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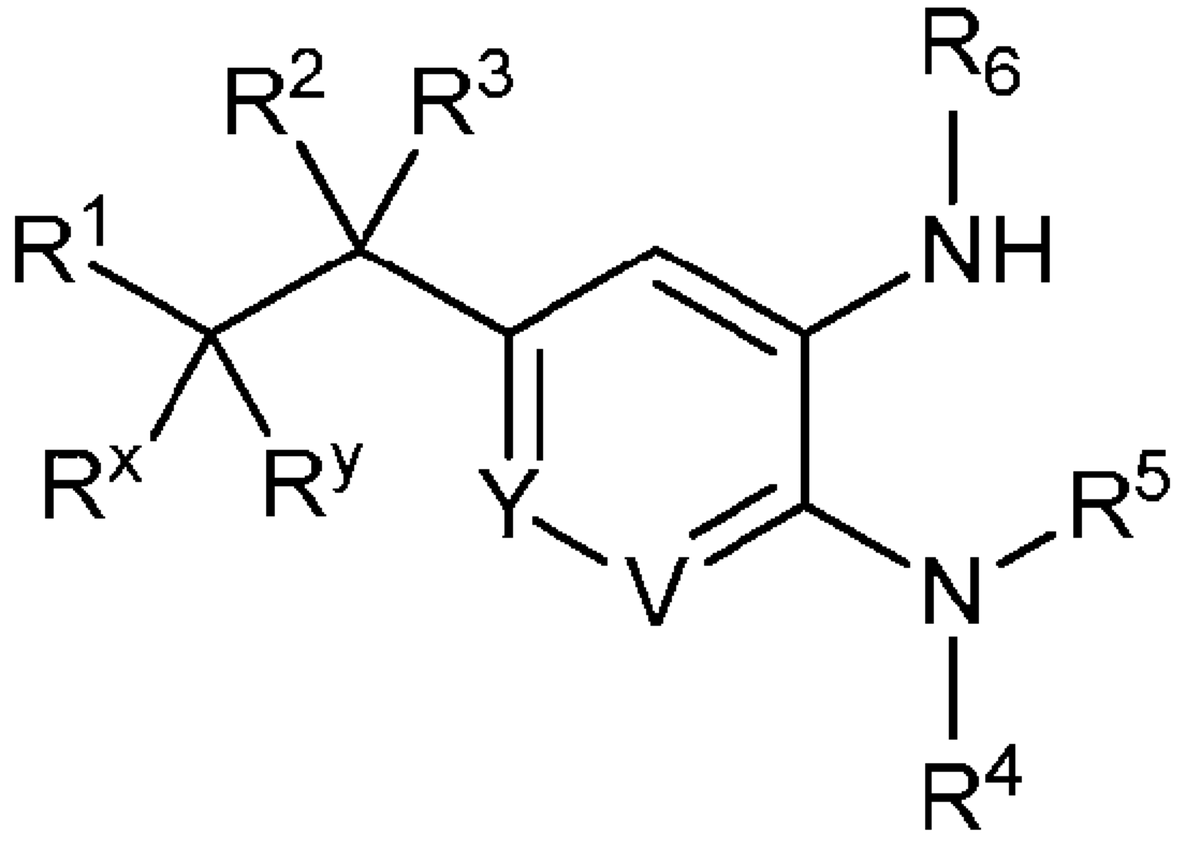
(54) Titre : INHIBITEURS DE L'INDOLEAMINE 2,3-DIOXYGENASE POUR LE TRAITEMENT DU CANCER
(54) Title: INHIBITORS OF INDOLEAMINE 2,3-DIOXYGENASE FOR THE TREATMENT OF CANCER



(I)

(57) Abrégé/Abstract:
There are disclosed compounds of formula (I) that modulate or inhibit the enzymatic activity of indoleamine-2,3-dioxygenase (IDO), pharmaceutical compositions containing said compounds and methods of treating proliferative disorders, such as cancer, viral infections and/or inflammatory disorders utilizing the compounds of the invention.

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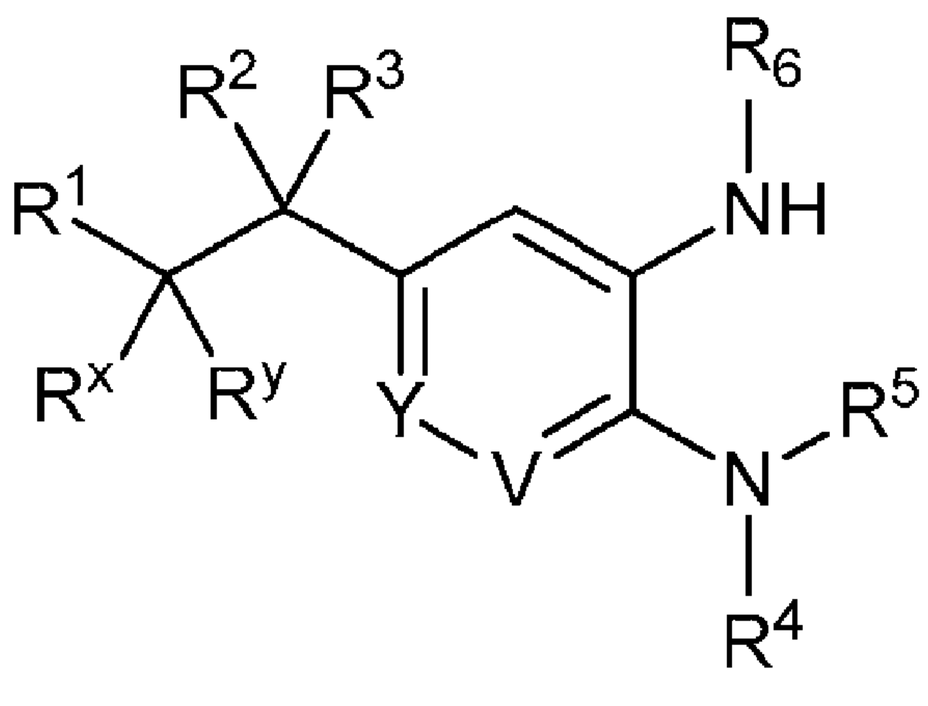
(54) **Title**: INHIBITORS OF INDOLEAMINE 2,3-DIOXYGENASE FOR THE TREATMENT OF CANCER



(I)

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INHIBITORS OF INDOLEAMINE 2,3-DIOXYGENASE FOR THE TREATMENT OF CANCER

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Serial No. 62/142,589, filed April 3, 2015, the entire content of which is incorporated herein by reference.

FIELD OF THE INVENTION

The invention relates generally to compounds that modulate or inhibit the enzymatic activity of indoleamine-2,3-dioxygenase (IDO), pharmaceutical compositions containing said compounds and methods of treating proliferative disorders, such as cancer, viral infections and/or autoimmune diseases utilizing the compounds of the invention.

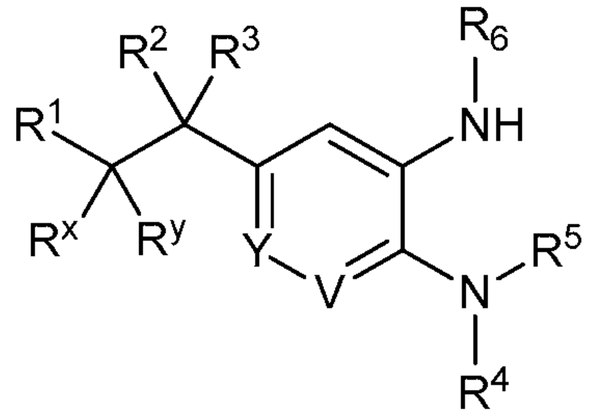
BACKGROUND OF THE INVENTION

Tryptophan is an amino acid which is essential for cell proliferation and survival. Indoleamine-2,3-dioxygenase is a heme-containing intracellular enzyme that catalyzes the first and rate-determining step in the degradation of the essential amino acid L-tryptophan to N-formyl-kynurenine. N-formyl-kynurenine is then metabolized by multiple steps to eventually produce nicotinamide adenine dinucleotide (NAD+). Tryptophan catabolites produced from N-formyl-kynurenine, such as kynurenine, are known to be preferentially cytotoxic to T-cells. Thus, an overexpression of IDO can lead to increased tolerance in the tumor microenvironment. IDO overexpression has been shown to be an independent prognostic factor for decreased survival in patients with melanoma, pancreatic, colorectal and endometrial cancers, among others. Moreover, IDO has been found to be implicated in neurologic and psychiatric disorders including mood disorders as well as other chronic diseases characterized by IDO activation and tryptophan depletion, such as viral infections, for example, AIDS, Alzheimer's disease, cancers including T-cell leukemia and colon cancer, autoimmune diseases, diseases of the eye such as cataracts, bacterial infections such as Lyme disease, and streptococcal infections.

Accordingly, an agent which is safe and effective in inhibiting the enzymatic function of IDO would be a most welcomed addition to the physician's armamentarium.

SUMMARY OF THE INVENTION

The present invention is directed to compounds of Formula I:



(I)

wherein:

Y is CF and V is CH; or Y is CH and V is CF; or Y is CF and V is CF;

R^1 is -COOH, -$COOC_1$-C_6 alkyl, -$CONH_2$, -CN, optionally substituted heterocyclyl, optionally substituted heteroaryl, -$NHCONHR^{13}$, -$CONHSO_2R^{14}$, -$CONHCOR^{13}$, -SO_2NHCOR^{13}, -$CONHSO_2NR^{13}R^{14}$, -SO_2NHR^{13}, -$NHCONHSO_2R^{13}$, -$CHCF_3OH$, -$COCF_3$, -CR^2R^3OH, or -$NHSO_2R^{13}$;

R^{13} is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_2-C_{10} alkenyl or optionally substituted C_2-C_{10} alkynyl;

R^{14} is H or optionally substituted C_1-C_{10} alkyl;

R^2 is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted heterocyclyl, or optionally substituted aryl;

R^3 is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted heterocyclyl, or optionally substituted aryl; or

R^2 and R^3 are taken together with the carbon to which they are attached to form an optionally substituted 3- to 6-membered carbocyclic or a 3- to 6-membered heterocyclic ring;

R^x is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10} alkoxy, or optionally substituted C_3-C_8 cycloalkyl;

R^y is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10} alkoxy, or optionally substituted C_3-C_8 cycloalkyl; or

R^x and R^y are taken together with the carbon to which they are attached to form a 3- to 7-membered heterocyclic ring containing 1-3 heteroatoms selected from -N-, -S-, and -O-;

R^4 is optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, optionally substituted C_1-C_{10} alkoxy, optionally substituted aryl, optionally substituted aryl-C_1-C_{10}-alkyl, optionally substituted 5- to 8-membered heteroaryl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted heterocyclyl;

R^5 is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, optionally substituted C_1-C_{10} alkoxy, optionally substituted aryl, optionally substituted aryl-C_1-C_{10}-alkyl, optionally substituted 5- to 8-membered heteroaryl, optionally substituted C_3-C_8 cycloalkyl or optionally substituted heterocyclyl; or

R^4 and R^5 are taken together with the nitrogen to which they are attached to form a 4- to 8-membered optionally substituted heterocyclic ring containing 0-3 additional heteroatoms selected from -N-, -S- and -O-; or

R^4 and R^5 are taken together with the nitrogen to which they are attached to form a 6- to 10-membered optionally substituted heterobicyclic ring containing 0-3 additional heteroatoms selected from -N-, -S-, and -O-;

R^6 is -C(O)NHR^8; and

R^8 is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted heterocyclyl;

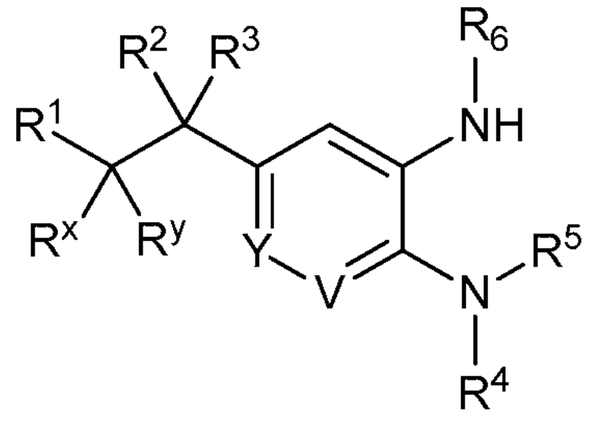
as well as stereoisomers thereof and tautomers thereof; and pharmaceutically acceptable salts thereof.

Compositions comprising compounds of Formula I, as well as methods of using compounds of Formula I in therapy, for example, in the treatment of cancer, are also described herein.

DETAILED DESCRIPTION OF THE INVENTION

I. COMPOUNDS OF THE INVENTION

The present invention is directed to compounds of Formula I:



(I)

wherein:

Y is CF and V is CH; or Y is CH and V is CF; or Y is CF and V is CF;

R^1 is -COOH, -COOC_1-C_6 alkyl, -$CONH_2$, -CN, optionally substituted heterocyclyl, optionally substituted heteroaryl, -$NHCONHR^{13}$, -$CONHSO_2R^{14}$, -$CONHCOR^{13}$, -SO_2NHCOR^{13}, -$CONHSO_2NR^{13}R^{14}$, -SO_2NHR^{13}, -$NHCONHSO_2R^{13}$, -$CHCF_3OH$, -$COCF_3$, -CR^2R^3OH, or -$NHSO_2R^{13}$;

R^{13} is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_2-C_{10} alkenyl or optionally substituted C_2-C_{10} alkynyl;

R^{14} is H or optionally substituted C_1-C_{10} alkyl;

R^2 is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted heterocyclyl, or optionally substituted aryl;

R^3 is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted heterocyclyl, or optionally substituted aryl; or

R^2 and R^3 are taken together with the carbon to which they are attached to form an optionally substituted 3- to 6-membered carbocyclic or a 3- to 6-membered heterocyclic ring;

R^x is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10} alkoxy, or optionally substituted C_3-C_8 cycloalkyl;

R^y is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10} alkoxy, or optionally substituted C_3-C_8 cycloalkyl; or

R^x and R^y are taken together with the carbon to which they are attached to form a 3- to 7-membered heterocyclic ring containing 1-3 heteroatoms selected from -N-, -S-, and -O-;

R^4 is optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, optionally substituted C_1-C_{10} alkoxy, optionally substituted aryl, optionally substituted aryl-C_1-C_{10}-alkyl, optionally substituted 5- to 8-membered heteroaryl, optionally substituted C_3-C_8 cycloalkyl or optionally substituted heterocyclyl;

R^5 is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, optionally substituted C_1-C_{10} alkoxy, optionally substituted aryl, optionally substituted aryl-C_1-C_{10}-alkyl, optionally substituted 5- to 8-membered heteroaryl, optionally substituted C_3-C_8 cycloalkyl or optionally substituted heterocyclyl; or

R^4 and R^5 are taken together with the nitrogen to which they are attached to form a 4- to 8-membered optionally substituted heterocyclic ring containing 0-3 additional heteroatoms selected from -N-, -S- and -O-; or

R^4 and R^5 are taken together with the nitrogen to which they are attached to form a 6- to 10-membered optionally substituted heterobicyclic ring containing 0-3 additional heteroatoms selected from -N-, -S-, and -O-;

R^6 is $-C(O)NHR^8$; and

R^8 is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted heterocyclyl;

as well as stereoisomers thereof and tautomers thereof; and also pharmaceutically acceptable salts thereof.

According to the invention, Y is CF and V is CH; or Y is CH and V is CF; or Y is CF and V is CF. In preferred aspects, Y is CF and V is CH. In other preferred aspects, Y is CH and V is CF. In some aspects, Y is CF and V is CF.

According to the invention, R^1 is -COOH, $-COOC_1$-C_6 alkyl, $-CONH_2$, -CN, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-NHCONHR^{13}$, $-CONHSO_2R^{14}$, $-CONHCOR^{13}$, $-SO_2NHCOR^{13}$, $-CONHSO_2NR^{13}R^{14}$, $-SO_2NHR^{13}$, $-NHCONHSO_2R^{13}$, $-CHCF_3OH$, $-COCF_3$, $-CR^2R^3OH$, or $-NHSO_2R^{13}$. In those aspects wherein R^1 is $-NHCONHR^{13}$, $-CONHSO_2R^{14}$, $-CONHCOR^{13}$, $-SO_2NHCOR^{13}$,

-$CONHSO_2NR^{13}R^{14}$, -SO_2NHR^{13}, -$NHCONHSO_2R^{13}$, or -$NHSO_2R^{13}$, R^{13} is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_2-C_{10} alkenyl or optionally substituted C_2-C_{10} alkynyl; and R^{14} is H or optionally substituted C_1-C_{10} alkyl. In those aspects wherein R^1 is -CR^2R^3OH, R^2 and R^3 are each independently H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_{3-6}cycloalkyl, or optionally substituted aryl.

In preferred aspects, R^1 is -COOH. In other aspects, R^1 is -$COOC_1$-C_6 alkyl, -$CONH_2$, -$CONHSO_2R^{14}$, -$CONHCOR^{13}$, -$CONHSO_2NR^{13}R^{14}$, or -$COCF_3$. In some aspects, R^1 is -CN. In other aspects, R^1 is optionally substituted heterocyclyl or optionally substituted heteroaryl. In other embodiments, R^1 is -$NHCONHR^{13}$, -$NHCONHSO_2R^{13}$, or -$NHSO_2R^{13}$. In still other aspects, R^1 is -SO_2NHCOR^{13} or -SO_2NHR^{13}. In some embodiments, R^1 is -$CHCF_3OH$ or -CR^2R^3OH.

According to the invention, R^2 is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted heterocyclyl, or optionally substituted aryl. In preferred aspects, R^2 is H.

In other aspects, R^2 is C_1-C_{10} alkyl, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or *t*-butyl. In some aspects, R^2 is substituted C_1-C_{10} alkyl, for example, substituted with 1, 2, or 3 independently selected substituents. When R^2 is substituted C_1-C_{10} alkyl, the C_1-C_{10} alkyl can be substituted with any substituent as defined herein. In preferred aspects, the substituted C_1-C_{10} alkyl is substituted with a substituent selected from -OH, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo, and haloalkyl.

In other aspects, R^2 is C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In other aspects, R^2 is substituted C_{3-6}cycloalkyl, for example, substituted with 1, 2, or 3 independently selected substituents. When R^2 is substituted C_{3-6}cycloalkyl the C_{3-6}cycloalkyl can be substituted with any substituent as defined herein. In preferred aspects, the substituted C_{3-6}cycloalkyl is substituted with a substituent selected from -OH, C_1-C_{10} alkyl, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo, and haloalkyl.

In other aspects, R^2 is heterocyclyl. The heterocyclyl can be any heterocyclyl defined herein, with a preferred heterocyclyl being an oxygen-containing heterocyclyl, *e.g.*, tetrahydropyranyl. In some aspects, the heterocyclyl is substituted heterocyclyl, for example, substituted with 1, 2, or 3 independently selected substituents. When R^2 is

substituted heterocyclyl, the heterocyclyl can be substituted with any substituent as defined herein. In preferred aspects, the substituted heterocyclyl is substituted with a substituent selected from -OH, C_1-C_{10} alkyl, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo, and haloalkyl.

In other aspects, R^2 is aryl, for example phenyl. In other aspects, R^2 is substituted aryl, for example, substituted with 1, 2, or 3 independently selected substituents. When R^2 is substituted aryl the aryl can be substituted with any substituent as defined herein. In preferred aspects, the substituted aryl is substituted with a substituent selected from -OH, C_1-C_{10} alkyl, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo, and haloalkyl.

According to the invention, R^3 is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted heterocyclyl, or optionally substituted aryl. In preferred aspects, R^3 is H.

In other aspects, R^3 is C_1-C_{10} alkyl, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or *t*-butyl. In some aspects, R^3 is substituted C_1-C_{10} alkyl, for example, substituted with 1, 2, or 3 independently selected substituents. When R^3 is substituted C_1-C_{10} alkyl, the C_1-C_{10} alkyl can be substituted with any substituent as defined herein. In preferred aspects, the substituted C_1-C_{10} alkyl is substituted with a substituent selected from -OH, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo, and haloalkyl.

In other aspects, R^3 is C_{3-6}cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In other aspects, R^2 is substituted C_{3-6}cycloalkyl, for example, substituted with 1, 2, or 3 independently selected substituents. When R^3 is substituted C_{3-6}cycloalkyl the C_{3-6}cycloalkyl can be substituted with any substituent as defined herein. In preferred aspects, the substituted C_{3-6}cycloalkyl is substituted with a substituent selected from -OH, C_1-C_{10} alkyl, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo, and haloalkyl.

In other aspects, R^3 is heterocyclyl. The heterocyclyl can be any heterocyclyl defined herein, with a preferred heterocyclyl being an oxygen-containing heterocyclyl, *e.g.*, tetrahydropyranyl. In some aspects, the heterocyclyl is substituted heterocyclyl, for example, substituted with 1, 2, or 3 independently selected substituents. When R^3 is substituted heterocyclyl, the heterocyclyl can be substituted with any substituent as defined herein. In preferred aspects, the substituted heterocyclyl is substituted with a

substituent selected from -OH, C_1-C_{10} alkyl, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo, and haloalkyl.

In other aspects, R^3 is aryl, for example phenyl. In other aspects, R^3 is substituted aryl, for example, substituted with 1, 2, or 3 independently selected substituents. When R^3 is substituted aryl the aryl can be substituted with any substituent as defined herein. In preferred aspects, the substituted aryl is substituted with a substituent selected from -OH, C_1-C_{10} alkyl, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo, and haloalkyl.

In alternative embodiments, R^2 and R^3 are taken together with the carbon to which they are attached to form a 3- to 6-membered carbocyclic ring, for example, R^2 and R^3 are taken together with the carbon to which they are attached to form a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl ring. In some embodiments, the 3- to 6-membered carbocyclic ring formed by the taking together of R^2 and R^3 is substituted, for example, with 1, 2, or 3 independently selected substituents. The 3- to 6-membered carbocyclic ring can be substituted with any substituent as defined herein. In preferred aspects, the 3- to 6-membered carbocyclic ring is substituted with a substituent selected from -OH, C_1-C_{10} alkyl, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo, and haloalkyl.

In alternative embodiments, R^2 and R^3 are taken together with the carbon to which they are attached to form a 3- to 6-membered heterocyclic ring, for example, R^2 and R^3 are taken together with the carbon to which they are attached to form a 3- to 6- membered heterocyclic ring including at least one heteroatom selected from O, N, and S (wherein the -S- is optionally oxidized to SO or SO_2). In some embodiments, the 3- to 6-membered heterocyclic ring formed by the taking together of R^2 and R^3 is substituted, for example, with 1, 2, or 3 independently selected substituents. The 3- to 6-membered heterocyclic ring can be substituted with any substituent as defined herein. In preferred aspects, the 3- to 6-membered heterocyclic ring is substituted with a substituent selected from -OH, C_1-C_{10} alkyl, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo, and haloalkyl.

In preferred aspects, one of R^2 and R^3 is H and the other is optionally substituted C_1-C_{10} alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted heterocyclyl, or optionally substituted aryl. In some preferred aspects, one of R^2 and R^3 is H and the other is C_1-C_{10} alkyl, for example, methyl, ethyl, propyl, butyl, isobutyl, or *t*-butyl. In those embodiments wherein the C_1-C_{10} alkyl is a substituted C_1-C_{10} alkyl, the C_1-C_{10} alkyl is substituted with 1 or 2 substituents independently selected from -OC_{1-6}alkyl (*e.g.*, -OCH_3)

and haloalkyl (*e.g.*, -CF_3). In some preferred aspects, one of R^2 and R^3 is H and the other is C_{3-6}cycloalkyl, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclobutyl, cyclopenyl, or cyclohexyl. In those embodiments wherein the C_{3-6}cycloalkyl is a substituted C_{3-6}cycloalkyl, the C_{3-6}cycloalkyl is substituted with 1 or 2 substituents independently selected from -OH, C_1-C_{10}alkyl (*e.g.*, methyl, ethyl, and the like), -OC_{1-6}alkyl (*e.g.*, -OCH_3), and haloalkyl (*e.g.*, -CF_3).

In other preferred aspects, R^2 and R^3 are each independently C_1-C_{10} alkyl, for example, methyl, ethyl, propyl, butyl, isobutyl, or *t*-butyl. In those embodiments wherein R^2 and R^3 are each independently a substituted C_1-C_{10} alkyl, each C_1-C_{10} alkyl is independently substituted with 1 or 2 substituents independently selected from -OH, -OC_{1-6}alkyl (*e.g.*, -OCH_3) and haloalkyl (*e.g.*, -CF_3).

According to the invention, R^x is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10} alkoxy, or optionally substituted C_3-C_8 cycloalkyl. In preferred aspects, R^x is H.

In other aspects, R^x is C_1-C_{10} alkyl, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or *t*-butyl. In some aspects, R^x is substituted C_1-C_{10} alkyl, for example, substituted with 1, 2, or 3 independently selected substituents. When R^x is substituted C_1-C_{10} alkyl, the C_1-C_{10} alkyl can be substituted with any substituent as defined herein. In preferred aspects, the substituted C_1-C_{10} alkyl is substituted with a substituent selected from -OH, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo, and haloalkyl.

In other aspects, R^x is C_1-C_{10} alkoxy, for example, methoxy, ethoxy, propoxy, butoxy, and the like. In some aspects, R^x is substituted C_1-C_{10} alkoxy, for example, substituted with 1, 2, or 3 independently selected substituents. When R^x is substituted C_1-C_{10} alkoxy, the C_1-C_{10} alkoxy can be substituted with any substituent as defined herein. In preferred aspects, the substituted C_1-C_{10} alkoxy is substituted with a substituent selected from -OH, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo, and haloalkyl.

In other aspects, R^x is C_3-C_8 cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In other aspects, R^x is substituted C_{3-6}cycloalkyl, for example, substituted with 1, 2, or 3 independently selected substituents. When R^x is substituted C_{3-6}cycloalkyl the C_{3-6}cycloalkyl can be substituted with any substituent as defined herein. In preferred aspects, the substituted C_3-C_8 cycloalkyl is substituted with a

substituent selected from -OH, C_1-C_{10} alkyl, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo, and haloalkyl.

According to the invention, R^y is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10} alkoxy, or optionally substituted C_3-C_8 cycloalkyl. In preferred aspects, R^y is H.

In other aspects, R^y is C_1-C_{10} alkyl, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or *t*-butyl. In some aspects, R^y is substituted C_1-C_{10} alkyl, for example, substituted with 1, 2, or 3 independently selected substituents. When R^y is substituted C_1-C_{10} alkyl, the C_1-C_{10} alkyl can be substituted with any substituent as defined herein. In preferred aspects, the substituted C_1-C_{10} alkyl is substituted with a substituent selected from -OH, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo, and haloalkyl.

In other aspects, R^y is C_1-C_{10} alkoxy, for example, methoxy, ethoxy, propoxy, butoxy, and the like. In some aspects, R^y is substituted C_1-C_{10} alkoxy, for example, substituted with 1, 2, or 3 independently selected substituents. When R^y is substituted C_1-C_{10} alkoxy, the C_1-C_{10} alkoxy can be substituted with any substituent as defined herein. In preferred aspects, the substituted C_1-C_{10} alkoxy is substituted with a substituent selected from -OH, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo, and haloalkyl.

In other aspects, R^y is C_3-C_8 cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In other aspects, R^y is substituted C_{3-6}cycloalkyl, for example, substituted with 1, 2, or 3 independently selected substituents. When R^y is substituted C_{3-6}cycloalkyl the C_{3-6}cycloalkyl can be substituted with any substituent as defined herein. In preferred aspects, the substituted C_3-C_8 cycloalkyl is substituted with a substituent selected from -OH, C_1-C_{10} alkyl, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo, and haloalkyl.

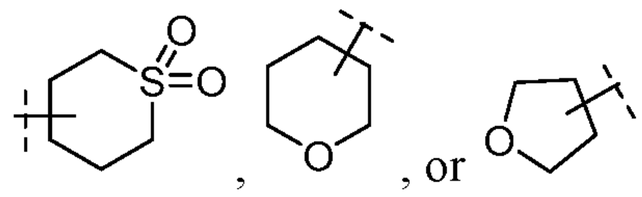
In alternative aspects, R^x and R^y are taken together with the carbon to which they are attached to form a 3- to 6-membered carbocyclic ring.

In alternative aspects, R^x and R^y are taken together with the carbon to which they are attached to form a 3- to 7-membered heterocyclic ring containing 1-3 heteroatoms, preferably 1 heteroatom selected from -N-, -S- (wherein the -S- is optionally oxidized to SO or SO_2) and -O-.

In most preferred embodiments, R^x and R^y are each H.

According to the invention, R^4 is optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, optionally substituted C_1-C_{10} alkoxy, optionally substituted aryl, optionally substituted aryl-C_1-C_{10}-alkyl, optionally substituted 5- to 8-membered heteroaryl, optionally substituted C_3-C_8 cycloalkyl or optionally substituted heterocyclyl. In preferred aspects, R^4 is C_1-C_{10} alkyl, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or *t*-butyl, with isobutyl being particularly preferred. In some aspects, R^4 is substituted C_1-C_{10} alkyl, for example, substituted with 1, 2, or 3 independently selected substituents. In preferred aspects, the substituted C_1-C_{10} alkyl is substituted 1, 2, or 3 substituents independently selected from -OH, $C_{3\text{-}6}$cycloalkyl, -O$C_{1\text{-}6}$alkyl, -O$C_{1\text{-}6}$haloalkyl, halo, and haloalkyl. In other preferred aspects, the substituted C_1-C_{10} alkyl is substituted 1 or 2 substituents independently selected from -OH, $C_{3\text{-}6}$cycloalkyl and -O$C_{1\text{-}6}$alkyl. In other preferred aspects, R^4 is C_3-C_8 cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some aspects, R^4 is substituted C_3-C_8 cycloalkyl, for example, substituted with 1, 2, or 3 independently selected substituents. In preferred aspects, the substituted C_3-C_8 cycloalkyl is substituted 1, 2, or 3 substituents independently selected from -OH, C_1-C_{10}alkyl, -O$C_{1\text{-}6}$alkyl, -O$C_{1\text{-}6}$haloalkyl, halo, and haloalkyl. In other preferred aspects, the substituted C_3-C_8 cycloalkyl is substituted 1 or 2 substituents independently selected from -OH, C_1-C_{10}alkyl, and -O$C_{1\text{-}6}$alkyl.

In other aspects, R^4 is heterocyclyl, preferably heterocycloalkyl. In other aspects, R^4 is substituted heterocyclyl, *e.g.*, substituted heterocycloalkyl, for example, substituted with 1, 2, or 3 independently selected substituents. When R^4 is a substituted heterocyclyl, *e.g.*, substituted heterocycloalkyl, the heterocyclyl can be substituted with any substituent as defined herein. In preferred aspects, the substituted heterocyclyl is substituted with a substituent selected from -OH, hydroxylC_1-C_{10}alkyl (*e.g.*, $(CH_3)_2(OH)C$-), C_1-C_{10} alkyl, $C_{3\text{-}6}$cycloalkyl, -O$C_{1\text{-}6}$alkyl, -O$C_{1\text{-}6}$haloalkyl, halo, haloalkyl, aryl, and alkaryl. The heterocyclyl can be any heterocyclyl , preferably any heterocycloalkyl group defined herein. Preferably, the heterocyclyl is a heterocycloalkyl that is tetrahydrothiopyranyl-dioxide, tetrahydropyranyl, or tetrahydrofuranyl:



any of which can be attached to Formula I through any ring carbon atom. A most preferred heterocycloalkyl is tetrahydropyranyl. In other aspects, the heterocycloalkyl is tetrahydrothiopyranyl-dioxide. In yet other aspects, the heterocycloalkyl is tetrahydrofuranyl.

According to the invention, R^5 is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, optionally substituted C_1-C_{10} alkoxy, optionally substituted aryl, optionally substituted aryl-C_1-C_{10}-alkyl, optionally substituted 5- to 8-membered heteroaryl, optionally substituted C_3-C_8 cycloalkyl or optionally substituted heterocyclyl. In some aspects, R^5 is H. In preferred aspects, R^5 is C_1-C_{10} alkyl, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or *t*-butyl, with isobutyl being particularly preferred. In some aspects, R^5 is substituted C_1-C_{10} alkyl, for example, substituted with 1, 2, or 3 independently selected substituents. In preferred aspects, the substituted C_1-C_{10} alkyl is substituted 1, 2, or 3 substituents independently selected from -OH, $C_{3\text{-}6}$cycloalkyl, -O$C_{1\text{-}6}$alkyl, -O$C_{1\text{-}6}$haloalkyl, halo, and haloalkyl. In other preferred aspects, the substituted C_1-C_{10} alkyl is substituted 1 or 2 substituents independently selected from -OH, $C_{3\text{-}6}$cycloalkyl and -O$C_{1\text{-}6}$alkyl.

In alternative embodiments, R^4 and R^5 are taken together with the nitrogen to which they are attached to form a 4- to 8-membered heterocyclic ring containing 0-3 additional heteroatoms, preferably 1 or 2 additional heteroatoms, selected from -N-, -S- (wherein the -S- can be oxidized to SO or SO_2), and -O-, for example, the ring formed by the taking together of R^4 and R^5 is a pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl. In some aspects, the 4- to 8-membered heterocyclic ring is substituted, for example, substituted with 1, 2, or 3 independently selected substituents. The substituents can be any substituent defined herein. In preferred aspects, the substituted 4- to 8-membered heterocyclic ring is substituted with a substituent selected from -OH, C_1-C_{10} alkyl, $C_{3\text{-}6}$cycloalkyl, -O$C_{1\text{-}6}$alkyl, O$C_{1\text{-}6}$haloalkyl, halo, haloalkyl, aryl, and alkaryl.

In alternative embodiments, R^4 and R^5 are taken together with the nitrogen to which they are attached to form a 6- to 10-membered optionally substituted heterobicyclic ring containing 0-3 additional heteroatoms, preferably 1 or 2 additional heteroatoms selected from -N-, -S- (wherein the -S- can be oxidized to SO or SO_2), and -O-. In some aspects, the 6- to 10-membered optionally substituted heterobicyclic ring is substituted,

for example, substituted with 1, 2, or 3 independently selected substituents. The substituents can be any substituent defined herein. In preferred aspects, the substituted 6- to 10-membered optionally substituted heterobicyclic ring is substituted with a substituent selected from -OH, C_1-C_{10} alkyl, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo, haloalkyl, aryl, and alkaryl.

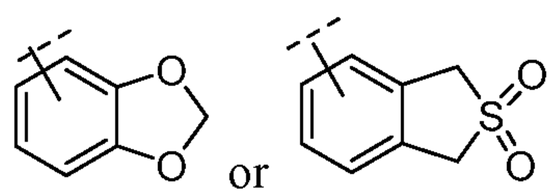
According to the invention, R^6 is -C(O)NHR^8 wherein R^8 is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted heterocyclyl.

In some aspects, R^8 is aryl, for example, phenyl. In some aspects, R^8 is substituted aryl, for example, substituted with 1, 2, or 3 independently selected substituents. In preferred aspects, the substituted aryl is substituted a substituent selected from -OH, C_1-C_{10} alkyl, C_{3-6}cycloalkyl,-CN, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo (*e.g.*, F and/or Cl), and haloalkyl.

In some aspects, R^8 is heteroaryl, for example, any heteroaryl group defined herein, in particular, isoxazolyl, pyridyl, pyrimidinyl, pyrazinyl, or pyridazinyl. In some aspects, R^8 is substituted heteroaryl, for example, substituted with 1, 2, or 3 independently selected substituents. In preferred aspects, the substituted heteroaryl is substituted with a substituent selected from -OH, C_1-C_{10} alkyl, C_{3-6}cycloalkyl,-CN, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo (*e.g.*, F and/or Cl), and haloalkyl.

In some aspects, R^8 is C_3-C_8 cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopenyl, or cyclohexyl. In some aspects, R^8 is substituted C_3-C_8 cycloalkyl, for example, substituted with 1, 2, or 3 independently selected substituents. In preferred aspects, the substituted C_3-C_8 cycloalkyl is substituted with a substituent selected from -OH, C_1-C_{10} alkyl, C_{3-6}cycloalkyl,-CN, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo (*e.g.*, F and/or Cl), and haloalkyl.

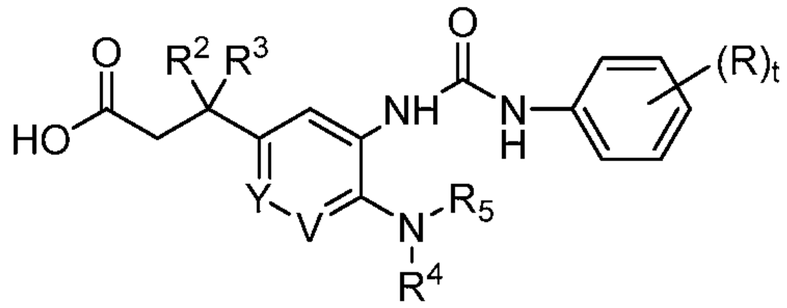
In some aspects, R^8 is heterocyclyl, for example, any heterocyclyl defined herein, in particular, benzodioxolyl or dihydrobenzothiophenyl-dioxide:



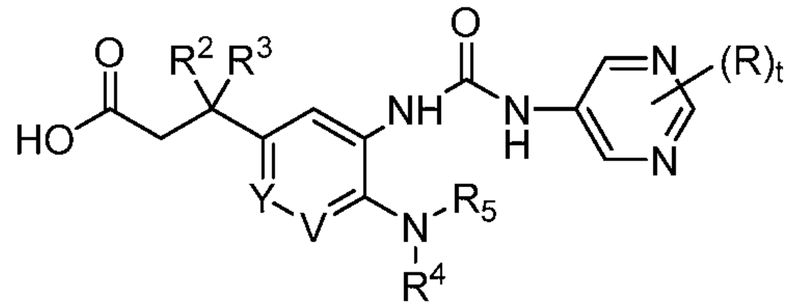
In some aspects, R^8 is substituted heterocyclyl, for example, substituted with 1, 2, or 3 independently selected substituents. In preferred aspects, the substituted heterocyclyl is

substituted with a substituent selected from -OH, C_1-C_{10} alkyl, C_{3-6}cycloalkyl,-CN, -OC_{1-6}alkyl, -OC_{1-6}haloalkyl, halo (*e.g.*, F and/or Cl), and haloalkyl.

Also within the scope of the invention are compounds of formulas IA and IB, and the pharmaceutically acceptable salts thereof.



IA-1



IA-2

wherein:

Y is CF and V is CH or Y is CH and V is CF;

t is 0, 1, 2, or 3, preferably 1 or 2;

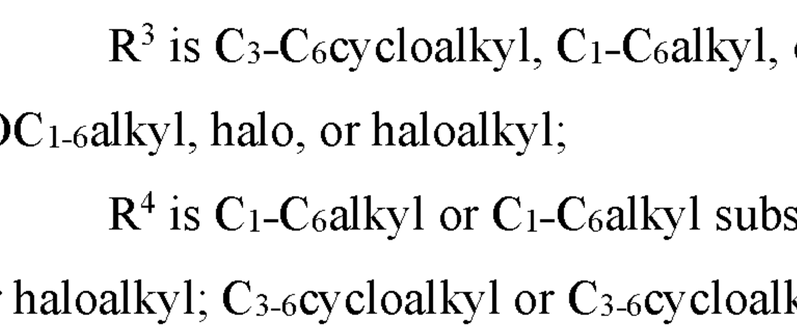
each R is independently F, Cl, C_1-C_6alkyl, C_1-C_6haloalkyl, -CN, -OC_1-C_6alkyl, or -OC_1-C_6haloalkyl;

R^2 is H, C_3-C_6cycloalkyl, C_1-C_6alkyl, or C_1-C_6alkyl substituted with C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl;

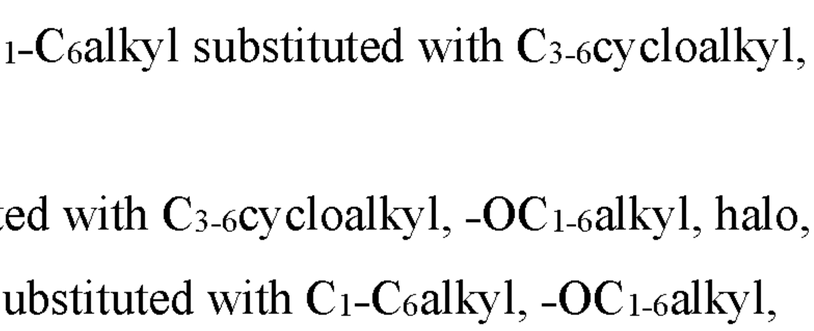
R^3 is C_3-C_6cycloalkyl, C_1-C_6alkyl, or C_1-C_6alkyl substituted with C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl;

R^4 is C_1-C_6alkyl or C_1-C_6alkyl substituted with C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl; C_{3-6}cycloalkyl or C_{3-6}cycloalkyl substituted with C_1-C_6alkyl, -OC_{1-6}alkyl, halo, or haloalkyl; or heterocycloalkyl or heterocycloalkyl substituted with C_1-C_6alkyl, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl; and

R^5 is C_1-C_6alkyl, or C_1-C_6alkyl substituted with C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl.



IB-1



IB-2

wherein:

Y is CF and V is CH or Y is CH and V is CF;

each s is independently 0, 1, or 2;

Z is N, O, S, SO, or SO_2;

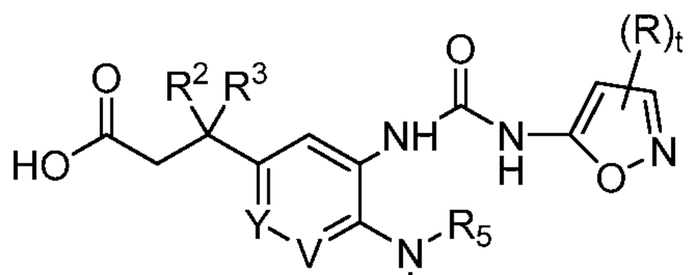
each t is 0, 1, 2, or 3;

each R is independently F, Cl, C_1-C_6alkyl, C_1-C_6haloalkyl, -CN, -OC_1-C_6alkyl, or -OC_1-C_6haloalkyl;

R^2 is H, C_3-C_6cycloalkyl, C_1-C_6alkyl, or C_1-C_6alkyl substituted with C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl; and

R^3 is C_3-C_6cycloalkyl, C_1-C_6alkyl, or C_1-C_6alkyl substituted with C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl.

Also within the scope of the invention are compounds of formulas IC and ID, and the pharmaceutically acceptable salts thereof.



IC-1

wherein:

Y is CF and V is CH or Y is CH and V is CF;

t is 0, 1, or 2, preferably 1;

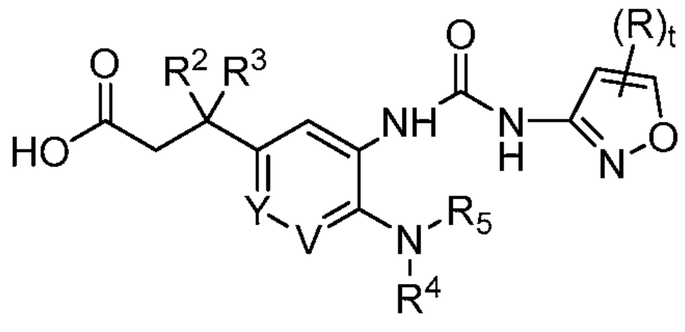
each R is independently F, Cl, C_1-C_6alkyl, C_1-C_6haloalkyl, -CN, -OC_1-C_6alkyl, or -OC_1-C_6haloalkyl;

R^2 is H, C_3-C_6cycloalkyl, C_1-C_6alkyl, or C_1-C_6alkyl substituted with C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl;

R^3 is C_3-C_6cycloalkyl, C_1-C_6alkyl, or C_1-C_6alkyl substituted with C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl;

R^4 is C_1-C_6alkyl or C_1-C_6alkyl substituted with C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl; C_{3-6}cycloalkyl or C_{3-6}cycloalkyl substituted with C_1-C_6alkyl, -OC_{1-6}alkyl, halo, or haloalkyl; or heterocycloalkyl or heterocycloalkyl substituted with C_1-C_6alkyl, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl; and

R^5 is C_1-C_6alkyl, or C_1-C_6alkyl substituted with C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl.



