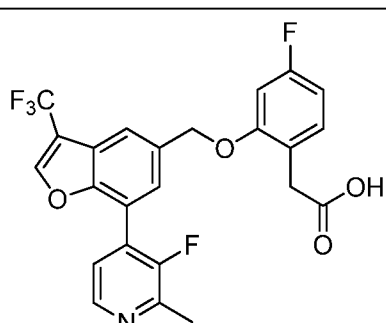
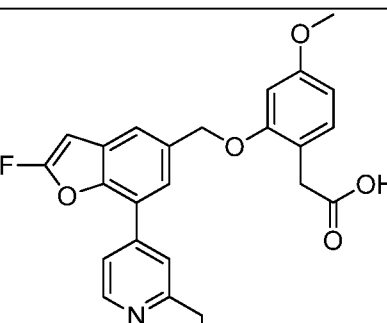
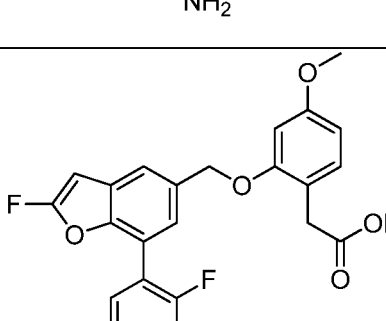
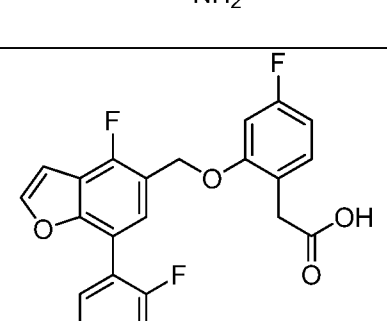
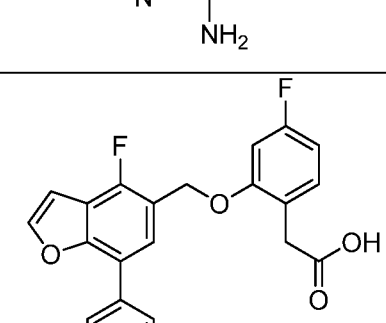
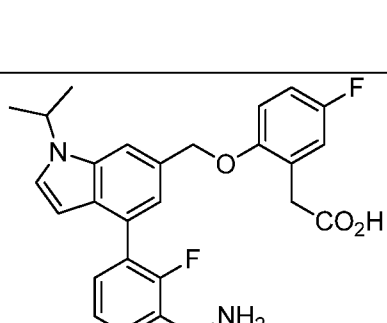
	
	
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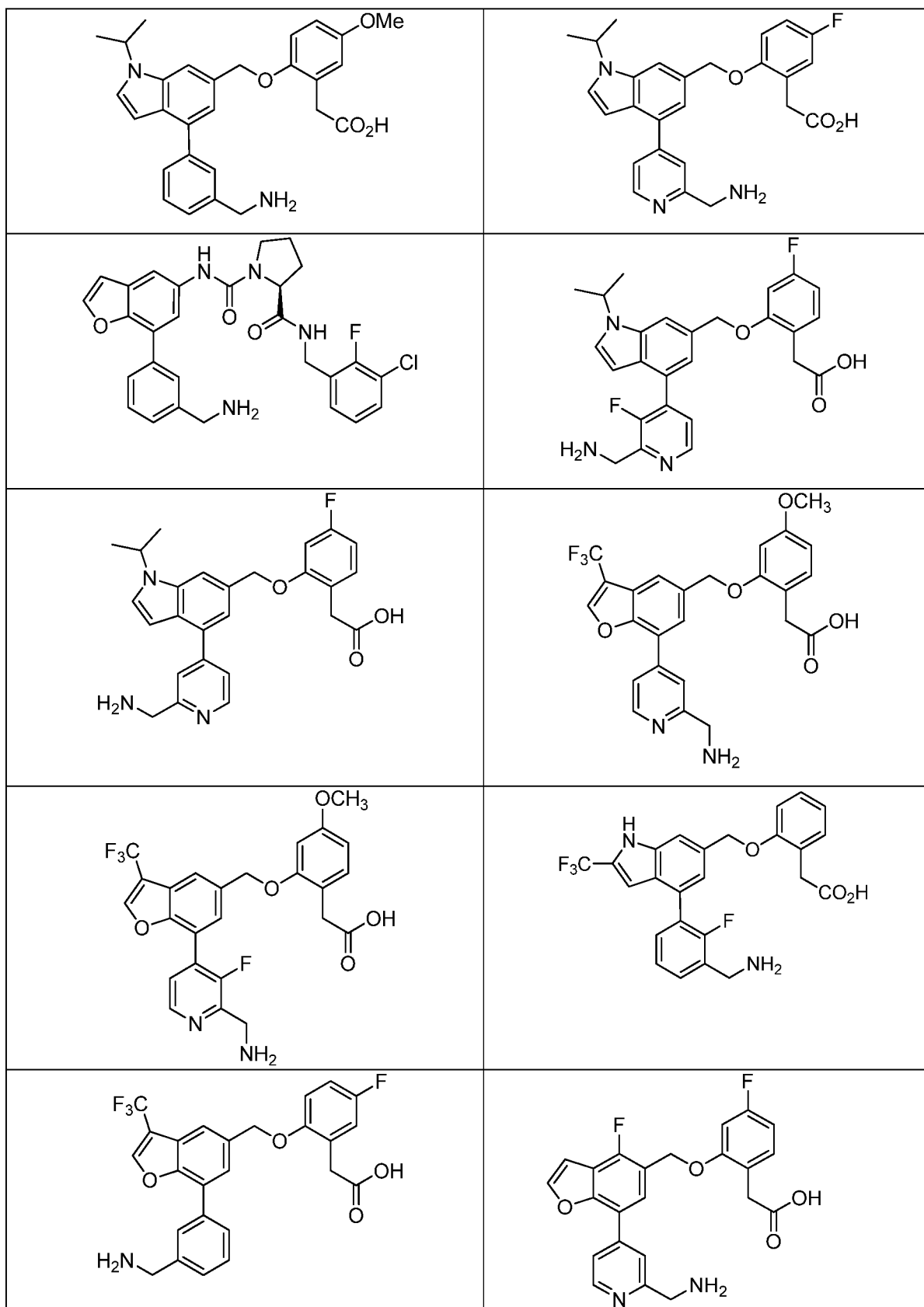
	