IC-2

wherein:

Y is CF and V is CH or Y is CH and V is CF;

each s is independently 0, 1, or 2;

Z is N, O, S, SO, or SO_2;

each t is 0, 1, or 2, preferably 1;

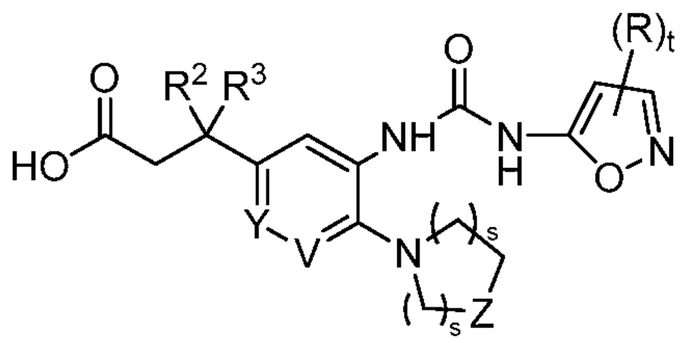
each R is independently F, Cl, C_1-C_6alkyl, C_1-C_6haloalkyl, -CN, -OC_1-C_6alkyl, or -OC_1-C_6haloalkyl;

R^2 is H, C_3-C_6cycloalkyl, C_1-C_6alkyl, or C_1-C_6alkyl substituted with C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl;

R^3 is C_3-C_6cycloalkyl, C_1-C_6alkyl, or C_1-C_6alkyl substituted with C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl;

R^4 is C_1-C_6alkyl or C_1-C_6alkyl substituted with C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl; C_{3-6}cycloalkyl or C_{3-6}cycloalkyl substituted with C_1-C_6alkyl, -OC_{1-6}alkyl, halo, or haloalkyl; or heterocycloalkyl or heterocycloalkyl substituted with C_1-C_6alkyl, C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl; and

R^5 is C_1-C_6alkyl, or C_1-C_6alkyl substituted with C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl.



ID-1

wherein:

Y is CF and V is CH or Y is CH and V is CF;

each s is independently 0, 1, or 2;

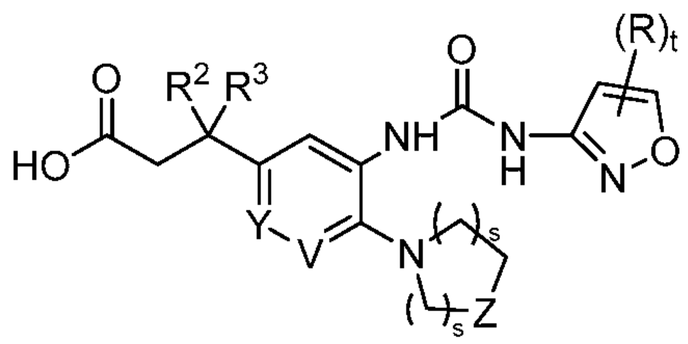
Z is N, O, S, SO, or SO_2;

each t is 0, 1, or 2, preferably 1;

each R is independently F, Cl, C_1-C_6alkyl, C_1-C_6haloalkyl, -CN, -OC_1-C_6alkyl, or -OC_1-C_6haloalkyl;

R^2 is H, C_3-C_6cycloalkyl, C_1-C_6alkyl, or C_1-C_6alkyl substituted with C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl; and

R^3 is C_3-C_6cycloalkyl, C_1-C_6alkyl, or C_1-C_6alkyl substituted with C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl.



ID-2

wherein:

Y is CF and V is CH or Y is CH and V is CF;

each s is independently 0, 1, or 2;

Z is N, O, S, SO, or SO_2;

each t is 0, 1, or 2, preferably 1;

each R is independently F, Cl, C_1-C_6alkyl, C_1-C_6haloalkyl, -CN, -OC_1-C_6alkyl, or -OC_1-C_6haloalkyl;

R^2 is H, C_3-C_6cycloalkyl, C_1-C_6alkyl, or C_1-C_6alkyl substituted with C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl; and

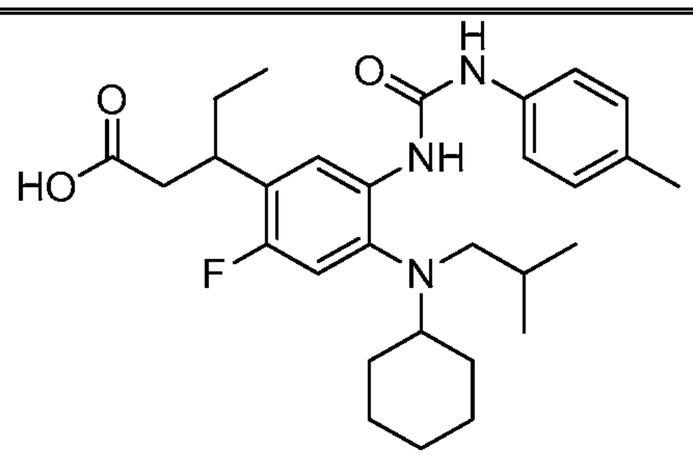
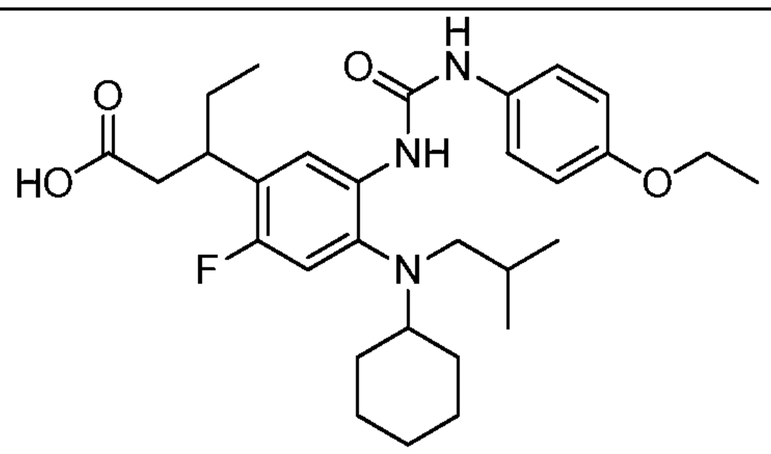
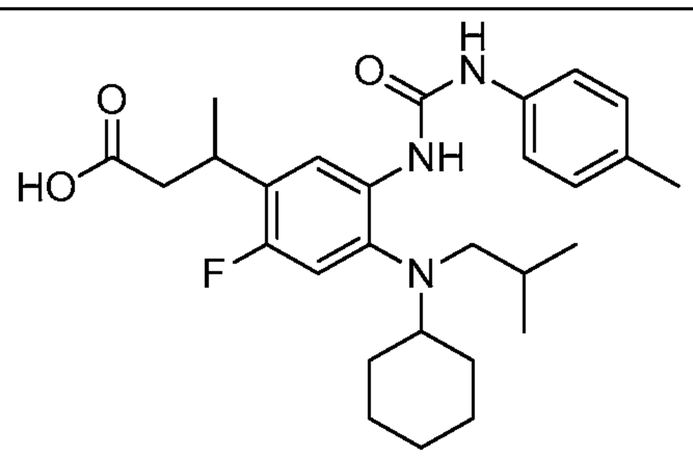
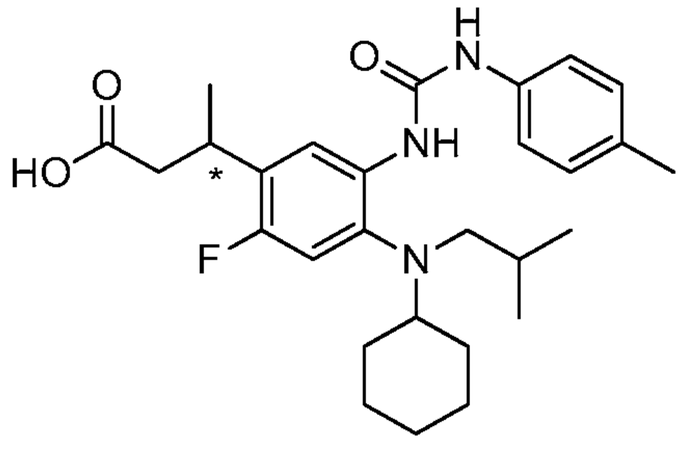
R^3 is C_3-C_6cycloalkyl, C_1-C_6alkyl, or C_1-C_6alkyl substituted with C_{3-6}cycloalkyl, -OC_{1-6}alkyl, halo, or haloalkyl.

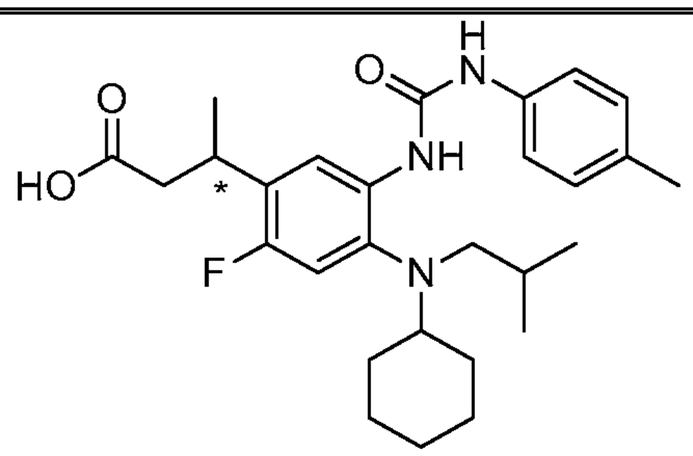
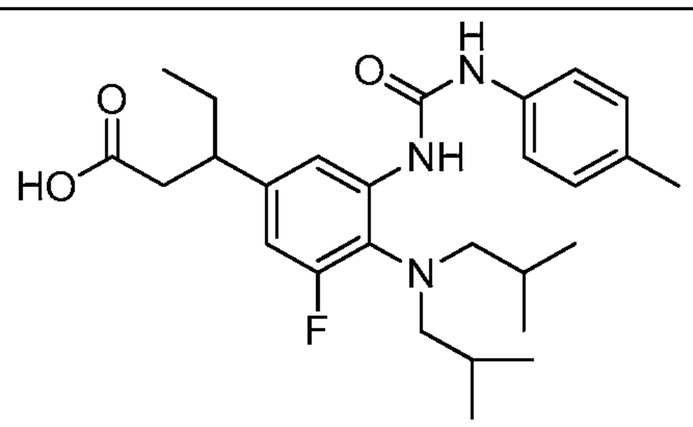
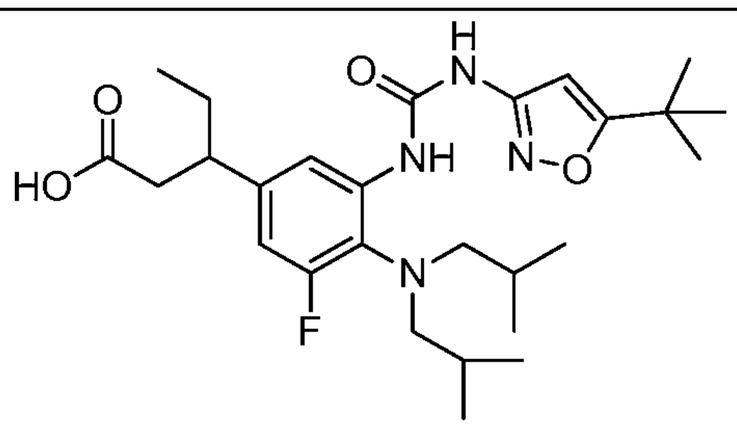
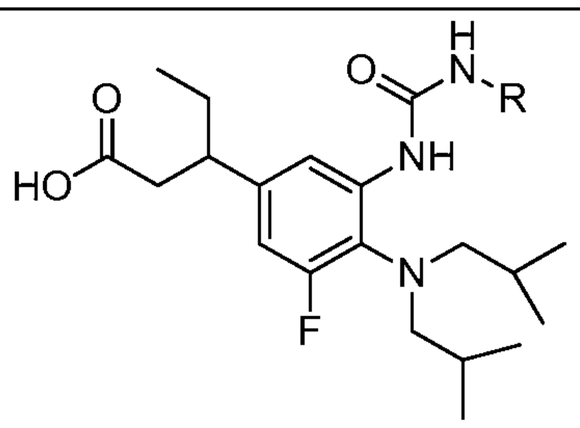
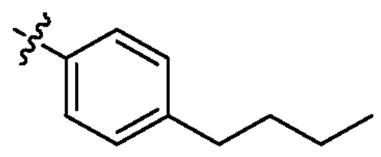
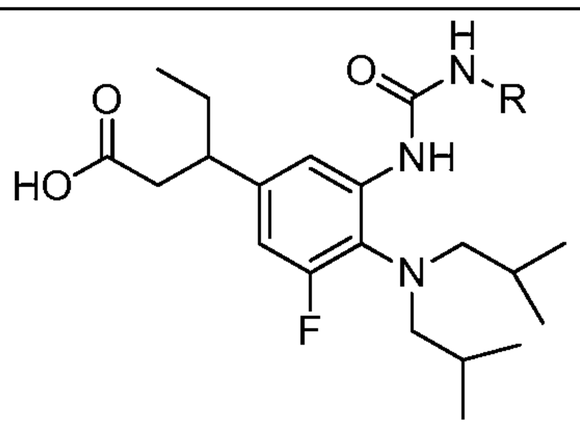
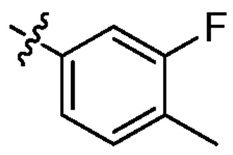
In another embodiment, the present invention provides a composition comprising one or more compounds of the present invention and/or a pharmaceutically acceptable salt thereof, a stereoisomer thereof, a tautomer thereof, or a solvate thereof.

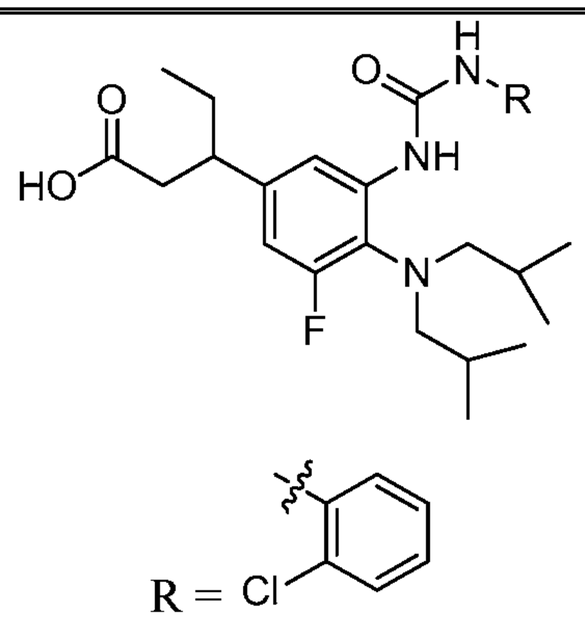
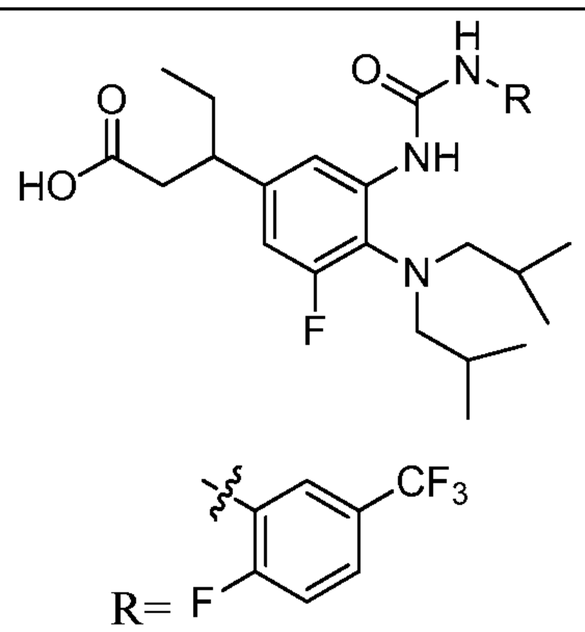
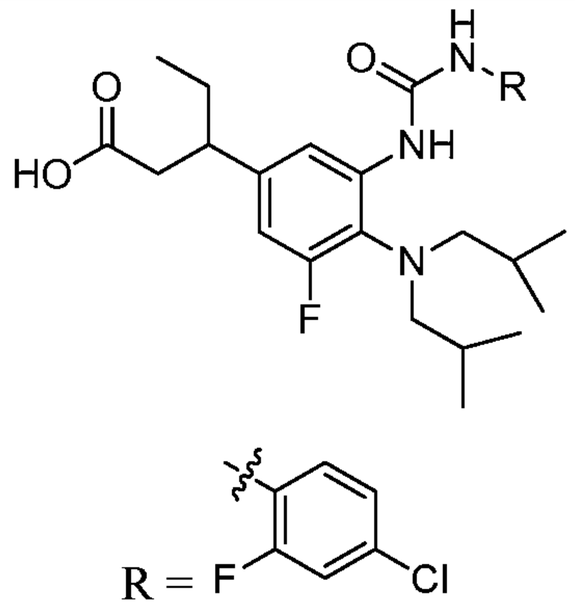
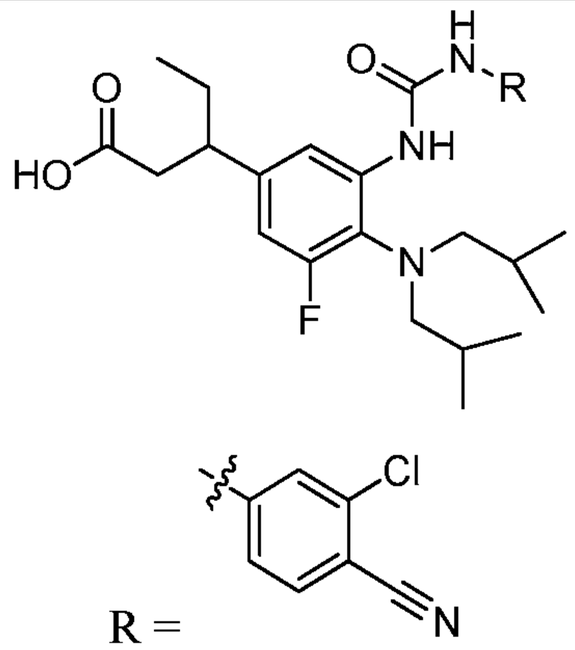
In another aspect, the invention provides a compound selected from the exemplified examples that are within the scope of Formula I, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof.

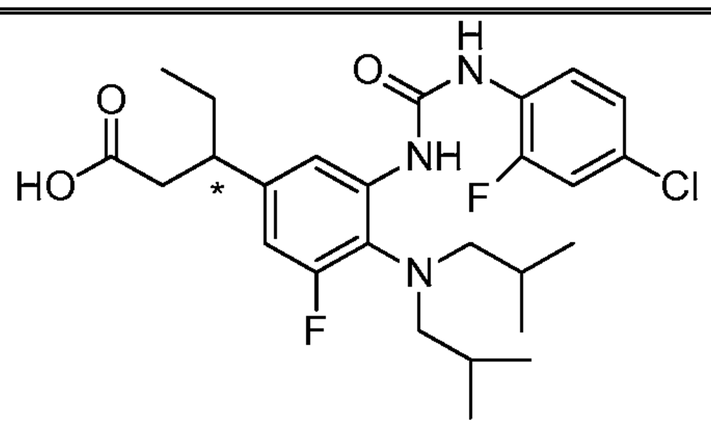
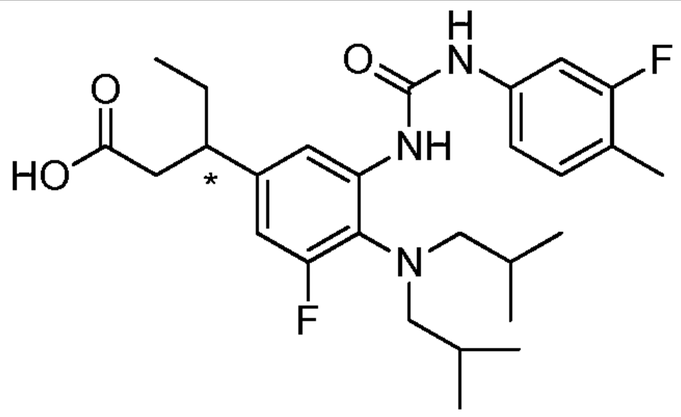
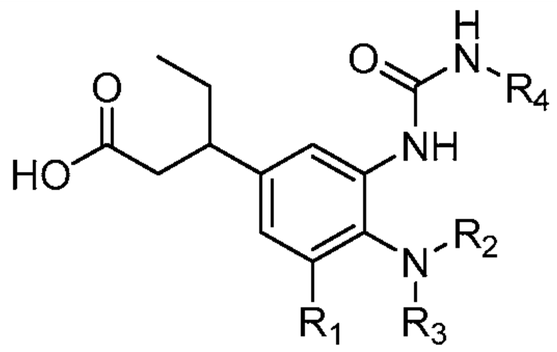
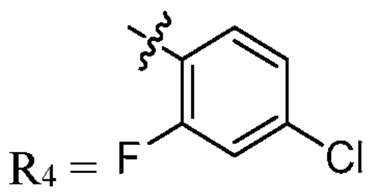
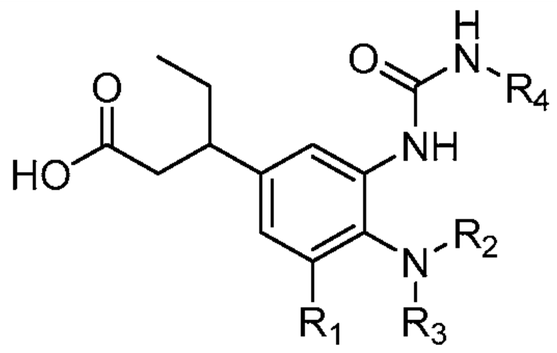
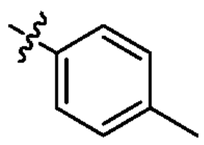
In another embodiment, the compounds of the invention have human IDO IC_{50} values > 50 nM. In another embodiment, the compounds of the invention have human IDO IC_{50} values ≤ 50 nM. In another embodiment, the compounds of the invention have human IDO IC_{50} values < 5 nM.

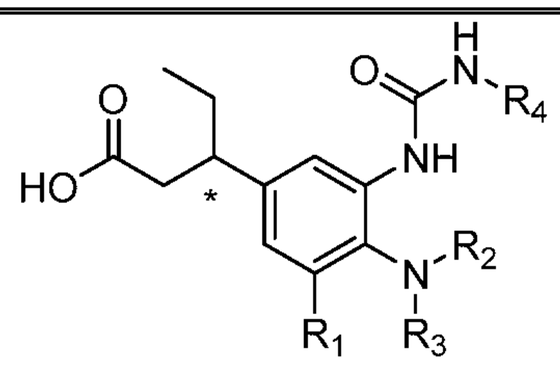
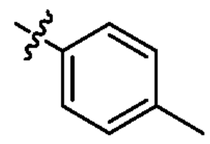
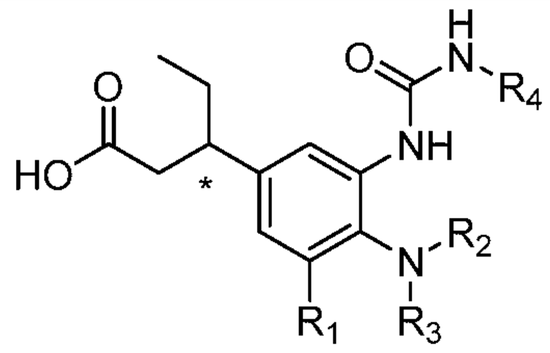
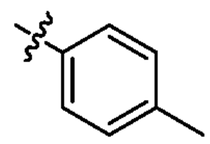
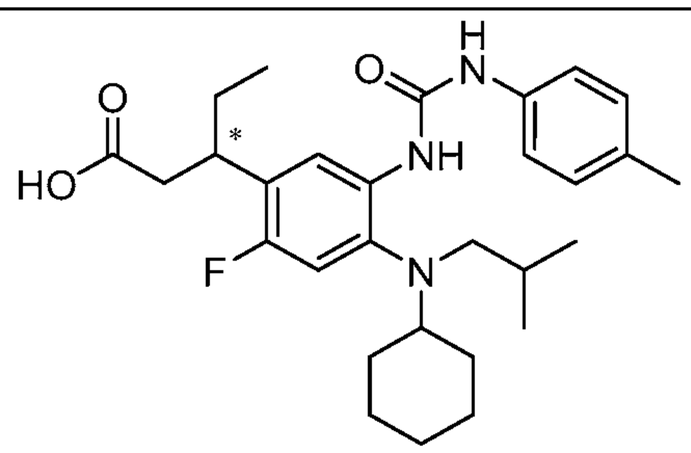
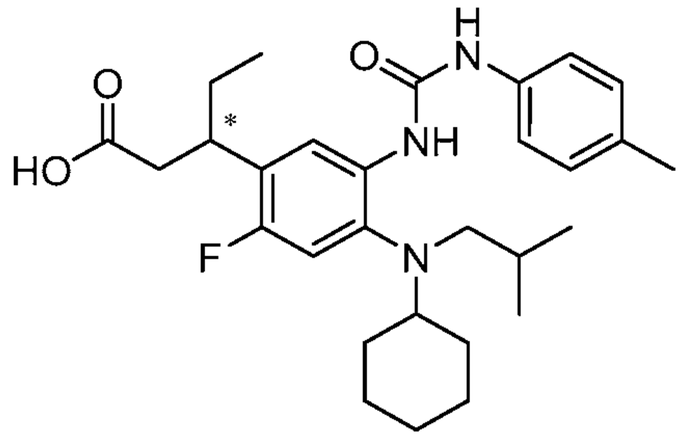
Preferred embodiments of the present invention are shown in the following Examples as well as Table A, below:

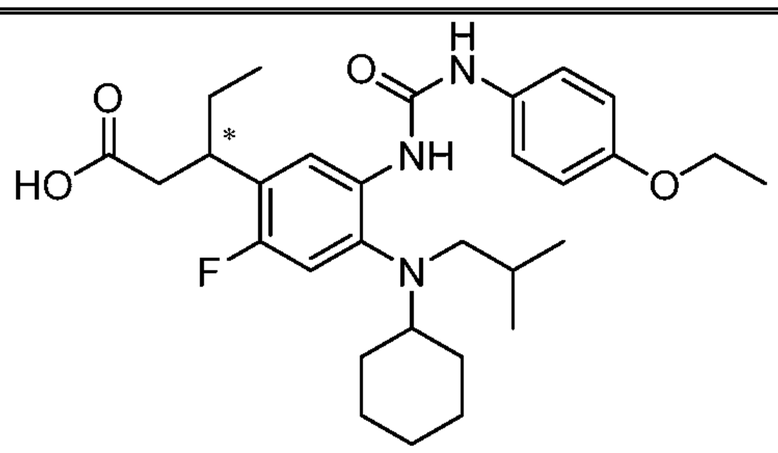
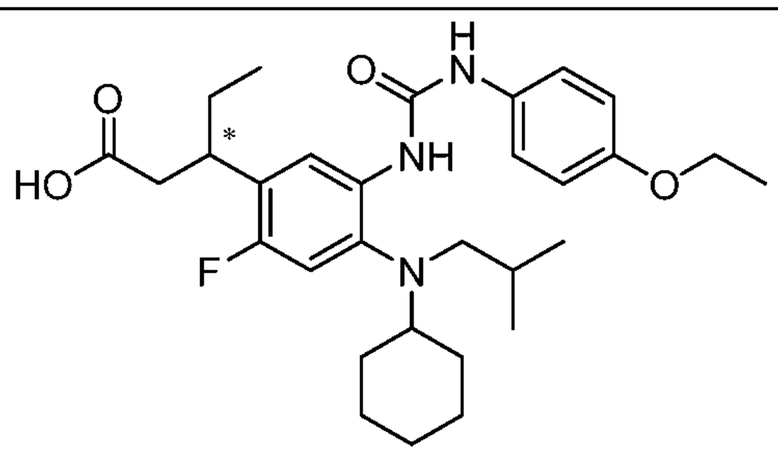
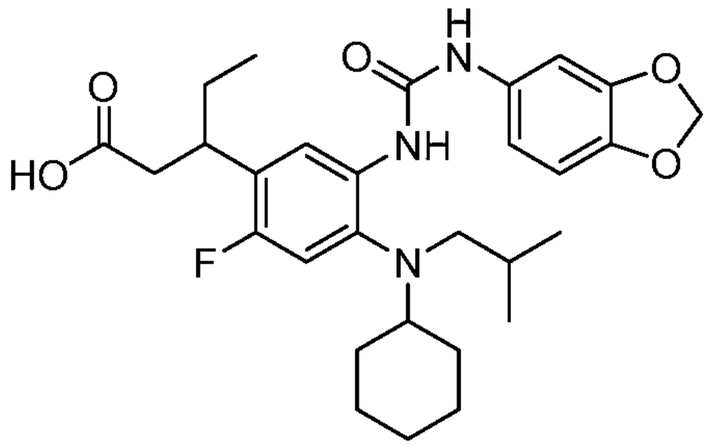
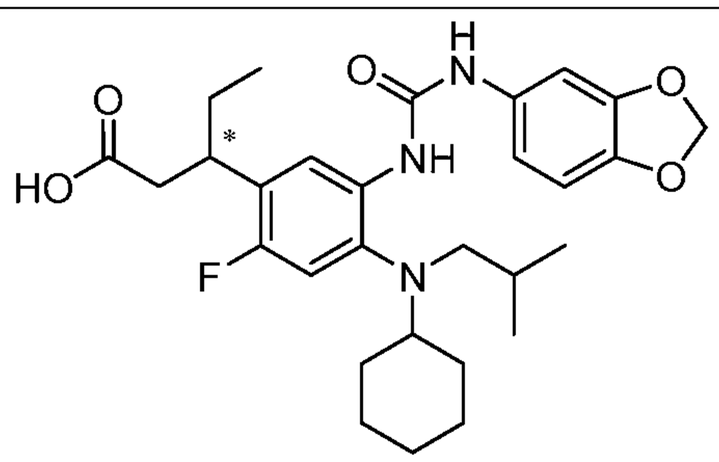
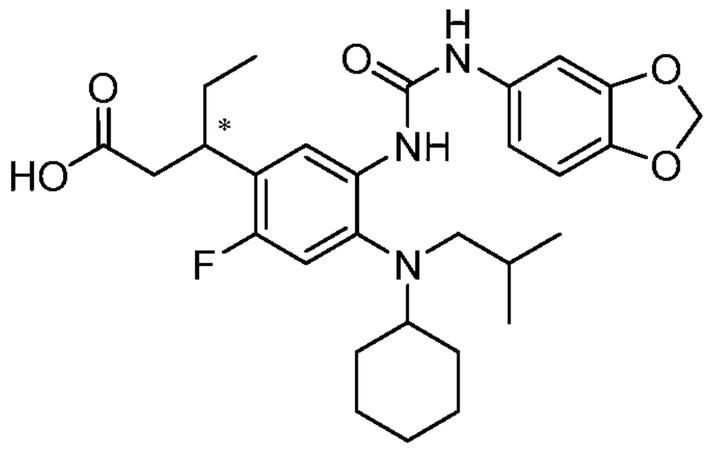
Ex. No.	Structure	Compound Name
951		(+/-)-3-(4-(cyclohexyl(isobutyl) amino)-2-fluoro-5-(3-(*p*-tolyl) ureido)phenyl)pentanoic acid
952		(+/-)-3-(4-(cyclohexyl(isobutyl) amino)-5-(3-(4-ethoxyphenyl) ureido)-2-fluorophenyl)pentanoic acid
955		(+/-)-3-(4-(cyclohexyl(isobutyl) amino)-2-fluoro-5-(3-(p-tolyl) ureido)phenyl)butanoic acid
956		3-(4-(cyclohexyl(isobutyl)amino)-2-fluoro-5-(3-(p-tolyl)ureido) phenyl)butanoic acid

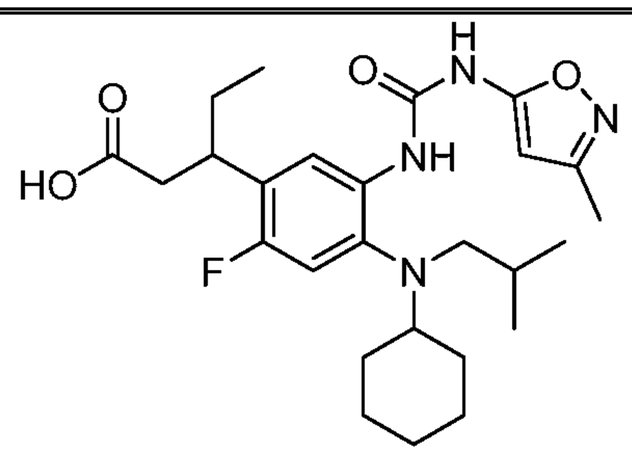
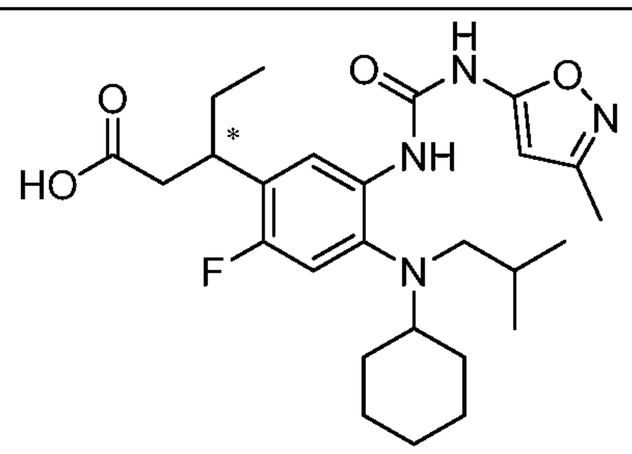
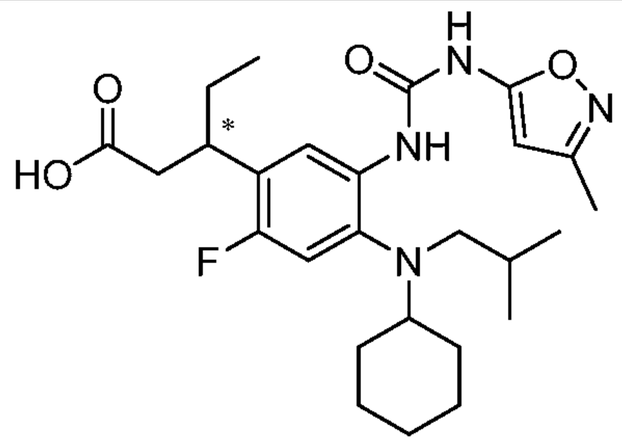
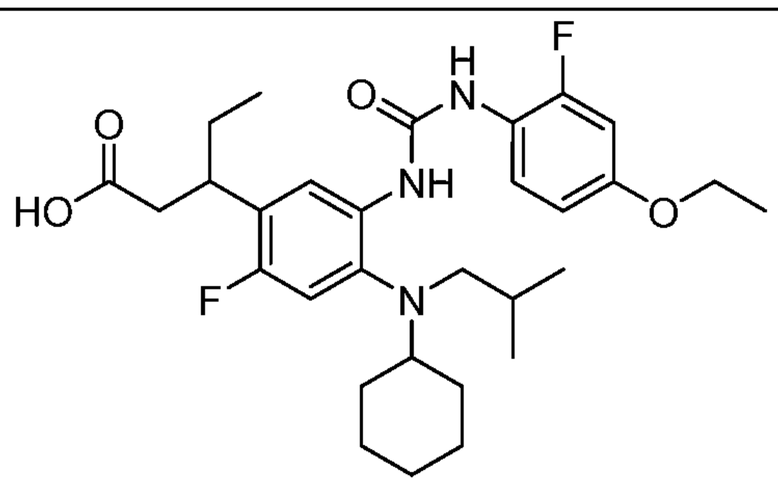
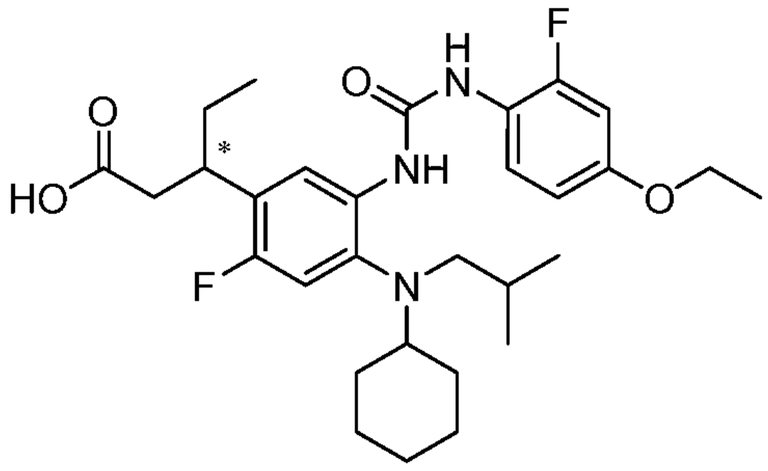
Ex. No.	Structure	Compound Name
957		3-(4-(cyclohexyl(isobutyl)amino)-2-fluoro-5-(3-(p-tolyl)ureido) phenyl)butanoic acid
970		(+/-)-3-(4-(diisobutylamino)-3-fluoro-5-(3-(p-tolyl)ureido) phenyl)pentanoic acid, TFA
971		(+/-)-3-(3-(3-(5-(*tert*-butyl) isoxazol-3-yl)ureido)-4-(diisobutylamino)-5-fluorophenyl) pentanoic acid, TFA
973	 	(+/-)-3-(3-(3-(4-butylphenyl) ureido)-4-(diisobutylamino)-5-fluorophenyl)pentanoic acid
974	 	(+/-)-3-(4-(diisobutylamino)-3-fluoro-5-(3-(3-fluoro-4-methylphenyl)ureido)phenyl) pentanoic acid

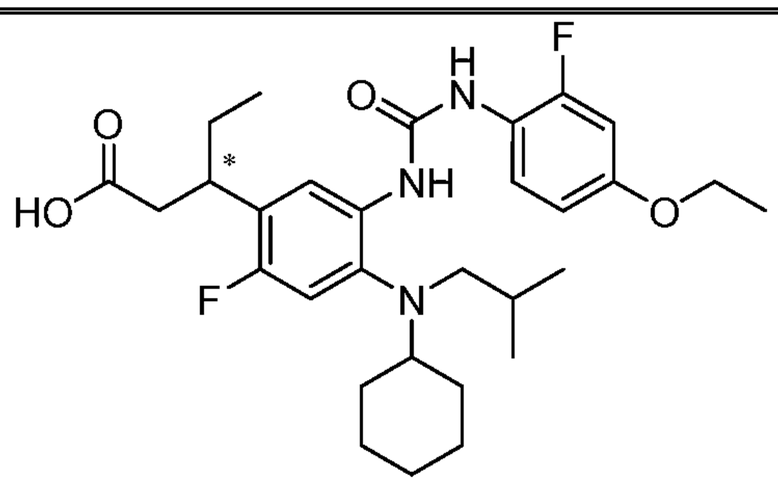
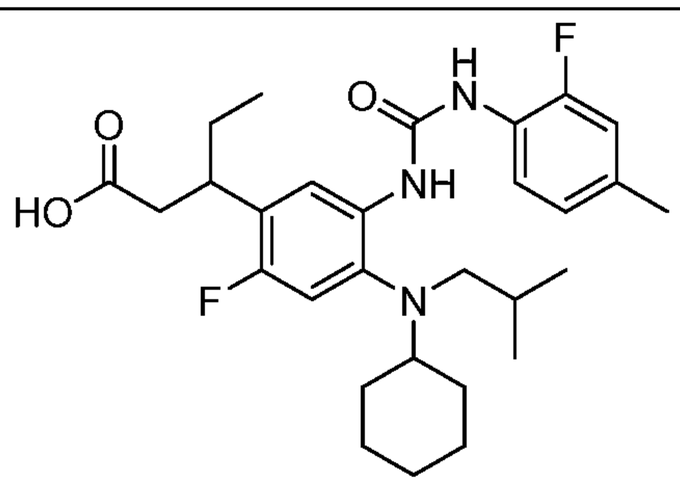
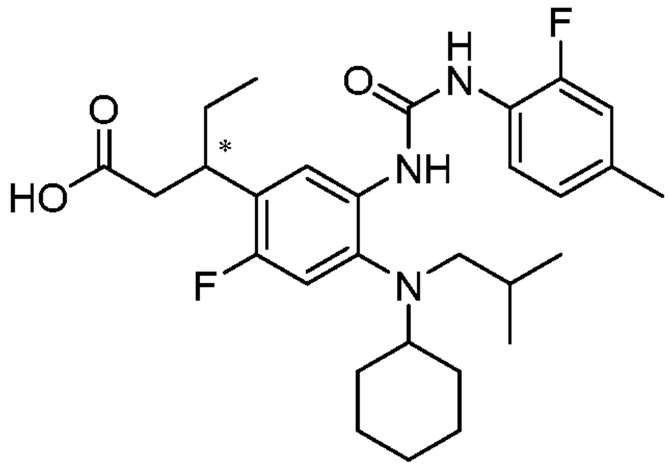
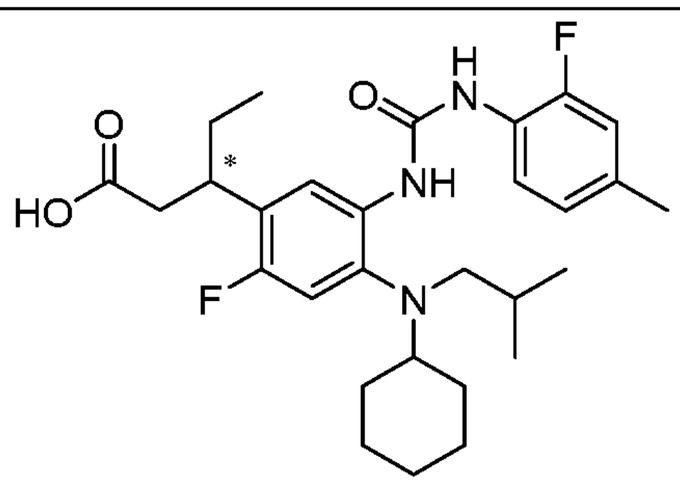
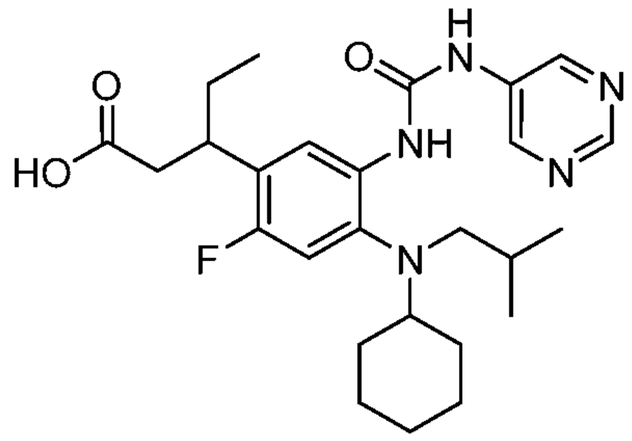
Ex. No.	Structure	Compound Name
975		(+/-)-3-(3-(3-(2-chlorophenyl) ureido)-4-(diisobutylamino)-5-fluorophenyl)pentanoic acid
976		(+/-)-3-(4-(diisobutylamino)-3-fluoro-5-(3-(2-fluoro-5-(trifluoromethyl)phenyl)ureido) phenyl)pentanoic acid
977		(+/-)-3-(3-(3-(4-chloro-2-fluorophenyl)ureido)-4-(diisobutylamino)-5-fluorophenyl) pentanoic acid
978		(+/-)-3-(3-(3-(3-chloro-4-cyanophenyl)ureido)-4-(diisobutylamino)-5-fluorophenyl) pentanoic acid

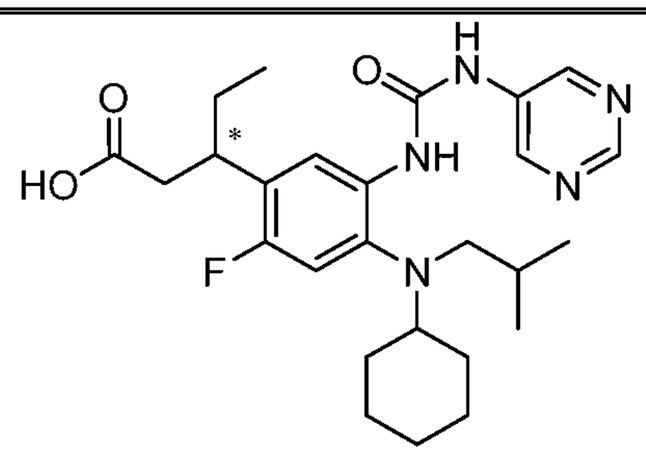
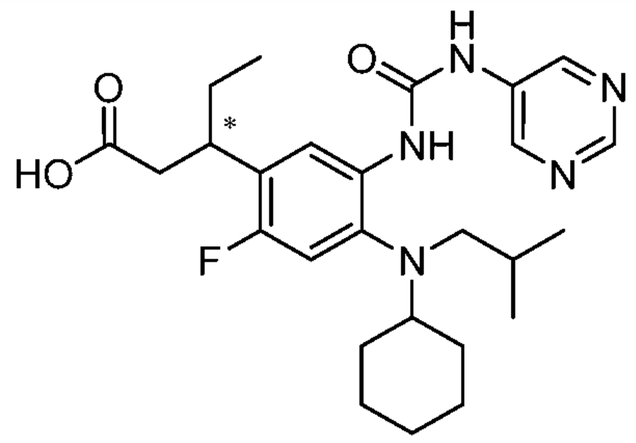
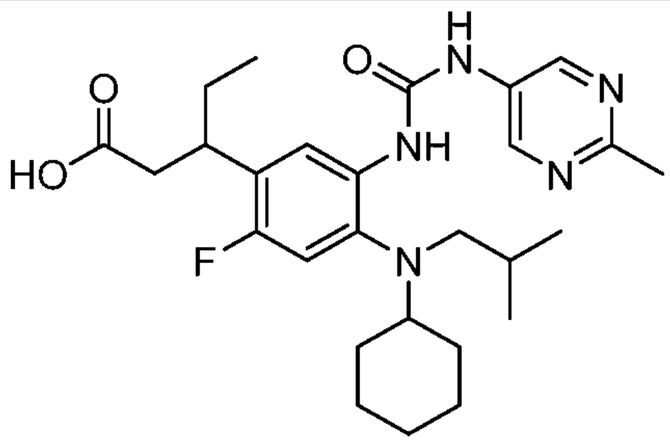
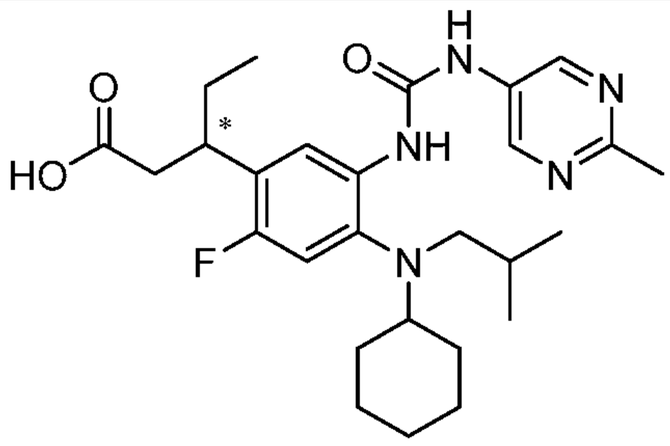
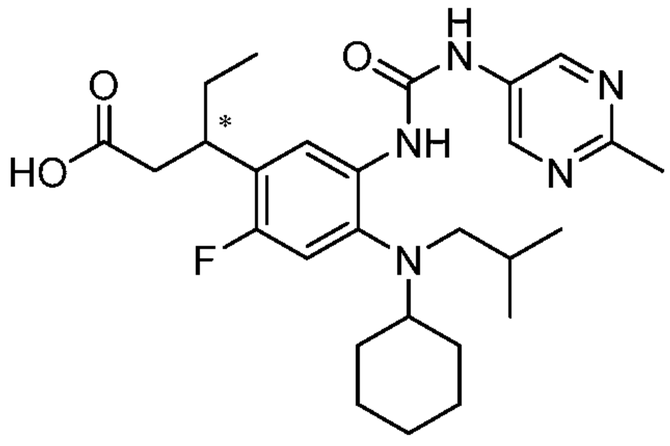
Ex. No.	Structure	Compound Name
981		3-(3-(3-(4-chloro-2-fluorophenyl) ureido)-4-(diisobutylamino)-5-fluorophenyl)pentanoic
982		3-(4-(diisobutylamino)-3-fluoro-5-(3-(3-fluoro-4-methylphenyl) ureido)phenyl)pentanoic acid
1090	 R_1 = F R_2 = isobutyl R_3 = cyclohexyl  R_4 =	3-(3-(3-(4-chloro-2-fluorophenyl) ureido)-4-(cyclohexyl(isobutyl) amino)-5-fluorophenyl)pentanoic acid
1091	 R_1 = F R_2 = isobutyl R_3 = cyclohexyl R_4 = 	3-(4-(cyclohexyl(isobutyl)amino)-3-fluoro-5-(3-(p-tolyl)ureido) phenyl)pentanoic acid

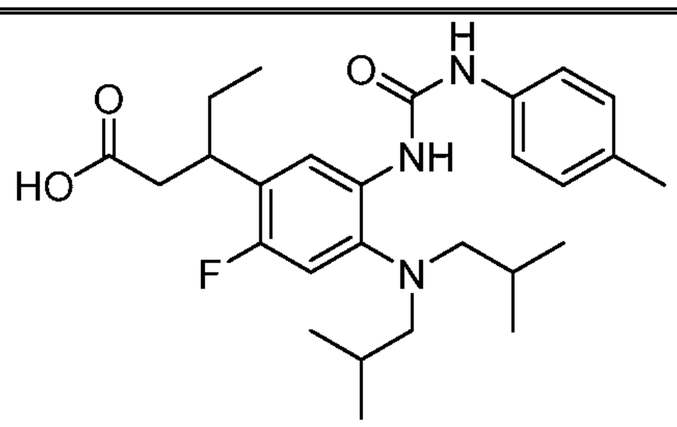
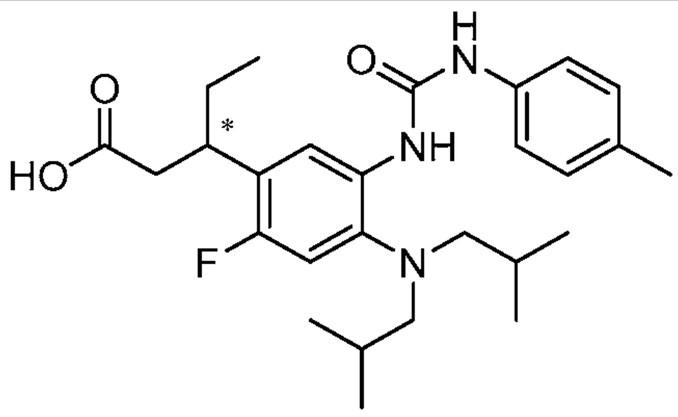
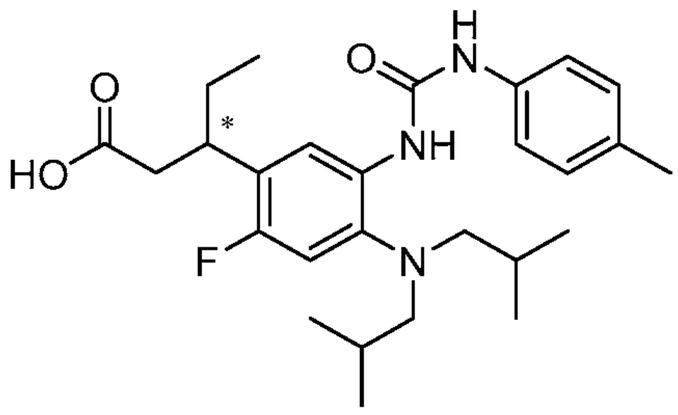
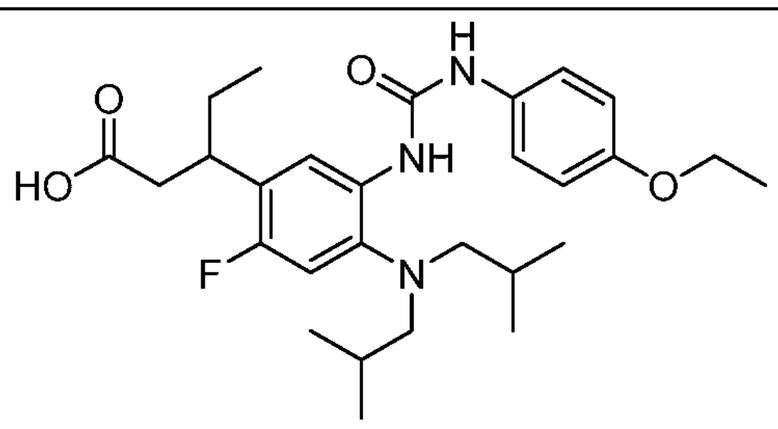
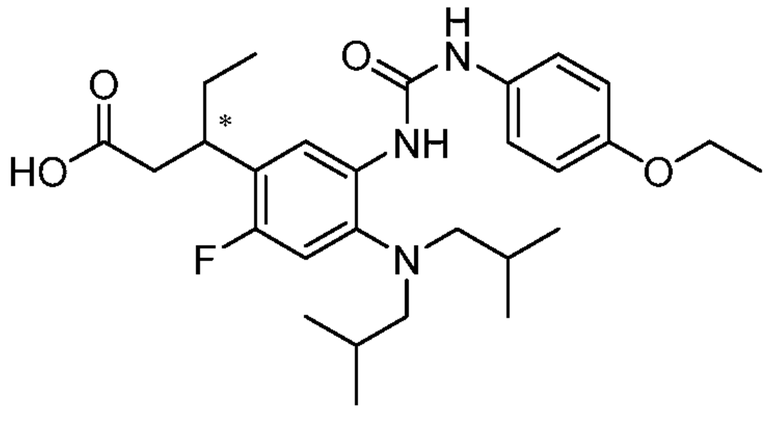
Ex. No.	Structure	Compound Name
1102E1	 R_1 = F R_2 = isobutyl R_3 = cyclohexyl R_4 = 	3-(4-(cyclohexyl(isobutyl)amino)-3-fluoro-5-(3-(p-tolyl)ureido) phenyl)pentanoic acid
1102E2	 R_1 = F R_2 = isobutyl R_3 = cyclohexyl R_4 = 	3-(4-(cyclohexyl(isobutyl)amino)-3-fluoro-5-(3-(p-tolyl)ureido) phenyl)pentanoic acid
1106		3-(4-(cyclohexyl(isobutyl)amino)-2-fluoro-5-(3-(*p*-tolyl)ureido) phenyl)pentanoic acid
1107		3-(4-(cyclohexyl(isobutyl)amino)-2-fluoro-5-(3-(*p*-tolyl)ureido) phenyl)pentanoic acid

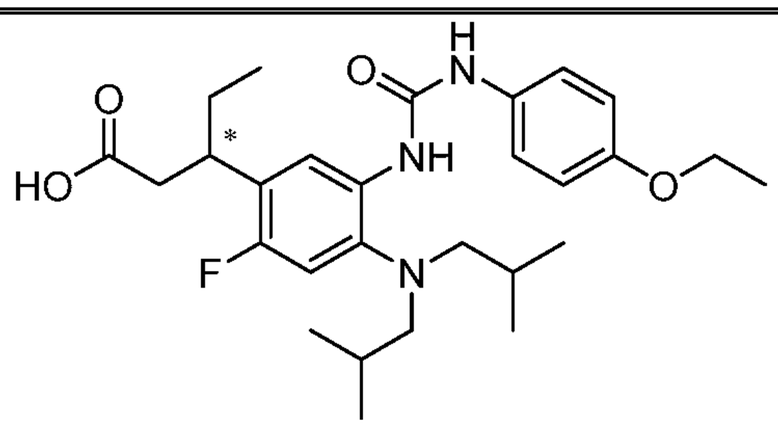
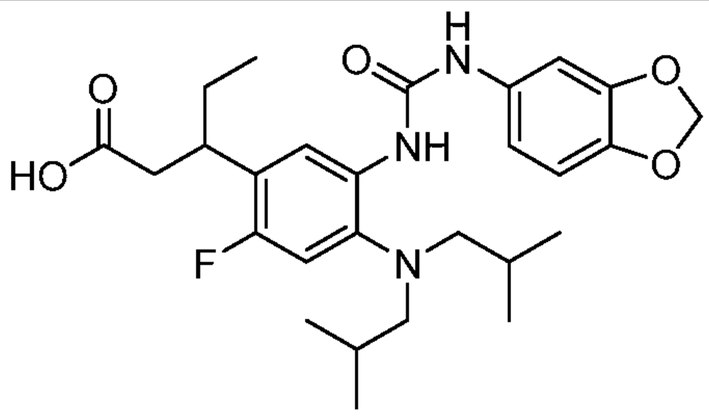
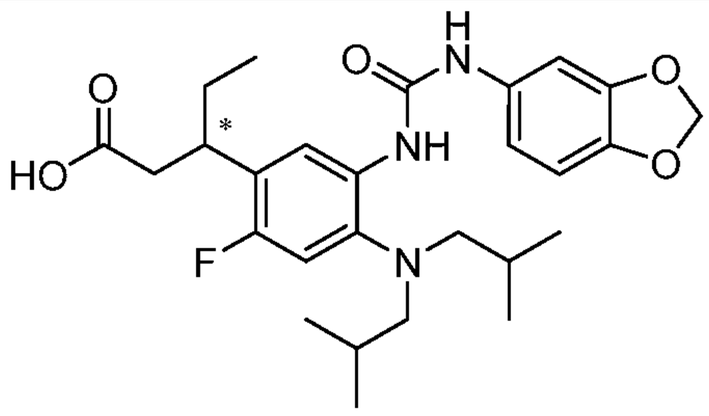
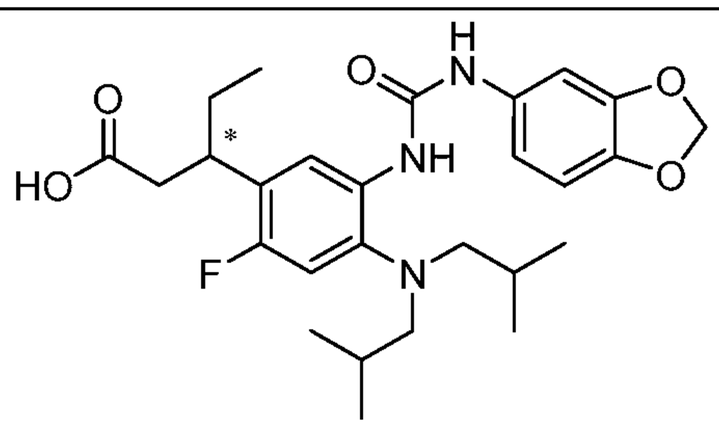
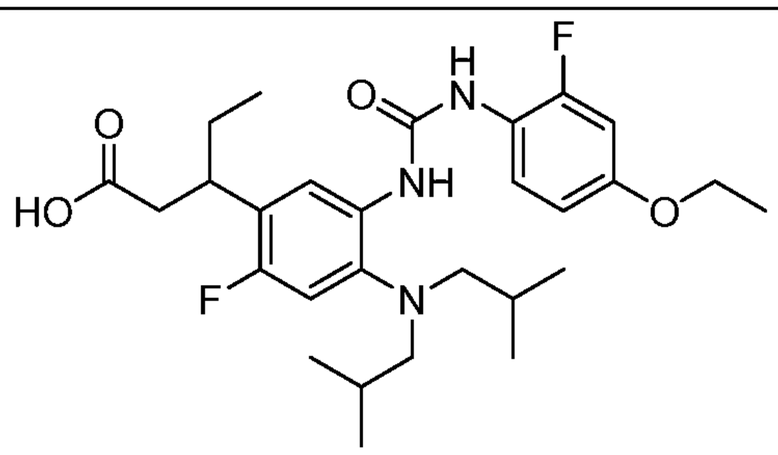
Ex. No.	Structure	Compound Name
1108		3-(4-(cyclohexyl(isobutyl)amino)-5-(3-(4-ethoxyphenyl)ureido)-2-fluorophenyl)pentanoic acid
1109		3-(4-(cyclohexyl(isobutyl)amino)-5-(3-(4-ethoxyphenyl)ureido)-2-fluorophenyl)pentanoic acid
1110		(±)-3-(5-(3-(benzo[d][1,3]dioxol-5-yl)ureido)-4-(cyclohexyl(isobutyl)amino)-2-fluorophenyl)pentanoic acid
1111		3-(5-(3-(benzo[d][1,3]dioxol-5-yl)ureido)-4-(cyclohexyl(isobutyl)amino)-2-fluorophenyl)pentanoic acid
1112		3-(5-(3-(benzo[d][1,3]dioxol-5-yl)ureido)-4-(cyclohexyl(isobutyl)amino)-2-fluorophenyl)pentanoic acid

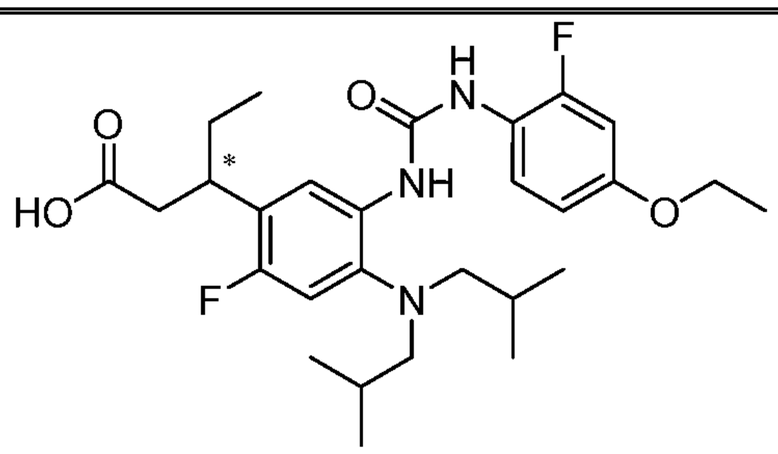
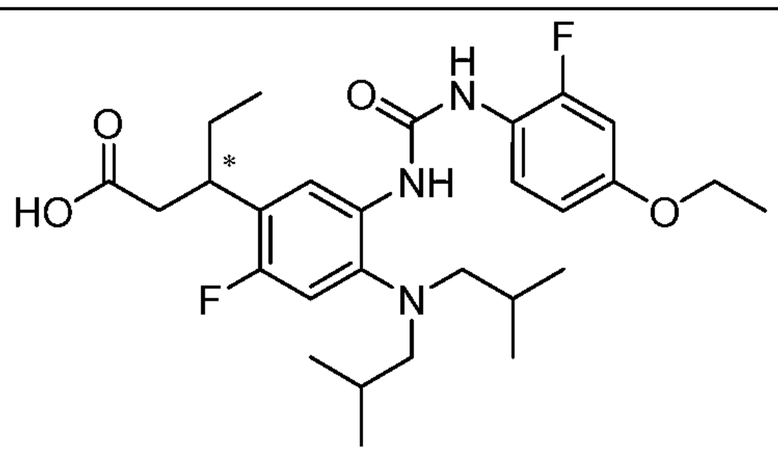
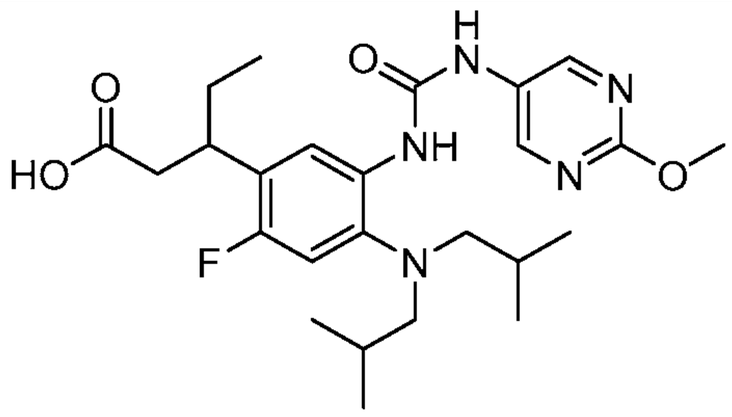
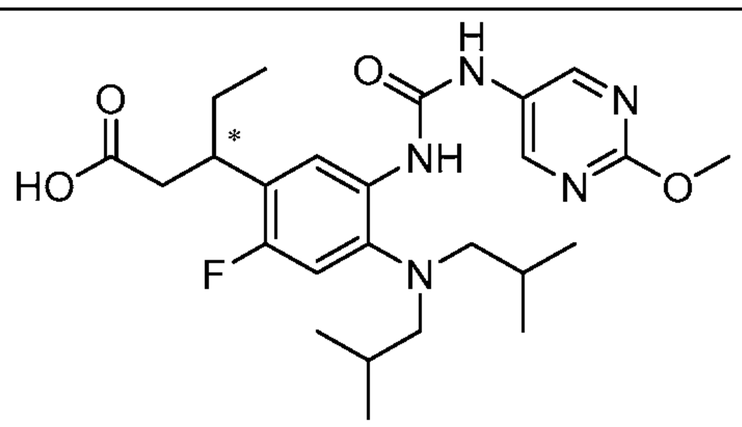
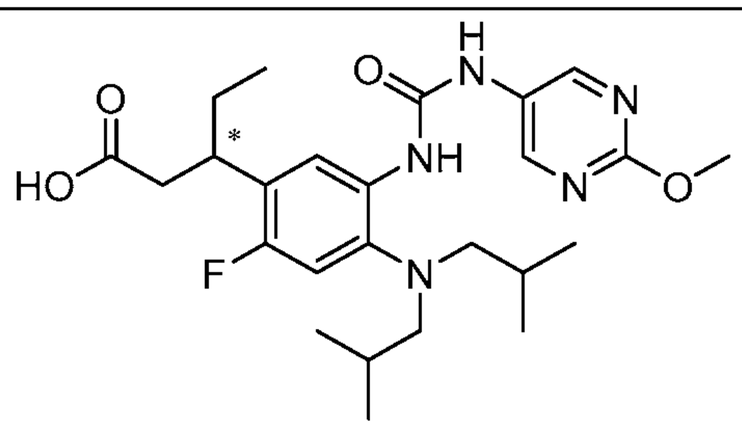
Ex. No.	Structure	Compound Name
1113		(±)-3-(4-(cyclohexyl(isobutyl) amino)-2-fluoro-5-(3-(3-methylisoxazol-5-yl)ureido) phenyl)pentanoic acid
1114		3-(4-(cyclohexyl(isobutyl)amino)-2-fluoro-5-(3-(3-methylisoxazol-5-yl)ureido)phenyl)pentanoic acid
1115		3-(4-(cyclohexyl(isobutyl)amino)-2-fluoro-5-(3-(3-methylisoxazol-5-yl)ureido)phenyl)pentanoic acid
1116		(±)-3-(4-(cyclohexyl(isobutyl) amino)-5-(3-(4-ethoxy-2-fluorophenyl)ureido)-2-fluorophenyl)pentanoic acid
1117		3-(4-(cyclohexyl(isobutyl)amino)-5-(3-(4-ethoxy-2-fluorophenyl) ureido)-2-fluorophenyl)pentanoic acid

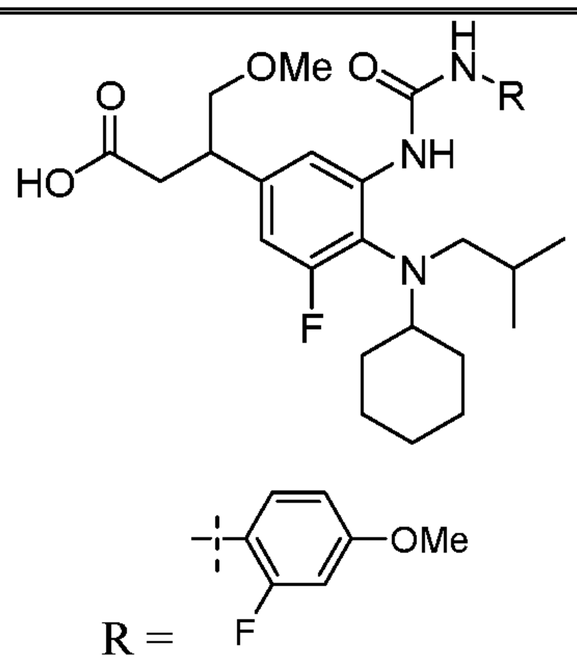
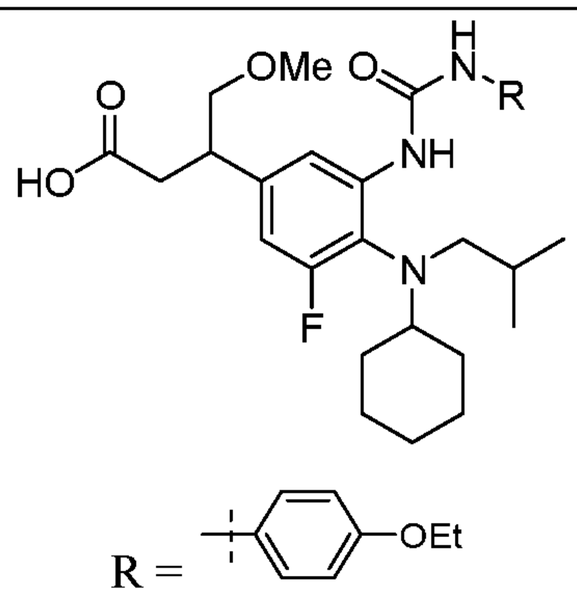
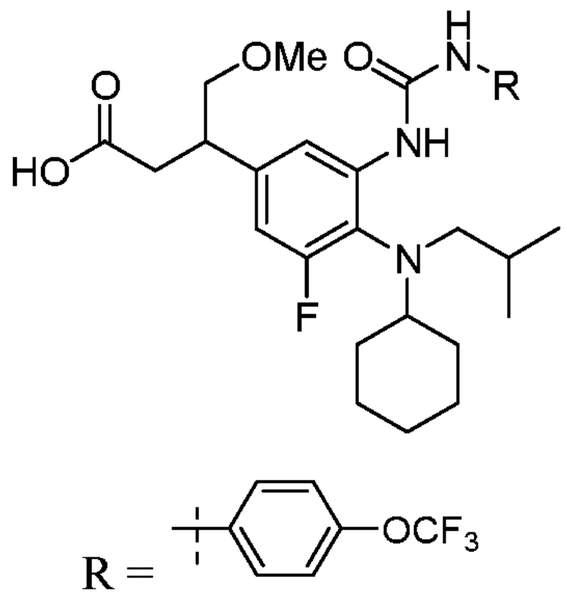
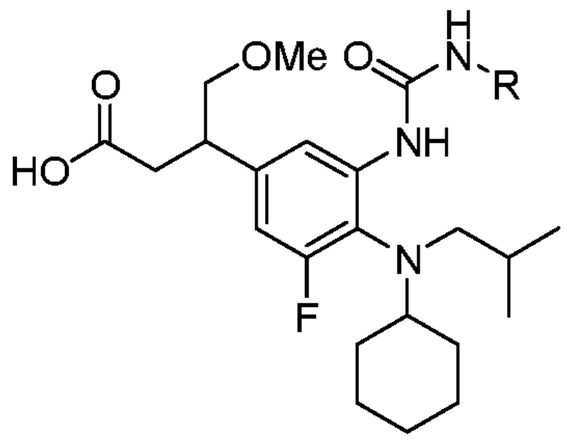
Ex. No.	Structure	Compound Name
1118		3-(4-(cyclohexyl(isobutyl)amino)-5-(3-(4-ethoxy-2-fluorophenyl) ureido)-2-fluorophenyl)pentanoic acid
1119		(±)-3-(4-(cyclohexyl(isobutyl) amino)-2-fluoro-5-(3-(2-fluoro-4-methylphenyl)ureido)phenyl) pentanoic acid
1120		3-(4-(cyclohexyl(isobutyl)amino)-2-fluoro-5-(3-(2-fluoro-4-methylphenyl)ureido)phenyl) pentanoic acid
1121		3-(4-(cyclohexyl(isobutyl)amino)-2-fluoro-5-(3-(2-fluoro-4-methylphenyl)ureido)phenyl) pentanoic acid
1122		(±)-3-(4-(cyclohexyl(isobutyl) amino)-2-fluoro-5-(3-(pyrimidin-5-yl)ureido)phenyl)pentanoic acid

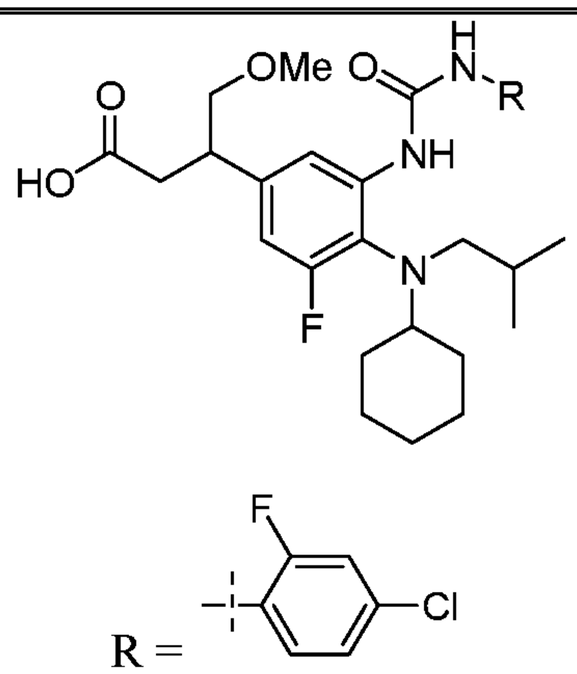
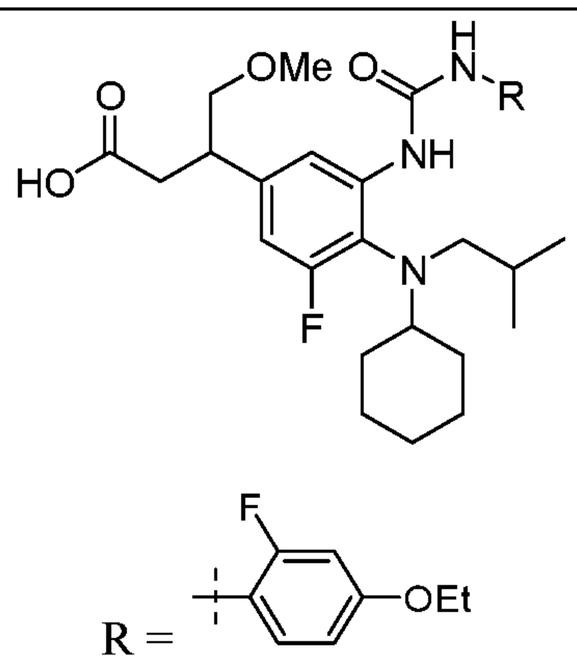
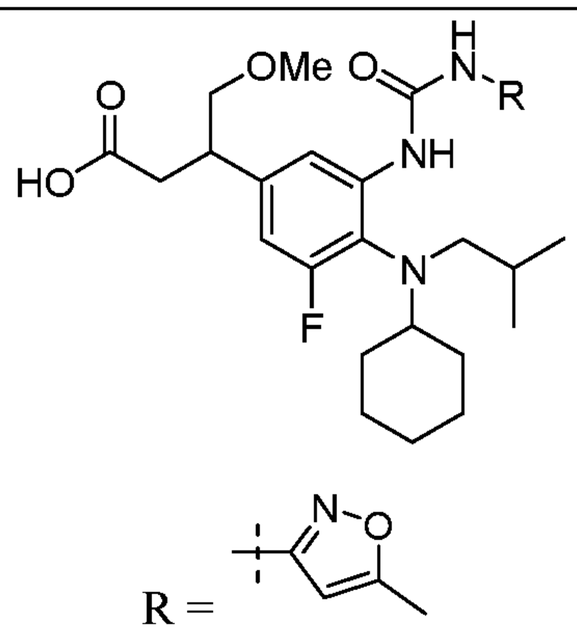
Ex. No.	Structure	Compound Name
1123		3-(4-(cyclohexyl(isobutyl)amino)-2-fluoro-5-(3-(pyrimidin-5-yl)ureido)phenyl)pentanoic acid
1124		3-(4-(cyclohexyl(isobutyl)amino)-2-fluoro-5-(3-(pyrimidin-5-yl)ureido)phenyl)pentanoic acid
1125		(±)-3-(4-(cyclohexyl(isobutyl) amino)-2-fluoro-5-(3-(2-methylpyrimidin-5-yl)ureido) phenyl)pentanoic acid
1126		3-(4-(cyclohexyl(isobutyl)amino)-2-fluoro-5-(3-(2-methylpyrimidin-5-yl)ureido)phenyl)pentanoic acid
1127		3-(4-(cyclohexyl(isobutyl)amino)-2-fluoro-5-(3-(2-methylpyrimidin-5-yl)ureido)phenyl)pentanoic acid

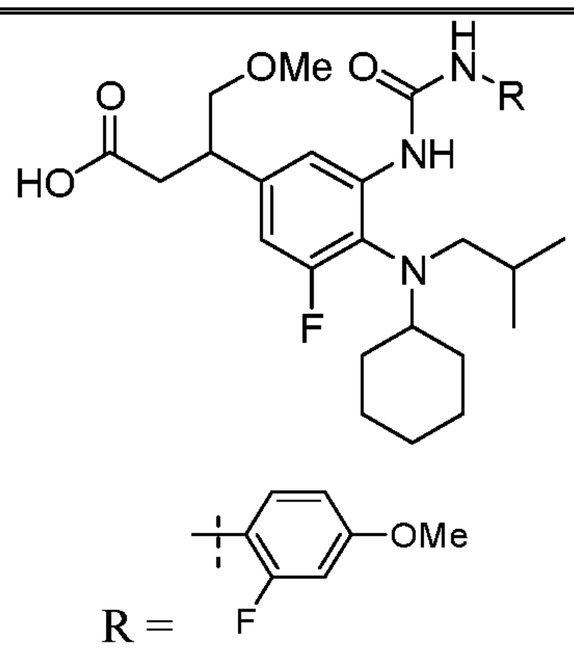
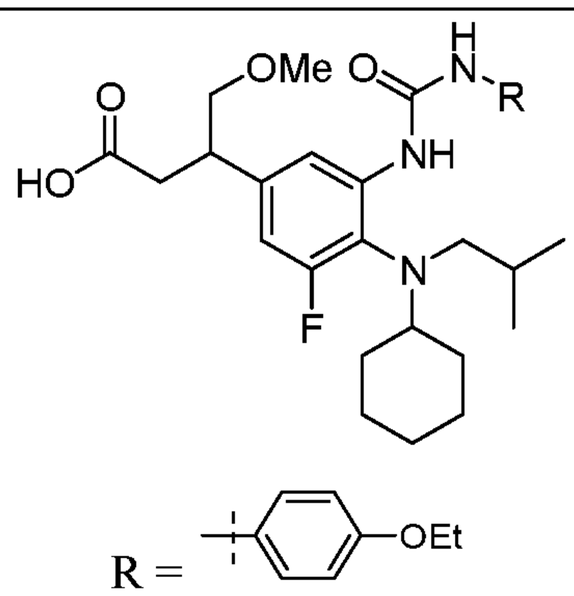
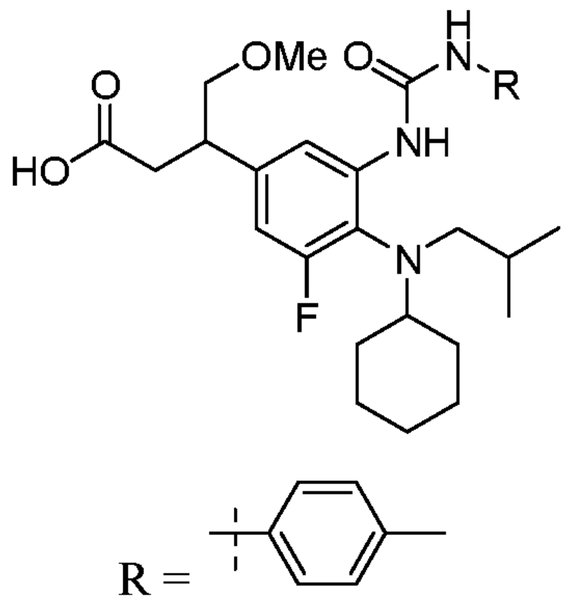
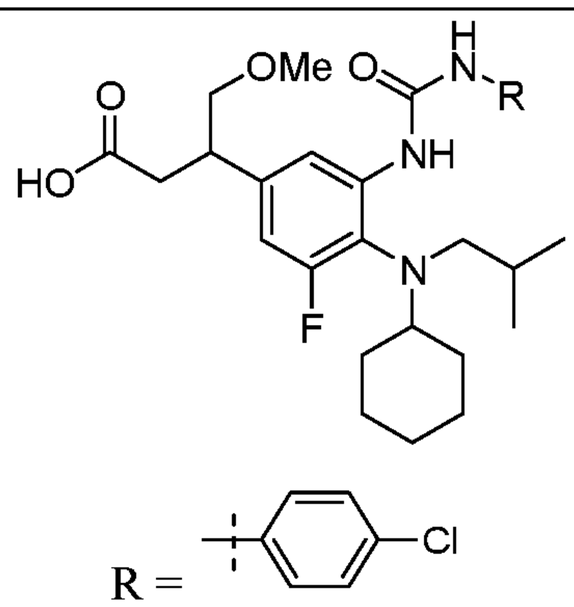
Ex. No.	Structure	Compound Name
1128		(±)-3-(4-(diisobutylamino)-2-fluoro-5-(3-(*p*-tolyl)ureido) phenyl)pentanoic acid
1129		3-(4-(diisobutylamino)-2-fluoro-5-(3-(*p*-tolyl)ureido)phenyl) pentanoic acid
1130		3-(4-(diisobutylamino)-2-fluoro-5-(3-(*p*-tolyl)ureido)phenyl) pentanoic acid
1131		(±)-3-(4-(diisobutylamino)-5-(3-(4-ethoxyphenyl)ureido)-2-fluorophenyl)pentanoic acid
1132		3-(4-(diisobutylamino)-5-(3-(4-ethoxyphenyl)ureido)-2-fluorophenyl)pentanoic acid

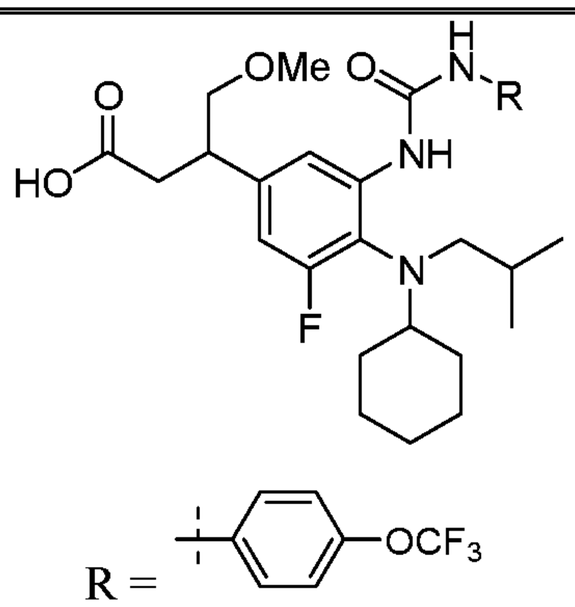
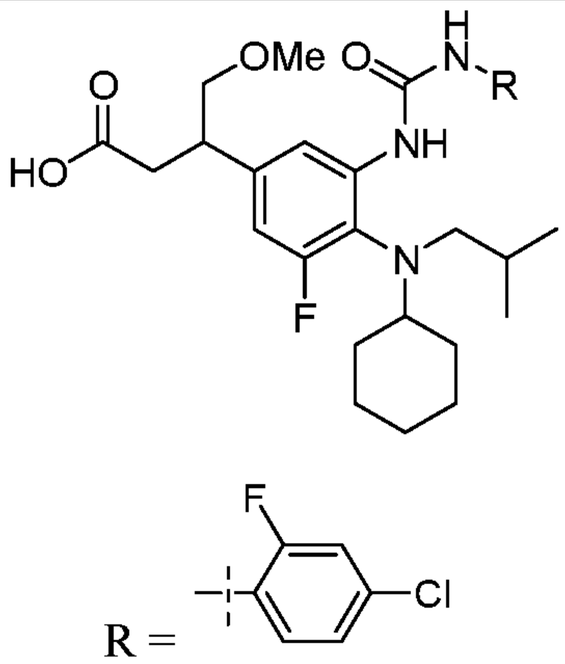
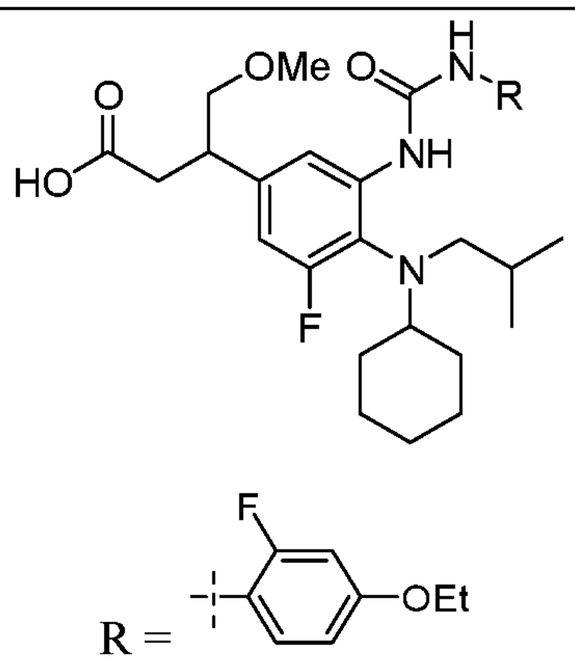
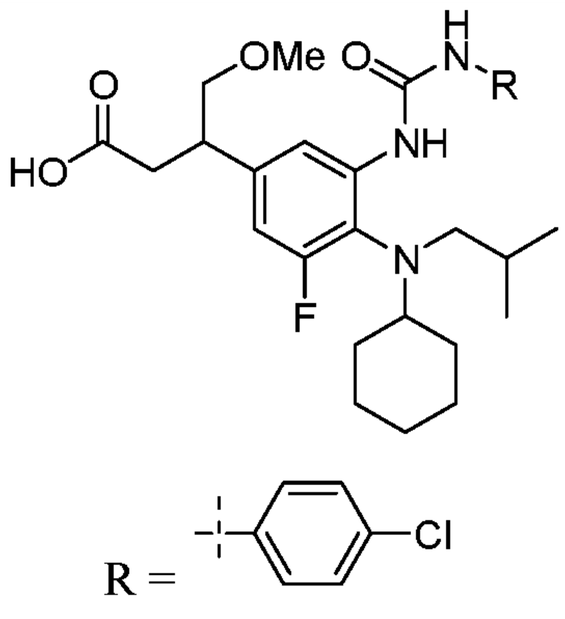
Ex. No.	Structure	Compound Name
1133		3-(4-(diisobutylamino)-5-(3-(4-ethoxyphenyl)ureido)-2-fluorophenyl)pentanoic acid
1134		(±)-3-(5-(3-(benzo[d][1,3]dioxol-5-yl)ureido)-4-(diisobutylamino)-2-fluorophenyl)pentanoic acid
1135		3-(5-(3-(benzo[d][1,3]dioxol-5-yl)ureido)-4-(diisobutylamino)-2-fluorophenyl)pentanoic acid
1136		3-(5-(3-(benzo[d][1,3]dioxol-5-yl)ureido)-4-(diisobutylamino)-2-fluorophenyl)pentanoic acid
1137		(±)-3-(4-(diisobutylamino)-5-(3-(4-ethoxy-2-fluorophenyl)ureido)-2-fluorophenyl)pentanoic acid