	
	
	
	

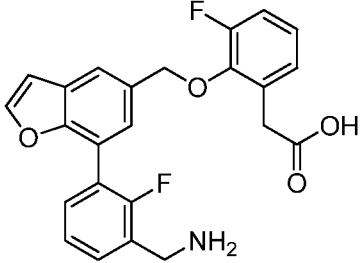
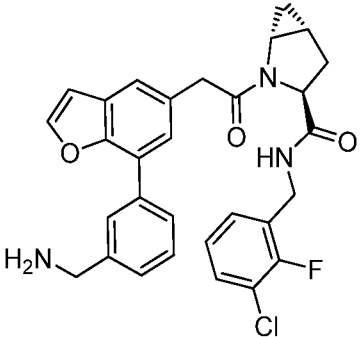
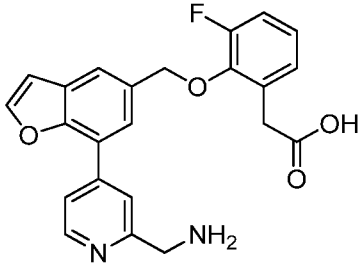
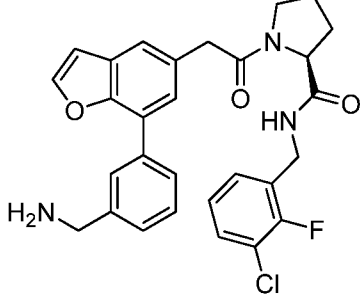
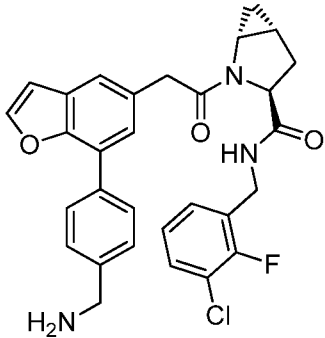
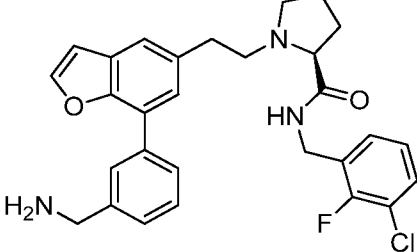
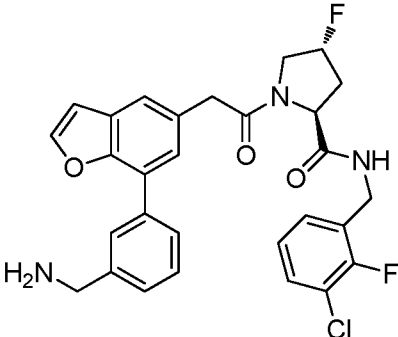
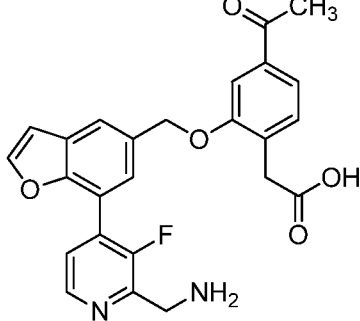
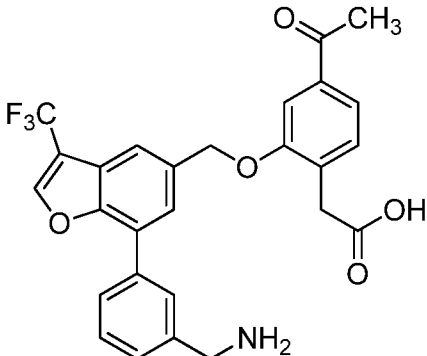
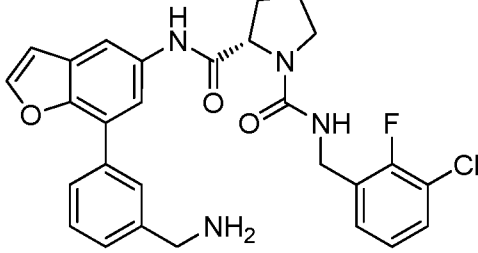
	
	
	
	
	