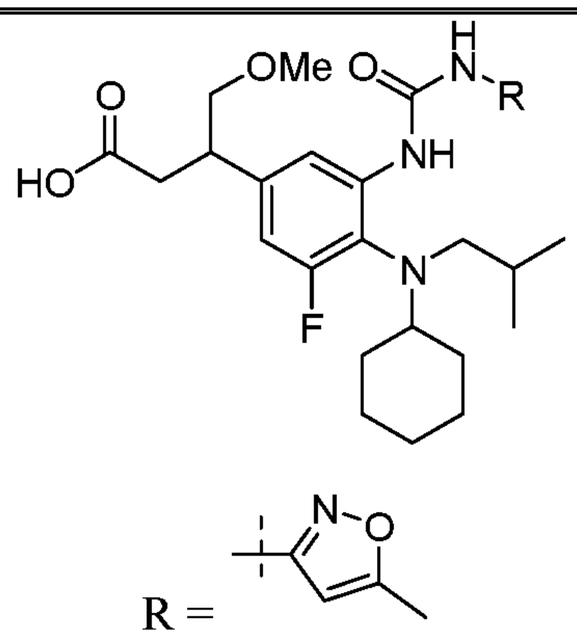
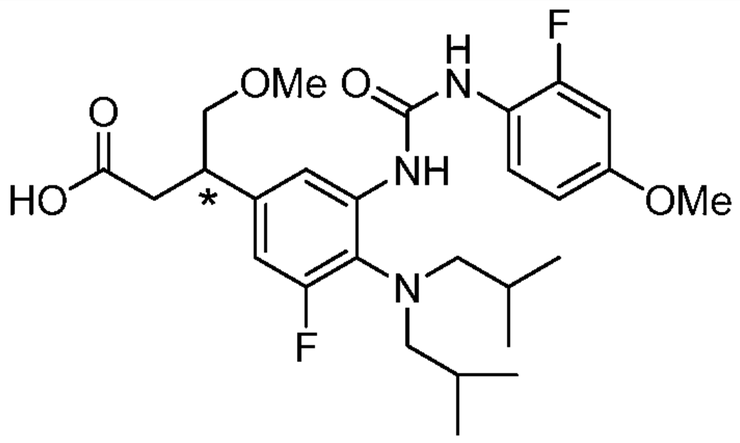
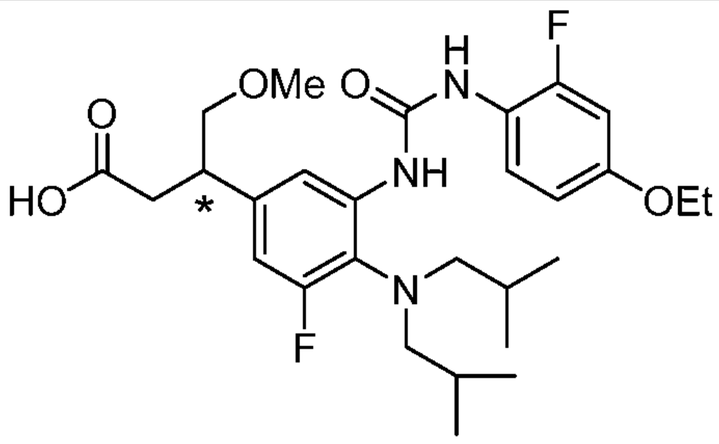
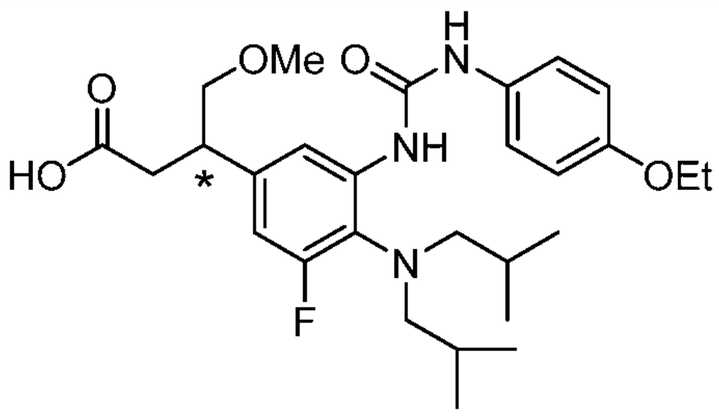
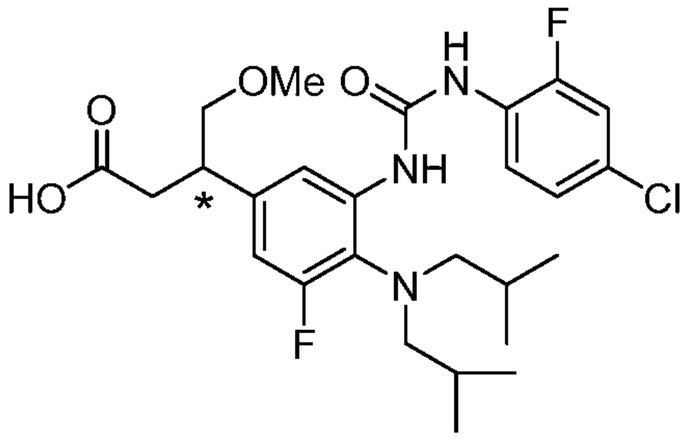
Ex. No.	Structure	Compound Name
1138		3-(4-(diisobutylamino)-5-(3-(4-ethoxy-2-fluorophenyl)ureido)-2-fluorophenyl)pentanoic acid
1139		3-(4-(diisobutylamino)-5-(3-(4-ethoxy-2-fluorophenyl)ureido)-2-fluorophenyl)pentanoic acid
1140		(±)-3-(4-(diisobutylamino)-2-fluoro-5-(3-(2-methoxypyrimidin-5-yl)ureido)phenyl)pentanoic acid
1141		3-(4-(diisobutylamino)-2-fluoro-5-(3-(2-methoxypyrimidin-5-yl)ureido)phenyl)pentanoic acid
1142		3-(4-(diisobutylamino)-2-fluoro-5-(3-(2-methoxypyrimidin-5-yl)ureido)phenyl)pentanoic acid

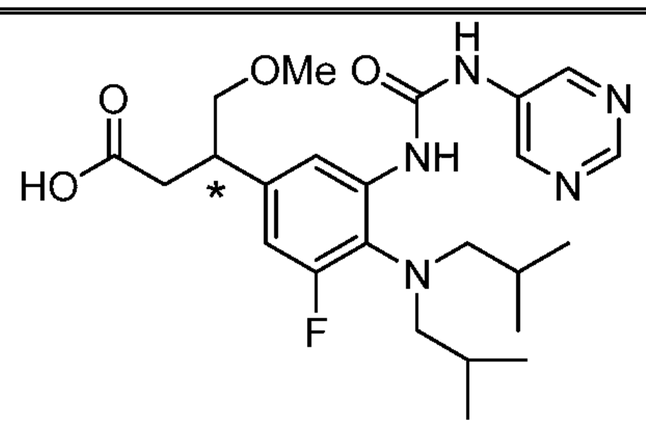
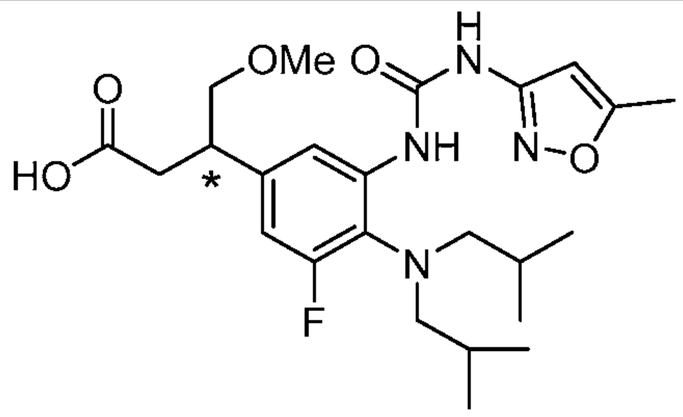
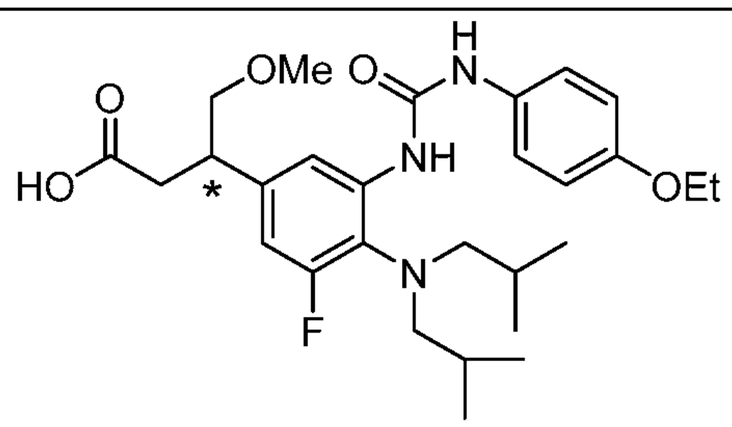
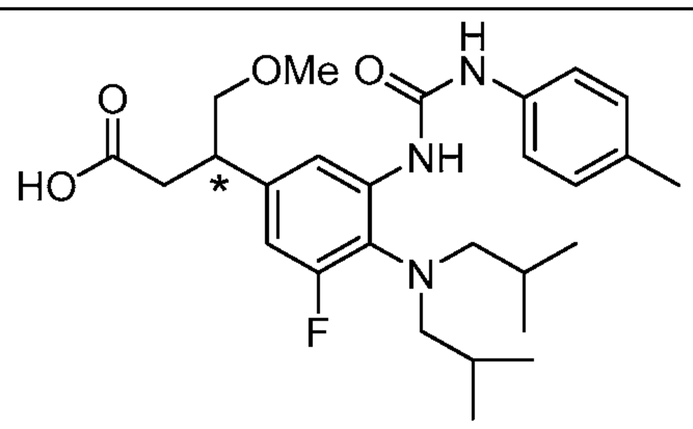
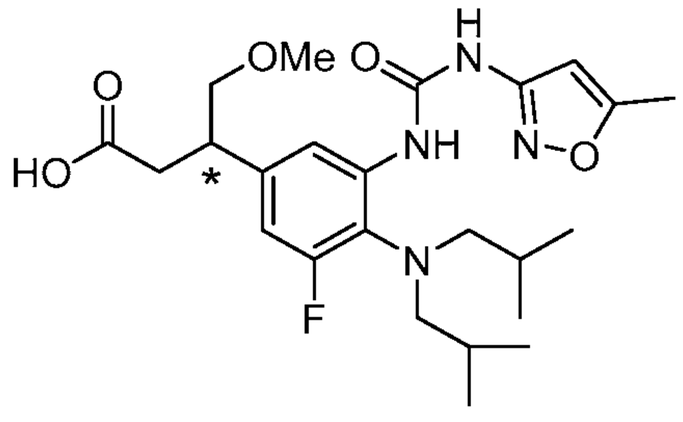
Ex. No.	Structure	Compound Name
1152		3-(4-(cyclohexyl(isobutyl)amino)-3-fluoro-5-(3-(2-fluoro-4-methoxyphenyl)ureido)phenyl)-4-methoxybutanoic acid
1153		3-(4-(cyclohexyl(isobutyl)amino)-3-(3-(4-ethoxyphenyl)ureido)-5-fluorophenyl)-4-methoxybutanoic acid
1154		3-(4-(cyclohexyl(isobutyl)amino)-3-fluoro-5-(3-(4-(trifluoromethoxy)phenyl) ureido)phenyl)-4-methoxybutanoic acid
1155		3-(4-(cyclohexyl(isobutyl)amino)-3-fluoro-5-(3-(p-tolyl)ureido) phenyl)-4-methoxybutanoic acid

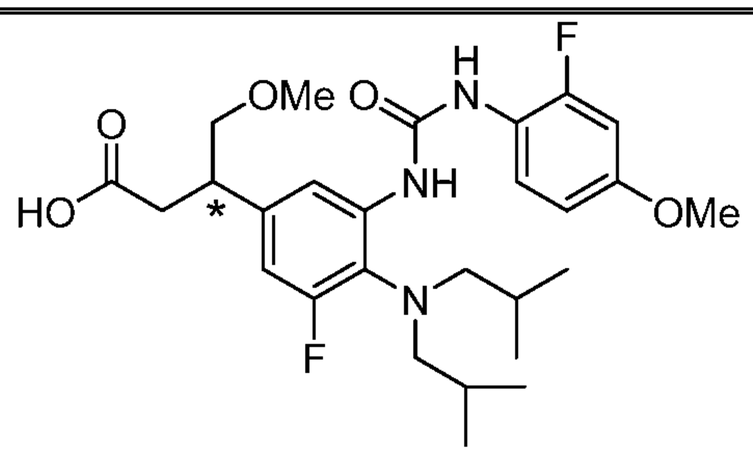
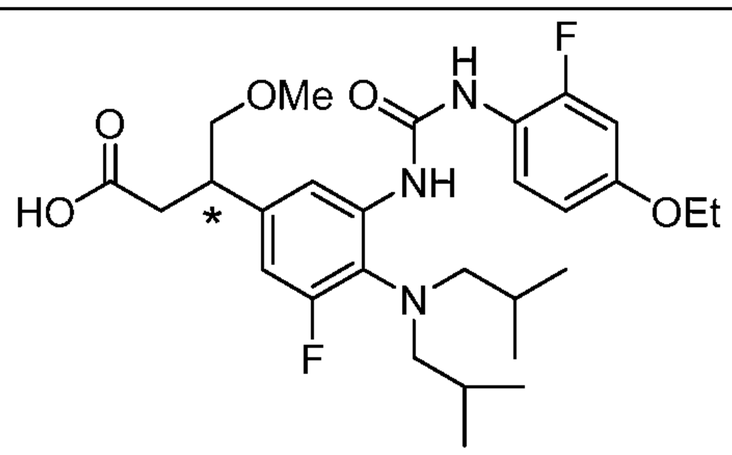
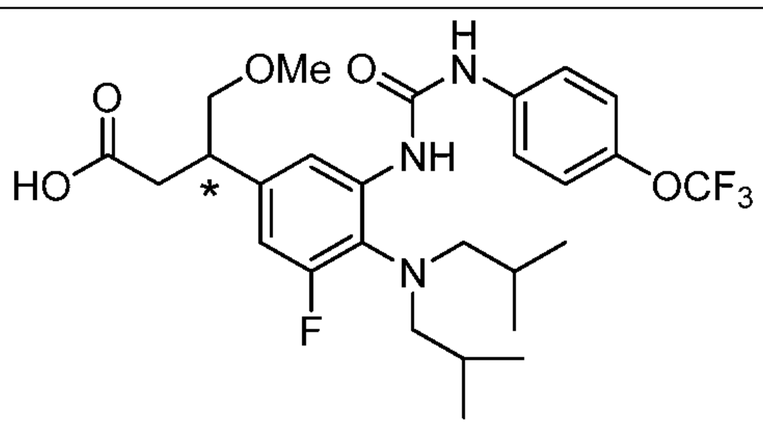
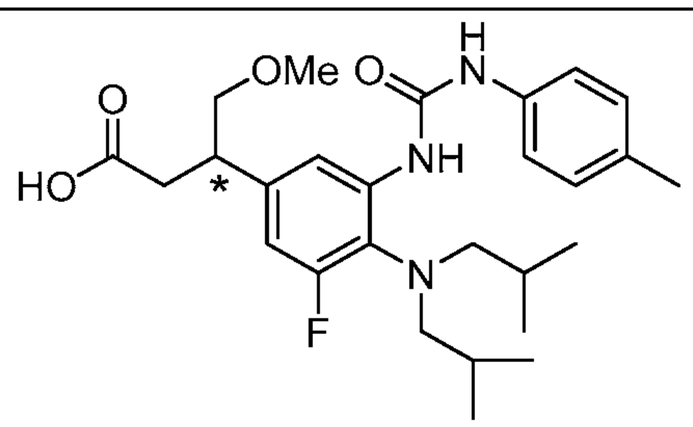
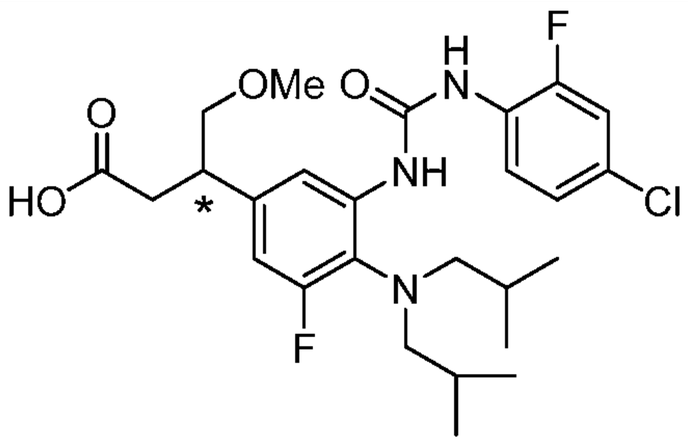
Ex. No.	Structure	Compound Name
1156		3-(3-(3-(4-chloro-2-fluorophenyl) ureido)-4-(cyclohexyl(isobutyl) amino)-5-fluorophenyl)-4-methoxybutanoic acid
1157		3-(4-(cyclohexyl(isobutyl)amino)-3-(3-(4-ethoxy-2-fluorophenyl) ureido)-5-fluorophenyl)-4-methoxybutanoic acid
1158		3-(4-(cyclohexyl(isobutyl)amino)-3-fluoro-5-(3-(5-methylisoxazol-3-yl)ureido)phenyl)-4-methoxybutanoic acid

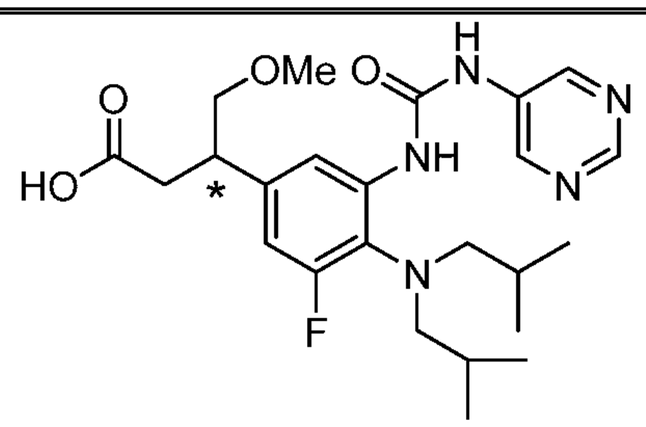
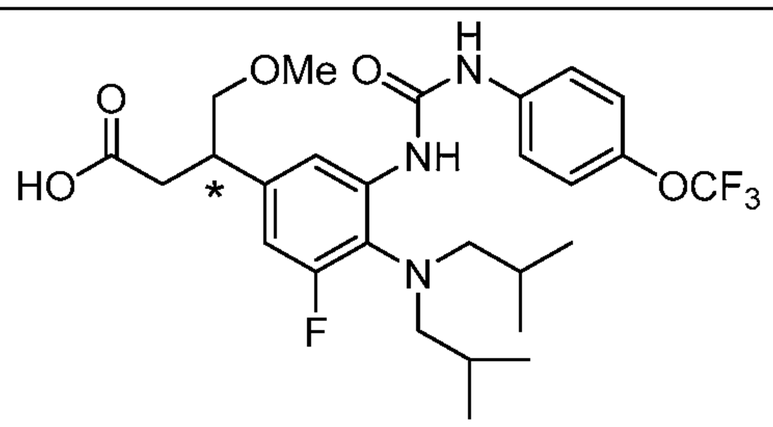
Ex. No.	Structure	Compound Name
1159		3-(4-(cyclohexyl(isobutyl)amino)-3-fluoro-5-(3-(2-fluoro-4-methoxyphenyl)ureido)phenyl)-4-methoxybutanoic acid
1160		3-(4-(cyclohexyl(isobutyl)amino)-3-(3-(4-ethoxyphenyl)ureido)-5-fluorophenyl)-4-methoxybutanoic acid
1161		3-(4-(cyclohexyl(isobutyl)amino)-3-fluoro-5-(3-(p-tolyl)ureido) phenyl)-4-methoxybutanoic acid
1162		3-(3-(3-(4-chlorophenyl)ureido)-4-(cyclohexyl(isobutyl)amino)-5-fluorophenyl)-4-methoxybutanoic acid

Ex. No.	Structure	Compound Name
1163		3-(4-(cyclohexyl(isobutyl)amino)-3-fluoro-5-(3-(4-(trifluoromethoxy)phenyl) ureido)phenyl)-4-methoxybutanoic acid
1164		3-(3-(3-(4-chloro-2-fluorophenyl) ureido)-4-(cyclohexyl(isobutyl) amino)-5-fluorophenyl)-4-methoxybutanoic acid
1165		3-(4-(cyclohexyl(isobutyl)amino)-3-(3-(4-ethoxy-2-fluorophenyl) ureido)-5-fluorophenyl)-4-methoxybutanoic acid
1166		3-(3-(3-(4-chlorophenyl)ureido)-4-(cyclohexyl(isobutyl)amino)-5-fluorophenyl)-4-methoxybutanoic acid

Ex. No.	Structure	Compound Name
1167		3-(4-(cyclohexyl(isobutyl)amino)-3-fluoro-5-(3-(5-methylisoxazol-3-yl)ureido)phenyl)-4-methoxybutanoic acid
1176		3-(4-(diisobutylamino)-3-fluoro-5-(3-(2-fluoro-4-methoxyphenyl) ureido)phenyl)-4-methoxybutanoic acid
1178		3-(4-(diisobutylamino)-3-(3-(4-ethoxy-2-fluorophenyl)ureido)-5-fluorophenyl)-4-methoxybutanoic acid
1179		3-(4-(diisobutylamino)-3-(3-(4-ethoxyphenyl)ureido)-5-fluorophenyl)-4-methoxybutanoic acid
1182		3-(3-(3-(4-chloro-2-fluorophenyl) ureido)-4-(diisobutylamino)-5-fluorophenyl)-4-methoxybutanoic acid

Ex. No.	Structure	Compound Name
1183		3-(4-(diisobutylamino)-3-fluoro-5-(3-(pyrimidin-5-yl)ureido) phenyl)-4-methoxybutanoic acid
1184		3-(4-(diisobutylamino)-3-fluoro-5-(3-(5-methylisoxazol-3-yl)ureido)phenyl)-4-methoxybutanoic acid
1185		3-(4-(diisobutylamino)-3-(3-(4-ethoxyphenyl)ureido)-5-fluorophenyl)-4-methoxybutanoic acid
1186		3-(4-(diisobutylamino)-3-fluoro-5-(3-(p-tolyl)ureido)phenyl)-4-methoxybutanoic acid
1188		3-(4-(diisobutylamino)-3-fluoro-5-(3-(5-methylisoxazol-3-yl)ureido)phenyl)-4-methoxybutanoic acid

Ex. No.	Structure	Compound Name
1189		3-(4-(diisobutylamino)-3-fluoro-5-(3-(2-fluoro-4-methoxyphenyl) ureido)phenyl)-4-methoxybutanoic acid
1191		3-(4-(diisobutylamino)-3-(3-(4-ethoxy-2-fluorophenyl)ureido)-5-fluorophenyl)-4-methoxybutanoic acid
1192		3-(4-(diisobutylamino)-3-fluoro-5-(3-(4-(trifluoromethoxy)phenyl) ureido)phenyl)-4-methoxybutanoic acid
1194		3-(4-(diisobutylamino)-3-fluoro-5-(3-(p-tolyl)ureido)phenyl)-4-methoxybutanoic acid
1195		3-(3-(3-(4-chloro-2-fluorophenyl) ureido)-4-(diisobutylamino)-5-fluorophenyl)-4-methoxybutanoic acid

Ex. No.	Structure	Compound Name
1196		3-(4-(diisobutylamino)-3-fluoro-5-(3-(pyrimidin-5-yl)ureido) phenyl)-4-methoxybutanoic acid
1197		3-(4-(diisobutylamino)-3-fluoro-5-(3-(4-(trifluoromethoxy)phenyl) ureido)phenyl)-4-methoxybutanoic acid

II. OTHER EMBODIMENTS OF THE INVENTION

In another embodiment, the present invention provides a composition comprising one or more compounds of the present invention and/or a pharmaceutically acceptable salt thereof, a stereoisomer thereof, a tautomer thereof, or a solvate thereof.

In another embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention and/or a pharmaceutically acceptable salt thereof, a stereoisomer thereof, a tautomer thereof, or a solvate thereof.

In another embodiment, the present invention provides a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention and/or a pharmaceutically acceptable salt thereof, a stereoisomer thereof, a tautomer thereof, or a solvate thereof.

In another embodiment, the present invention provides a process for making a compound of the present invention and/or a pharmaceutically acceptable salt thereof, a stereoisomer thereof, a tautomer thereof, or a solvate thereof.

In another embodiment, the present invention provides an intermediate for making a compound of the present invention and/or a pharmaceutically acceptable salt thereof, a stereoisomer thereof, a tautomer thereof, or a solvate thereof.

In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of various types of cancer, viral infections and/or autoimmune diseases, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of one or more compounds of the present invention and/or a pharmaceutically acceptable salt thereof, a stereoisomer thereof or a tautomer thereof, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent, such as a chemotherapeutic agent or a signal transductor inhibitor.

In another embodiment, the present invention provides a compound of the present invention, and/or a pharmaceutically acceptable salt thereof, a stereoisomer thereof or a tautomer thereof, for use in therapy.

In another embodiment, the present invention provides a combined preparation of a compound of the present invention, and/or a pharmaceutically acceptable salt thereof, a stereoisomer thereof or a tautomer thereof, and additional therapeutic agent(s) for simultaneous, separate or sequential use in therapy.

In another embodiment, the present invention provides a combined preparation of a compound of the present invention, and/or a pharmaceutically acceptable salt thereof, a stereoisomer thereof or a tautomer thereof, and additional therapeutic agent(s) for simultaneous, separate or sequential use in the treatment and/or prophylaxis of multiple diseases or disorders associated with the enzymatic activity of IDO.

In another aspect, the invention provides a method of treating a patient suffering from or susceptible to a medical condition that is sensitive to enzymatic activity of IDO. A number of medical conditions can be treated. The method comprises administering to the patient a therapeutically effective amount of a composition comprising a compound described herein and/or a pharmaceutically acceptable salt thereof, a stereoisomer thereof or a tautomer thereof. For example, the compounds described herein may be used to treat or prevent viral infections, proliferative diseases (*e.g.*, cancer), and autoimmune diseases.

III. THERAPEUTIC APPLICATIONS

The compounds and pharmaceutical compositions of the present invention are useful in treating or preventing any disease or conditions that are sensitive to enzymatic activity of IDO. These include viral and other infections (*e.g.*, skin infections, GI

infection, urinary tract infections, genito-urinary infections, systemic infections), proliferative diseases (*e.g.*, cancer), and autoimmune diseases (*e.g.*, rheumatoid arthritis, lupus). The compounds and pharmaceutical compositions may be administered to animals, preferably mammals (*e.g.*, domesticated animals, cats, dogs, mice, rats), and more preferably humans. Any method of administration may be used to deliver the compound or pharmaceutical composition to the patient. In certain embodiments, the compound or pharmaceutical composition is administered orally. In other embodiments, the compound or pharmaceutical composition is administered parenterally.

Compounds of the invention can modulate activity of the enzyme indoleamine-2,3-dioxygenase (IDO). The term "modulate" is meant to refer to an ability to increase or decrease activity of an enzyme or receptor. Accordingly, compounds of the invention can be used in methods of modulating IDO by contacting the enzyme with any one or more of the compounds or compositions described herein. In some embodiments, compounds of the present invention can act as inhibitors of IDO. In further embodiments, the compounds of the invention can be used to modulate activity of IDO in cell or in an individual in need of modulation of the enzyme by administering a modulating (*e.g.*, inhibiting) amount of a compound of the invention.

Compounds of the invention can inhibit activity of the enzyme indoleamine-2,3-dioxygenase (IDO). For example, the compounds of the invention can be used to inhibit activity of IDO in cell or in an individual in need of modulation of the enzyme by administering an inhibiting amount of a compound of the invention.

The present invention further provides methods of inhibiting the degradation of tryptophan in a system containing cells expressing IDO such as a tissue, living organism, or cell culture. In some embodiments, the present invention provides methods of altering (*e.g.*, increasing) extracellular tryptophan levels in a mammal by administering an effective amount of a compound of composition provided herein. Methods of measuring tryptophan levels and tryptophan degradation are routine in the art.

The present invention further provides methods of inhibiting immunosuppression such as IDO-mediated immunosuppression in a patient by administering to the patient an effective amount of a compound or composition recited herein. IDO-mediated immunosuppression has been associated with, for example, cancers, tumor growth, metastasis, viral infection, and viral replication.

The present invention further provides methods of treating diseases associated with activity or expression, including abnormal activity and/or overexpression, of IDO in an individual (*e.g.*, patient) by administering to the individual in need of such treatment a therapeutically effective amount or dose of a compound of the present invention or a pharmaceutical composition thereof. Example diseases can include any disease, disorder or condition that is directly or indirectly linked to expression or activity of the IDO enzyme, such as over expression or abnormal activity. An IDO-associated disease can also include any disease, disorder or condition that can be prevented, ameliorated, or cured by modulating enzyme activity. Examples of IDO-associated diseases include cancer, viral infection such as HIV infection, HCV infection, depression, neurodegenerative disorders such as Alzheimer's disease and Huntington's disease, trauma, age-related cataracts, organ transplantation (*e.g.*, organ transplant rejection), and autoimmune diseases including asthma, rheumatoid arthritis, multiple sclerosis, allergic inflammation, inflammatory bowel disease, psoriasis and systemic lupus erythematosus.

As used herein, the term "cell" is meant to refer to a cell that is *in vitro*, *ex vivo* or *in vivo*. In some embodiments, an *ex vivo* cell can be part of a tissue sample excised from an organism such as a mammal. In some embodiments, an *in vitro* cell can be a cell in a cell culture. In some embodiments, an *in vivo* cell is a cell living in an organism such as a mammal.

As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" the IDO enzyme with a compound of the invention includes the administration of a compound of the present invention to an individual or patient, such as a human, having IDO, as well as, for example, introducing a compound of the invention into a sample containing a cellular or purified preparation containing the IDO enzyme.

The term "IDO inhibitor" refers to an agent capable of inhibiting the activity of indoleamine-2,3-dioxygenase (IDO) and thereby reversing IDO-mediated immunosuppression. The IDO inhibitor may inhibit IDO1 and/or IDO2 (INDOL1). An IDO inhibitor may be a reversible or irreversible IDO inhibitor. "A reversible IDO inhibitor" is a compound that reversibly inhibits IDO enzyme activity either at the catalytic site or at a non-catalytic site and "an irreversible IDO inhibitor" is a compound that irreversibly destroys IDO enzyme activity.

Types of cancers that may be treated with the compounds of this invention include, but are not limited to, brain cancers, skin cancers, bladder cancers, ovarian cancers, breast cancers, gastric cancers, pancreatic cancers, prostate cancers, colon cancers, blood cancers, lung cancers and bone cancers. Examples of such cancer types include neuroblastoma, intestine carcinoma such as rectum carcinoma, colon carcinoma, familiar adenomatous polyposis carcinoma and hereditary non-polyposis colorectal cancer, esophageal carcinoma, labial carcinoma, larynx carcinoma, hypopharynx carcinoma, tongue carcinoma, salivary gland carcinoma, gastric carcinoma, adenocarcinoma, medullary thyroid carcinoma, papillary thyroid carcinoma, renal carcinoma, kidney parenchymal carcinoma, ovarian carcinoma, cervix carcinoma, uterine corpus carcinoma, endometrium carcinoma, chorion carcinoma, pancreatic carcinoma, prostate carcinoma, testis carcinoma, breast carcinoma, urinary carcinoma, melanoma, brain tumors such as glioblastoma, astrocytoma, meningioma, medulloblastoma and peripheral neuroectodermal tumors, Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma, acute lymphatic leukemia (ALL), chronic lymphatic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), adult T-cell leukemia lymphoma, diffuse large B-cell lymphoma (DLBCL), hepatocellular carcinoma, gall bladder carcinoma, bronchial carcinoma, small cell lung carcinoma, non-small cell lung carcinoma, multiple myeloma, basalioma, teratoma, retinoblastoma, choroid melanoma, seminoma, rhabdomyosarcoma, craniopharyngioma, osteosarcoma, chondrosarcoma, myosarcoma, liposarcoma, fibrosarcoma, Ewing sarcoma and plasmacytoma.

Thus, according to another embodiment, the invention provides a method of treating an autoimmune disease by providing to a patient in need thereof a compound or composition of the present invention. Examples of such autoimmune diseases include, but are not limited to, collagen diseases such as rheumatoid arthritis, systemic lupus erythematosus, Sharp's syndrome, CREST syndrome (calcinosis, Raynaud's syndrome, esophageal dysmotility, telangiectasia), dermatomyositis, vasculitis (Morbus Wegener's) and Sjögren's syndrome, renal diseases such as Goodpasture's syndrome, rapidly-progressing glomerulonephritis and membranoproliferative glomerulonephritis type II, endocrine diseases such as type-I diabetes, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), autoimmune parathyroidism, pernicious anemia, gonad insufficiency, idiopathic Morbus Addison's, hyperthyreosis, Hashimoto's thyroiditis and

primary myxedema, skin diseases such as pemphigus vulgaris, bullous pemphigoid, herpes gestationis, epidermolysis bullosa and erythema multiforme major, liver diseases such as primary biliary cirrhosis, autoimmune cholangitis, autoimmune hepatitis type-1, autoimmune hepatitis type-2, primary sclerosing cholangitis, neuronal diseases such as multiple sclerosis, myasthenia gravis, myasthenic Lambert-Eaton syndrome, acquired neuromyotomy, Guillain-Barré syndrome (Muller-Fischer syndrome), stiff-man syndrome, cerebellar degeneration, ataxia, opsoclonus, sensoric neuropathy and achalasia, blood diseases such as autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura (Morbus Werlhof), infectious diseases with associated autoimmune reactions such as AIDS, malaria and Chagas disease.

One or more additional pharmaceutical agents or treatment methods such as, for example, anti-viral agents, chemotherapeutics or other anticancer agents, immune enhancers, immunosuppressants, radiation, anti-tumor and anti-viral vaccines, cytokine therapy (*e.g.*, IL2 and GM-CSF), and/or tyrosine kinase inhibitors can be optionally used in combination with the compounds of the present invention for treatment of IDO-associated diseases, disorders or conditions. The agents can be combined with the present compounds in a single dosage form, or the agents can be administered simultaneously or sequentially as separate dosage forms.

Suitable chemotherapeutic or other anticancer agents include, for example, alkylating agents (including, without limitation, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes) such as uracil mustard, chlormethine, cyclophosphamide (CYTOXAN®), ifosfamide, melphalan, chlorambucil, pipobroman, triethylene-melamine, triethylenethiophosphoramine, busulfan, carmustine, lomustine, streptozocin, dacarbazine, and temozolomide.

In the treatment of melanoma, suitable agents for use in combination with the compounds of the present invention include: dacarbazine (DTIC), optionally, along with other chemotherapy drugs such as carmustine (BCNU) and cisplatin; the "Dartmouth regimen", which consists of DTIC, BCNU, cisplatin and tamoxifen; a combination of cisplatin, vinblastine, and DTIC, temozolomide or YERVOY®. Compounds according to the invention may also be combined with immunotherapy drugs, including cytokines such as interferon alpha, interleukin 2, and tumor necrosis factor (TNF) in the treatment of melanoma.

Compounds of the invention may also be used in combination with vaccine therapy in the treatment of melanoma. Anti-melanoma vaccines are, in some ways, similar to the anti-virus vaccines which are used to prevent diseases caused by viruses such as polio, measles, and mumps. Weakened melanoma cells or parts of melanoma cells called antigens may be injected into a patient to stimulate the body's immune system to destroy melanoma cells.

Melanomas that are confined to the arms or legs may also be treated with a combination of agents including one or more compounds of the invention, using a hyperthermic isolated limb perfusion technique. This treatment protocol temporarily separates the circulation of the involved limb from the rest of the body and injects high doses of chemotherapy into the artery feeding the limb, thus providing high doses to the area of the tumor without exposing internal organs to these doses that might otherwise cause severe side effects. Usually the fluid is warmed to 102° to 104° F. Melphalan is the drug most often used in this chemotherapy procedure. This can be given with another agent called tumor necrosis factor (TNF).

Suitable chemotherapeutic or other anticancer agents include, for example, antimetabolites (including, without limitation, folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors) such as methotrexate, 5-fluorouracil, floxuridine, cytarabine, 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, pentostatine, and gemcitabine.

Suitable chemotherapeutic or other anticancer agents further include, for example, certain natural products and their derivatives (for example, vinca alkaloids, antitumor antibiotics, enzymes, lymphokines and epipodophyllotoxins) such as vinblastine, vincristine, vindesine, bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, ara-C, paclitaxel (Taxol), mithramycin, deoxycoformycin, mitomycin-C, L-asparaginase, interferons (especially IFN-a), etoposide, and teniposide.

Other cytotoxic agents include navelbene, CPT-11, anastrazole, letrazole, capecitabine, reloxafine, and droloxafine.

Also suitable are cytotoxic agents such as epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes such as cisplatin and carboplatin; biological response modifiers; growth

inhibitors; antihormonal therapeutic agents; leucovorin; tegafur; and haematopoietic growth factors.

Other anticancer agent(s) include antibody therapeutics such as trastuzumab (HERCEPTIN®), antibodies to costimulatory molecules such as CTLA-4, 4-1BB and PD-1, or antibodies to cytokines (IL-1O or TGF-β).

Other anticancer agents also include those that block immune cell migration such as antagonists to chemokine receptors, including CCR2 and CCR4.

Other anticancer agents also include those that augment the immune system such as adjuvants or adoptive T cell transfer.

Anticancer vaccines include dendritic cells, synthetic peptides, DNA vaccines and recombinant viruses.

The pharmaceutical composition of the invention may optionally include at least one signal transduction inhibitor (STI). A "signal transduction inhibitor" is an agent that selectively inhibits one or more vital steps in signaling pathways, in the normal function of cancer cells, thereby leading to apoptosis. Suitable STIs include, but are not limited to: (i) bcr/abl kinase inhibitors such as, for example, STI 571 (GLEEVEC®); (ii) epidermal growth factor (EGF) receptor inhibitors such as, for example, kinase inhibitors (IRESSA®, SSI-774) and antibodies (Imclone: C225 [Goldstein et al., *Clin. Cancer Res.*, 1:1311-1318 (1995)], and Abgenix: ABX-EGF); (iii) her-2/neu receptor inhibitors such as farnesyl transferase inhibitors (FTI) such as, for example, L-744,832 (Kohl et al., *Nat. Med.*, 1(8):792-797 (1995)); (iv) inhibitors of Akt family kinases or the Akt pathway, such as, for example, rapamycin (see, for example, Sekulic et al., *Cancer Res.*, 60:3504-3513 (2000)); (v) cell cycle kinase inhibitors such as, for example, flavopiridol and UCN-O1 (see, for example, Sausville, *Curr. Med. Chem. Anti-Canc. Agents*, 3:47-56 (2003)); and (vi) phosphatidyl inositol kinase inhibitors such as, for example, LY294002 (see, for example, Vlahos et al., *J. Biol. Chem.*, 269:5241-5248 (1994)). Alternatively, at least one STI and at least one IDO inhibitor may be in separate pharmaceutical compositions. In a specific embodiment of the present invention, at least one IDO inhibitor and at least one STI may be administered to the patient concurrently or sequentially. In other words, at least one IDO inhibitor may be administered first, at least one STI may be administered first, or at least one IDO inhibitor and at least one STI may

be administered at the same time. Additionally, when more than one IDO inhibitor and/or STI is used, the compounds may be administered in any order.

The present invention further provides a pharmaceutical composition for the treatment of a chronic viral infection in a patient comprising at least one IDO inhibitor, optionally, at least one chemotherapeutic drug, and, optionally, at least one antiviral agent, in a pharmaceutically acceptable carrier. The pharmaceutical compositions may include at least one IDO inhibitor of the instant invention in addition to at least one established (known) IDO inhibitor. In a specific embodiment, at least one of the IDO inhibitors of the pharmaceutical composition is selected from the group consisting of compounds of formulas I and (II).

Also provided is a method for treating a chronic viral infection in a patient by administering an effective amount of the above pharmaceutical composition.

In a specific embodiment of the present invention, at least one IDO inhibitor and at least one chemotherapeutic agent may be administered to the patient concurrently or sequentially. In other words, at least one IDO inhibitor may be administered first, at least one chemotherapeutic agent may be administered first, or at least one IDO inhibitor and the at least one STI may be administered at the same time. Additionally, when more than one IDO inhibitor and/or chemotherapeutic agent is used, the compounds may be administered in any order. Similarly, any antiviral agent or STI may also be administered at any point in comparison to the administration of an IDO inhibitor.

Chronic viral infections that may be treated using the present combinatorial treatment include, but are not limited to, diseases caused by: hepatitis C virus (HCV), human papilloma virus (HPV), cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), varicella zoster virus, Coxsackie virus, human immunodeficiency virus (HIV). Notably, parasitic infections (*e.g.*, malaria) may also be treated by the above methods wherein compounds known to treat the parasitic conditions are optionally added in place of the antiviral agents.

In yet another embodiment, the pharmaceutical compositions comprising at least one IDO inhibitor of the instant invention may be administered to a patient to prevent arterial restenosis, such as after balloon endoscopy or stent placement. In a particular embodiment, the pharmaceutical composition further comprises at least one taxane (*e.g.*, paclitaxel (Taxol); see, *e.g.*, Scheller et al., *Circulation*, 110:810-814 (2004)).

Suitable antiviral agents contemplated for use in combination with the compounds of the present invention can comprise nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors and other antiviral drugs.

Examples of suitable NRTIs include zidovudine (AZT); didanosine (ddI); zalcitabine (ddC); stavudine (d4T); lamivudine (3TC); abacavir (1592U89); adefovir dipivoxil [bis(POM)-PMEA]; lobucavir (BMS-180194); BCH-I0652; emtricitabine [(-)-FTC]; beta-L-FD4 (also called beta-L-D4C and named beta-L-2′,3′-dicleoxy-5-fluoro-cytidene); DAPD, ((-)-beta-D-2,6-diamino-purine dioxolane); and lodenosine (FddA). Typical suitable NNRTIs include nevirapine (BI-RG-587); delaviradine (BHAP, U-90152); efavirenz (DMP-266); PNU-142721; AG-1549; MKC-442 (1-(ethoxy-methyl)-5-(1-methylethyl)-6-(phenylmethyl)-(2,4(1H,3H)-pyrimidinedione); and (+)-calanolide A (NSC-675451) and B. Typical suitable protease inhibitors include saquinavir (Ro 31-8959); ritonavir (ABT-538); indinavir (MK-639); nelfinavir (AG-1343); amprenavir (141W94); lasinavir (BMS-234475); DMP-450; BMS-2322623; ABT-378; and AG-1549. Other antiviral agents include hydroxyurea, ribavirin, IL-2, IL-12, pentafuside and Yissum Project No.11607.

Combination with an Immuno-Oncology Agent

Further provided herein are methods of treatment wherein a compound of Formula I is administered with one or more immuno-oncology agents. The immuno-oncology agents used herein, also known as cancer immunotherapies, are effective to enhance, stimulate, and/or upregulate immune responses in a subject.

In one aspect, the Compound of Formula I is sequentially administered prior to administration of the immuno-oncology agent. In another aspect, the Compound of Formula I is administered concurrently with the immunology-oncology agent. In yet another aspect, the Compound of Formula I is sequentially administered after administration of the immuno-oncology agent.

In another aspect, the Compound of Formula I may be co-formulated with an immuno-oncology agent.

Immuno-oncology agents include, for example, a small molecule drug, antibody, or other biologic or small molecule. Examples of biologic immuno-oncology agents

include, but are not limited to, cancer vaccines, antibodies, and cytokines. In one aspect, the antibody is a monoclonal antibody. In another aspect, the monoclonal antibody is humanized or human.

In one aspect, the immuno-oncology agent is (i) an agonist of a stimulatory (including a co-stimulatory) receptor or (ii) an antagonist of an inhibitory (including a co-inhibitory) signal on T cells, both of which result in amplifying antigen-specific T cell responses (often referred to as immune checkpoint regulators).

Certain of the stimulatory and inhibitory molecules are members of the immunoglobulin super family (IgSF). One important family of membrane-bound ligands that bind to co-stimulatory or co-inhibitory receptors is the B7 family, which includes B7-1, B7-2, B7-H1 (PD-L1), B7-DC (PD-L2), B7-H2 (ICOS-L), B7-H3, B7-H4, B7-H5 (VISTA), and B7-H6. Another family of membrane bound ligands that bind to co-stimulatory or co-inhibitory receptors is the TNF family of molecules that bind to cognate TNF receptor family members, which includes CD40 and CD40L, OX-40, OX-40L, CD70, CD27L, CD30, CD30L, 4-1BBL, CD137 (4-1BB), TRAIL/Apo2-L, TRAILR1/DR4, TRAILR2/DR5, TRAILR3, TRAILR4, OPG, RANK, RANKL, TWEAKR/Fn14, TWEAK, BAFFR, EDAR, XEDAR, TACI, APRIL, BCMA, LTβR, LIGHT, DcR3, HVEM, VEGI/TL1A, TRAMP/DR3, EDAR, EDA1, XEDAR, EDA2, TNFR1, Lymphotoxin α/TNFβ, TNFR2, TNFα, LTβR, Lymphotoxin α 1β2, FAS, FASL, RELT, DR6, TROY, NGFR.