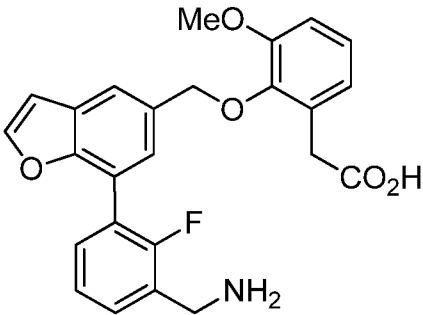
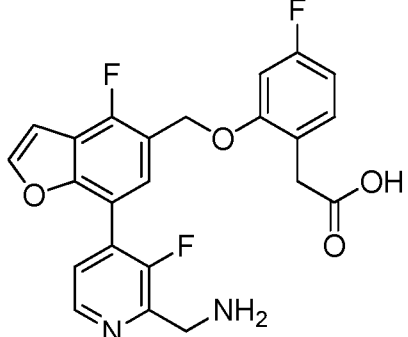
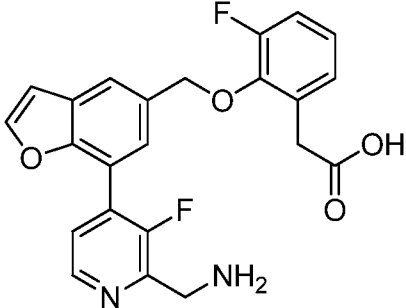
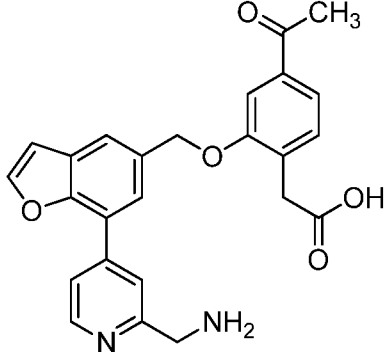
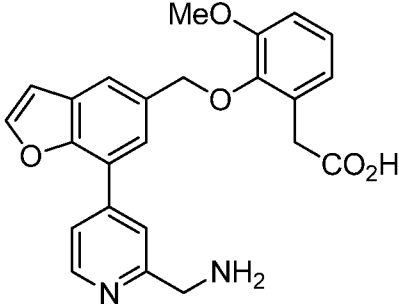
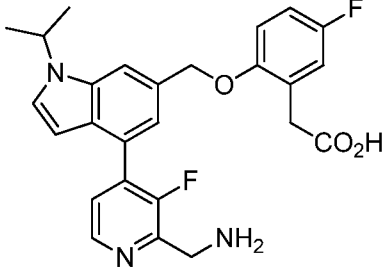
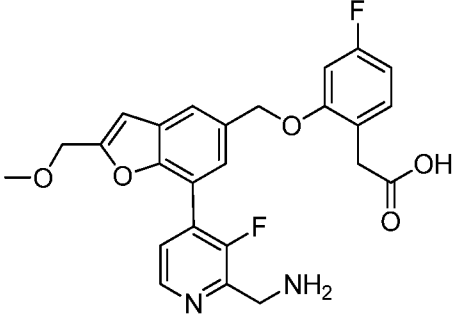
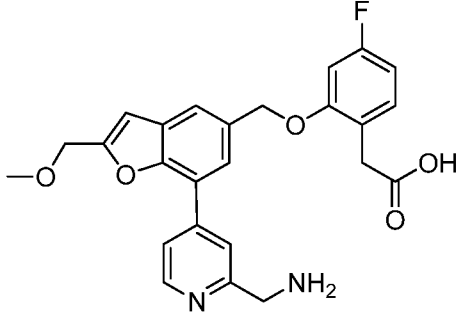
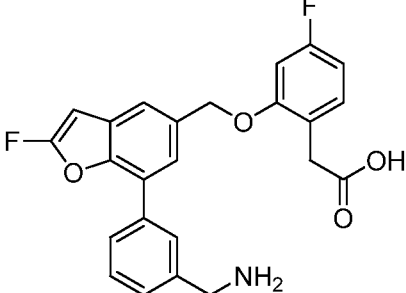
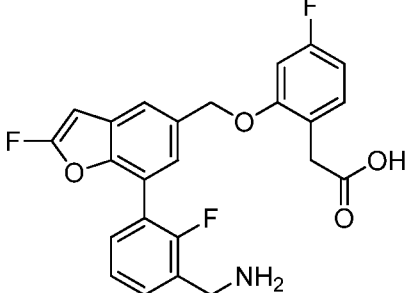
	
	
	
	
	

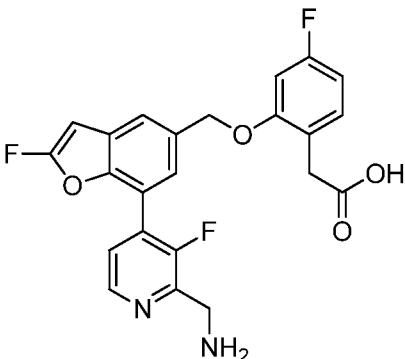
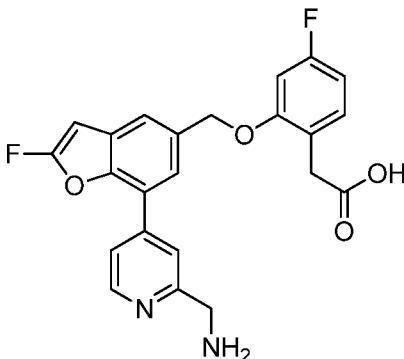
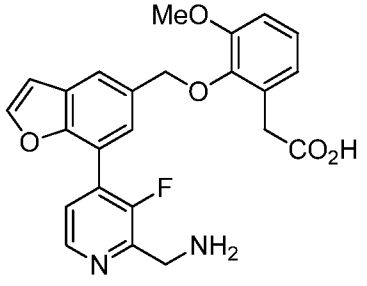
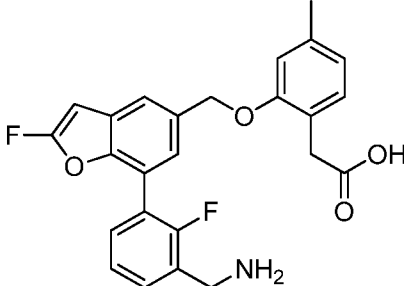
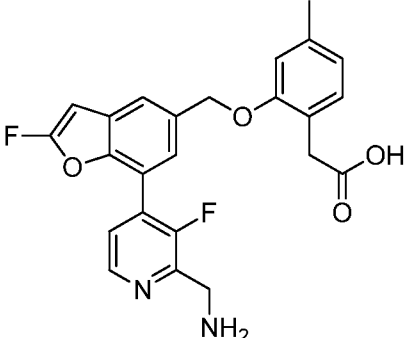
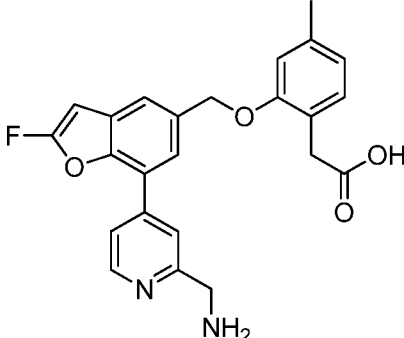
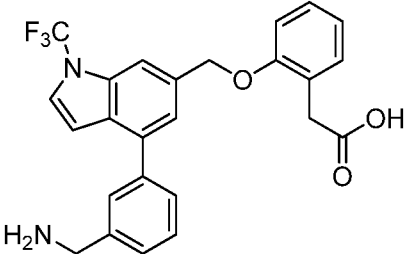
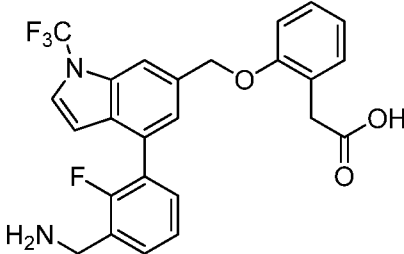
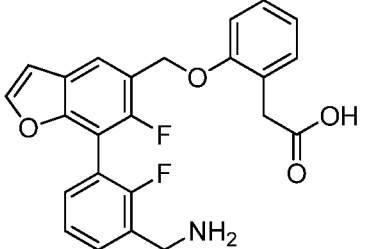
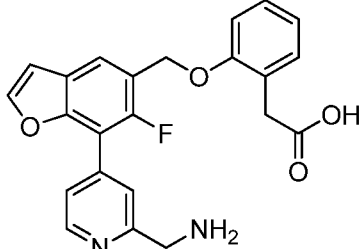
	