In another aspect, the immuno-oncology agent is a cytokine that inhibits T cell activation (*e.g.*, IL-6, IL-10, TGF-ß, VEGF, and other immunosuppressive cytokines) or a cytokine that stimulates T cell activation, for stimulating an immune response.

In one aspect, T cell responses can be stimulated by a combination of the Compound of Formula I and one or more of (i) an antagonist of a protein that inhibits T cell activation (*e.g.*, immune checkpoint inhibitors) such as CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, TIM-3, Galectin 9, CEACAM-1, BTLA, CD69, Galectin-1, TIGIT, CD113, GPR56, VISTA, 2B4, CD48, GARP, PD1H, LAIR1, TIM-1, and TIM-4, and (ii) an agonist of a protein that stimulates T cell activation such as B7-1, B7-2, CD28, 4-1BB (CD137), 4-1BBL, ICOS, ICOS-L, OX40, OX40L, GITR, GITRL, CD70, CD27, CD40, DR3 and CD28H.

Other agents that can be combined with the Compound of Formula I for the treatment of cancer include antagonists of inhibitory receptors on NK cells or agonists of activating receptors on NK cells. For example, the Compound of Formula I can be combined with antagonists of KIR, such as lirilumab.

Yet other agents for combination therapies include agents that inhibit or deplete macrophages or monocytes, including but not limited to CSF-1R antagonists such as CSF-1R antagonist antibodies including RG7155 (WO 11/70024, WO 11/107553, WO 11/131407, WO 13/87699, WO 13/119716, WO 13/132044) or FPA-008 (WO 11/140249, WO 13/169264, WO 14/036357).

In another aspect, the Compound of Formula I can be used with one or more of agonistic agents that ligate positive costimulatory receptors, blocking agents that attenuate signaling through inhibitory receptors, antagonists, and one or more agents that increase systemically the frequency of anti-tumor T cells, agents that overcome distinct immune suppressive pathways within the tumor microenvironment (*e.g.*, block inhibitory receptor engagement (*e.g.*, PD-L1/PD-1 interactions), deplete or inhibit Tregs (*e.g.*, using an anti-CD25 monoclonal antibody (*e.g.*, daclizumab) or by *ex vivo* anti-CD25 bead depletion), inhibit metabolic enzymes such as IDO, or reverse/prevent T cell anergy or exhaustion) and agents that trigger innate immune activation and/or inflammation at tumor sites.

In one aspect, the immuno-oncology agent is a CTLA-4 antagonist, such as an antagonistic CTLA-4 antibody. Suitable CTLA-4 antibodies include, for example, YERVOY® (ipilimumab) or tremelimumab.

In another aspect, the immuno-oncology agent is a PD-1 antagonist, such as an antagonistic PD-1 antibody. Suitable PD-1 antibodies include, for example, OPDIVO® (nivolumab), KEYTRUDA® (pembrolizumab), or MEDI-0680 (AMP-514; WO 2012/145493). The immuno-oncology agent may also include pidilizumab (CT-011), though its specificity for PD-1 binding has been questioned. Another approach to target the PD-1 receptor is the recombinant protein composed of the extracellular domain of PD-L2 (B7-DC) fused to the Fc portion of IgG1, called AMP-224

In another aspect, the immuno-oncology agent is a PD-L1 antagonist, such as an antagonistic PD-L1 antibody. Suitable PD-L1 antibodies include, for example,

MPDL3280A (RG7446; WO 2010/077634), durvalumab (MEDI4736), BMS-936559 (WO 2007/005874), and MSB0010718C (WO 2013/79174).

In another aspect, the immuno-oncology agent is a LAG-3 antagonist, such as an antagonistic LAG-3 antibody. Suitable LAG3 antibodies include, for example, BMS-986016 (WO 10/19570, WO 14/08218), or IMP-731 or IMP-321 (WO 08/132601, WO 09/44273).

In another aspect, the immuno-oncology agent is a CD137 (4-1BB) agonist, such as an agonistic CD137 antibody. Suitable CD137 antibodies include, for example, urelumab and PF-05082566 (WO 12/32433).

In another aspect, the immuno-oncology agent is a GITR agonist, such as an agonistic GITR antibody. Suitable GITR antibodies include, for example, BMS-986153, BMS-986156, TRX-518 (WO 06/105021, WO 09/009116) and MK-4166 (WO 11/028683).

In another aspect, the immuno-oncology agent is an IDO antagonist. Suitable IDO antagonists include, for example, INCB-024360 (WO 2006/122150, WO 07/75598, WO 08/36653, WO 08/36642), indoximod, or NLG-919 (WO 09/73620, WO 09/1156652, WO 11/56652, WO 12/142237).

In another aspect, the immuno-oncology agent is an OX40 agonist, such as an agonistic OX40 antibody. Suitable OX40 antibodies include, for example, MEDI-6383 or MEDI-6469.

In another aspect, the immuno-oncology agent is an OX40L antagonist, such as an antagonistic OX40 antibody. Suitable OX40L antagonists include, for example, RG-7888 (WO 06/029879).

In another aspect, the immuno-oncology agent is a CD40 agonist, such as an agonistic CD40 antibody. In yet another embodiment, the immuno-oncology agent is a CD40 antagonist, such as an antagonistic CD40 antibody. Suitable CD40 antibodies include, for example, lucatumumab or dacetuzumab.

In another aspect, the immuno-oncology agent is a CD27 agonist, such as an agonistic CD27 antibody. Suitable CD27 antibodies include, for example, varlilumab.

In another aspect, the immuno-oncology agent is MGA271 (to B7H3) (WO 11/109400).

The present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of IDO-associated diseases or disorders, obesity, diabetes and other diseases referred to herein which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention. Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

The combination therapy is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single dosage form having a fixed ratio of each therapeutic agent or in multiple, single dosage forms for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. Combination therapy also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients and non-drug therapies (*e.g.*, surgery or radiation treatment). Where the combination therapy further comprises a non-drug treatment, the non-drug treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and non-drug treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the non-drug treatment is

temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

PHARMACEUTICAL COMPOSITIONS AND DOSING

The invention also provides pharmaceutically acceptable compositions which comprise a therapeutically effective amount of one or more of the compounds of Formula I, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents, and optionally, one or more additional therapeutic agents described above.

The compounds of this invention can be administered for any of the uses described herein by any suitable means, for example, orally, such as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions (including nanosuspensions, microsuspensions, spray-dried dispersions), syrups, and emulsions; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection, or infusion techniques *(e.g.*, as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally, including administration to the nasal membranes, such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

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

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (*e.g.*, lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another

organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient.

The term "pharmaceutical composition" means a composition comprising a compound of the invention in combination with at least one additional pharmaceutically acceptable carrier. A "pharmaceutically acceptable carrier" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals, including, *i.e.*, adjuvant, excipient or vehicle, such as diluents, preserving agents, fillers, flow regulating agents, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms.

Pharmaceutically acceptable carriers are formulated according to a number of factors well within the purview of those of ordinary skill in the art. These include, without limitation: the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and the therapeutic indication being targeted. Pharmaceutically acceptable carriers include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi-solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, *e.g.*, stabilization of the active agent, binders, etc., well known to those of ordinary skill in the art. Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources such as, for example, Allen, Jr., L.V. et al., *Remington: The Science and Practice of Pharmacy* (2 Volumes), 22nd Edition, Pharmaceutical Press (2012).

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to about 5000 mg per day, preferably between about 0.01 to about 1000 mg per day, and most preferably between about 0.1 to about 250 mg per day. Intravenously, the most preferred doses will range from about 0.01 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, *e.g.*, oral tablets, capsules, elixirs, and syrups, and consistent with conventional pharmaceutical practices.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 2000 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.1-95% by weight based on the total weight of the composition.

A typical capsule for oral administration contains at least one of the compounds of the present invention (250 mg), lactose (75 mg), and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

A typical injectable preparation is produced by aseptically placing at least one of the compounds of the present invention (250 mg) into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectable preparation.

The present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, a therapeutically effective amount of at least one of the compounds of the present invention, alone or in combination with a pharmaceutical carrier. Optionally, compounds of the present invention can be used alone, in combination with other compounds of the invention, or in combination with one or more other therapeutic agent(s), *e.g.*, an anticancer agent or other pharmaceutically active material.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

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

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

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, oral, intravenous, intracerebroventricular and subcutaneous doses of the compounds of this invention for a patient will range from about 0.01 to about 50 mg per kilogram of body weight per day.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain aspects of the invention, dosing is one administration per day.

While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation (composition).

DEFINITIONS

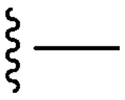
Unless specifically stated otherwise herein, references made in the singular may also include the plural. For example, "a" and "an" may refer to either one, or one or more.

Unless otherwise indicated, any heteroatom with unsatisfied valences is assumed to have hydrogen atoms sufficient to satisfy the valences.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof where such isomers exist. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are within the scope of the invention. Many geometric isomers of C=C double bonds, C=N double bonds, ring systems, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. *Cis*- and *trans*- (or *E*- and *Z*-) geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. The present compounds can be isolated in optically active or racemic forms. Optically active forms may be prepared by resolution of racemic forms or by synthesis from optically active starting materials. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. When enantiomeric or diastereomeric products are prepared, they may be separated by conventional methods, for example, by chromatography or fractional crystallization. Depending on the process conditions the end products of the present invention are obtained either in free (neutral) or salt form. Both the free form and the salts of these end products are within the scope of the invention. If so desired, one form of a compound may be converted into another form. A free base or acid may be converted into a salt; a salt may be converted into the free compound or another salt; a mixture of isomeric compounds of the present invention may be separated into the individual isomers. Compounds of the present invention, free form and salts thereof, may exist in multiple tautomeric forms, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the

molecules are consequently rearranged. It should be understood that all tautomeric forms, insofar as they may exist, are included within the invention.

When a substituent is noted as "optionally substituted", the substituents are selected from, for example, substituents such as alkyl, cycloalkyl, aryl, heterocyclo, halo, hydroxy, alkoxy, oxo, alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, arylalkylamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or arylalkyl; alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, arylalkylthio, alkylthiono, arylthiono, arylalkylthiono, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, sulfonamido, *e.g.*, $-SO_2NH_2$, substituted sulfonamido, nitro, cyano, carboxy, carbamyl, *e.g.*, $-CONH_2$, substituted carbamyl, *e.g.*, -CONHalkyl, -CONHaryl, -CONHarylalkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or arylalkyl; alkoxycarbonyl, aryl, substituted aryl, guanidino, heterocyclyl, *e.g.*, indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, homopiperazinyl and the like, and substituted heterocyclyl, unless otherwise defined.

For purposes of clarity and in accordance with standard convention in the art, the symbol  is used in formulas and tables to show the bond that is the point of attachment of the moiety or substituent to the core/nucleus of the structure.

Additionally, for purposes of clarity, where a substituent has a dash (-) that is not between two letters or symbols; this is used to indicate a point of attachment for a substituent. For example, $-CONH_2$ is attached through the carbon atom.

Additionally, for purposes of clarity, when there is no substituent shown at the end of a solid line, this indicates that there is a methyl (CH_3) group connected to the bond.

As used herein, the term "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "C_1-C_6 alkyl" denotes alkyl having 1 to 6 carbon atoms. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, *t*-butyl), and pentyl (*e.g.*, n-pentyl, isopentyl, neopentyl).

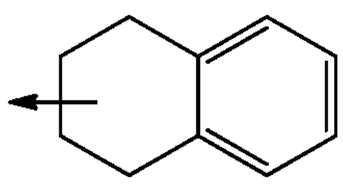
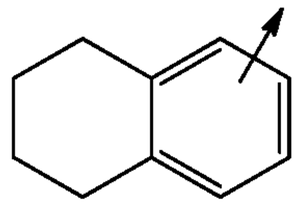
The term "alkenyl" denotes a straight- or branch-chained hydrocarbon radical containing one or more double bonds and typically from 2 to 20 carbon atoms in length.

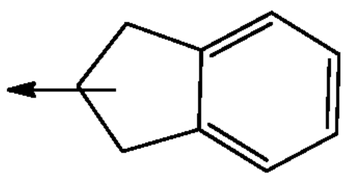
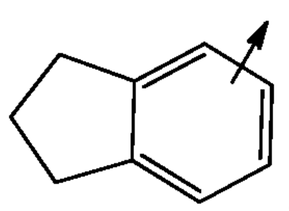
For example, "C_2-C_8 alkenyl" contains from two to eight carbon atoms. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, heptenyl, octenyl and the like.

The term "alkynyl" denotes a straight- or branch-chained hydrocarbon radical containing one or more triple bonds and typically from 2 to 20 carbon atoms in length. For example, "C_2-C_8 alkenyl" contains from two to eight carbon atoms. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butynyl, heptynyl, octynyl and the like.

The term "alkoxy" or "alkyloxy" refers to an -O-alkyl group. "C_{1-6} alkoxy" (or alkyloxy), is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. Example alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy (*e.g.*, n-propoxy and isopropoxy), and *t*-butoxy. Similarly, "alkylthio" or "thioalkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example, methyl-S- and ethyl-S-.

The term "aryl", either alone or as part of a larger moiety such as "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic and tricyclic ring systems having a total of 5 to 15 ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains three to seven ring members. In certain embodiments of the invention, "aryl" refers to an aromatic ring system which includes, but not limited to phenyl, biphenyl, indanyl, 1-naphthyl, 2-naphthyl and terahydronaphthyl. The term "aralkyl" or "arylalkyl" refers to an alkyl residue attached to an aryl ring. Non-limiting examples include benzyl, phenethyl and the like. The fused aryls may be connected to another group either at a suitable position on the cycloalkyl ring or the aromatic ring. For example:

Arrowed lines drawn from the ring system indicate that the bond may be attached to any of the suitable ring atoms.

The term "cycloalkyl" refers to cyclized alkyl groups. C_{3-6} cycloalkyl is intended to include C_3, C_4, C_5, and C_6 cycloalkyl groups. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and norbornyl. Branched cycloalkyl groups such as 1-methylcyclopropyl and 2-methylcyclopropyl are included in the definition of "cycloalkyl". The term "cycloalkenyl" refers to cyclized alkenyl groups. C_{4-6} cycloalkenyl is intended to include C_4, C_5, and C_6 cycloalkenyl groups. Example cycloalkenyl groups include, but are not limited to, cyclobutenyl, cyclopentenyl, and cyclohexenyl.

The term "cycloalkylalkyl" refers to a cycloalkyl or substituted cycloalkyl bonded to an alkyl group connected to the carbazole core of the compound.

"Halo" or "halogen" includes fluoro, chloro, bromo, and iodo. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogens. Examples of haloalkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl. Examples of haloalkyl also include "fluoroalkyl" that is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more fluorine atoms.

"Haloalkoxy" or "haloalkyloxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. For example, "C_{1-6} haloalkoxy", is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 haloalkoxy groups. Examples of haloalkoxy include, but are not limited to, trifluoromethoxy, 2,2,2-trifluoroethoxy, and pentafluorothoxy. Similarly, "haloalkylthio" or "thiohaloalkoxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example, trifluoromethyl-S-, and pentafluoroethyl-S-.

The term "benzyl", as used herein, refers to a methyl group on which one of the hydrogen atoms is replaced by a phenyl group.

As used herein, the term "heterocycle", "heterocyclyl", or "heterocyclic group" is intended to mean a stable 3-, 4-, 5-, 6-, or 7-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered polycyclic heterocyclic ring that is saturated,

partially unsaturated, or fully unsaturated, and that contains carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O and S; and including any polycyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, wherein p is 0, 1 or 2). The nitrogen atom may be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, if defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. When the term "heterocycle" is used, it is intended to include heteroaryl.

Examples of heterocycles include, but are not limited to, acridinyl, azetidinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, imidazolopyridinyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolopyridinyl, isoxazolyl, isoxazolopyridinyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolopyridinyl, oxazolidinylperimidinyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolopyridinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidonyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl,

quinoxalinyl, quinuclidinyl, tetrazolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thiazolopyridinyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

As used herein, the term "bicyclic heterocycle" or "bicyclic heterocyclic group" is intended to mean a stable 9- or 10-membered heterocyclic ring system which contains two fused rings and consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, O and S. Of the two fused rings, one ring is a 5- or 6-membered monocyclic aromatic ring comprising a 5-membered heteroaryl ring, a 6-membered heteroaryl ring or a benzo ring, each fused to a second ring. The second ring is a 5- or 6-membered monocyclic ring which is saturated, partially unsaturated, or unsaturated, and comprises a 5-membered heterocycle, a 6-membered heterocycle or a carbocycle (provided the first ring is not benzo when the second ring is a carbocycle).

The bicyclic heterocyclic group may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The bicyclic heterocyclic group described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1.

Examples of a bicyclic heterocyclic group are, but not limited to, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, indolyl, isoindolyl, indolinyl, 1H-indazolyl, benzimidazolyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydro-quinolinyl, 2,3-dihydro-benzofuranyl, chromanyl, 1,2,3,4-tetrahydro-quinoxalinyl and 1,2,3,4-tetrahydro-quinazolinyl.

As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended to mean stable monocyclic and polycyclic aromatic hydrocarbons that include at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include, without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrroyl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-

thiadiazolyl, isothiazolyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, benzodioxolanyl and benzodioxane. Heteroaryl groups are substituted or unsubstituted. The nitrogen atom is substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, if defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, wherein p is 0, 1 or 2).

Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more, preferably one to three, atoms (*i.e.*, C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Examples of bridged rings include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

The term "heterocyclylalkyl" refers to a heterocyclyl or substituted heterocyclyl bonded to an alkyl group connected to the core of the compound.

The term "counter ion" is used to represent a negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate or a positively charged species such as sodium (Na+), potassium (K+), ammonium (R_nNH_m+ where n=0-4 and m=0-4) and the like.

The term "electron withdrawing group" (EWG) refers to a substituent which polarizes a bond, drawing electron density towards itself and away from other bonded atoms. Examples of EWGs include, but are not limited to, CF_3, CF_2CF_3, CN, halogen, haloalkyl, NO_2, sulfone, sulfoxide, ester, sulfonamide, carboxamide, alkoxy, alkoxyether, alkenyl, alkynyl, OH, C(O)alkyl, CO_2H, phenyl, heteroaryl, -O-phenyl, and -O-heteroaryl. Preferred examples of EWG include, but are not limited to, CF_3, CF_2CF_3, CN, halogen, $SO_2(C_{1-4}$ alkyl), $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl)$_2$, and heteroaryl. More preferred examples of EWG include, but are not limited to, CF_3 and CN.

As used herein, the term "amine protecting group" means any group known in the art of organic synthesis for the protection of amine groups which is stable to an ester reducing agent, a disubstituted hydrazine, R4-M and R7-M, a nucleophile, a hydrazine reducing agent, an activator, a strong base, a hindered amine base and a cyclizing agent. Such amine protecting groups fitting these criteria include those listed in Wuts, P.G.M. et al., *Protecting Groups in Organic Synthesis*, Fourth Edition, Wiley (2007) and *The*

Peptides: Analysis, Synthesis, Biology, Vol. 3, Academic Press, New York (1981). The disclosure of which is hereby incorporated by reference. Examples of amine protecting groups include, but are not limited to, the following: (1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; (2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); (3) aliphatic carbamate types such as *tert*-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; (4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; (5) alkyl types such as triphenylmethyl and benzyl; (6) trialkylsilane such as trimethylsilane; (7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl; and (8) alkyl types such as triphenylmethyl, methyl, and benzyl; and substituted alkyl types such as 2,2,2-trichloroethyl, 2-phenylethyl, and *t*-butyl; and trialkylsilane types such as trimethylsilane.

As referred to herein, the term "substituted" means that at least one hydrogen atom is replaced with a non-hydrogen group, provided that normal valencies are maintained and that the substitution results in a stable compound. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N, or N=N).

In cases wherein there are nitrogen atoms (*e.g.*, amines) on compounds of the present invention, these may be converted to N-oxides by treatment with an oxidizing agent (*e.g.*, mCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

When any variable occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R, then said group may optionally be substituted with up to three R groups, and at each occurrence R is selected independently from the definition of R. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom in which such substituent is bonded to the rest of the

compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

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

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Allen, Jr., L.V., ed., *Remington: The Science and Practice of Pharmacy*, 22nd Edition, Pharmaceutical Press, London, UK (2012). The disclosure of which is hereby incorporated by reference.

In addition, compounds of formula I may have prodrug forms. Any compound that will be converted *in vivo* to provide the bioactive agent (*i.e.*, a compound of formula

I) is a prodrug within the scope and spirit of the invention. Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) Bundgaard, H., ed., *Design of Prodrugs*, Elsevier (1985), and Widder, K. et al., eds., *Methods in Enzymology*, 112:309-396, Academic Press (1985);

b) Bundgaard, H., Chapter 5: "Design and Application of Prodrugs", *A Textbook of Drug Design and Development*, pp. 113-191, Krogsgaard-Larsen, P. et al., eds., Harwood Academic Publishers (1991);

c) Bundgaard, H., *Adv. Drug Deliv. Rev.*, 8:1-38 (1992);

d) Nielsen, N.M. et al., *J. Pharm. Sci.*, 77:285 (1988);

e) Kakeya, N. et al., *Chem. Pharm. Bull.*, 32:692 (1984); and

g) Rautio, J., ed., *Prodrugs and Targeted Delivery (Methods and Principles in Medicinal Chemistry)*, Vol. 47, Wiley-VCH (2011).

Compounds containing a carboxy group can form physiologically hydrolyzable esters that serve as prodrugs by being hydrolyzed in the body to yield formula I compounds *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula I include C_{1-6}alkyl, C_{1-6}alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C_{1-6} alkanoyloxy-C_{1-6}alkyl (*e.g.*, acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl), C_{1-6}alkoxycarbonyloxy-C_{1-6}alkyl (*e.g.*, methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl), and other well-known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

Preparation of prodrugs is well known in the art and described in, for example, King, F.D., ed., *Medicinal Chemistry: Principles and Practice*, The Royal Society of Chemistry, Cambridge, UK (Second Edition, reproduced, 2006); Testa, B. et al., *Hydrolysis in Drug and Prodrug Metabolism. Chemistry, Biochemistry and Enzymology*,

VCHA and Wiley-VCH, Zurich, Switzerland (2003); Wermuth, C.G., ed., *The Practice of Medicinal Chemistry*, Third Edition, Academic Press, San Diego, CA (2008).

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ^{13}C and ^{14}C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

The term "solvate" means a physical association of a compound of this invention with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The solvent molecules in the solvate may be present in a regular arrangement and/or a non-ordered arrangement. The solvate may comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include, but are not limited to, hydrates, ethanolates, methanolates, and isopropanolates. Methods of solvation are generally known in the art.

As used herein, the term "patient" refers to organisms to be treated by the methods of the present invention. Such organisms preferably include, but are not limited to, mammals (*e.g.*, murines, simians, equines, bovines, porcines, canines, felines, and the like), and most preferably refers to humans.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent, *i.e.*, a compound of the invention, that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. An effective amount can be administered in one or more administrations,

applications or dosages and is not intended to be limited to a particular formulation or administration route. The term also includes within its scope amounts effective to enhance normal physiological function.

As used herein, the term "treating" includes any effect, *e.g.*, lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

As used herein, the term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo*.

Examples of bases include, but are not limited to, alkali metals (*e.g.*, sodium) hydroxides, alkaline earth metals (*e.g.*, magnesium), hydroxides, ammonia, and compounds of formula NW_4^+, wherein W is C_{1-4} alkyl, and the like.

For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

METHODS OF PREPARATION

The compounds of the present invention may be prepared by methods such as those illustrated in the following Schemes utilizing chemical transformations known to those skilled in the art. Solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. Starting materials are commercially available or readily prepared by one of ordinary skill in the art. These Schemes are illustrative and are not meant to limit the possible techniques one skilled in the art may use to manufacture compounds disclosed herein. Different methods may be evident to those skilled in the art. Additionally, the various steps in the synthesis may be performed in an alternate sequence or order to give the desired compound(s). Further, the representation of the reactions in these Schemes as discrete steps does not preclude their being performed in tandem, either by telescoping multiple steps in the same reaction vessel or by performing multiple steps without purifying or characterizing the intermediate(s). In addition, many of the compounds prepared by the methods below can

be further modified using conventional chemistry well known to those skilled in the art. All documents cited herein are incorporated herein by reference in their entirety.

References to many of these chemical transformations employed herein can be found in Smith, M.B. et al., *March's Advanced Organic Chemistry Reactions, Mechanisms, and Structure*, Fifth Edition, Wiley-Interscience, New York (2001), or other standard texts on the topic of synthetic organic chemistry. Certain transformations may require that reactive functional groups be masked by protecting group(s). A convenient reference which provides conditions for introduction, removal, and relative susceptibility to reaction conditions of these groups is Greene, T.W. et al., *Protective Groups in Organic Synthesis*, Third Edition, Wiley-Interscience, New York (1999).

EXAMPLES

The invention is now described with reference to the following Examples. These Examples are provided for the purpose of illustration only and the invention should in no way be construed as being limited to these Examples but rather should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

Abbreviations as used herein, are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "L" for liter or liters, "mL" for milliliter or milliliters, "μL" for microliter or microliters, "N" for normal, "M" for molar, "mmol" for millimole or millimoles, "min" for minute or min, "h" for hour or h, "rt" for room temperature, "*Tr*" for retention time, "atm" for atmosphere, "psi" for pounds per square inch, "conc." For concentrate or concentrated, "aq" for "aqueous", "sat" or "sat'd" for saturated, "MW" for molecular weight, "mp" for melting point, "MS" or "Mass Spec" for mass spectrometry, "ESI" for electrospray ionization mass spectroscopy, "HR" for high resolution, "HRMS" for high resolution mass spectrometry, "LCMS" for liquid chromatography mass spectrometry, "HPLC" for high pressure liquid chromatography, "RP HPLC" for reverse phase HPLC, "TLC" or "tlc" for thin layer chromatography, "NMR" for nuclear magnetic resonance spectroscopy, "nOe" for nuclear Overhauser effect spectroscopy, "^{1}H" for proton, "δ" for delta, "s" for singlet, "d" for doublet, "t" for

triplet, "q" for quartet, "m" for multiplet, "br" for broad, "Hz" for hertz, and "α", "β", "R", "S", "E", and "Z" are stereochemical designations familiar to one skilled in the art.

Me	methyl
Et	ethyl
Pr	propyl
i-Pr	isopropyl
Bu	butyl
i-Bu	isobutyl
t-Bu	*tert*-butyl
Ph	phenyl
Bn	benzyl
Hex	hexanes
MeOH	methanol
EtOH	ethanol
i-PrOH or IPA	isopropanol
AcOH or HOAc	acetic acid
BOP	(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
$CDCl_3$	deutero-chloroform
$CHCl_3$	chloroform
cDNA	complimentary DNA
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
DIAD	Diisopropyl azodicarboxylate
EDTA	ethylenediaminetetraacetic acid
EtOAc	ethyl acetate
Et_2O	diethyl ether
$AlCl_3$	aluminum chloride
Boc	*tert*-butyloxycarbonyl
CH_2Cl_2	dichloromethane
CH_3CN or ACN	acetonitrile

Cs_2CO_3	cesium carbonate
HCl	hydrochloric acid
H_2SO_4	sulfuric acid
Hunig's base	diisopropylethylamine
K_2CO_3	potassium carbonate
mCPBA or m-CPBA	*meta*-chloroperbenzoic acid
Pd/C	palladium on carbon
PS	polystyrene
SiO_2	silica oxide
$SnCl_2$	tin(II) chloride
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
$TMSCHN_2$	trimethylsilyldiazomethane
KOAc	potassium acetate
LHMDS	Lithium hexamethyldisilazide
$MgSO_4$	magnesium sulfate
NMP	N-Methylpyrrolidone
MsOH or MSA	methylsulfonic acid
NaCl	sodium chloride
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
Na_2SO_3	sodium sulfite
Na_2SO_4	sodium sulfate
NH_3	ammonia
NH_4Cl	ammonium chloride
NH_4OH	ammonium hydroxide
LG	leaving group
RT	Room temperature
SFC	Supercritical Fluid Chromatography

The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent or solvent mixture appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

The novel compounds of this invention may be prepared using the reactions and techniques described in this section. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. Restrictions to the substituents that are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

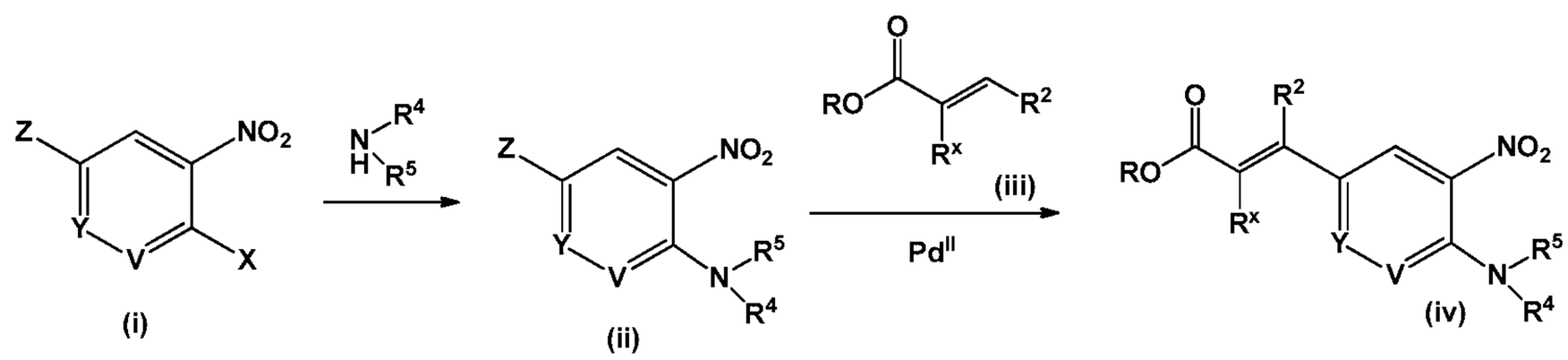
SYNTHESIS

The compounds of Formula I may be prepared by the exemplary processes described in the following Schemes and working Examples, as well as relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples. Protection and de-protection in the processes below may be carried out by procedures generally known in the art (see, for example, Greene, T.W. et al., *Protecting Groups in Organic Synthesis*, Third Edition, Wiley (1999)). General methods of organic synthesis and functional group transformations are found in: Trost, B.M. et al., eds., *Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic*

Chemistry, Pergamon Press, New York, NY (1991); March, J., *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, Fourth Edition, Wiley & Sons, New York, NY (1992); Katritzky, A.R. et al., eds., *Comprehensive Organic Functional Groups Transformations*, First Edition, Elsevier Science Inc., Tarrytown, NY (1995); Larock, R.C., *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, NY (1989), and references therein.

Compounds (i), where X = F and Z can be Br, Cl and I are commercially available or can be prepared utilizing standard transformations known to those of ordinary proficiency in the art of organic/medicinal chemistry. Treatment of compounds (i), with amines HNR^4R^5 (Scheme 1) and a suitable base in a solvent such as THF, DMF, NMP, or the like affords intermediates (ii). Generally heating is required. Suitable bases include, but are not limited to aliphatic tertiary amines or an excess of the reacting primary or secondary amine HNR^4R^5. Treatment of compounds (ii) under standard Heck palladium coupling conditions such as a Pd^{II} catalyst $Pd(OAc)_2$ and olefin containing compounds (iii) in a solvent such as THF, yields compounds (iv). Reduction of the olefin and the nitroaromatic found in compounds (iv) can be accomplished under reductive conditions such as but not limited to Pd/C under an atmosphere of H_2 and in a solvent such as ethyl acetate or methanol to afford saturated aniline compounds (v). Treatment of anilines (*v*) with an isocyanate $R^7N=C=O$, affords urea compounds (vi). Typically, this reaction is performed in a solvent such as THF at a temperature between ambient and the boiling point of the solvent. Esters (vi) may be converted to the corresponding carboxylic acids of the invention I under various conditions familiar to those of ordinary skill in the art. Generally this is effected using an alkali metal hydroxide (MOH) in aqueous solution, preferably with an organic co-solvent such as methanol or THF.

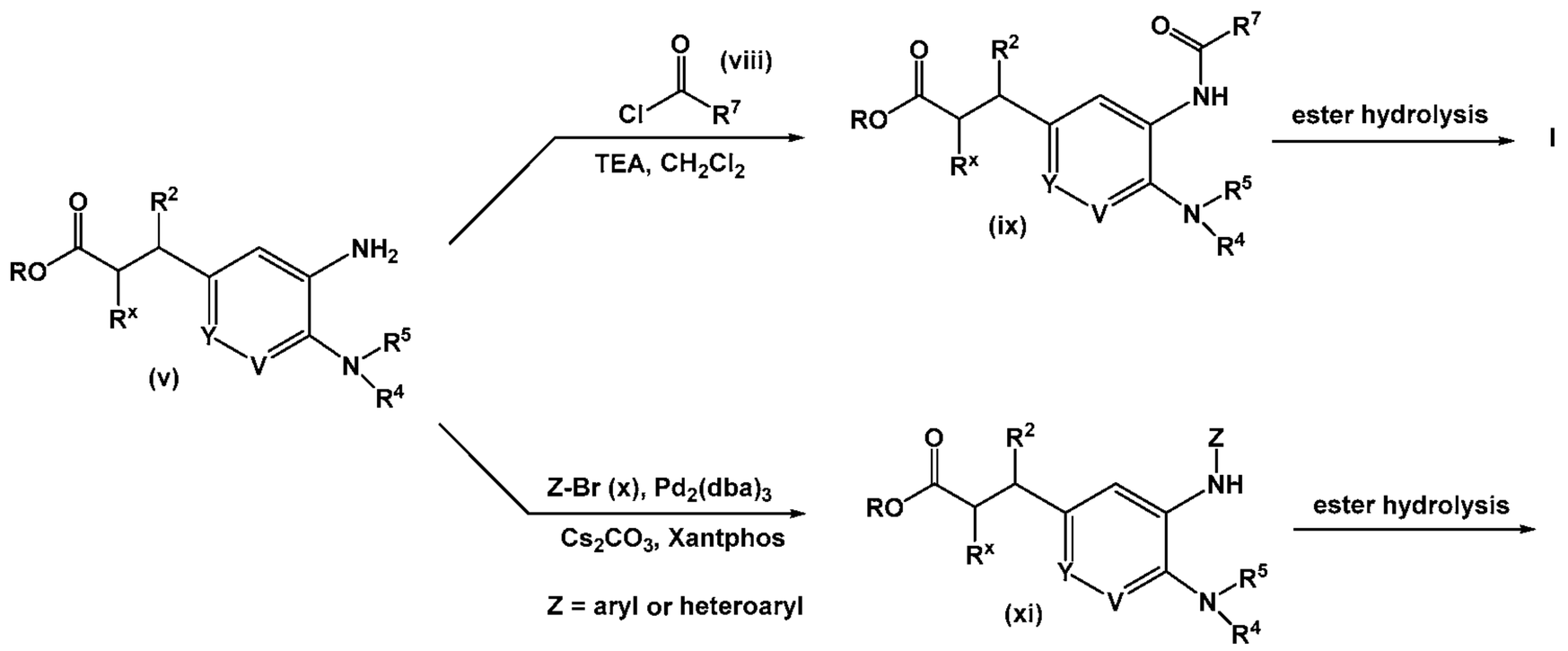
Scheme 1



As shown in Scheme 2, compounds (v) (prepared by the methods described above) may be coupled with carboxylic acids using peptide coupling reagents such as BOP, PyBOP, HATU or a similar reagent and a suitable base in a solvent such as THF, DMF, NMP, or the like to afford intermediates (ix). The use of such peptide coupling reagents has been reviewed by Han, S.-Y. et al., *Tetrahedron*, 60:2447-2467 (2004). Suitable bases include, but are not limited to aliphatic tertiary amines. Alternatively, amines (v) could react with acid chlorides of the formula R^7COCl to give amides (ix), again in a solvent in the presence of a base. Conversion of (ix) to compounds of the invention I is accomplished by hydrolysis of the ester by methods described previously to afford a compound of the invention I.

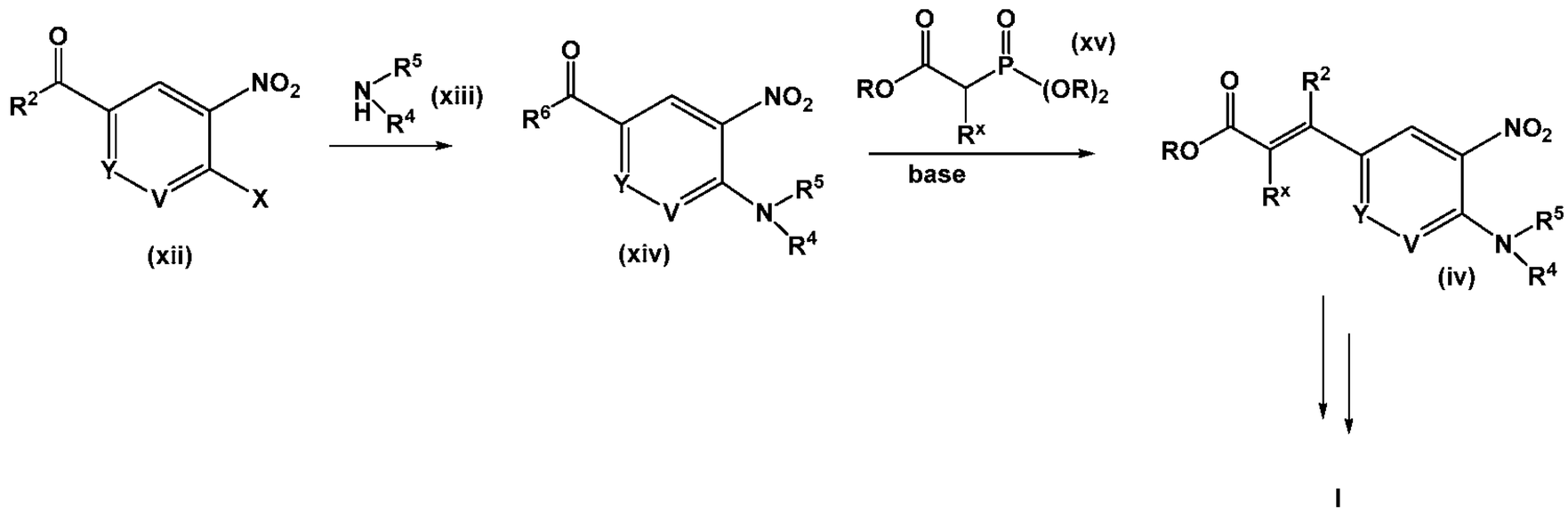
Amines of general structure (v) can also undergo a palladium catalyzed coupling to both aryl and heteroaryl halides (x) to afford N-arylated compounds of general structure (xi). Coupling can be accomplished by utilizing conditions established by Buchwald and Hartwig (*i.e.*, $Pd_2(dba)_3$, Xantphos and base) that are well-known to one skilled in the art (Surry, D.S. et al., *Chem. Sci.*, 2:27-50 (2011)). Compounds of general structure (xi) can then be converted to compounds of the invention I via hydrolysis of the ester via methods already described herein (Scheme 2).

Scheme 2



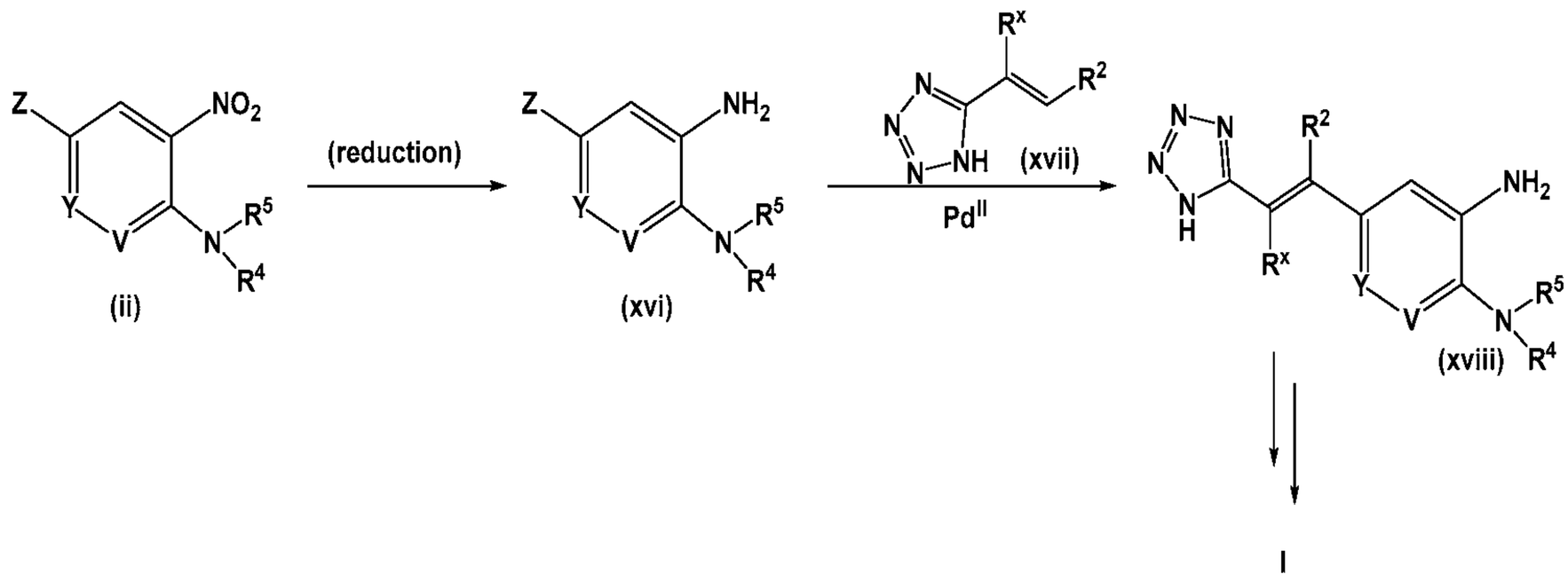
Treatment of carbonyl containing compounds (xii), where X = F and Z can be Br, Cl and I, with amines HNR^4R^5 (xiii) (Scheme 3) and a suitable base in a solvent such as THF, DMF, NMP, or the like affords intermediates (xiv). Generally heating is required. Suitable bases include, but are not limited to aliphatic tertiary amines or an excess of the reacting primary or secondary amine HNR^4R^5. Olefination of the carbonyl aldehyde or ketone can be accomplished by many methods that are well-known to those skilled in the art, such as Horner-Wadsworth-Emmons conditions as shown in Scheme 3. In practice the carbonyl compounds (xiv) can be treated with a phosphonic ester (xv) in the presence of a base such as sodium hexamethyldisilazane (NaHMDS) to afford olefins (iv). Olefins (iv) can be converted to compounds of the invention I by methods described in Scheme 1.

Scheme 3



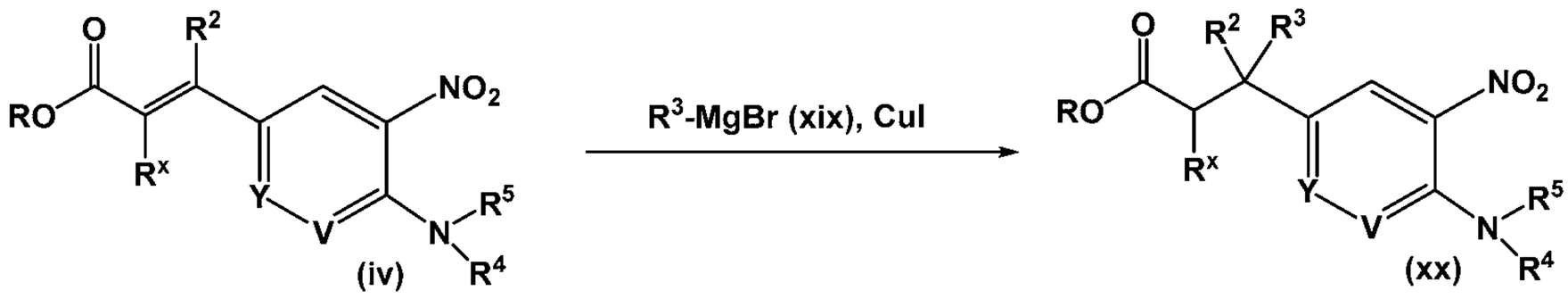
In Scheme 4 reduction of the nitro group in compounds (ii) to afford anilines (xvi) can be effected by various means including catalytic hydrogenation and dissolving metal reductions both in their various forms. See: House, H.O. et al., *Modern Synthetic Reactions*, Second Edition, Menlo Park, California (1972). A preferred method for effecting this reduction without removal of the halogen substituent Z involves stirring a solution of (ii) in a wet alcoholic solvent with an acid such as ammonium chloride and finely divided zinc. The anilines (xvi) can be couple to the olefins (xvii) under standard Heck coupling conditions with a Pd^{II} catalyst such as $Pd(OAc)_2$ to afford the olefins (xviii). The aniline compounds (xviii) can then be converted to compounds of the invention I by treatment previously described in Schemes 1 and 2.

Scheme 4



In Scheme 5, olefins (iv) may be treated with an appropriate organometallic, such as an alkyl cuprate, to afford compounds (xx) where R^3 has been installed beta to the ester carbonyl. These reactions are well known to those skilled in the art and comprise an alkyl or aryl Grignard reagent such as R^3-MgBr and a Cu^I reagent such as copper(I)iodide. The cuprate that is so-formed can then add in a 1,4 sense to the unsaturated ester (iv) to give the compounds (xx) which can be converted to compounds of the invention I by methods described previously.

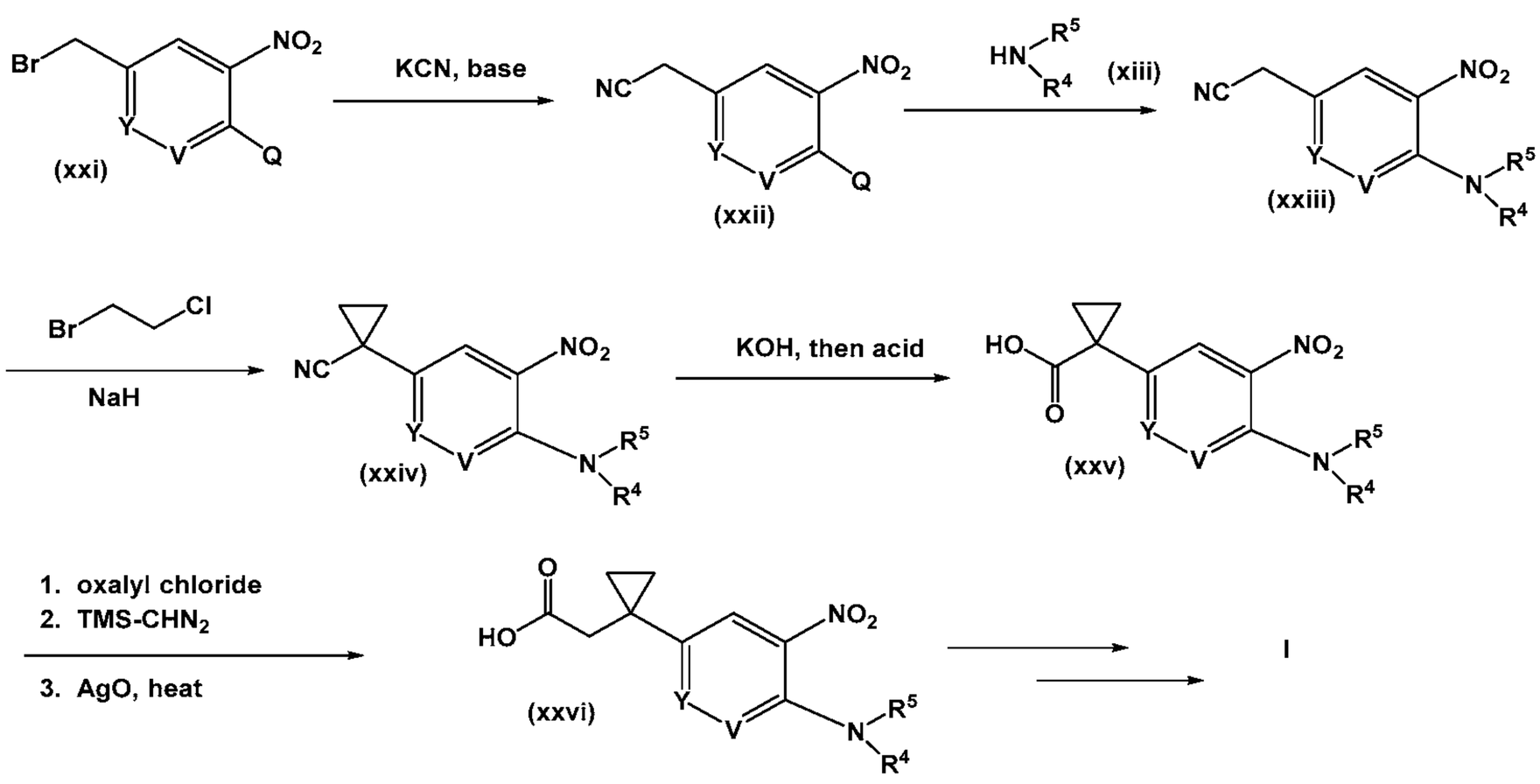
Scheme 5



I

Scheme 6 below demonstrates the preparation of compounds of the invention I where R^2 and R^3 have been joined to form a cyclopropane. The benzyl bromide (xxi) can be purchased or synthesized by one of ordinary skills in the art. Treatment of (xvii) with a cyanide anion source, such as potassium cyanide, in the presence of a base, such as potassium carbonate will afford the nitrile compounds (xxii). Treatment of (xxii) with HNR^4R^5, as described previously, will afford amines of general structure (xxiii). Cyclopropane formation can be accomplished by several methods known to one skilled in the art. One method uses 1-bromo-2-chloroethane in the presence of a strong base such as sodium hydride to afford the cyclopropane (xxiv). Hydrolysis of the nitrile (xxiv) can be accomplished by first treating with a strong base, such as potassium hydroxide, at elevated temperatures to afford the corresponding carboxylic acids (xxv). A one carbon homologation of the acid (xxv) can be accomplished by several methods known to one skilled in the art. Scheme 6 depicts a three step homologation process from (xxv) to produce the compounds of general structure (xxvi) (Qiao, J. et al., PCT Publication No. WO 2003/099276). The compounds of general structure (xxvi) can then be converted to compounds of the invention I by methods discussed previously.

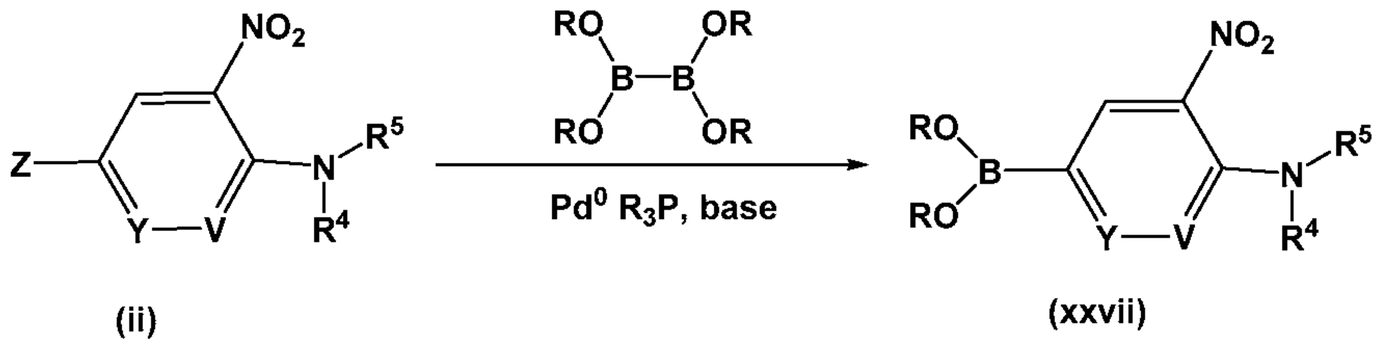
Scheme 6

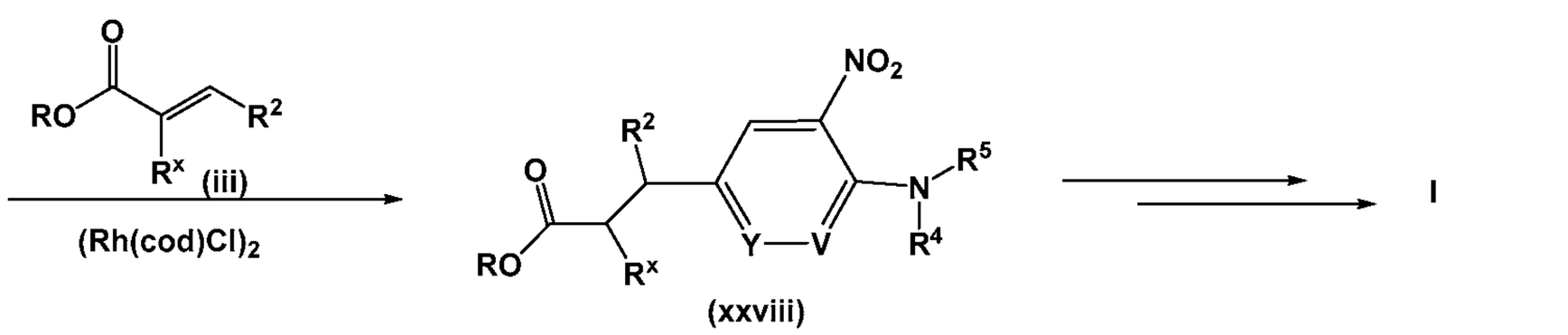


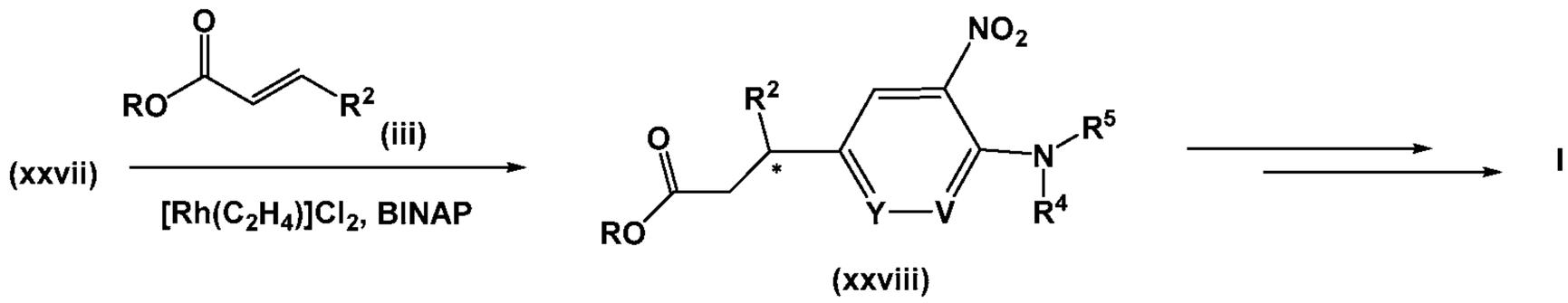
Scheme 7 below shows an alternative preparation of compounds of the invention I. The boronate (xxvii) can be prepared from the previously discussed aryl halide (ii) under standard condition utilizing a Pd catalyst such as $Pd(PPh_3)_4$ or 1,1′-bis(diphenylphosphino)ferrocenedichloro palladium(II). Rhodium catalyzed 1,4-conjugate addition of the boronic ester (xxvii) and an unsaturated ester (iii) are well known (Zou, G. et al., *Dalton Trans.*, 28:3055 (2007)) and can be accomplished using a rhodium^{I} catalyst, for example, $[Rh(COD)Cl]_2$ in the presence of a strong base such as NaOH to afford saturated esters of the general structure (xxvii). The ester (xxvii) can then be converted to compounds of the invention I by methods previously described herein.

In another embodiment, the conjugate addition with boronates of general structure (xxvii), where R^x is hydrogen, and the unsaturated ester (iii) can be accomplished with a chiral catalyst to give products of general structure (xxviii) with enhanced optical purity at the benzylic position (see Scheme 7 below). One can accomplish this transformation using the conditions developed by Hayashi whereby chlorobis(ethylene)rhodium(I)dimer is combined with (R)- or (S)-BINAP as the chiral ligand (Hayashi et al., *J. Am. Chem. Sci.*, 124:5052 (2002)). The desired stereochemistry at the benzylic position of compounds of general structure (xxviii) can be obtained by the appropriate choice of (R)- or (S)-BINAP used in the conjugate addition.

Scheme 7

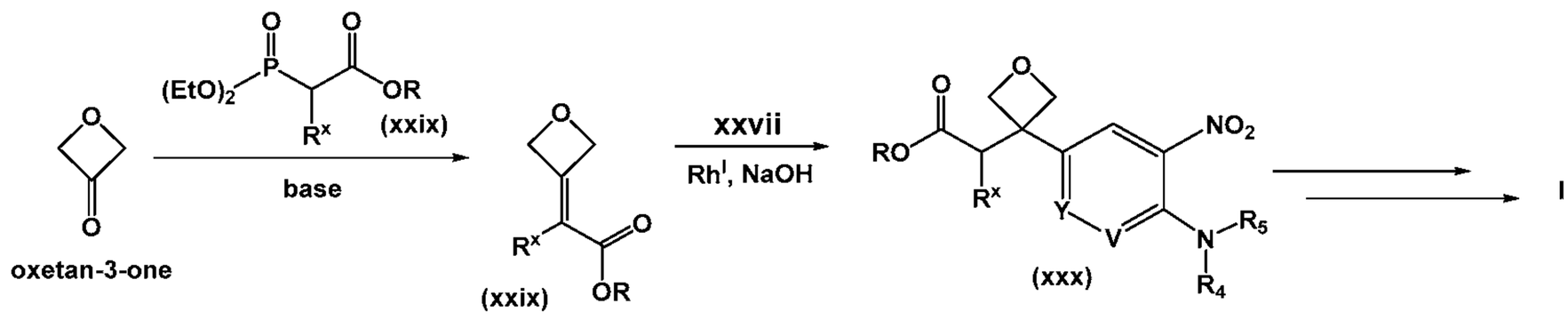






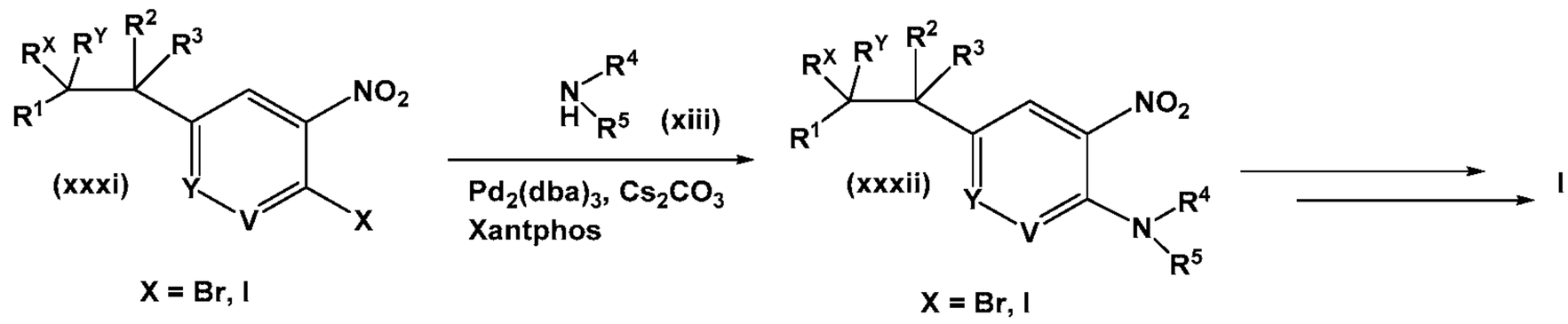
Oxetanes of the invention I can also be prepared in a similar manner, as depicted in Scheme 8. Oxetan-3-one is commercially available and can be treated under standard Horner-Wadsworth Emmons olefination conditions using a phosphonate in the presence of a base such as lithium hexamethyldisilazane (LiHMDS) to afford the unsaturated ester (xxix). Rhodium catalyzed 1,4-conjugate addition of the boronic acid (xxvii) to the unsaturated ester (xxix) can then be accomplished using a rhodium^{I} catalyst, for example, $[Rh(COD)Cl]_2$ in the presence of a strong base such as NaOH to afford the oxetanes (xxx). The oxetanes (xxx) can be converted to compounds of the invention I by methods previously described.

Scheme 8



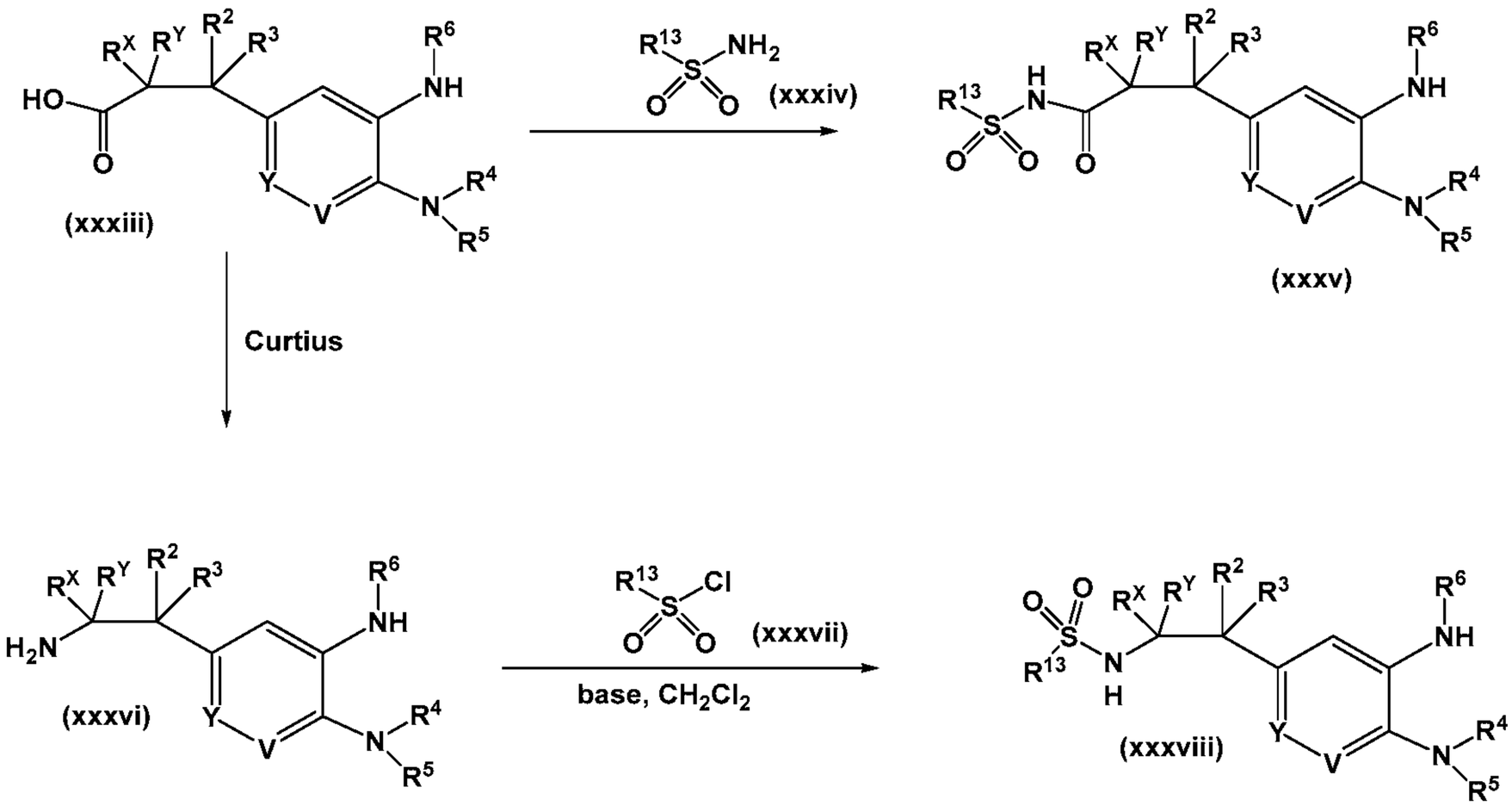
In another embodiment shown in Scheme 9, an aryl halide of general structure (xxxi) can be treated with an amine of general structure (xiii) and a palladium catalyst under standard coupling conditions established by Buchwald and Hartwig (*i.e.*, $Pd_2(dba)_3$, Xantphos and base) that are well-known to one skilled in the art (Surry, D.S. et al., *Chem. Sci.*, 2:27-50 (2011)) to give the product of general structure (xxxii). This compound can then be converted to a compound of the invention I by methods already discussed herein.

Scheme 9



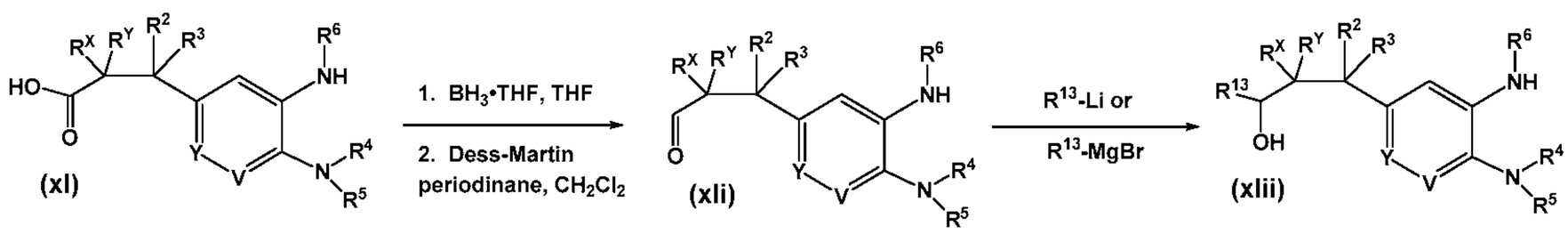
Scheme 10 shows another embodiment where the carboxylic acid of general structure (xxxiii) can be converted to an acyl sulfonamide of general structure (xxxv) by sequential treatment with an activating agent, such as CDI (carbonyl diimidazole), followed by addition of a sulfonamide (xxxiv) in the presence of a base such as DBU with or without heating. Numerous sulfonamides (xxxiv) are commercially available. The acylsulfonamide (xxxv) is a compound of the invention (I). The carboxylic acid (xxxiii) can also be treated under conditions known to affect a Curtius rearrangement, such as heating with DPPA in toluene, followed by a strong base such as LiOH, to afford an amine of general structure (xxxvi). The amine (xxxvi) can then be treated with a sulfonyl chloride of general structure (xxxvii) and a base, such as diisopropyl ethyl amine, to afford a sulfonamide a general structure (xxxviii) which is a compound of the invention I.

Scheme 10



In another embodiment shown in Scheme 11, the carboxylic acid (xl) can be reduced to the corresponding primary alcohol by treatment with a reducing agent, such as borane•THF in a solvent such as THF at elevated temperatures. Subsequent oxidation of the resulting primary alcohol by an appropriate oxidant, such as Dess-Martin periodinane, in a solvent such as dichloromethane will afford the aldehyde of general structure (xli). Treatment of the aldehyde (xli) with an alkyl lithium or Grignard reagent in a solvent such as THF, will afford a secondary alcohol of general structure (xlii), which is a compound of the invention I.

Scheme 11



HPLC/MS AND PREPARATORY/ANALYTICAL HPLC METHODS EMPLOYED IN CHARACTERIZATION OR PURIFICATION OF EXAMPLES

Analytical HPLC/MS was performed using the following methods:

Method A: Waters Acquity SDS using the following method: Linear Gradient of 2% to 98% Solvent B over 1.00 min; UV visualization at 220 or 254 nm; Column: BEH C18 2.1 mm × 50 mm; 1.7 μm particle (heated to temp. 50 °C); Flow rate: 0.8 ml/min; Mobile Phase A: 100% water, 0.05% TFA; Mobile Phase B: 100% acetonitrile, 0.05% TFA.

Method B: Column: Waters Acquity UPLC BEH C18, 2.1 × 50 mm, 1.7-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Temperature: 50 °C; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.00 mL/min; Detection: UV at 220 nm.

Method C: Column: Waters Acquity UPLC BEH C18, 2.1 × 50 mm, 1.7-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Temperature: 50 °C; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.11 mL/min; Detection: UV at 220 nm.

Method D: Column: Waters XBridge C18, 4.6 × 150 mm, 3.5-μm particles; Mobile Phase A: 10 mM ammonium bicarbonate pH9.5 / methanol 95/5; Mobile Phase B: 10 mM ammonium bicarbonate pH9.5 / methanol 5/95; Temperature: 40 °C; Gradient: 10-100-100% B at 0-25-30 minutes; Flow: 1.0 mL/min; Detection: UV at 220 and 254 nm.

Analytical chiral SFC chromatography was performed on a Berger or Aurora Analytical SFC using the following method:

Method E: Aurora SFC, Column: WHELK-O1® Komosil 250 × 4.6 mm ID, 5 μm, Flow rate: 2.0 mL/min, Mobile Phase: 90/10 CO_2/MeOH.

Method F: Instrument: Berger SFC MGII; Column: PHENOMENEX® Lux Cellulose-2 Axia Pack 25 × 3 cm ID, 5 μm; Mobile Phase A: 88/12 CO_2/(MeOH/ACN 50/50); 85.0 mL/min; Detection: UV at 220; Sample Prep: 600μL of 30 mg dissolved in 5 mL MeOH.

Method G: Instrument: Aurora analytical SFC; Column: PHENOMENEX® Lux Cellulose-2 250 × 4.6 mm ID, 3 μm; Flow rate: 2.0 mL/min; Mobile Phase: 85/15 CO_2/(MeOH/ACN 50/50).

Method H: Column: WHELK-O1® (R,R), KROMASIL®, 250 mm × 30 mm, 5 μ. Mobile Phase: 85 mL/min. of 85:15 CO_2:MeOH.

Method I: Column: WHELK-O1® (R,R), KROMASIL®, 250 mm × 30 mm, 5 μ. Mobile Phase: 85 mL/min. of 93:7 CO_2:MeOH.

Method J: Column: WHELK-O1® (R,R), KROMASIL®, 250 mm × 30 mm, 5 μ. Mobile Phase: 85 mL/min. of 90:10 CO_2:MeOH.

Method K: Column: PHENOMENEX® Lux Cellulose-2, 250 mm × 30 mm, 5 μ. Mobile Phase: 85 mL/min. of 85:15 CO_2:MeOH.

Method L: Column: PHENOMENEX® Lux Cellulose-2, 250 mm × 30 mm, 5 μ. Mobile Phase: 85 mL/min. of 84:16 CO_2:MeOH + 0.1% each of formic acid and diethylamine.

Method M: Column: PHENOMENEX® Lux Cellulose-2, 250 mm × 30 mm, 5 μ. Mobile Phase: 85 mL/min. of 92:8 CO_2:MeOH + 0.1% each of formic acid and diethylamine.

Method N: Kinetex XB-C18 (75 × 3) mm, 2.6 μm; Mobile Phase A: 10 mM NH_4OAc in water:acetonitrile (98:02); Mobile Phase B: 10 mM NH_4OAc in water:acetonitrile (02:98); Gradient: 20-100% B over 4 minutes, Flow rate: 1 mL/min, then a 0.6 minute hold at 100% B Flow rate: 1.5 mL/min; then Gradient: 100-20% B over 0.1 minutes, Flow rate: 1.5 mL/min.

Method O: Column: Ascentis Express C18 (50 × 2.1) mm, 2.7 μm; Flow rate: 1.1 mL/min; Gradient time 3 min; Temperature: 50 °C, 0% Solvent B to 100% Solvent B; monitoring at 220 nm (Solvent A: 95% water: 5% acetonitrile; 10 mM NH_4OAc; Solvent B: 5% water: 95% acetonitrile; 10 mM NH_4OAc).

Method P: Column: Ascentis Express C18 (50 × 4.6) mm, 2.7 µm, Flow rate: 4 mL/min; Gradient: 0 to 100% Solvent B over 4 min; Temperature: 50 °C. Monitoring at 220 nm (Solvent A: 95:05 water: CH_3CN with 10 mM NH_4OAc and Solvent B: 05:95 water: CH_3CN with 10 mM NH_4OAc).

Method Q: Column: Ascentis Express C18 (50 × 4.6) mm, 2.7 µm, Flow rate: 4 mL/min; Gradient: 0 to 100% Solvent B over 4 min; Temperature: 50 °C; monitoring at 220 nm (Solvent A: 95:05 water: CH_3CN with 0.1% TFA and Solvent B: 05:95 water: CH_3CN with 0.1% TFA).

Method R: Column: Ascentis Express C18 (50 × 2.1) mm, 2.7 µm, Flow rate: 1.1 mL/min; Gradient: 0 to 100% Solvent B over 3 min; Temperature: 50 °C; monitoring at 220 nm (Solvent A: 95:05 water: CH_3CN with 0.1% TFA and Solvent B: 05:95 water: CH_3CN with 0.1% TFA).

Method S: Column: CHIRALPAK® ASH (250 × 4.6) mm, 5.0 µm; Isocratic Mode, CO_2: Co-solvent (85:15), Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 15%, Column Temperature: 22.1 °C; Back Pressure: 100 bars; Total Flow: 3 g/min; CO_2 flow: 2.55 g/min; Co-solvent flow: 0.45 g/min.

Method T: Column: Acquity BEH C18 (2.1 × 50 mm) 1.7 µm; Mobile Phase A: Buffer: ACN (95:5); Mobile Phase B: Buffer: ACN (5:95), Buffer: 5 mM ammonium acetate; Gradient: 20-90% B over 1.1 minutes, then a 0.6 minute hold at 90% B, Flow rate: 0.5 mL/min.

Method U: Column: Kinetex XB-C18 (75 × 3) mm, 2.6 µm; Mobile Phase A: 10 mM NH_4COOH in water:acetonitrile (98:02; Mobile Phase B: 10 mM NH_4COOH in water:acetonitrile (02:98); Gradient: 20-100% B over 4 minutes, Flow rate: 1 mL/min, then a 0.6 minute hold at 100% B Flow rate: 1.5 mL/min; then Gradient: 100-20% B over 0.1 minutes, Flow rate: 1.5 mL/min.

Method V: Column: CHIRALPAK® ASH (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 20%, Column Temperature: 20.2 °C; Back Pressure: 100 bars; Total Flow: 3 g/min; CO_2 flow: 2.4 g/min; Co-solvent flow: 0.6 g/min.

Method W: Column: CHIRALPAK® ASH (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 30%, Column

Temperature: 20.2 °C; Back Pressure: 100 bars; Total Flow: 3 g/min; CO_2 flow: 2.1 g/min; Co-solvent flow: 0.9 g/min.

Method X: Column: CHIRALPAK® ASH (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 25%, Column Temperature: 24.3 °C; Back Pressure: 100 bars; Total Flow: 3 g/min; CO_2 flow: 2.5 g/min; Co-solvent flow: 0.75 g/min.

Method Y: Column: CHIRALPAK® ASH (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 25%, Column Temperature: 27.1 °C; Back Pressure: 100 bars; Total Flow: 3 g/min; CO_2 flow: 2.25 g/min; Co-solvent flow: 0.75 g/min.

Method Z: Column: CHIRALCEL®-OJH (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 30%, Column Temperature: 26 °C; Back Pressure: 100 bars; Total Flow: 3 g/min; CO_2 flow: 2.1 g/min; Co-solvent flow: 0.9 g/min.

Method AA: Column: Acquity BEH C18 (2.1 × 50 mm) 1.7 µm; Mobile Phase A: 0.1% TFA in water; Mobile Phase B: acetonitrile; Gradient: 2-98% B over 1 minute, then a 0.6 minute hold at 98% B.

Method AB: Column: Lux Cellulose-4 (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 30%, Column Temperature: 24.2 °C; Back Pressure: 100 bars; Total Flow: 3 g/min; CO_2 flow: 2.1 g/min; Co-solvent flow: 0.9 g/min.

Method AC: Column: CHIRALCEL®-ASH (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 30%, Column Temperature: 26 °C; Back Pressure: 100 bars; Total Flow: 3 g/min; CO_2 flow: 2.1 g/min; Co-solvent flow: 0.9 g/min.

Method AD: Kinetex XB-C18 (75 × 3) mm, 2.6 µm; Mobile Phase A: 0.1% HCOOH in water; Mobile Phase B: 100% acetonitrile; Gradient: 20-100% B over 4 minutes; Flow rate: 1 mL/min, then a 0.6 minute hold at 100% B Flow rate: 1.5 mL/min; Flow rate: 1.5 mL/min.

Method AE: Column: HP-5MS (Part Number: AGILENT® 19091S-433); (250 × 30) mm; 0.25 µm; Injection volume 3 µl, run time 17 min (GCMS).

Method AF: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.25% DEA in methanol; Co-solvent percentage: 30%, Column Temperature: 25 °C; Back Pressure: 100 bars; Total Flow: 3 g/min; CO_2 flow: 2.1 g/min; Co-solvent flow: 0.9 g/min.

Method AG: Column: CHIRALCEL®-ASH (250 × 21) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.25% DEA in methanol; Co-solvent percentage: 45%, Column Temperature: 25 °C; Back Pressure: 100 bars; Total Flow: 75 g/min.

Method AH: Column: CHIRALCEL®-ASH (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 40%, Column Temperature: 25 °C; Back Pressure: 100 bars; Total Flow: 4 g/min.

Method AI: Column: CHIRALCEL®-ASH (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 30%, Column Temperature: 24.7 °C; Back Pressure: 95 bars; Total Flow: 4 g/min; CO_2 flow: 2.4 g/min; Co-solvent flow: 1.6 g/min.

Method AJ: Column: CHIRALPAK® AD-H (250 × 30) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.25% DEA in methanol; Co-solvent percentage: 30%, Column Temperature: 25 °C; Back Pressure: 100 bars; Total Flow: 120 g/min.

Method AK: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.25% DEA in methanol; Co-solvent percentage: 40%, Column Temperature: 25 °C; Back Pressure: 100 bars; Total Flow: 4 g/min; CO_2 flow: 2.4 g/min; Co-solvent flow: 1.6 g/min.

Method AM: Column: CHIRALPAK® IA (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 30%, Column Temperature: 21 °C; Back Pressure: 100 bars; Total Flow: 3 g/min; CO_2 flow: 2.1 g/min; Co-solvent flow: 0.9 g/min.

Method AN: Column: CHIRALPAK® IA (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 20%, Column Temperature: 21 °C; Back Pressure: 100 bars; Total Flow: 3 g/min; CO_2 flow: 2.4 g/min; Co-solvent flow: 0.6 g/min.

Method AU: Column: XBridge C18 (50 × 3.0) mm, 1.7 µm; Flow rate: 1.0 mL/min; Gradient time 0 min 0% Solvent B to 2 min 100% Solvent B, then a 1.0 minute

hold at 100% B, monitoring at 220 nm (Solvent A: 10 mM 98% ammonium formate, 2% acetonitrile; Solvent B: 10 mM 2% ammonium formate, 98% acetonitrile).

Method AV: Column: Acquity BEH C8 (2.1 × 50 mm) 1.7 μm; Mobile Phase A: Buffer: ACN (95:5); Mobile Phase B: Buffer: ACN (5:95), Buffer: 5 mM ammonium acetate; Gradient: 20-90% B over 1.1 minutes, then a 0.6 minute hold at 90% B, Flow rate: 0.5 mL/min.

Method AQ: Column: CHIRALPAK® OD-H (250 × 4.6) mm, 5.0 μm, Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 40%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method AR: Column: Lux Cellulose-2 (250 × 4.6) mm, 5.0 μm; Isocratic Mode, Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 10%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method AS: Column: Whelk-O1 (R,R) (4.6 × 250) mm, 5 μ; Co-solvent: 0.2% DEA in IPA; Co-solvent percentage: 15%, Column Temperature: 20.6 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method AT: Column: Ascentis Express C18 (50 × 2.1) mm, 1.7 μm; Flow rate: 1.0 mL/min; Gradient time 0 min 20% Solvent B to 4 min 100% Solvent B, then a 0.6 minute hold at 100% B, monitoring at 220 nm (Solvent A: 10 mM 98% ammonium formate, 2% acetonitrile; Solvent B: 10 mM 2% ammonium formate, 98% acetonitrile).

Method AU: Column: Waters XBridge C18 (19 × 150) mm, 5-μm particles; Mobile Phase A: 10 mM ammonium acetate; Mobile Phase B: acetonitrile; Gradient: 5-45% B over 25 minutes, then a 5-minute hold at 100% B; Flow: 15 mL/min.

Method AV: Column: Lux Cellulose-2 (250 × 4.6) mm, 5.0 μm; Isocratic Mode, Co-solvent: 25% (0.2% DEA in methanol; Co-solvent percentage: 75%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min; CO_2 flow: 2.1 g/min; Co-solvent flow: 0.9 g/min.

Method AW: Column: YMC Amylose SA (250 × 4.6) mm, 5.0 μm; Isocratic Mode, Co-solvent: (0.2% DEA in ethanol; Co-solvent percentage: 20%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min; CO_2 flow: 2.1 g/min; Co-solvent flow: 0.9 g/min.

Method AX: Column: CHIRALPAK® IC (250 × 4.6) mm, 5.0 μm; Isocratic Mode, Co-solvent: 0.25% DEA in ethanol; Co-solvent percentage: 30%, Column

Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min; CO_2 flow: 2.1 g/min; Co-solvent flow: 0.9 g/min.

Method AY: Column: Acquity BEH C18 (3.0 × 50 mm) 1.7 µm; Mobile Phase A: Buffer: ACN (95:5); Mobile Phase B: Buffer: ACN (5:95), Buffer: 5 mM ammonium acetate; Gradient: 20-90% B over 1.1 minutes, then 1.7 minute hold at 90% B, Flow rate: 0.7 mL/min.

Method AZ: Column: CHIRALPAK® AD-H (250 × 30) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 30%, Column Temperature: 25 °C; Back Pressure: 100 bars; Total Flow: 120 g/min.

Method BA: Column: Acquity UPLC BEH C18 (3 × 50 mm) 1.7 µm; Mobile Phase A: Buffer: ACN (95:5); Mobile Phase B: Buffer: ACN (5:95), Buffer: 5 mM ammonium acetate; Gradient: 20-90% B over 1.1 minutes, then a 0.6 minute hold at 90% B, Flow rate: 0.7 mL/min.

Method BB: Column: ZORBAX® SBC18 (4.6 × 50) mm, 5 µm; Mobile Phase A: 10 mM NH_4COOH in water:acetonitrile (98:02; Mobile Phase B: 10 mM NH_4COOH in water:acetonitrile (02:98); Gradient: 0-100% B over 4 minutes, Flow rate: 1.5 mL/min, then a 0.6 minute hold at 100% B Flow rate: 1.5 mL/min; then Gradient: 100-30% B over 0.1 minutes, Flow rate: 1.5 mL/min.

Method BC: Column: Acquity BEH C18 (2.1 × 50 mm) 1.7 µm; Mobile Phase A: 0.1% TFA in water; Mobile Phase B: 0.1% TFA in acetonitrile; Gradient: 10-90% B over 1.0 minutes, then a 0.6 minute hold at 90% B, Flow rate: 0.7 mL/min.

Method BD: Column: Kinetex SBC18 (4.6 × 50 mm - 5 µm), Mobile Phase A: 10 mM NH_4COOH in water:ACN (98:02), Mobile Phase B: 10 mM NH_4COOH in water:ACN (02:98), Buffer: 10 mM ammonium acetate; Gradient: 30-100% B over 4.0 minutes, then a 0.6 minute hold at 100% B, Flow rate: 1.5 mL/min.

Method BE: Gemini-Kinetex nx-C18 (4.6 × 50 mm - 5 µm), Mobile Phase A: 10 mM NH_4COOH in water:ACN(98:02), Mobile Phase B: 10 mM NH_4COOH in water:ACN (02:98), Buffer: 10 mM ammonium acetate; Gradient: 30-100% B over 4.0 minutes, then a 0.6 minute hold at 100% B, Flow rate: 1.5 mL/min.

Method BF: Column: CHIRALCEL®-OJH (250 × 4.6) mm, 5.0 µm; Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 20%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method BG: Column: Whelk-O1 (R,R) (250 × 4.6) mm, 5 µ; Co-solvent: 0.2% DEA in ethanol; Co-solvent percentage: 5%, Column Temperature: 22.2 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method BH: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5.0 µm; Co-solvent: 0.2% DEA in IPA; Co-solvent percentage: 15%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method BI: Column: CHIRALPAK® AD-H (250 × 3.0) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 30%, Column Temperature: 25 °C; Back Pressure: 100 bars.

Method BJ: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5.0 µm; Co-solvent: 0.2% DEA in methanol + IPA (1:1); Co-solvent percentage: 10%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method BK: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5.0 µm; Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 10%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method BL: Column: CHIRALPAK® OD-H (250 × 2.1) mm, 5.0 µm, Co-solvent: 0.2% DEA in IPA; Co-solvent percentage: 15%, Column Temperature: 30 °C.

Method BM: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5.0 µm; Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 25%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method BN: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5.0 µm; Co-solvent: 0.1% NH_4OH in IPA; Co-solvent percentage: 10%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method BO: Column: Ascentis Express C18 (50 × 2.1 mm) 2.7 µm, Mobile Phase A: 10 mM NH_4COOH in water:ACN (98:02), Mobile Phase B: 10 mM NH_4COOH in water:ACN (02:98); Gradient: 0-100% B over 1.5 minutes, then a 1.7 minute hold at 100% B, Flow rate: 1.0 mL/min.

Method BP: Column: Whelk-O1 (R,R) (250 × 4.6) mm, 5 µ; Co-solvent: 0.2% DEA in IPA; Co-solvent percentage: 10%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method BQ: Column: CHIRALPAK® IC (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in methanol:IPA (1:1); Co-solvent percentage: 10%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method BR: Column: CHIRALPAK® OJ-H (250 × 4.6 mm), 5 µ; Mobile Phase: 0.2% TEA in n-hexane:EtOH (70:30), Flow:1.0 mL/min.

Method BS: Column: CHIRALCEL®-OJH (250 × 4.6) mm, 5.0 µm; Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 25%, Column Temperature: 28 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method BT: Column: CHIRALCEL®-OJH (250 × 4.6) mm, 5.0 µm; Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 15%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 60 g/min.

Method BU: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in IPA+ACN; Co-solvent percentage: 10%, Column Temperature: 25 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method BV: Column: Lux Amylose 2 (250 × 21.2) mm, Mobile Phase A: 0.2% DEA in hexane; Mobile Phase B: EtOH; Flow: 25 mL/min.

Method BW: Column: Lux Cellulose-2 (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 25% (0.1% NH_4OH in methanol); Co-solvent percentage: 75%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method BX: Column: Lux Cellulose-2 (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in ethanol; Co-solvent percentage: 20%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method BY: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in ethanol; Co-solvent percentage: 25%, Column Temperature: 25.7 °C; Back Pressure: 100 bars; CO_2 Flow rate: 2.25 g/min; Co solvent Flow rate: 0.75 g/min; Total Flow: 3 g/min.

Method BZ: Column: CHIRALCEL®-OJH (250 × 4.6) mm, 5.0 µm; Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 10%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 mL/min.

Method CA: Column: YMC Amylose SA (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in IPA; Co-solvent percentage: 15%, Column Temperature: 35 °C; Back Pressure: 100 bars; Total Flow: 60.0 g/min.

Method CB: Column: CHIRALPAK® ASH (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in hexane:IPA (98:02); Total Flow: 1.0 mL/min.

Method CC: Column: Lux Cellulose-4 (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 30% (0.1% NH_4OH in methanol); Co-solvent percentage: 30%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 60 g/min.

Method CD: Column: CHIRALCEL®-OJH (250 × 4.6) mm, 5.0 µm; Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 30%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 mL/min.

Method CE: Column: CHIRALCEL®-OJH (250 × 2.1) mm, 5.0 µm; Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 20%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 60 mL/min.