	
	
	
	

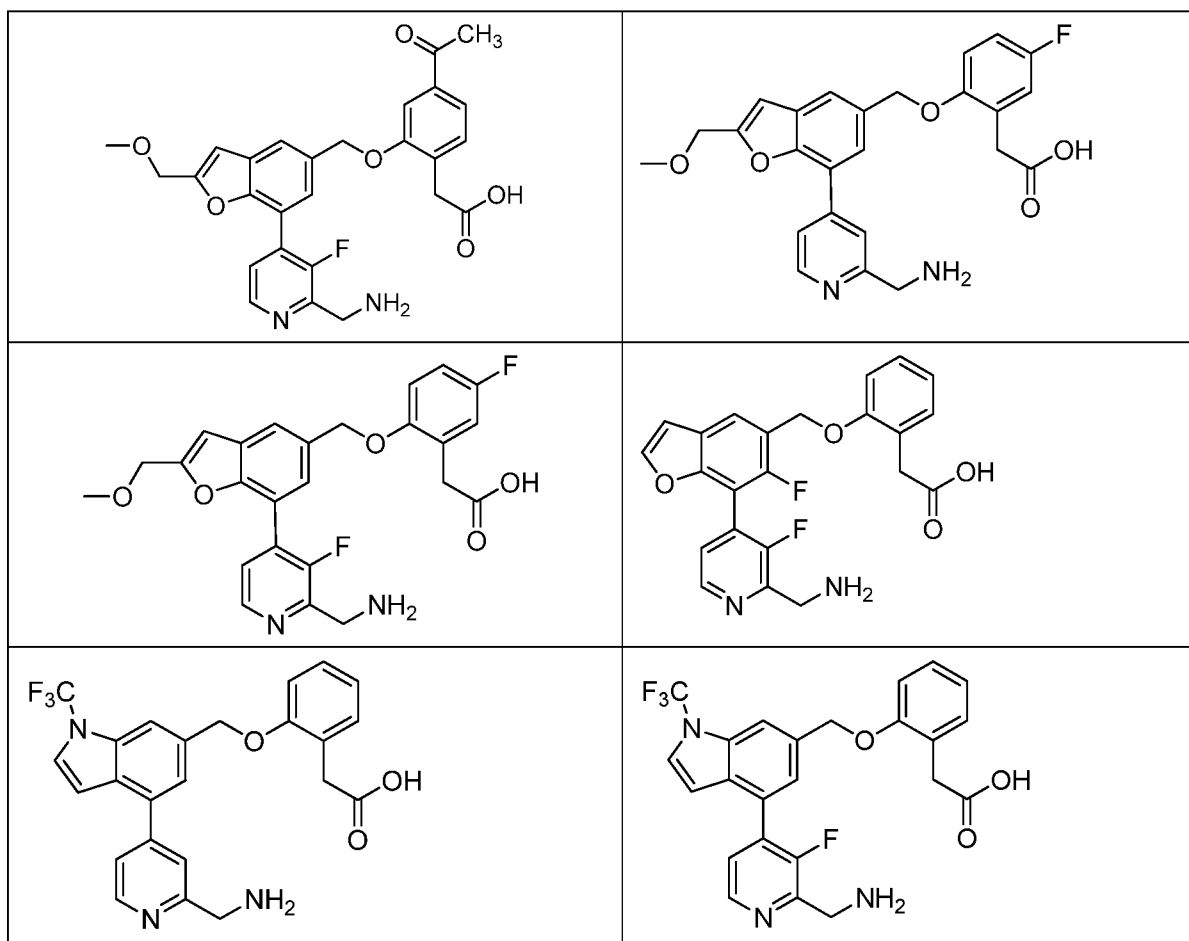
	
	
	
	
	



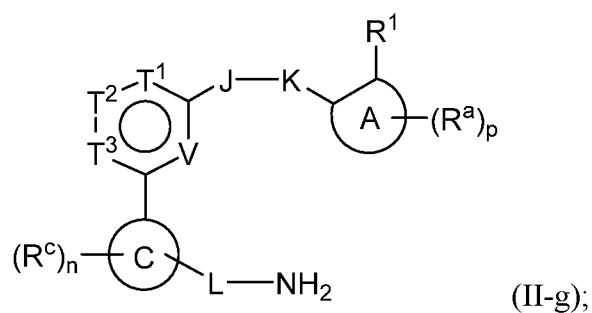
	
	
	
	
	



45. A compound of formula (II-g), or a pharmaceutically acceptable salt or prodrug thereof:



wherein:

ring $\textcircled{\text{A}}$ is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

ring $\textcircled{\text{C}}$ is aryl or heteroaryl;

R^a , independently for each occurrence, is halogen, cyano, hydroxy, $-\text{NH}_2$, $-\text{NH}(\text{Ac})$, $-\text{NH}(\text{alkyl})$, $-\text{NH}(\text{cycloalkyl})$, $-\text{NH}(\text{heterocycloalkyl})$, $-\text{NH}(\text{aryl})$, -