Method CF: Column: CHIRALCEL®-OJH (250 × 4.6) mm, 5.0 µm; Co-solvent: 0.2% DEA in IPA:ACN (1:1); Co-solvent percentage: 20%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 mL/min.

Method CG: Column: CHIRALPAK® IC (250 × 3.0) mm, 5.0 µm; Co-solvent: 0.2% DEA in methanol: IPA (1:1); Co-solvent percentage: 10%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 110 g/min.

Method CH: Column: Lux Amylose 2 (250 × 4.6) mm, 5.0 µm; Mobile Phase A: 0.2% DEA in hexane; Mobile Phase B: EtOH; Flow: 1 mL/min.

Method CI: Column: Kineticsx 2.6 µ EVO c18 100 Au. Mobile Phase A; 5 mM NH_4C0AC in water:ACN (95: 05), Mobile Phase B: 5 mM NH_4C0AC in water:ACN (05:95), Buffer: 5 mM ammonium acetate; Flow rate: 0.7 mL/min.

Method CJ: Column: CHIRALCEL®-OJH (250 × 4.6) mm, 5.0 µm; Co-solvent: 0.2% DEA in n-hexane:EtOH (98:2Total Flow: 1 mL/min.

Method CK: Column: Lux Cellulose-4 (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in IPA; Co-solvent percentage: 15%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method CL: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 30%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 4 g/min.

Method CM: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5.0 µm; Co-solvent: 0.2% DEA in IPA; Co-solvent percentage: 30%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 4 g/min.

Method CN: Column: CHIRALPAK® IC (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in methanol:ACN (1:1); Co-solvent percentage: 25%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method CO: Column: Lux Cellulose-4 (250 × 4.6) mm, 5.0 µm; Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 10%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method CP: Column: ZORBAX® AQ (4.6 × 50) mm, 5 µm; Mobile Phase A: 10 mM NH_4COOH in water:acetonitrile (98:02); Mobile Phase B: 10 mM NH_4COOH in water:acetonitrile (02:98); Gradient: 30-100% B over 4 minutes, Flow rate: 1.5 mL/min, then a 0.6 minute hold at 100% B Flow rate: 1.5 mL/min; then Gradient: 100-30% B over 0.1 minutes, Flow rate: 1.5 mL/min.

Method CQ: Column: Gemini nx-C18 (50 × 4.6) mm, 5 µm; Mobile Phase A: 10 mM NH_4COOH in water:acetonitrile (98:02); Mobile Phase B: 10 mM NH_4COOH in water:acetonitrile (02:98); Gradient: 30-100% B over 4 minutes, Flow rate: 1.5 mL/min, then a 0.6 minute hold at 100% B Flow rate: 1.5 mL/min; then Gradient: 100-30% B over 0.1 minutes, Flow rate: 1.5 mL/min.

Method CR: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5.0 µm; Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 20%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method CS: Column: XBridge C18 (50 × 4.6) mm, 5 µm, Flow rate: 4.0 mL/min; Gradient: 0 to 100% Solvent B over 3 min; Temperature: 35 °C; monitoring at 220 nm (Solvent A: 95:05 water: CH_3CN with 0.1% TFA and Solvent B: 05:95 water: CH_3CN with 0.1% TFA).

Method CT: Column: CHIRALPAK® IA (250 × 4.6) mm, 5.0 µm; Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 15%, Column Temperature: 21.7 °C; Back Pressure: 96 bars; Total Flow: 3 g/min; CO_2 flow: 2.55 g/min; Co-solvent flow: 0.45 g/min.

Method CU: Column: CHIRALPAK® ASH (250 × 4.6) mm, 5.0 µm; Co-solvent: 0.2% DEA in IPA; Co-solvent percentage: 20%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 mL/min.

Method CV: Column: Lux Cellulose-4 (250 × 4.6) mm, 5.0 µm; Co-solvent: 0.2% DEA in IPA:methanol, (1:1); Co-solvent percentage: 10%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method CW: Column: CHIRALPAK® AD-H (250 × 30) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 30%, Column Temperature: 21.6 °C; Back Pressure: 104 bars; Total Flow: 3 g/min. CO_2 Flow rate: 2.1; Co solvent Flow rate: 0.9.

Method CX: Column: Lux Amylose-2 (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 15% (0.2% DEA in IPA; Column Temperature: 30 °C; Back Pressure: 101 bars; Total Flow: 3 g/min; CO_2 flow: 2.55 g/min; Co-solvent flow: 0.45 g/min.

Method CY: Column: Lux Cellulose-4 (250 × 4.6) mm, 5.0 µm; Mobile Phase: 0.2% TFA in n-hexane:methanol:ethanol (97:03), Flow rate: 1.0 mL/min.

Method CZ: Column: XBridge C18 (50 × 4.6) mm, 5.0 µm; Mobile Phase A: 0.1%TFA in water; Mobile Phase B: acetonitrile; Gradient: 5-95% B over 4 minutes, Temp : 35 °C; Flow Rate : 4.0 mL/min.

Method DA: Column: R,R-WHELK (250 × 4.6) mm, 5 µm, Mobile Phase: 0.2% EA in n-hexane:IPA (99:01), Flow: 1.0 mL/min.

Method DB: Column: Lux Cellulose-4 (250 × 4.6) mm, 5 µm, Co-solvent 0.2% DEA in methanol, Column Temperature 19.4 °C, CO_2 Flow Rate 1.8 g/min, Co-solvent Flow Rate 1.2 g/min, Co-solvent 40%, Total Flow 3 g/min, Back Pressure 104 bars.

Method DC: Column: XBridge C18 (50 × 4.6) mm, 5 µm, Solvent A : 10 mM NH_4OAc, Solvent B : acetonitrile, Temp: 35 °C, Gradient: 5-95% B over 4 minutes, Flow Rate : 4.0 ml/min.

Method DD: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5 µm, Co-solvent 0.2% DEA in methanol, Column Temperature 19.5 °C, CO_2 Flow Rate 2.25 g/min, Co-solvent Flow Rate 0.75 g/min, Co-solvent 25%; Total Flow 3 g/min; Back Pressure 100 bars.

Method DE: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5 µm, Column Temperature 27 °C, Co-solvent 0.2% DEA in methanol, CO_2 Flow Rate 2.25 g/min, Co-

solvent Flow Rate 0.75 g/min, Co-solvent 25%, Total Flow 3 g/min, Back Pressure 98 bars.

Method DF: Column: CHIRALPAK® IA (250 × 4.6) mm, 5 µ, Co-solvent 0.1% NH_4OH in IPA, Column Temperature 19.3 °C, CO_2 Flow Rate 1.8 g/min, Co-solvent Flow Rate 1.2 g/min, Co-solvent 40%, Total Flow 3 g/min, Back Pressure 100 bars.

Method DG: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5 µm, Co-solvent; 0.2% DEA in IPA, Column Temperature: 15.3 °C, CO_2 Flow Rate: 2.4 g/min, Co-solvent Flow Rate: 3 g/min, Co-solvent: 99%, Back Pressure 100 bars.

Method DH: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5 µm, Co-solvent: 0.2% DEA in IPA, Column Temperature: 27.7 °C, CO_2 Flow Rate: 2.4 g/min, Co-solvent Flow Rate: 0.6 g/min, Co-solvent: 20%, Total Flow; 3 g/min, Back Pressure; 100 bars.

Method DI: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5 µm, Co-solvent: 0.1% NH_4OH in IPA, Column Temperature: 21.4 °C, CO_2 Flow Rate: 2.25 g/min, Co-solvent Flow Rate: 0.75 g/min, Co-solvent: 25%, Total Flow: 3 g/min, Back Pressure: 102 bars.

Method DJ: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5 µm, Co-solvent: IPA, Column Temperature: 20.6 °C, CO_2 Flow Rate: 2.7 g/min, Co-solvent Flow Rate: 0.3 g/min, Co-solvent: 10%, Total Flow: 3, Back Pressure: 100.

Method DK: Column: CHIRALPAK®-IA (250 × 4.6), 5 µm, Mobile Phase: -0.2% DEA in n-hexane:EtOH (60:40), Flow: 1.0 ml/min.

Method DL: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in IPA+ACN; Co-solvent percentage: 10%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method DM: Column: XBridge BEH C8 (2.1 × 50 mm) 2.5 µm; Mobile Phase A: Buffer: ACN (95:5); Mobile Phase B: Buffer: ACN (5:95), Buffer: 5 mM ammonium acetate; Gradient: 20-90% B over 1.1 minutes, then a 1.7 minute hold at 90% B, Flow rate: 0.5 mL/min.

Method DN: Column: CHIRALCEL®-OJH (250 × 4.6) mm, 5.0 µm; Isocratic Mode, Co-solvent: 0.2% DEA in ethanol; Co-solvent percentage: 10%, Column Temperature: 25.8 °C; Back Pressure: 100 bars; Total Flow: 3 g/min; CO_2 flow: 2.7 g/min; Co-solvent flow: 0.3 g/min.

Method DO: Column: Acquity BEH C18 (2.1 × 50 mm) 1.7 μm; Mobile Phase A: Buffer: ACN (95:5); Mobile Phase B: Buffer: ACN (5:95), Buffer: 5 mM ammonium acetate; Gradient: 20-90% B over 1.1 minutes, then a 0.6 minute hold at 90% B, Flow rate: 0.7 mL/min.

Method DP: Column: CHIRALCEL® OD-H (250 × 4.6) mm, 5 μm; Co-solvent: 0.2% DEA in MeOH; CO_2 Flow Rate: 2.4 g/min; Co-solvent Flow Rate:0.6; Co-solvent 20%; Total Flow: g/mon3; Back Pressure: 100 bars.

Method DQ: Column: CHIRALCEL® IE (250 × 4.6) mm, 5 μm; Mobile Phase: 0.2% DEA in hexane:ethanol:methanol (1:1) (95:05) Flow: 1.0 ml/min.

Method DR: Kinetex C18 (75 × 3) mm, 2.6 μm; Mobile Phase A: 10 mM NH_4OAc in water:acetonitrile (98:02); Mobile Phase B: 10 mM NH_4OAc in water:acetonitrile (02:98); Gradient: 80-98% B over 2.5 minutes, Flow rate: 1 mL/min, then a 1.0 minute hold at 98% B Flow rate: 1.0 mL/min; then Gradient: 100-20% B over 0.1 minutes, Flow rate 1.0 mL/min.

Method DS: Column: CHIRALPAK® AD-H (250 × 4.6) mm, 5.0 μm; Co-solvent: 0.2% DEA in methanol; Co-solvent percentage: 15%, Column Temperature: 30 °C; Back Pressure: 100 bars; Total Flow: 3 g/min.

Method DT: Column: CHIRALPAK® AS, 250 mm × 30 mm, 5 μ. Mobile Phase: 85 mL/min. of 88:12 CO_2:MeOH.

Method DU: Column: WHELK-O1® (R,R), KROMASIL®, 250 mm × 4.6 mm, 5 μ. Mobile Phase: 2 mL/min. of 85:15 CO_2:MeOH.

Method DV: Column: WHELK-O1® (R,R), KROMASIL®, 250 mm × 4.6 mm, 5 μ. Mobile Phase: 2 mL/min. of 90:10 CO_2:MeOH.

Method DW: Column: PHENOMENEX® Lux Cellulose-2, 250 mm × 4.6 mm, 5 μ. Mobile Phase: 2 mL/min. of 85:15 CO_2:MeOH.

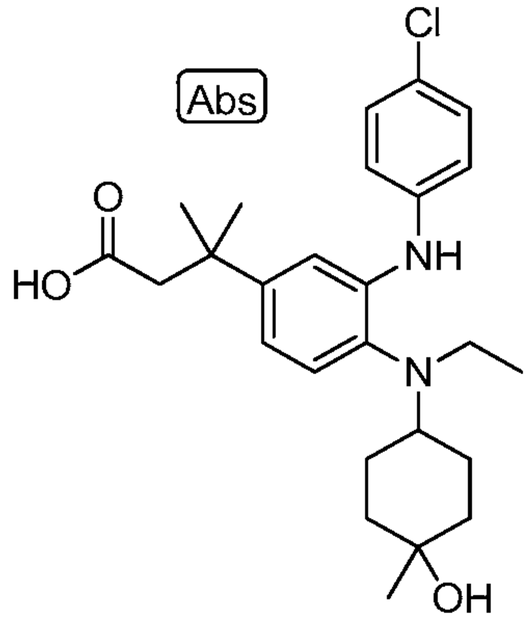
Method DX: Column: PHENOMENEX® Lux Cellulose-2, 250 mm × 4.6 mm, 5 μ. Mobile Phase: 2 mL/min. of 90:10 CO_2:MeOH + 0.1% each of formic acid and diethylamine.

Method DY: Column: PHENOMENEX® Lux Cellulose-2, 250 mm × 4.6 mm, 5 μ. Mobile Phase: 2 mL/min. of 80:20 CO_2:MeOH + 0.1% each of formic acid and diethylamine.

Method DZ: Column: CHIRALPAK® AS, 250 mm × 4.6 mm, 5 μ. Mobile Phase: 2 mL/min. of 90:10 CO_2:MeOH.

Example 1

3-(3-((4-Chlorophenyl)amino)-4-(ethyl(4-hydroxy-4-methylcyclohexyl)amino)phenyl)-3-methylbutanoic acid



1A. 8-Methyl-1,4-dioxaspiro[4.5]decan-8-ol

A stirred solution of 1,4-dioxaspiro[4.5]decan-8-one (5 g, 32.0 mmol) in dry THF (70 mL) was cooled to -70 °C and methylmagnesium bromide (23.48 mL, 70.4 mmol) in ether was added dropwise over 10 min. The cooling bath was allowed to warm to room temperature and the mixture was stirred overnight. The mixture was quenched with sat. aq. NH_4Cl (75 mL) and extracted with diethyl ether (2 × 300 mL). The combined ether extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford 1A (yellow liquid, 5.1 g, 29.6 mmol, 92% yield) which was used in next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 - 3.90 (m, 4H), 1.91 - 1.84 (m, 2H), 1.71 - 1.65 (m, 3H), 1.63 - 1.57 (m, 3H), 1.22 (s, 3H).

1B. 4-Hydroxy-4-methylcyclohexanone

Compound 1A (5.1 g, 29.6 mmol) was dissolved in THF (100 mL), followed by addition of 1N aqueous HCl (44.4 mL, 44.4 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. The resulting reaction liquid was concentrated under reduced pressure and then extracted with 10% MeOH/DCM (2 × 200 mL). The combined organic layer were washed with brine (50 mL), dried over anhydrous

sodium sulfate and concentrated under reduced pressure to afford 1B (yellow liquid, 3.1 g, 24.19 mmol, 82% yield) which was used in next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.81 - 2.65 (m, 2H), 2.32 - 2.15 (m, 2H), 2.01 - 1.75 (m, 4H), 1.36 (s, 3H).

1C. 4-(Ethylamino)-1-methylcyclohexanol (diastereomeric mixture)

To a stirred solution of 1B (3.2 g, 24.97 mmol), ethanamine (13.73 mL, 27.5 mmol) in dry MeOH (50 mL) under nitrogen atmosphere molecular sieves (5.0 g) was added and the reaction stirred at room temperature overnight. Reaction mixture was cooled to 0 °C and was added $NaBH_4$ (1.889 g, 49.9 mmol) in portionwise in 10 minutes. Reaction stirred at room temperature for 3 h. Reaction mixture was concentrated under reduced pressure to get semi-solid. To this was added sat. $NaHCO_3$ (100 mL) and was stirred overnight. Reaction mixture was dissolved in EtOAc (400 ml), washed with water (100 ml), brine (100 ml), dried over Na_2SO_4 and concentrated under reduced pressure to get 1C (light yellow liquid, 3.1 g, 19.71 mmol, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (q, J = 7.2 Hz, 2H), 2.45 - 2.35 (m, 1H), 1.92 - 1.61 (m, 4H), 1.51 - 1.35 (m, 4H), 1.23 (s, 3H), 1.10 (t, J = 7.2 Hz, 3H).

1D. Dimethyl 2-(2-(4-fluorophenyl) propan-2-yl) malonate

To a stirred solution of (4-fluorophenyl)magnesium bromide (54.1 mL, 54.1 mmol) in diethyl ether (70 mL) at -10 °C was added copper(I) chloride (2.68 g, 27.1 mmol). Then dimethyl 2-(propan-2-ylidene)malonate (6.99 g, 40.6 mmol) in 10 mL ether was added in dropwise over 2 min. Reaction mixture was stirred for 20 minutes at room temperature, followed by reflux for 3 h. Reaction mixture was cooled to room temperature and quenched with ice cold 1 N HCl. The aqueous layer was extracted with diethyl ether (50 mL), dried over sodium sulfate, concentrated under reduced pressure to give 1D (light yellow liquid, 495 mg, 1.856 mmol, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 - 7.31 (m, 2H), 6.99 - 6.94 (m, 2H), 3.75 (s, 1H), 3.58 (s, 6H), 1.56 (s, 6H).

1E. Methyl 3-(4-fluorophenyl)-3-methylbutanoate

To a stirred solution of 1D (12.5 g, 46.6 mmol), in DMSO (5.0 mL) and water (0.15 mL) mixture, lithium chloride (3.95 g, 93 mmol) was added. Reaction mixture

heated to 180 °C and stirred for 5 h. Reaction mixture was cooled to room temperature, partitioned between diethyl ether (50 mL) and water (25 mL). Aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layer was washed with brine (25 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash chromatography gave 1E (gummy liquid, 6.2 g, 29.5 mmol, 63% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.34 - 7281 (m, 2H), 7.02 - 6.94 (m, 2H), 3.52 (s, 3H), 2.60 (s, 2H), 1.48 (s, 6H).

1F. Methyl 3-(4-fluoro-3-nitrophenyl)-3-methylbutanoate

To a stirred solution of 1E (0.200 g, 0.892 mmol) in H_2SO_4 (2.0 mL) at 0 °C, nitric acid (0.092 mL, 1.338 mmol) was slowly added under nitrogen atmosphere and maintained at same temperature for 1 h. Reaction mixture quenched with ice and extracted with DCM (2 × 10 mL). Organic layer dried over sodium sulfate and concentrated under reduced pressure to get light yellow liquid. Purification via flash chromatography gave 1F (colorless liquid, 100 mg, 0.392 mmol, 42% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.05 - 8.02 (m, 1H), 7.65 - 7.61 (m, 1H), 7.25 - 7.19 (m, 1H), 3.53 (s, 3H), 2.65 (s, 2H), 1.47 (s, 6H).

1G. Methyl 3-(4-(ethyl(4-hydroxy-4-methylcyclohexyl)amino)-3-nitrophenyl)-3-methylbutanoate (diastereomeric mixture)

To a solution of 1F (1.0 g, 3.92 mmol) in dioxane (10 mL) was added DIPEA (2.053 mL, 11.75 mmol), followed by 1C (0.924 g, 5.88 mmol). Reaction mixture was heated to 135 °C and was stirred overnight. LCMS indicated completion of reaction. Reaction mixture was concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography (ethyl acetate in pet ether as eluent) to afford 1G (yellow liquid, 1.1 g, 2.354 mmol, 60.1% yield). LC-MS Anal. Calc'd. $C_{21}H_{32}N_2O_5$ for 392.2, found [M+H] 393.2, T_r = 3.3 min (Method N).

1H. Methyl 3-(3-amino-4-(ethyl(4-hydroxy-4-methylcyclohexyl)amino)phenyl)-3-methylbutanoate

The solution of methyl 1G (850 mg, 2.166 mmol) in ethyl acetate (10.0 mL) was charged to a sealable hydrogen flask. The solution was sequentially evacuated and purged

with nitrogen gas. To this 10% Pd on carbon (157 mg, 0.147 mmol) was added under nitrogen atmosphere. The reaction mixture was stirred under hydrogen atmosphere (40 psi) at room temperature for 16 h. The reaction mixture was filtered through a CELITE® pad and the residue on the pad was thoroughly rinsed with MeOH (3 × 20 mL). The combined filtrate was concentrated under reduced pressure to afford 1H (diastereomer mixture). LC-MS Anal. Calc'd. $C_{21}H_{34}N_2O_3$ for 362.3, found [M+H] 363.4, T_r = 2.68 min (Method U).

Chiral separation of diastereomeric mixture 1H (Method AM) gave Diastereomer 1 T_r = 3.76 min (Method AM), Diastereomer 2 T_r = 6.37 min (Method AM).

1H Diastereomer 1 (yellow liquid, 90 mg, 0.248 mmol, 12% yield): LC-MS Anal. Calc'd. $C_{21}H_{34}N_2O_3$ for 362.3, found [M+H] 363.4, T_r = 2.79 min (Method U).

1H Diastereomer 2 (yellow liquid, 650 mg, 1.793 mmol, 83% yield): LC-MS Anal. Calc'd. $C_{21}H_{34}N_2O_3$ for 362.3, found [M+H] 363.4, T_r = 2.96 min (Method U).

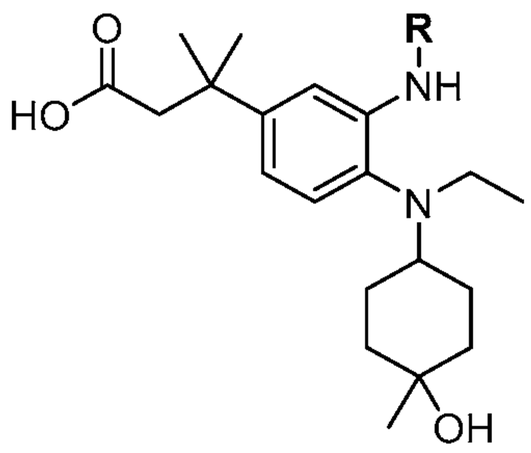
1I. Methyl 3-(3-((4-chlorophenyl)amino)-4-(ethyl(4-hydroxy-4-methylcyclohexyl)amino) phenyl)-3-methylbutanoate

The mixture of 1H Diastereomer 2 (100 mg, 0.276 mmol), 1-bromo-4-chlorobenzene (58.1 mg, 0.303 mmol), Xantphos (31.9 mg, 0.055 mmol) and Cs_2CO_3 (270 mg, 0.828 mmol) in dioxane (2.0 mL) was stirred at room temperature. Argon gas was bubbled through the mixture for 10 min. Bis(dibenzylideneacetone)palladium (15.86 mg, 0.028 mmol) was added and argon gas was bubbled through the mixture for 5 min. The reaction mixture was sealed and placed in preheated oil bath at 110 °C for 18 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford a residue. The residue was reconstituted in a mixture of DCM (50 mL) and water (10 mL). The organic layer was separated and was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue of 1I (131 mg, 0.116 mmol, 42% yield) which was used in next step without further purification. LC-MS Anal. Calc'd. $C_{27}H_{37}ClN_2O_3$ for 472.3, found [M+H] 473.5, T_r = 2.13 min (Method BA).

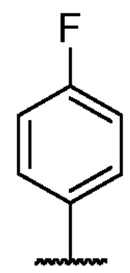
Example 1. 3-(3-((4-Chlorophenyl)amino)-4-(ethyl(4-hydroxy-4-methylcyclohexyl) amino)phenyl)-3-methylbutanoic acid

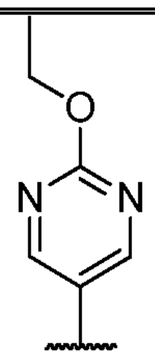
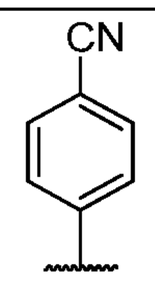
To a stirred solution of above residue 1I (0.116 mmol) in mixture of THF (1.0 mL), MeOH (1.0 mL) and water (0.5 mL) was added $LiOH•H_2O$ (33.0 mg, 1.380 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure. The aqueous residue so obtained was acidified with 1N HCl to pH ~2. The aqueous layer was diluted with water (5 mL) and extracted with ethyl acetate (2 × 20 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LC/MS to afford Example 1 (17.9 mg, 0.039 mmol, 14% yield). LC-MS Anal. Calc'd. $C_{26}H_{35}ClN_2O_3$ for 458.234, found [M+H] 459.2, T_r = 2.3 min (Method O). ^1H NMR (400 MHz, DMSO-d_6) δ 7.61 - 7.52 (m, 3H), 7.22 - 7.19 (m, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 3.71 - 3.50 (m, 3H), 2.70 (s, 2H), 1.83 - 1.73 (m, 6H), 1.45 - 1.31 (m, 8H), 1.19 (s, 3H), 1.05 (t, *J* = 6.9 Hz, 3H).

Examples 2 to 4



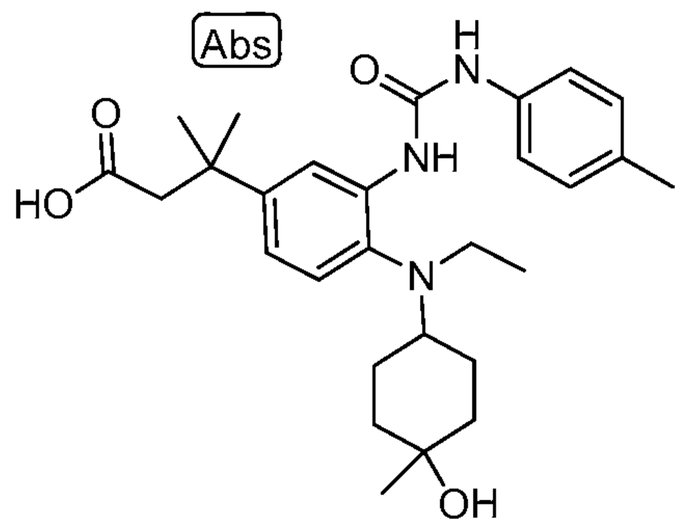
Examples 2 to 4 were prepared from 1H Diastereomer 2 and the corresponding halides following the procedure described for the synthesis of Example 1.

Ex. No.	Name	R	T_r (min) Method O	$[M+H]^+$
2	3-(4-(ethyl(4-hydroxy-4-methylcyclohexyl)amino)-3-((4-fluorophenyl)amino)phenyl)-3-methylbutanoic acid		2.148	443.3

Ex. No.	Name	R	T_r (min) Method O	$[M+H]^+$
3	3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(4-hydroxy-4-methylcyclohexyl) amino)phenyl)-3-methylbutanoic acid		1.638	471.4
4	3-(3-((4-cyanophenyl)amino)-4-(ethyl (4-hydroxy-4-methylcyclohexyl)amino) phenyl)-3-methylbutanoic acid		1.703	450.4

Example 5

3-(4-(Ethyl(4-hydroxy-4-methylcyclohexyl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)-3-methylbutanoic acid



5A. Methyl 3-(4-(ethyl(4-hydroxy-4-methylcyclohexyl)amino)-3-(3-(*p*-tolyl)ureido) phenyl)-3-methylbutanoate

To a stirred solution of 1H Diastereomer 2 (0.035 g, 0.097 mmol) in dry THF (1.0 mL), 1-isocyanato-4-methylbenzene (0.013 g, 0.097 mmol) was added at room temperature and was stirred for 12 h. Reaction mixture was diluted with DCM (50 mL), filtered through CELITE®, concentrated under reduced pressure to get the crude compound. The residue was purified via flash silica gel column chromatography (conditions: 0-10% MeOH/$CHCl_3$, 12 g silica gel column) to afford 5A (yellow liquid, 45 mg, 0.091 mmol, 94% yield). LC-MS Anal. Calc'd. $C_{29}H_{41}N_3O_4$ for 495.3, found $[M+H]$ 496.3, T_r = 1.52 min (Method BA).

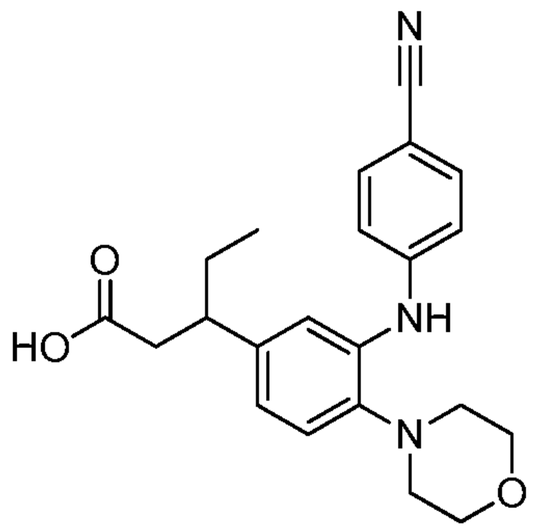
Example 5. 3-(4-(Ethyl(4-hydroxy-4-methylcyclohexyl)amino)-3-(3-(*p*-tolyl)ureido) phenyl)-3-methylbutanoic acid

Example 5 was prepared from 5A following the procedure described for the synthesis of Example 1 from 1I. LC-MS Anal. Calc'd. $C_{28}H_{39}N_3O_4$ for 481.294, found [M+H] 482.3, T_r = 1.893 min (Method O). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.40 (s, 1H), 8.43 (s, 1H), 8.27 (s, 1H), 7.38 - 7.36 (m, 2H), 7.15 - 7.05 (m, 3H), 6.98 - 6.93 (m, 1H), 3.00 (s, 2H), 2.72 - 2.65 (m, 1H), 2.25 (s, 3H), 1.59 - 1.53 (m, 6H), 1.38 (s, 6H), 1.27 - 1.21 (m, 2H), 1.05 (s, 3H), 0.85 - 0.81 (m, 3H). (2H peak is buried under solvent peak).

Example 6

(Enantiomer 1 and Enantiomer 2)

3-(3-((4-Cyanophenyl)amino)-4-morpholinophenyl)pentanoic acid



6A. Methyl 3-(4-morpholino-3-nitrophenyl)pentanoate

To a solution of 41B (2.0 g, 7.84 mmol) in NMP (15 mL) was added DIPEA (4.11 mL, 23.51 mmol), followed by morpholine (0.819 g, 9.40 mmol). Reaction mixture was heated to 120 °C and was stirred overnight. LCMS indicated completion of reaction. The reaction mixture was cooled to room temperature and diluted with diethyl ether. The organic layer was washed with 10% aq. AcOH solution, 10% $NaHCO_3$ solution, brine, dried over Na_2SO_4 and was concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography (0-100% ethyl acetate in pet ether as eluent to afford 6A (orange liquid, 2.4 g, 7.45 mmol, 95% yield). LC-MS Anal. Calc'd. $C_{16}H_{22}N_2O_5$ for 322.2, found [M+H] 323.2, T_r = 2.678 min (Method U).

6B. Methyl 3-(3-amino-4-morpholinophenyl)pentanoate

The solution of 6A (2.4 g, 7.45 mmol) in ethyl acetate (10.0 mL) was charged to a sealable hydrogen flask. The solution was sequentially evacuated and purged with nitrogen gas. To this 10% Pd on carbon (0.396 g, 0.372 mmol) was added under nitrogen atmosphere. The reaction mixture was stirred under hydrogen atmosphere (40 psi) at room temperature for 3 h. The reaction mixture was filtered through a CELITE® pad and the residue on the pad was thoroughly rinsed with MeOH (3 × 20 mL). The combined filtrate was concentrated under reduced pressure to afford 6B (enantiomeric mixture). LC-MS Anal. Calc'd. $C_{16}H_{24}N_2O_3$ for 292.2, found [M+H] 293.2, T_r = 3.028 min (Method BE).

Chiral separation of Enantiomeric mixture 6B (Method AF) gave Enantiomer 1 T_r = 5.12 min (Method AF), Enantiomer 2 T_r = 5.79 min (Method AF).

6B Enantiomer 1 (brown semi-solid, 0.8 g, 2.72 mmol, 36.6% yield): LC-MS Anal. Calc'd. $C_{16}H_{24}N_2O_3$ for 292.2, found [M+H] 293.2, T_r = 2.064 min (Method BE).

6B Enantiomer 2 (brown semi-solid, 0.85 g, 2.75 mmol, 36.9% yield); LC-MS Anal. Calc'd. $C_{16}H_{24}N_2O_3$ for 292.2, found [M+H] 293.2, T_r = 2.067 min (Method BE)

6C. Methyl 3-(3-((4-cyanophenyl)amino)-4-morpholinophenyl)pentanoate

Compound 6C was prepared from 6B Enantiomer 1 and 4-bromobenzonitrile following the procedure described for the synthesis of 1I. LC-MS Anal. Calc'd. $C_{23}H_{27}N_3O_3$ 393.2, found [M+H] 394.2, T_r = 1.41 min (Method BA).

Example 6 Enantiomer 1. 3-(3-((4-Cyanophenyl)amino)-4-morpholinophenyl)pentanoic acid

Example 6 Enantiomer 1 was prepared from 6C following the procedure described for the synthesis of Example 1 from 1I. LC-MS Anal. Calc'd. $C_{22}H_{25}N_3O_3$ for 379.2, found [M+H] 380.2, T_r = 1.527 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.53 (d, J = 6.4 Hz, 2H), 7.04 - 6.92 (m, 5H), 3.56 - 3.55 (m, 4H), 2.80 - 2.79 (m, 5H), 2.58 - 2.39 (m, 2H), 1.65 - 1.45 (m, 2H), 0.73 (t, J = 7.2 Hz, 3H).

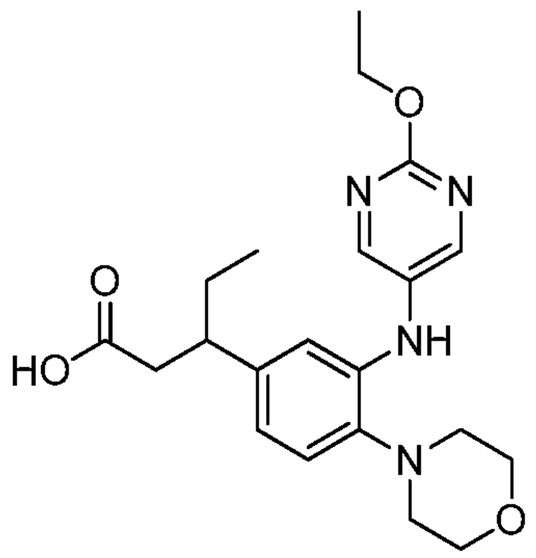
Example 6 Enantiomer 2. 3-(3-((4-Cyanophenyl)amino)-4-morpholinophenyl)pentanoic acid

Example 6 Enantiomer 2 was prepared from 6B Enantiomer 2 following the procedure described for the synthesis of Example 6 Enantiomer 1. LC-MS Anal. Calc'd. $C_{22}H_{25}N_3O_3$ for 379.2, found [M+H] 380.2, T_r = 1.527 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.53 (d, *J* = 6.4 Hz, 2H), 7.04 - 6.92 (m, 5H), 3.56 - 3.55 (m, 4H), 2.80 - 2.79 (m, 5H), 2.58 - 2.39 (m, 2H), 1.65 - 1.45 (m, 2H), 0.73 (t, *J* = 7.2 Hz, 3H).

Example 7

(Enantiomer 1 and Enantiomer 2)

3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-morpholinophenyl)pentanoic acid



Example 7 Enantiomer 1. 3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-morpholinophenyl) pentanoic acid

Example 7 Enantiomer 1 was prepared from 6B Enantiomer 1 and 5-bromo-2-ethoxypyrimidine following the procedure described for the synthesis of Example 6 Enantiomer 1. LC-MS Anal. Calc'd. $C_{21}H_{28}N_4O_4$ for 400.2, found [M+H] 401.3, T_r = 1.113 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 2H), 7.33 (s, 1H), 6.98 (d, *J* = 1.6 Hz, 1H), 6.72 - 6.71 (m, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.60 - 3.55 (m, 4H), 2.81 - 2.72 (m, 5H), 2.52 - 2.34 (m, 2H), 1.57 - 1.4 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.70 (t, *J* = 7.2 Hz, 3H).

Example 7 Enantiomer 2. 3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-morpholinophenyl) pentanoic acid

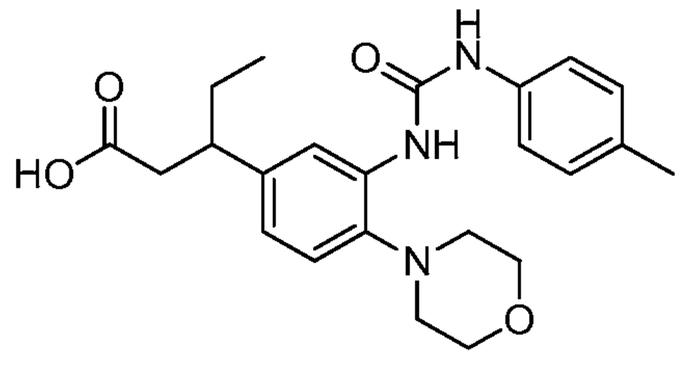
Example 7 Enantiomer 2 was prepared from 6B Enantiomer 2 and 5-bromo-2-ethoxypyrimidine following the procedure described for the synthesis of Example 6 Enantiomer 1. LC-MS Anal. Calc'd. $C_{21}H_{28}N_4O_4$ for 400.2, found [M+H] 401.3, T_r =

1.113 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 2H), 7.33 (s, 1H), 6.97 (d, J = 1.6 Hz, 1H), 6.77 - 6.71 (m, 2H), 4.30 (q, J = 7.2 Hz, 2H), 3.60 - 3.55 (m, 4H), 2.81 - 2.72 (m, 6H), 2.52 - 2.34 (m, 2H), 1.56 - 1.4 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H), 0.70 (t, J = 7.2 Hz, 3H).

Example 8

(Enantiomer 1 and Enantiomer 2)

3-(4-Morpholino-3-(3-(*p*-tolyl)ureido)phenyl)pentanoic acid



Example 8 Enantiomer 1. 3-(4-Morpholino-3-(3-(*p*-tolyl)ureido)phenyl)pentanoic acid

Example 8 Enantiomer 1 was prepared from 6B Enantiomer 1 and 1-isocyanato-4-methylbenzene following the procedure described for the synthesis of Example 5. LC-MS Anal. Calc'd. $C_{23}H_{29}N_3O_4$ for 411.2, found [M+H] 412.2, T_r = 1.524 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.43 (s, 1H), 8.07 (s, 1H), 7.96 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.11 -7.08 (m, 3H), 6.79 (dd, J = 8.4, 2.0 Hz, 1H), 3.82 - 3.80 (m, 4H), 2.82 - 2.75 (m, 5H), 2.53 - 2.44 (m, 2H), 2.25 (s, 3H), 1.63 - 1.60 (m, 1H), 1.55 - 1.48 (m, 1H), 0.73 (t, J = 7.2 Hz, 3H).

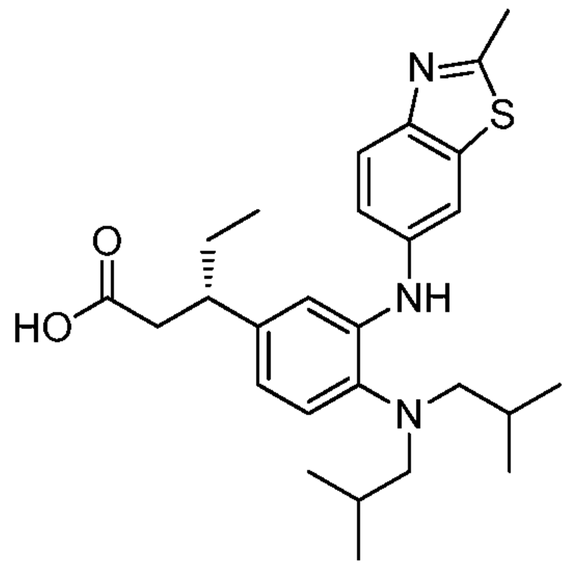
Example 8 Enantiomer 2. 3-(4-Morpholino-3-(3-(*p*-tolyl)ureido)phenyl)pentanoic acid

Example 8 Enantiomer 2 was prepared from 6B Enantiomer 2 and 1-isocyanato-4-methylbenzene following the procedure described for the synthesis of Example 5. LC-MS Anal. Calc'd. $C_{23}H_{29}N_3O_4$ for 411.2, found [M+H] 412.2, T_r = 1.274 min (Method O). ^{1}H NMR (400 MHz, MeOD) δ 8.00 (d, J = 2.0 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.17 -7.14 (m, 3H), 6.88 (dd, J = 8.4, 2.0 Hz, 1H), 3.86 - 3.84 (m, 4H), 2.96 - 2.83 (m, 5H), 2.66 - 2.32 (m, 2H), 2.32 (s, 3H), 1.75 - 1.66 (m, 1H), 1.65 - 1.62 (m, 1H), 0.82 (t, J = 7.2 Hz, 3H).

Example 9

(Enantiomer 1)

(S)-3-(4-(Diisobutylamino)-3-((2-methylbenzo[d]thiazol-6-yl) amino)phenyl)pentanoic acid



9A. N,N-Diisobutyl-2-nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

The mixture of 4-bromo-N,N-diisobutyl-2-nitroaniline (1 g, 3.04 mmol), bis(pinacolato)diboron (1.018 g, 4.01 mmol) and potassium acetate (0.894 g, 9.11 mmol) in DMSO (10 mL) was stirred at room temperature. Argon gas was bubbled through the mixture for 5 min. $PdCl_2$ (dppf)•CH_2Cl_2 Adduct (0.074 g, 0.091 mmol) was added and argon gas was bubbled through the mixture for 5 min. The reaction mixture was heated at 80 °C for 6 h. The reaction mixture was cooled to room temperature and diluted with dichloromethane (200 mL). The organic layer was washed with water (2 × 50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography (conditions: 0-100% ethyl acetate in pet ether or gradient of ethyl acetate in pet ether) to afford 9A (gummy, 1.0 g, 2.66 mmol, 87% yield). LC-MS Anal. Calc'd. for $C_{20}H_{33}BN_2O_4$ 376.253, found [M+H] 377.3, T_r = 4.48 min (Method U).

9B. (S)-Methyl 3-(4-(diisobutylamino)-3-nitrophenyl)pentanoate

In a pressure tube equipped with Teflon cap, 9A (200 mg, 0.531 mmol), 1,4-dioxane (5.0 mL) were added followed by (E)-methyl pent-2-enoate (72.8 mg, 0.638 mmol), (R)-BINAP (7.28 mg, 0.012 mmol) and 1M solution of sodium hydroxide (0.485 mL, 0.485 mmol). Argon gas was bubbled through the mixture for 10 min and chlorobis(ethylene)rhodium(I) dimer (3.10 mg, 7.97 μmol) was added at room

temperature. Argon gas was bubbled through the mixture for 5 min. The tube was then screw-capped and heated at 50 °C for 3 h. The reaction mixture was cooled to room temperature, quenched with acetic acid (0.027 mL, 0.478 mmol) and was stirred for 5 minutes before it was diluted with water (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL). Combined organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography (conditions: 0-100% ethyl acetate in pet ether or gradient of ethyl acetate in pet ether) to afford 9B (yellow liquid, 150 mg, 0.412 mmol, 77% yield). LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_4$ 364.2, found [M+H] 365.4, T_r = 4.12 min (Method U). (Absolute stereochemistry of the product assigned based on the expected product enantiomer from the use of (R)-BINAP in the conjugate addition)

9C. (S)-Methyl 3-(3-amino-4-(diisobutylamino)phenyl)pentanoate

The solution of 9B (0.150 g, 0.412 mmol) in ethyl acetate (20.0 mL) was charged to a sealable hydrogen flask. The solution was sequentially evacuated and purged with nitrogen gas. To this 10% Pd on carbon (0.030 g, 0.028 mmol) was added under nitrogen atmosphere. The reaction mixture was stirred under hydrogen atmosphere (40 psi) at room temperature for 4 h. The reaction mixture was filtered through a CELITE® pad and the residue on the pad was thoroughly rinsed with MeOH (3 × 20 mL). The combined filtrate was concentrated under reduced pressure to afford 9C (120 mg, 0.359 mmol, 87% yield). LC-MS Anal. Calc'd. $C_{20}H_{34}N_2O_2$ for 334.3, found [M+H] 335.3, T_r = 1.90 min (Method BA).