NH(heteroaryl), -N(alkyl)₂, -NHC(O)(alkyl), -CH(alkyl)NH₂, -CH(hydroxyalkyl)NH₂, -CH(haloalkyl)NH₂, -CH(cycloalkyl)NH₂, -CH(heterocycloalkyl)NH₂, -CH(aryl)NH₂, -CH(heteroaryl)NH₂, -CH₂NHC(O)(alkyl), -C(O)NH₂, -C(O)(alkyl), -SO₂NH₂, -SO₂(cycloalkyl), -SO₂(heterocycloalkyl), -SO₂(alkyl), -SO₂(aryl), or -SO₂(heteroaryl); or is selected from the group consisting of substituted or unsubstituted aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl;

T¹ is N, CH, NR^{T1}, or CR^{T1};

T² is NR^{T2} or CR^{T2};

T³ is N, CH, NR^{T3}, or CR^{T3};

wherein:

(a) T¹ is CR^{T1} or NR^{T1}, wherein R^{T1} and R^{T2}, taken together with the intervening atoms, form an optionally substituted cycloalkyl, aryl, or heteroaryl ring; and

T³ is N or CH; or

(b) T³ is CR^{T3} or NR^{T3}; wherein R^{T3} and R^{T2}, taken together with the intervening atoms, form an optionally substituted heteroaryl ring; and

T¹ is N or CH; and

at least one of (a) T² is NR^{T2}, (b) T³ is N, or (c) T¹ is NR^{T1};

R¹ is selected from the group consisting of -NH₂, -COOH, -CH₂COOH, -CH(NH(CO)(alkyl))COOH, -CH(NH(CO)(arylalkyl))COOH, -CH(NH(CO)(cycloalkyl))COOH, -CH(NH(CO)(aryl substituted cycloalkyl))COOH, -CH(NH(CO)(heteroaryl substituted cycloalkyl))COOH, -CH(S(alkyl))COOH, -CO(NH)CH₂(substituted or unsubstituted aryl), -CO(NH)CH₂(substituted or unsubstituted heteroaryl), -CO(NH)(substituted or unsubstituted aryl), -CO(NH)(substituted or unsubstituted heteroaryl), and -CH₂(tetrazolyl);

n is 0, 1, 2, 3, or 4;

p is 0, 1, 2, 3, or 4;

J is -C(O)-, -NH-, -CH₂-, -O-, -S-, -S(O)-, -SO₂-, -N(alkyl)-, -CH(alkyl)-, -CH(cycloalkyl)-, -N((C(O)O)arylalkyl)-, -N((C(O)O)heteroarylalkyl)-, or -N(C(O)arylalkyl)-;

K is $-\text{C}(\text{O})-$, $-\text{NH}-$, $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{SO}_2-$, $-\text{N}(\text{alkyl})-$, $-\text{CH}(\text{alkyl})-$, $-\text{CH}(\text{cycloalkyl})-$, $-\text{N}((\text{C}(\text{O})\text{O})\text{arylalkyl})-$, $-\text{N}((\text{C}(\text{O})\text{O})\text{heteroarylalkyl})-$, or $-\text{N}(\text{C}(\text{O})\text{arylalkyl})-$;

R^c , independently for each occurrence, is selected from the group consisting of halogen, $-\text{OH}$, $-\text{NR}^j\text{R}^k$, alkoxy, alkyl, cycloalkyl, and heterocycloalkyl;

L is selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CHR}^2-$, $-\text{CF}_2-$, $-\text{CFR}^2-$, $-\text{C}(\text{O})-$, $-\text{C}(=\text{NR}^L)-$, $-\text{C}(=\text{CHR}^L)-$, $-\text{S}(\text{O})_2-$, and $-\text{S}(\text{O})-$; wherein R^L is H or alkyl;

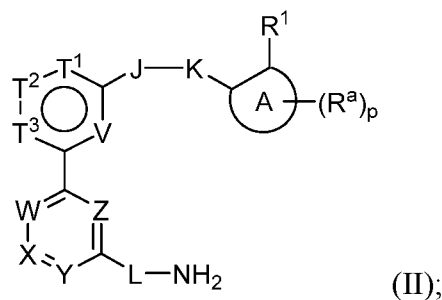
or wherein R^L and an occurrence of R^c taken together with the intervening atoms form a substituted or unsubstituted heteroaryl ring;

R^2 is alkyl, cycloalkyl, hydroxyalkyl, or haloalkyl;

V is N or CH; and

the stereochemical configuration at any chiral center is *R*, *S*, or a mixture of *R* and *S*.

46. The compound of claim 45, having the structure of formula (II):



wherein:

ring A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^a , independently for each occurrence, is selected from the group consisting of halogen, cyano, hydroxy, $-\text{NH}_2$, $-\text{NH}(\text{Ac})$, $-\text{NH}(\text{alkyl})$, $-\text{N}(\text{alkyl})_2$, $-\text{NHC}(\text{O})(\text{alkyl})$, $-\text{CH}_2\text{NHC}(\text{O})(\text{alkyl})$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})(\text{alkyl})$, optionally substituted aryl, optionally substituted heteroaryl, cycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl;

T^1 is N, CH, $\text{NR}^{\text{T}1}$, or $\text{CR}^{\text{T}1}$;

T^2 is $\text{NR}^{\text{T}2}$ or $\text{CR}^{\text{T}2}$;

T^3 is N, CH, $\text{NR}^{\text{T}3}$, or $\text{CR}^{\text{T}3}$;

wherein:

(a) T^1 is CR^{T1} or NR^{T1} , wherein R^{T1} and R^{T2} , taken together with the intervening atoms, form an optionally substituted cycloalkyl, aryl, or heteroaryl ring; and

T^3 is N or CH; or

(b) T^3 is CR^{T3} or NR^{T3} ; wherein R^{T3} and R^{T2} , taken together with the intervening atoms, form an optionally substituted heteroaryl ring; and

T^1 is N or CH; and

at least one of (a) T^2 is NR^{T2} , (b) T^3 is N, or (c) T^1 is NR^{T1} ;

R^1 is selected from the group consisting of $-NH_2$, $-CH_2COOH$,

$-CH(NH(CO)(alkyl))COOH$, $-CH(NH(CO)(cycloalkyl))COOH$,

$-CO(NH)CH_2aryl$, $-CO(NH)CH_2heteroaryl$, $-CO(NH)aryl$, and

$-CO(NH)heteroaryl$;

p is 0, 1, or 2;

J is $-C(O)-$, $-NH-$, $-CH_2-$, $-O-$, $-S-$, $-S(O)-$, $-SO_2-$, $-N(alkyl)-$, or $-CH(alkyl)-$;

K is $-C(O)-$, $-NH-$, $-O-$, $-CH_2-$, $-S-$, $-S(O)-$, $-SO_2-$, $-N(alkyl)-$, or $-CH(alkyl)-$;

wherein at least one of J and K is $-C(O)-$, $-CH_2-$, or $-CH(alkyl)-$;

W is N, CH, or CR^c ;

X is N, CH, or CR^c ;

Y is N, CH, or CR^c ;

Z is N, CH, or CR^c ;

R^c , independently for each occurrence, is selected from the group consisting of halogen, $-OH$, $-NR^jR^k$, alkoxy, and alkyl;

L is selected from the group consisting of a bond, $-CH_2-$, $-CH_2CH_2-$, $-CHR^2-$,

$-CF_2-$, $-CFR^2-$, $-C(O)-$, $-C(=NR^L)-$, and $-C(=CHR^L)-$;

wherein R^L is H or alkyl;

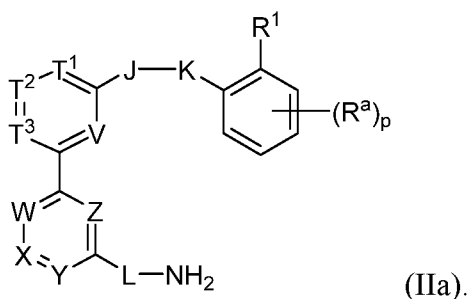
or wherein R^L and an occurrence of R^c taken together with the intervening atoms form a substituted or unsubstituted heteroaryl ring;

R^2 is alkyl, hydroxyalkyl, or haloalkyl; and

V is N or CH.

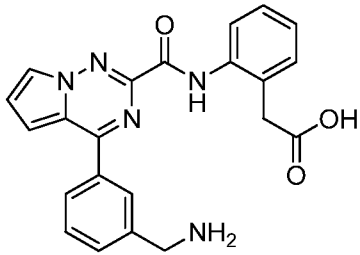
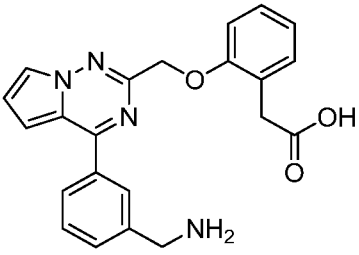
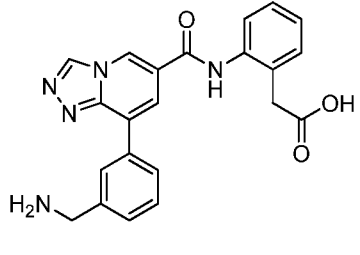
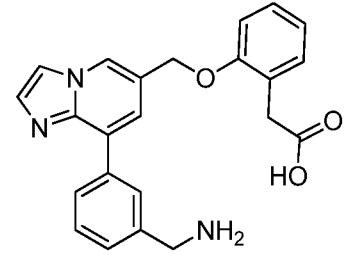
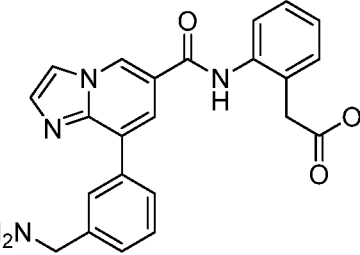
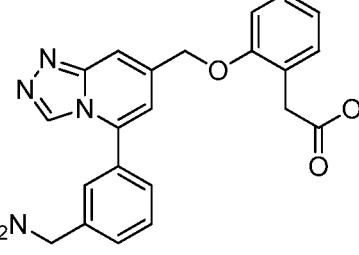
47. The compound of claim 45 or 46, wherein ring  is phenyl, thiophenyl, furyl, pyrazole, or pyridinyl.

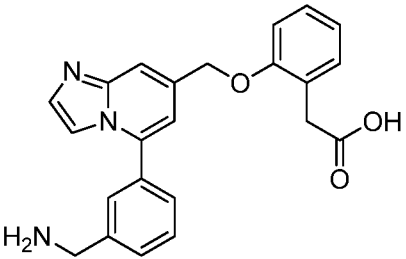
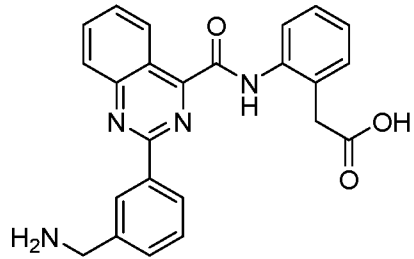
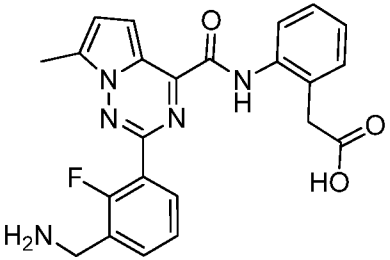
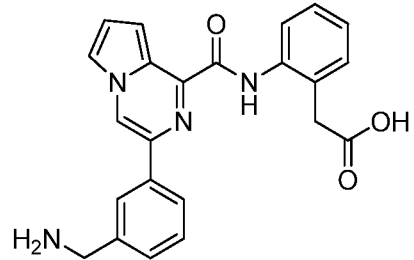
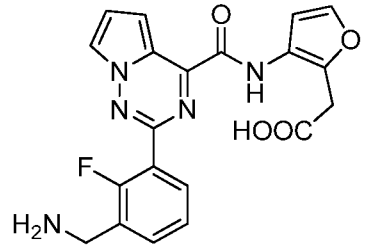
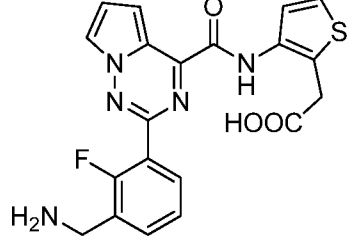
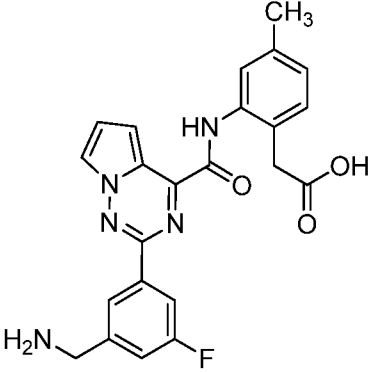
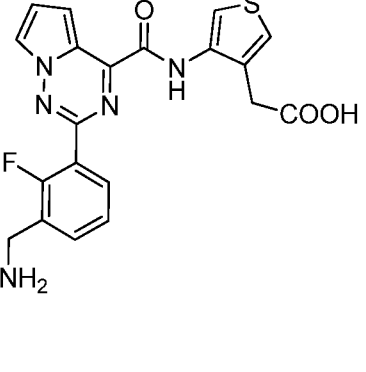
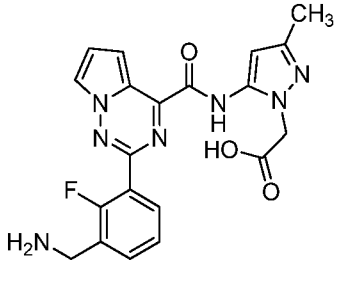
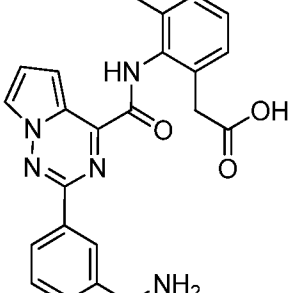
48. The compound of claim 45 or 46, having the structure of formula (IIa):

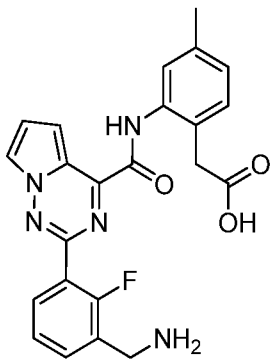
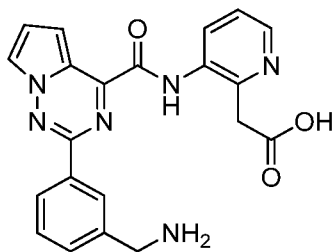
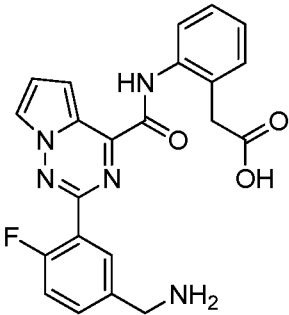
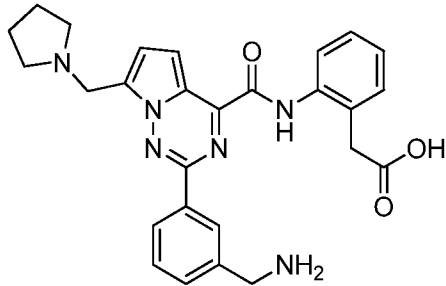
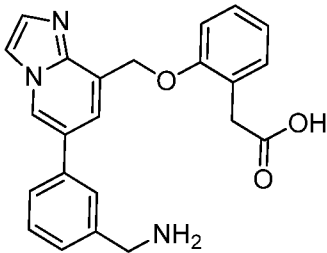
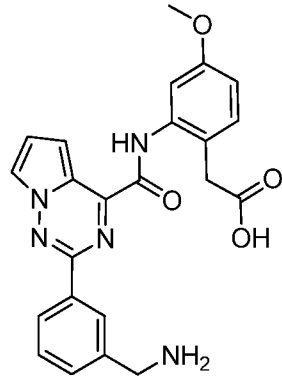
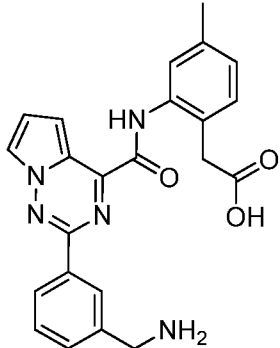
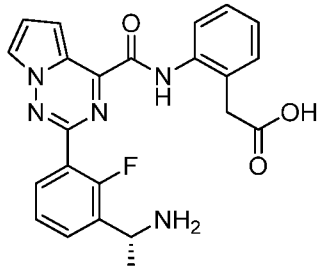
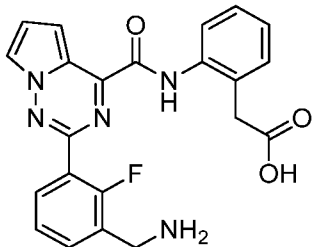
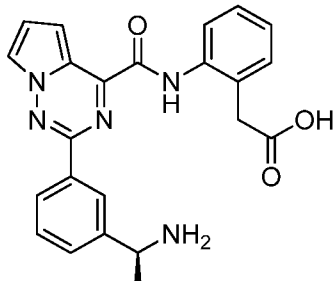


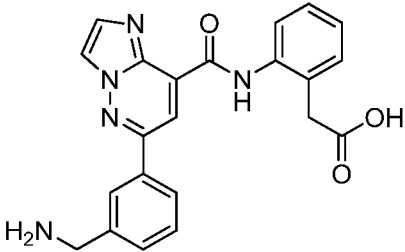
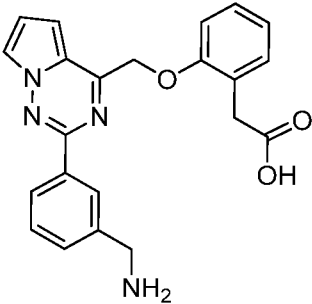
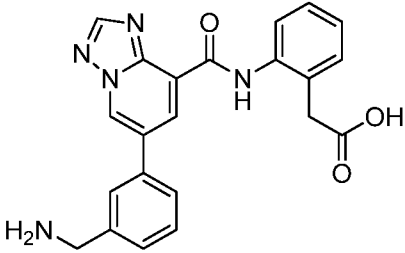
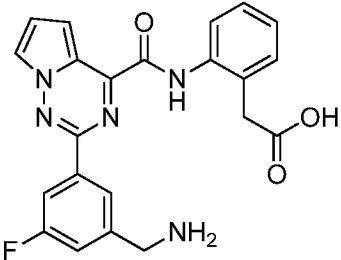
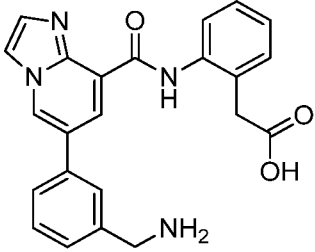
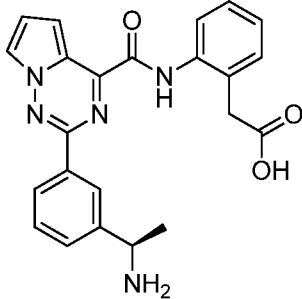
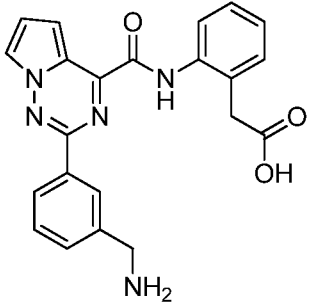
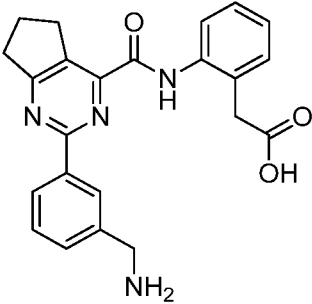
49. The compound of any one of claims 45-48, wherein p is 1.
50. The compound of claim 49, wherein R^a is alkyl or alkoxy.
51. The compound of any one of claims 45-48, wherein p is 0.
52. The compound of any one of claims 45-51, wherein R^1 is $-\text{CH}_2\text{COOH}$.
53. The compound of any one of claims 45-52, wherein $-\text{J}-\text{K}-$ is selected from the group consisting of $-\text{C}(\text{O})-\text{NH}-$, $-\text{NH}-\text{C}(\text{O})-$, and $-\text{CH}_2\text{O}-$.
54. The compound of claim 53, wherein $-\text{J}-\text{K}-$ is $-\text{CH}_2\text{O}-$.
55. The compound of any one of claims 45-54, wherein V is CH.
56. The compound of any one of claims 45-55, wherein each of W, X, Y, and Z is CH.
57. The compound of any one of claims 45-55, wherein at least one of W, X, Y, and Z is CR^c .
58. The compound of claim 57, wherein Z is CR^c .
59. The compound of claim 57 or 58, wherein Y is CR^c .
60. The compound of any one of claims 57-59, wherein R^c is halogen, e.g., fluoride.

61. The compound of any one of claims 45-55 and 57, wherein at least one of W, X, Y, and Z is N.
62. The compound of claim 61 wherein Z is N.
63. The compound of claim 61, wherein Y is N.
64. The compound of any one of claims 45-63, wherein L is $-\text{CH}_2-$.
65. The compound of any one of claims 45-64, wherein T^1 is $\text{CR}^{\text{T}1}$; and $\text{R}^{\text{T}1}$ and $\text{R}^{\text{T}2}$, taken together with the intervening atoms, form an optionally substituted heteroaryl ring, such as pyrrole, imidazole, or 1,2,4-triazole.
66. The compound of any one of claims 45-64, wherein T^3 is $\text{CR}^{\text{T}3}$; and $\text{R}^{\text{T}3}$ and $\text{R}^{\text{T}2}$, taken together with the intervening atoms, form an optionally substituted heteroaryl ring, such as pyrrole, imidazole, 1,2,4-triazole, or pyridine.
67. The compound of claim 45 or 46, selected from the following table:

68. A pharmaceutical composition, comprising a compound of any one of claims 1-67, or a pharmaceutically acceptable salt or prodrug thereof; and a pharmaceutically acceptable carrier.
69. A method of treating or preventing a disease or condition characterized by aberrant complement system activity, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-67, or a pharmaceutically acceptable salt or prodrug thereof.

70. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is an immunological disorder.
71. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is a disease of the central nervous system.
72. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is a neurodegenerative disease or neurological disease.
73. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is a renal disease.
74. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is a cardiovascular disease.
75. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is selected from the group consisting of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, organ transplant rejection, myasthenia gravis, neuromyelitis optica, membranoproliferative glomerulonephritis, dense-deposit disease, cold agglutinin disease, and catastrophic antiphospholipid syndrome.
76. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is selected from the group consisting of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), warm autoimmune hemolytic anemia, IgA nephropathy, C3 glomerulonephritis, and focal segmental glomerulosclerosis.
77. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is a hematological disorder.
78. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is an ocular disorder or an eye disorder.

79. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is macular degeneration, age-related macular degeneration (AMD), macular edema, diabetic macular edema, choroidal neovascularization (CNV), uveitis, Behcet's uveitis, proliferative diabetic retinopathy, non-proliferative diabetic retinopathy, glaucoma, hypertensive retinopathy, a corneal neovascularization disease, post-corneal transplant rejection, a corneal dystrophic disease, an autoimmune dry eye disease, Stevens-Johnson syndrome, Sjogren's syndrome, an environmental dry eye disease, Fuchs' endothelial dystrophy, retinal vein occlusion, or post-operative inflammation.