Example 9. (S)-3-(4-(Diisobutylamino)-3-((2-methylbenzo[d]thiazol-6-yl)amino)phenyl) pentanoic acid

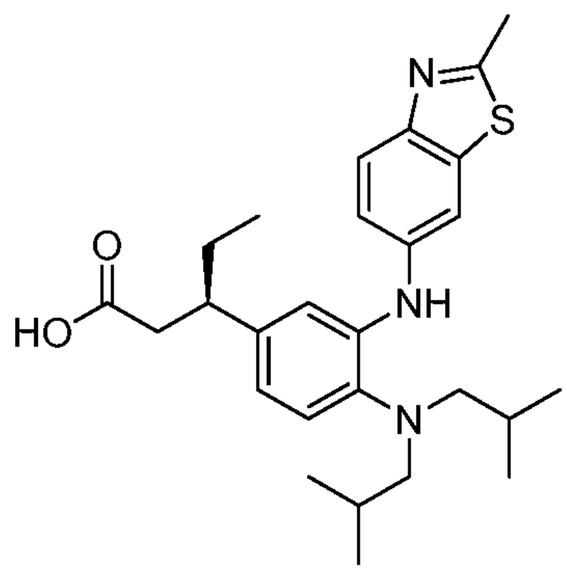
The mixture of 9C (100 mg, 0.276 mmol), 6-bromo-2-methylbenzo[d]thiazole (32.7 mg, 0.143 mmol), Xantphos (41.5 mg, 0.072 mmol) and sodium *tert*-butoxide (41.4 mg, 0.430 mmol) in dioxane (2.0 mL) was stirred at room temperature. Argon gas was bubbled through the mixture for 10 min. Bis(dibenzylideneacetone)palladium (8.25 mg, 0.014 mmol) was added and argon gas was bubbled through the mixture for 5 min. The reaction mixture was sealed and placed in preheated oil bath at 110 °C for 18 h. The

reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford a residue. The residue was reconstituted in a mixture of DCM (50 mL) and water (10 mL). The organic layer was separated and was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LC/MS to afford Example 9 (14.2 mg, 0.030 mmol, 21% yield). LC-MS Anal. Calc'd. $C_{27}H_{37}N_3O_2S$ for 467.3, found [M+H] 468.4, T_r = 2.616 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.0 (bs, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.64 (s, 1H), 7.16 - 7.11 (m, 3H), 6.73 (dd, *J* = 8.8, 2.0 Hz, 2H), 2.9 - 2.79 (m, 1H), 2.72 (s, 3H), 2.61 - 2.40 (m, 6H), 1.71 - 1.63 (m, 3H), 1.61 - 1.45 (m, 1H), 0.84 - 0.83 (m, 12H), 0.73 (t, *J* = 7.2 Hz, 3H).

Example 10

(Enantiomer 2)

(R)-3-(4-(Diisobutylamino)-3-((2-methylbenzo[d]thiazol-6-yl)amino) phenyl)pentanoic acid



10A. (R)-Methyl 3-(4-(diisobutylamino)-3-nitrophenyl)pentanoate

10A was prepared from 9A and (S)-BINAP following the procedure described for the synthesis of 9B. LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_4$ 364.2, found [M+H] 365.4. T_r = 4.2 min (Method U). (Absolute stereochemistry of the product assigned based on the expected product enantiomer from the use of (S)-BINAP in the conjugate addition)

10B. (R)-Methyl 3-(3-amino-4-(diisobutylamino)phenyl)pentanoate

10B was prepared from 10A following the procedure described for the synthesis of 9C. LC-MS Anal. Calc'd. $C_{20}H_{34}N_2O_2$ for 334.3, found [M+H] 335.3, T_r = 1.87 min

(Method BA). Chiral purity T_r = 18.9 min with ee 90% (Method CY) as single enantiomer.

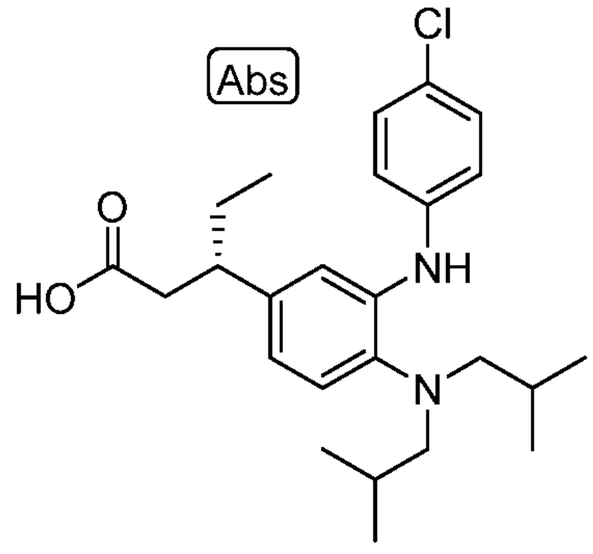
Example 10. (R)-3-(4-(Diisobutylamino)-3-((2-methylbenzo[d]thiazol-6-yl)amino) phenyl)pentanoic acid

Example 10 was prepared from 10B following the procedure described for the synthesis of Example 9. LC-MS Anal. Calc'd. $C_{27}H_{37}N_3O_2S$ for 467.3, found [M+H] 468.4, T_r = 2.616 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.0 (br.s., 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.63 (s, 1H), 7.16 - 7.11 (m, 3H), 6.73 (d, *J* = 8.8 Hz, 2H), 2.9 - 2.79 (m, 1H), 2.72 (s, 3H), 2.61 - 2.40 (m, 6H), 1.71 - 1.63 (m, 3H), 1.61 - 1.45 (m, 1H), 0.84 - 0.83 (m, 12H), 0.73 (t, *J* = 7.2 Hz, 3H).

Example 11

(Enantiomer 1)

(S)-3-(3-((4-Chlorophenyl)amino)-4-(diisobutylamino)phenyl)pentanoic acid

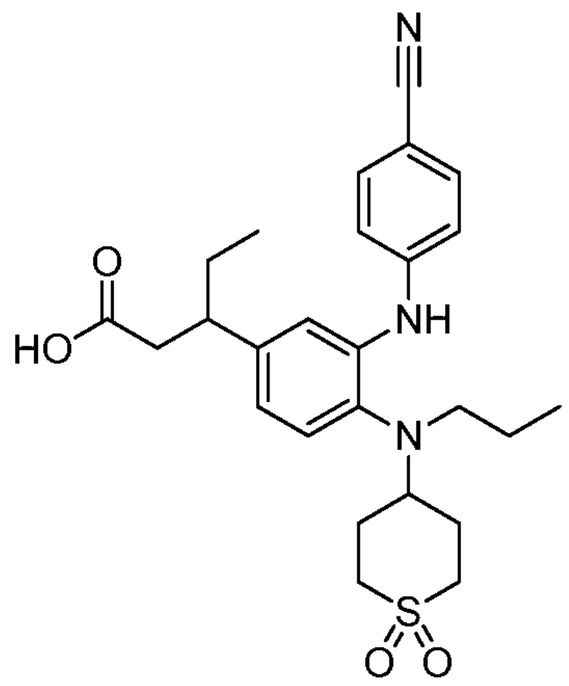


Example 11 was prepared from 9C and 1-bromo-4-chlorobenzene following the procedure described for the synthesis of Example 9. LC-MS Anal. Calc'd. $C_{25}H_{35}ClN_2O_2$ for 430.2, found [M+H] 431.2, T_r = 2.862 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.0 (bs, 1H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.19 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.04 - 7.02 (m, 3H), 6.73 (dd, *J* = 8.4, 1.6 Hz, 1H), 2.82 - 2.76 (m, 1H), 2.66 - 2.32 (m, 6H), 1.67 - 1.57 (m, 3H), 1.52 - 1.46 (m, 1H), 0.82 (d, *J* = 6.4 Hz, 12H), 0.72 (t, *J* = 7.2 Hz, 3H).

Example 12

(Enantiomer 1 and Enantiomer 2)

3-(3-((4-Cyanophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)phenyl)pentanoic acid



12A. N-Propyltetrahydro-2h-thiopyran-4-amine

To a stirred solution of dihydro-2H-thiopyran-4(3H)-one (5.0 g, 43.0 mmol) in dry MeOH (80 mL), propan-1-amine (2.80 g, 47.3 mmol) was added. Then molecular sieves (5.0 g) were added to the reaction mixture. Reaction mixture was stirred at RT overnight. Reaction mixture was cooled to 0 °C and added $NaBH_4$ (3.26 g, 86 mmol) portionwise in 10 minutes. It was stirred at room temperature for 3 h. Reaction mixture was concentrated under reduced pressure to get semi-solid. To this was added sat. aq. $NaHCO_3$ (200 mL) and was stirred overnight. Mixture was extracted with EtOAc (400 mL), washed with water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get 12A (light yellow liquid, 5.5 g, 34.5 mmol, 80% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 2.74 - 2.51 (m, 6H), 2.49 - 2.35 (m, 1H), 2.21 - 2.1 (m, 2H), 1.56 - 1.41 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H).

12B. Methyl 3-(3-nitro-4-(propyl(tetrahydro-2H-thiopyran-4-yl)amino)phenyl)pentanoate

To a solution of 41B (2.0 g, 7.84 mmol) in NMP (20 mL) was added DIPEA (4.11 mL, 23.51 mmol), followed by 12A (1.872 g, 11.75 mmol). Reaction mixture was heated to 135 °C and was stirred overnight. Reaction mixture was cooled to RT and was diluted with EtOAc (100 mL), washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated to get crude compound as yellow liquid. The residue was purified via flash silica gel column chromatography (conditions: 0-100% ethyl acetate in pet ether or gradient of ethyl acetate in pet ether) to afford 12B (yellow liquid, 0.6 g, 1.521 mmol,

20% yield). LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_4S$ 394.2, found [M+H] 395.2. T_r = 3.75 min (Method BE).

12C. Methyl 3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)-3-nitrophenyl)pentanoate

To a stirred solution of 12B (0.6 g, 1.521 mmol) in acetonitrile (7.0 mL), water (5.38 mL) at 0 °C was added sodium bicarbonate (1.278 g, 15.21 mmol), followed by OXONE® (2.337 g, 3.80 mmol). The mixture was stirred at the same temperature for 20 min and at RT. The reaction mixture was diluted with ethyl acetate (100 mL) and filtered through CELITE®. The filtrate was concentrated under reduced pressure and diluted with ethyl acetate (25 mL), washed with water (10 mL), dried over sodium sulfate, concentrated under reduced pressure to get orange liquid. The residue was purified via flash silica gel column chromatography (conditions: 0-100% ethyl acetate in pet ether or gradient of ethyl acetate in pet ether) to afford 12C (yellow liquid, 500 mg, 1.172 mmol, 77% yield). LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_6S$ 426.2, found [M+H] 427.2. T_r = 2.65 min (Method BE).

12D. Methyl 3-(3-amino-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)phenyl)pentanoate

The solution of methyl 12C (450 mg, 1.055 mmol) in ethyl acetate (10.0 mL) was charged to a sealable hydrogen flask. The solution was sequentially evacuated and purged with nitrogen gas. To this 10% Pd on carbon (76 mg, 0.072 mmol) was added under nitrogen atmosphere. The reaction mixture was stirred under hydrogen atmosphere (40 psi) at room temperature for 16 h. The reaction mixture was filtered through a CELITE® pad and the residue on the pad was thoroughly rinsed with MeOH (3 × 20 mL). The combined filtrate was concentrated under reduced pressure to afford 12D. LC-MS Anal. Calc'd. $C_{20}H_{32}N_2O_4S$ for 396.2, found [M+H] 397.4, T_r = 1.27 min (Method BA).

Chiral separation of mixture 12D (Method BS) gave Diastereomer 1 T_r = 3.43 min (Method BS), Diastereomer 2 T_r = 7.73 min (Method BS).

12D Enantiomer 1 (absolute stereochemistry unknown, yellow liquid, 130 mg, 0.328 mmol, 31.1% yield): LC-MS Anal. Calc'd. $C_{20}H_{32}N_2O_4S$ for 396.2, found [M+H] 397.4, T_r = 1.27 min (Method BA).

12D Enantiomer 2 (absolute stereochemistry unknown, yellow liquid, 130 mg, 0.328 mmol, 31.1% yield): LC-MS Anal. Calc'd. $C_{20}H_{32}N_2O_4S$ for 396.2, found [M+H] 397.4, T_r = 1.27 min (Method BA).

Example 12 Enantiomer 1. 3-(3-((4-Cyanophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)phenyl)pentanoic acid

Example 12 Enantiomer 1 was prepared from 12D Enantiomer 1 following the procedure described for the synthesis of Example 9 (absolute stereochemistry unknown). LC-MS Anal. Calc'd. $C_{26}H_{33}N_3O_4S$ for 483.219, found [M+H] 484.3, T_r = 1.463 min (Method Q). ^{1}H NMR (400 MHz, MeOD) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.96 - 6.93 (m, 1H), 3.21 - 3.16 (m, 1H), 3.01 - 2.96 (m, 7H), 2.68 - 2.64 (m, 1H), 2.57 - 2.53 (m, 1H), 2.17 - 2.13 (m, 4H), 1.74 - 1.60 (m, 2H), 1.38 -1.30 (m, 2H), 0.86 - 0.83 (m, 6H).

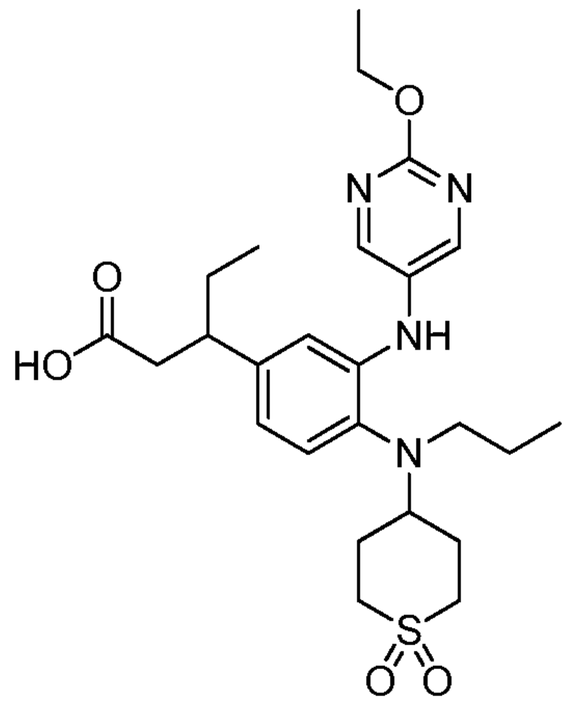
Example 12 Enantiomer 2. 3-(3-((4-Cyanophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)phenyl)pentanoic acid

Example 12 Enantiomer 2 was prepared from 12D Enantiomer 2 following the procedure described for the synthesis of Example 9 (absolute stereochemistry unknown). LC-MS Anal. Calc'd. $C_{26}H_{33}N_3O_4S$ for 483.219, found [M+H] 484.3, T_r = 2.015 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.17 - 7.11 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.92 - 6.90 (m, 1H), 3.21 - 3.16 (m, 1H), 3.05 - 2.81 (m, 7H), 2.61 - 2.42 (m, 2H), 2.06 - 1.91 (m, 4H), 1.62 - 1.45 (m, 2H), 1.23 - 1.18 (m, 2H), 0.75 - 0.71 (m, 6H).

Example 13

(Enantiomer 1 and Enantiomer 2)

3-(4-((1,1-Dioxidotetrahydro-2h-thiopyran-4-yl)(propyl)amino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl)pentanoic acid



Example 13 Enantiomer 1. 3-(4-((1,1-Dioxidotetrahydro-2h-thiopyran-4-yl)(propyl) amino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl)pentanoic acid

Example 13 Enantiomer 1 was prepared from 12D Enantiomer 1 and 5-bromo-2-ethoxypyrimidine following the procedure described for the synthesis of Example 1 (absolute stereochemistry unknown). LC-MS Anal. Calc'd. $C_{25}H_{36}N_4O_5S$ for 504.241, found [M+H] 504.3., T_r = 1.619 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 2H), 7.22 (s, 1H), 7.11 (d, *J* = 8.0 Hz, 1H). 6.76 - 6.75 (m, 1H), 6.66 - 6.64 (m, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.30 - 3.01 (m, 5H), 2.91 - 2.85 (m, 2H), 2.8 - 2.72 (m, 1H), 2.52 - 2.41 (m, 2H), 2.2 - 1.9 (m, 4H), 1.64 - 1.46 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.27 - 1.22 (m, 2H), 0.77 (t, *J* = 7.2 Hz, 3H), 0.69 (t, *J* = 7.2 Hz, 3H).

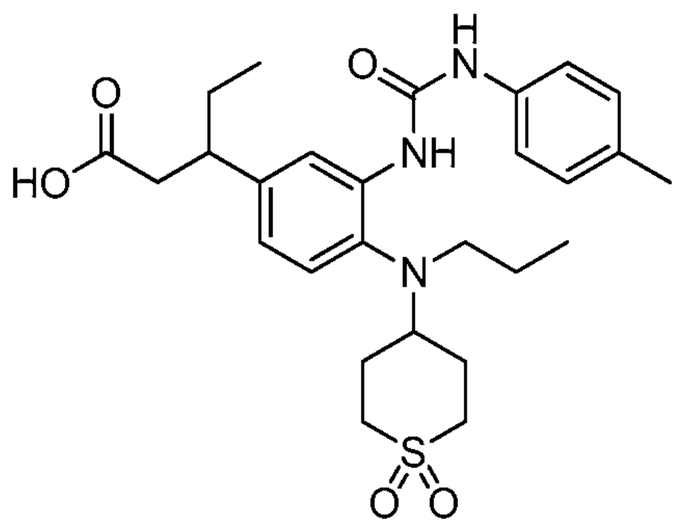
Example 13 Enantiomer 2. 3-(4-((1,1-Dioxidotetrahydro-2h-thiopyran-4-yl)(propyl) amino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl)pentanoic acid

Example 13 Enantiomer 2 was prepared from 12D Enantiomer 2 and 5-bromo-2-ethoxypyrimidine following the procedure described for the synthesis of Example 1 (absolute stereochemistry unknown). LC-MS Anal. Calc'd. $C_{25}H_{36}N_4O_5S$ for 504.241, found [M+H] 505.1., T_r = 1.955 min (Method O). ^{1}H NMR (400 MHz, MeOD) δ 8.41 (s, 2H), 7.21 (d, *J* = 8.0 Hz, 1H). 6.82 (d, *J* = 1.6 Hz, 1H), 6.75 (dd, *J* = 8.0, 1.6 Hz, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 3.33 - 3.25 (m, 3H), 3.08 - 2.95 (m, 4H), 2.9 - 2.82 (m, 1H), 2.12 - 1.92 (m, 2H), 2.31 - 2.21 (m, 4H), 1.69 - 1.51 (m, 2H), 1.45 - 1.30 (m, 5H), 0.86 (t, *J* = 7.2 Hz, 3H), 0.79 (t, *J* = 7.2 Hz, 3H).

Example 14

(Enantiomer 1 and Enantiomer 2)

3-(4-((1,1-Dioxidotetrahydro-2h-thiopyran-4-yl)(propyl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)pentanoic acid



Example 14 Enantiomer 1. 3-(4-((1,1-Dioxidotetrahydro-2h-thiopyran-4-yl)(propyl) amino)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoic acid

Example 14 Enantiomer 1 was prepared from 12D Enantiomer 1 and 1-isocyanato-4-methylbenzene following the procedure described for the synthesis of Example 5 (absolute stereochemistry unknown). LC-MS Anal. Calc'd. $C_{27}H_{37}N_3O_5S$ for 515.3, found [M+H] 516.4., T_r = 1.7 min (Method O).^{1}H NMR (400 MHz, MeOD) δ 8.08 (d, *J* = 2.0 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.22 - 7.15 (m, 3H), 6.90 (dd, *J* = 8.4, 2.0 Hz, 1H), 3.20 - 3.05 (m, 5H), 2.96 - 2.93 (m, 3H), 2.63 - 2.53 (m, 2H), 2.33 (s, 3H), 2.23 - 2.20 (m, 2H), 2.11 2.06 (m, 2H), 1.77 - 1.62 (m, 2H), 1.34 - 1.28 (m, 2H), 0.85 - 0.81 (m, 6H).

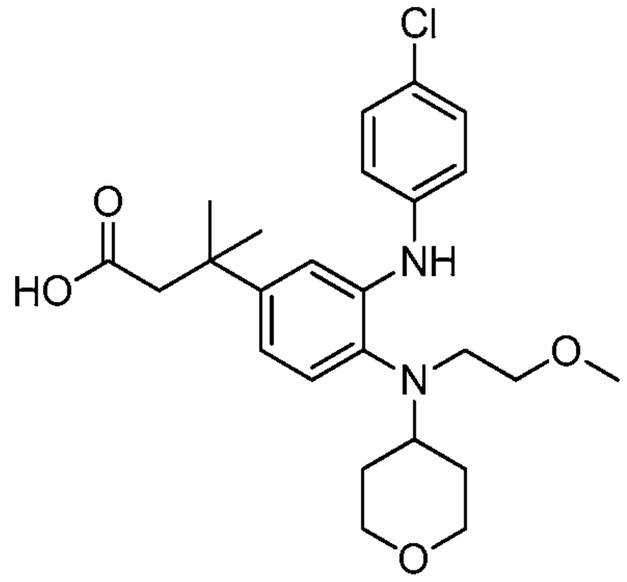
Example 14 Enantiomer 2. 3-(4-((1,1-Dioxidotetrahydro-2h-thiopyran-4-yl)(propyl) amino)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoic acid

Example 14 Enantiomer 2 was prepared from 12D Enantiomer 2 and 1-isocyanato-4-methylbenzene following the procedure described for the synthesis of Example 5 (absolute stereochemistry unknown). LC-MS Anal. Calc'd. $C_{27}H_{37}N_3O_5S$ for 515.3, found [M+H] 516.4, T_r = 1.427 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, 1H), 8.34 (s, 1H), 8.10 (d, *J* = 2.0 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.79 (dd, *J* = 8.4, 2.0 Hz, 1H), 3.17 - 3.05 (m, 5H), 2.90 - 2.86 (m, 3H), 2.53 - 2.44 (m, 2H), 2.24 - 2.18 (m, 5H), 1.9 - 1.81 (m, 2H), 1.69 -

1.59 (m, 1H), 1.55 - 1.46 (m, 1H), 1.23 - 1.17 (m, 2H), 0.77 (t, *J* = 7.2 Hz, 3H), 0.70 (t, *J* = 7.2 Hz, 3H).

Example 15

3-(3-((4-Chlorophenyl)amino)-4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoic acid



15A. Diethyl 2-(2-(4-fluorophenyl)propan-2-yl)malonate

To a stirred solution of magnesium (0.139 g, 5.71 mmol) and pinch of iodine in dry diethyl ether (5.0 mL), 1-bromo-4-fluorobenzene (0.500 g, 2.86 mmol) in 2 mL THF was added at room temperature. Reaction was stirred for 30 minutes at room temperature. Reaction mixture was cooled to -10 °C and diethyl isopropylidenemalonate (1.144 g, 5.71 mmol) dissolved in 1 mL THF was added dropwise over 2 minutes. Reaction mixture was stirred for 20 minutes at room temperature, followed by reflux for 3 h. Reaction mixture was cooled to rt and quenched with ice cold 1 N HCl. The aqueous layer was extracted with diethyl ether (50 mL), dried over sodium sulfate, concentrated under reduced pressure to give 15A (light yellow liquid, 550 mg, 1.856 mmol, 65% yield). LC-MS Anal. Calc'd. for $C_{16}H_{21}FO_4$ 296.14, found [M+H] 297.2, T_r = 1.47 min (Method BA).

15B. Ethyl 3-(4-fluorophenyl)-3-methylbutanoate

To a stirred solution of 15A (0.500 g, 1.687 mmol), in DMSO (5.0 mL), water (0.15 mL) mixture lithium chloride (0.143 g, 3.37 mmol) was added. Reaction mixture heated to 180 °C and stirred for 12 h. Reaction mixture was cooled to room temperature, partitioned between diethyl ether (50 mL) and water (25 mL). Aqueous layer was extracted with ether (2 × 25 mL). The combined organic layer was washed with brine (25

mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash chromatography gave 15B (light yellow liquid, 255 mg, 1.137 mmol, 67% yield). LC-MS Anal. Calc'd. for $C_{13}H_{17}FO_2$ 224.12, found [M+H] 225.2, T_r = 2.87 min (Method N).

15C. Ethyl 3-(4-fluoro-3-nitrophenyl)-3-methylbutanoate

To a stirred solution of 15B (0.200 g, 0.892 mmol) in H_2SO_4 (2.0 mL) at 0 °C, nitric acid (0.092 mL, 1.338 mmol) was slowly added under nitrogen atmosphere and maintained at same temperature for 1 h. Reaction mixture quenched with ice and extracted with DCM (2 × 10 mL). Organic layer dried over sodium sulfate and concentrated under reduced pressure to get light yellow liquid. Purification via flash chromatography gave 15C (colorless liquid, 210 mg, 0.780 mmol, 87% yield). LC-MS Anal. Calc'd. for $C_{13}H_{16}FNO_4$ 269.10, found [M+H] 270.2, T_r = 2.967 min (Method N).

15D. N-(2-Methoxyethyl)tetrahydro-2H-pyran-4-amine

To a stirred solution of dihydro-2H-pyran-4(3H)-one (27.7 mL, 300 mmol) in methanol (300 mL) under nitrogen atmosphere was added 2-methoxyethanamine (25.8 mL, 300 mmol), followed by 4 A° molecular sieves (2 g). The reaction mixture was stirred for 12 h at room temperature. To this was added $NaBH_4$ (34.0 g, 899 mmol) portionwise at 0 °C and the reaction mixture was stirred at room temperature for 3 h. Reaction mixture was quenched with water (10 mL) and concentrated under reduced pressure to get semi-solid which was quenched with 10% sodium bicarbonate (500 mL) and it was extracted with ethyl acetate (2 × 200 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to get 15D (yellow liquid, 30 g, 188 mmol, 62% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.89 - 3.56 (m, 6H), 3.37 (s, 3H), 2.86 - 2.67 (m, 3H), 1.98 - 1.67 (m, 4H).

15E. Ethyl 3-(4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)-3-methylbutanoate

In a sealed tube 15C (2 g, 7.43 mmol) in N-methyl-2-pyrrolidinone (10 mL) were added DIPEA (3.89 mL, 22.28 mmol) and 15D (2.365 g, 14.86 mmol). The reaction

mixture was stirred at 135 °C for 36 h. TLC indicated completion of reaction. Reaction mixture was cooled to room temperature, quenched with water (20 mL) and was extracted with MTBE (3 × 30 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash chromatography gave 15E (yellow liquid, 810 mg, 1.923 mmol, 25% yield). LC-MS Anal. Calc'd. for $C_{21}H_{32}N_2O_6$ 408.22, found [M+H] 409.5, T_r = 1.41 min. (Method AY).

15F. Ethyl 3-(3-amino-4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoate

The solution of 15E (0.810 g, 1.983 mmol) in ethyl acetate (8 mL) was charged to a sealable hydrogen flask. The solution was sequentially evacuated and purged with nitrogen gas. To this 10% Pd on carbon (0.106 g, 0.099 mmol) was added under nitrogen atmosphere. The reaction mixture was stirred under hydrogen atmosphere (40 psi). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through a CELITE® pad and the residue on the pad was thoroughly rinsed with ethyl acetate (3 × 15 mL). The combined filtrate was concentrated under reduced pressure to get crude compound. Purification via flash chromatography gave 15F (yellow liquid, 500 mg, 1.281 mmol, 64% yield). LC-MS Anal. Calc'd. for $C_{21}H_{34}N_2O_4$ 378.26, found [M+H] 379.3, T_r = 1.34 min (Method AY).

15G. Ethyl 3-(3-((4-chlorophenyl)amino)-4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoate

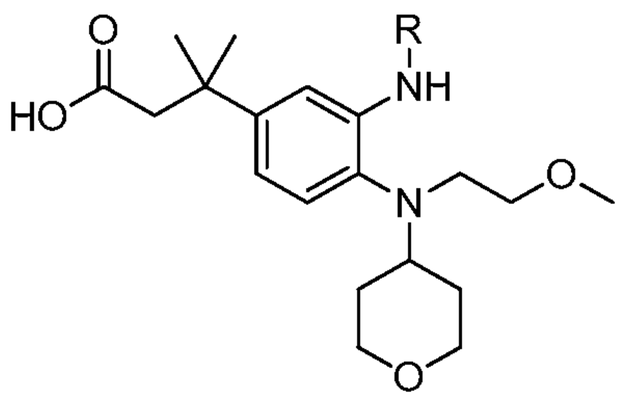
The mixture of 15F (0.050 g, 0.132 mmol), 1-bromo-4-chlorobenzene (0.030 g, 0.159 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (7.64 mg, 0.013 mmol) and Cs_2CO_3 (0.065 g, 0.198 mmol) in 1,4-dioxane (1.5 mL) was stirred at room temperature. Argon gas was bubbled through the mixture for 5 min. Bis(dibenzylideneacetone)palladium (3.80 mg, 6.60 µmol) was added and argon gas was bubbled through the mixture for another 5 min. The reaction mixture was sealed and placed in preheated oil bath at 110 °C for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford a residue. The residue was reconstituted in a mixture of ethyl acetate (15 mL) and water (15 mL). The organic layer

was separated and aqueous layer was extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography to afford 15G (yellow liquid, 50 mg, 0.082 mmol, 61% yield). LC-MS Anal. Calc'd. for $C_{27}H_{37}ClN_2O_4$ 488.2, found [M+H] 489.4, T_r = 1.84 min. (Method AY).

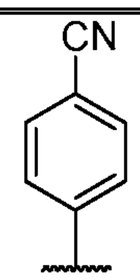
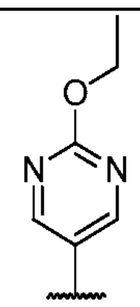
Example 15. 3-(3-((4-Chlorophenyl)amino)-4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoic acid

To a stirred solution of 15G (0.050 g, 0.102 mmol) in mixture of THF (0.7 mL), methanol (0.7 mL) and water (0.1 mL) was added $LiOH•H_2O$ (0.017 g, 0.409 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure. The aqueous residue so obtained was acidified with aqueous citric acid. The aqueous layer was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LC/MS to afford Example 15 (16.7 mg, 0.036 mmol, 35% yield). LC-MS Anal. Calc'd. for $C_{25}H_{33}ClN_2O_4$ 460.2, found [M+H] 461.1, T_r = 2.13 min. (Method O). ^1H NMR (400 MHz, DMSO-d_6) δ 7.49 (s, 1H), 7.13 - 7.30 (m, 3H), 7.18 (m, 1H), 7.09 (m, 2H), 6.91 (m, 1H), 3.67 - 3.85 (m, 4H), 3.07 - 3.22 (m, 7H), 2.89 - 3.03 (m, 1H), 2.26 - 2.40 (m, 2H), 1.65 (m, 4H), 1.27 - 1.44 (m, 6H).

Examples 16 and 17

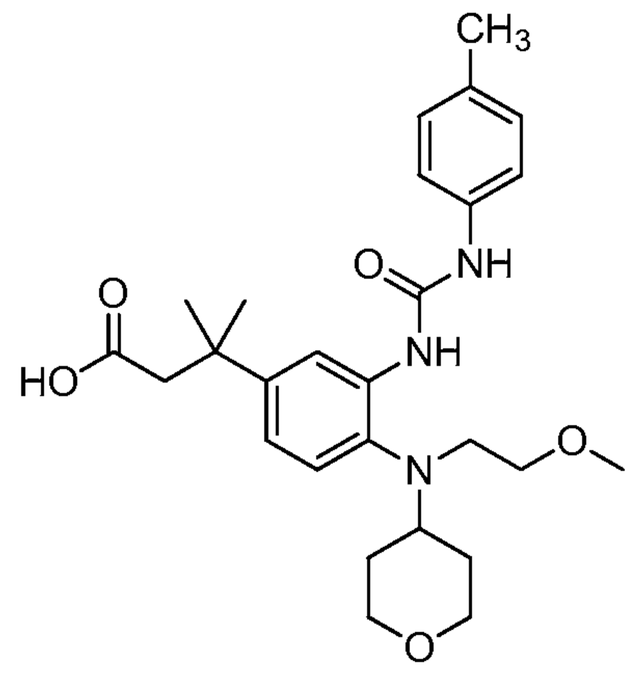


Examples 16 and 17 were prepared following the procedure for Example 15 by using the corresponding halides.

Ex. No.	Name	R	T_r (min) Method O	$[M+H]^+$
16	3-(3-((4-cyanophenyl)amino)-4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoic acid		1.766	452.1
17	3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoic acid		1.619	473.1

Example 18

3-(4-((2-Methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)-3-methylbutanoic acid



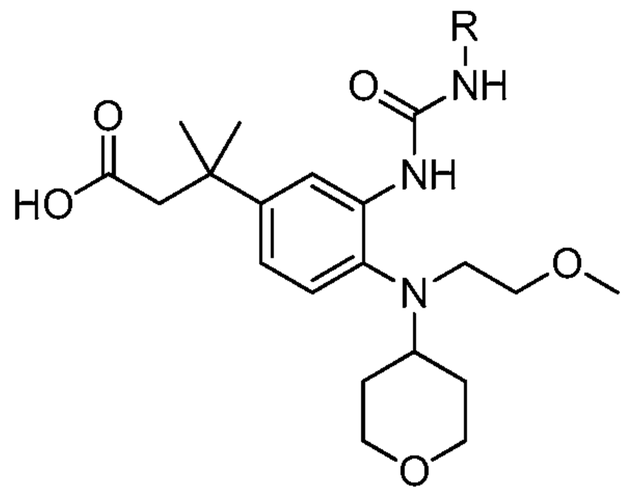
18A. Ethyl 3-(4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)-3-methylbutanoate

To a stirred solution of 15F (0.035 g, 0.092 mmol) in tetrahydrofuran (1 mL) was added 1-isocyanato-4-methylbenzene (0.015 g, 0.111 mmol). The reaction mixture was stirred at room temperature for 12 h. LCMS indicated completion of reaction. The reaction mixture was concentrated under reduced pressure to get 18A (yellow liquid, 45 mg, 0.069 mmol, 75% yield). LC-MS Anal. Calc'd. for $C_{29}H_{41}N_3O_5$ 511.3, found [M+H] 512.5, T_r = 1.53 min. (Method AY).

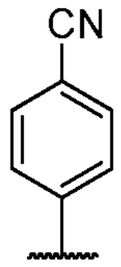
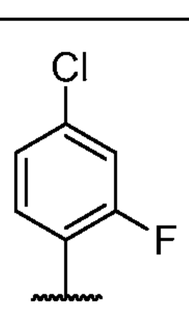
Example 18. 3-(4-((2-Methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)-3-methylbutanoic acid

Example 18 was prepared from 18A following the procedure described for the synthesis of Example 15 from 15G. LC-MS Anal. Calc'd. for $C_{27}H_{37}N_3O_5$ 483.3, found [M+H] 484.1. T_r = 1.71 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.40 (s, 1H), 8.20 - 8.31 (m, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.15 - 7.23 (m, 1H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.87 - 7.01 (m, 1H), 4.13 - 4.20 (m, 4H), 3.05 - 3.14 (m, 5H), 2.88 - 3.02 (m, 2H), 2.64 - 2.74 (m, 1H), 2.30 - 2.39 (m, 2H), 2.17 - 2.27 (m, 3H), 1.69 (m, 4H), 1.32 - 1.42 (m, 6H).

Examples 19 and 20

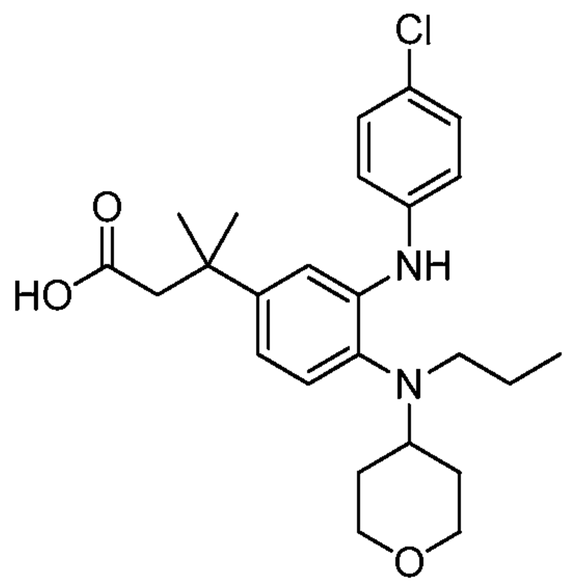


Examples 19 and 20 were prepared following the procedure for Example 18 by using the corresponding isocyanates.

Ex. No.	Name	R	T_r (min) Method O	$[M+H]^+$
19	3-(3-(3-(4-cyanophenyl)ureido)-4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoic acid		1.56	495.3
20	3-(3-(3-(4-chloro-2-fluorophenyl) ureido)-4-((2-methoxyethyl) (tetrahydro-2H-pyran-4-yl)amino) phenyl)-3-methylbutanoic acid		2.02	522.1

Example 21

3-(3-((4-Chlorophenyl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoic acid



21A. N-Propyltetrahydro-2H-pyran-4-amine

To a stirred solution of dihydro-2H-pyran-4(3H)-one (9.26 mL, 100 mmol) in tetrahydrofuran (100 mL), methanol (100 mL) under nitrogen atmosphere was added propan-1-amine (8.25 mL, 100 mmol), followed by 4 A° molecular sieves (4 g). The reaction mixture was stirred for 12 h at room temperature. To this was added $NaBH_4$ (11.34 g, 300 mmol) portionwise at 0 °C and the reaction mixture was stirred at room temperature for 3 h. Reaction mixture was quenched with water (10 mL) and concentrated under reduced pressure to get semi-solid which was quenched with 10% sodium bicarbonate (500 mL) and it was extracted with ethyl acetate (2 × 200 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to give 21A (yellow liquid, 8.4 g, 58.6 mmol, 58% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.82 - 3.27 (m, 4H), 2.49 (m, 1H), 2.56 (m, 2H), 1.73 - 1.63 (m, 4H), 1.41 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H).

21B. Methyl 3-methyl-3-(3-nitro-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) butanoate

In a sealed tube 15C (0.600 g, 2.351 mmol) in N-methyl-2-pyrrolidinone (3 mL) were added DIPEA (1.232 mL, 7.05 mmol) and 21A (0.673 g, 4.70 mmol). The reaction mixture was stirred at 135 °C for 15 h. LCMS indicated completion of reaction. Reaction mixture was cooled to room temperature, quenched with water (20 mL) and it was extracted with MTBE (2 × 30 mL). The combined organic layer was washed with brine

(20 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash chromatography gave 21B (yellow liquid, 230 mg, 0.608 mmol, 25% yield). LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_5$ 378.21, found [M+H] 379.5, T_r = 1.55 min (Method AY).

21C. Methyl 3-(3-amino-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoate

The solution of 21B (0.230 g, 0.608 mmol) in ethyl acetate (3 mL) was charged to a sealable hydrogen flask. The solution was sequentially evacuated and purged with nitrogen gas. To this 10% Pd on carbon (0.032 g, 0.030 mmol) was added under nitrogen atmosphere. The reaction mixture was stirred under hydrogen atmosphere (40 psi). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through a CELITE® pad and the residue on the pad was thoroughly rinsed with ethyl acetate (3 × 15 mL). The combined filtrate was concentrated under reduced pressure to get 21C (yellow liquid, 160 mg, 0.459 mmol, 76% yield). LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_3$ 348.2, found [M+H] 349.6, T_r = 1.52 min. (Method AY).

21D. Methyl 3-(3-((4-chlorophenyl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoate

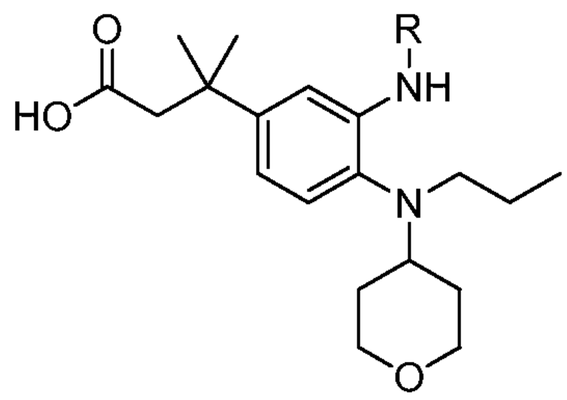
The mixture of 21C (0.050 g, 0.143 mmol), 1-bromo-4-chlorobenzene (0.033 g, 0.172 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.042 g, 0.072 mmol) and Cs_2CO_3 (0.140 g, 0.430 mmol) in 1,4-dioxane (2 mL) was stirred at room temperature. Argon gas was bubbled through the mixture for 5 min. Bis(dibenzylideneacetone)palladium (8.25 mg, 0.014 mmol) was added and argon gas was bubbled through the mixture for 5 min. The reaction mixture was sealed and placed in preheated oil bath at 110 °C for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford a residue. The residue was reconstituted in a mixture of ethyl acetate (15 mL) and water (15 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography gave 21D (yellow liquid, 60 mg,

0.131 mmol, 91% yield). LC-MS Anal. Calc'd. for $C_{26}H_{35}ClN_2O_3$ 458.2, found [M+H] 459.6, T_r = 2.20 min. (Method AY).

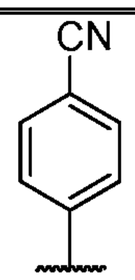
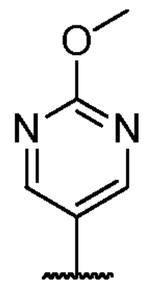
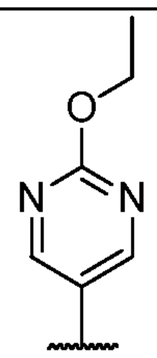
Example 21. 3-(3-((4-Chlorophenyl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)-3-methylbutanoic acid

To a stirred solution of 21D (0.060 g, 0.131 mmol) in mixture of tetrahydrofuran (1 mL), methanol (1 mL) and water (0.2 mL) was added $LiOH•H_2O$ (0.022 g, 0.523 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure. The aqueous residue so obtained was acidified with aqueous citric acid. The aqueous layer was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LCMS to afford Example 21 (14.4 mg, 0.031 mmol, 23% yield). LC-MS Anal. Calc'd. for $C_{25}H_{33}ClN_2O_3$ 444.2, found [M+H] 445.2, T_r = 2.39 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (s, 1H), 7.13 - 7.30 (m, 3H), 7.18 (m, 1H), 7.09 (m, 2H), 6.91 (m, 1H), 3.67 - 3.85 (m, 4H), 3.07 - 3.22 (m, 4H), 2.89 - 3.03 (m, 1H), 2.26 - 2.40 (m, 2H), 1.65 (m, 4H), 1.27 - 1.44 (m, 6H), 0.79 (t, *J* = 7.2 Hz, 3H).

Examples 22 to 24

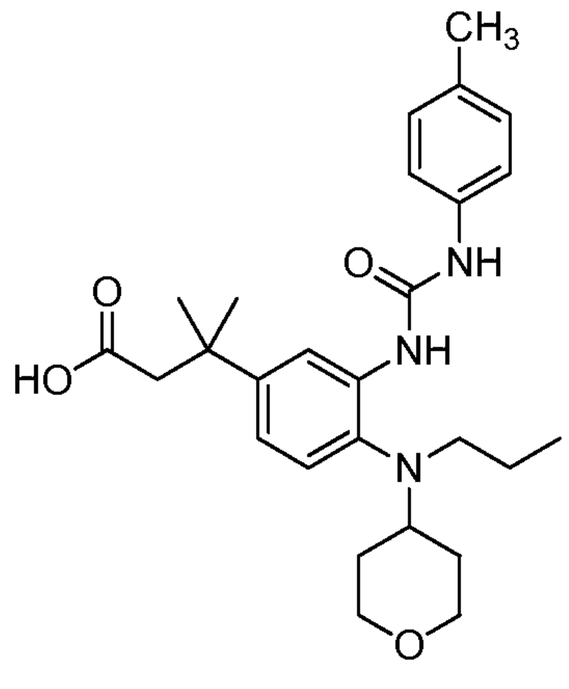


Examples 22 to 24 were prepared following the procedure for Example 21 by using the corresponding halides.

Ex. No.	Name	R	T_r (min) Method O	$[M+H]^+$
22	3-(3-((4-cyanophenyl)amino)-4-(propyl (tetrahydro-2H-pyran-4-yl)amino) phenyl)-3-methylbutanoic acid		2.036	436.2
23	3-(3-((2-methoxypyrimidin-5-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoic acid		1.766	443.3
24	3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoic acid		1.879	457.3

Example 25

3-Methyl-3-(4-(propyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido) phenyl)butanoic acid



25A. Ethyl 3-(4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)-3-methylbutanoate

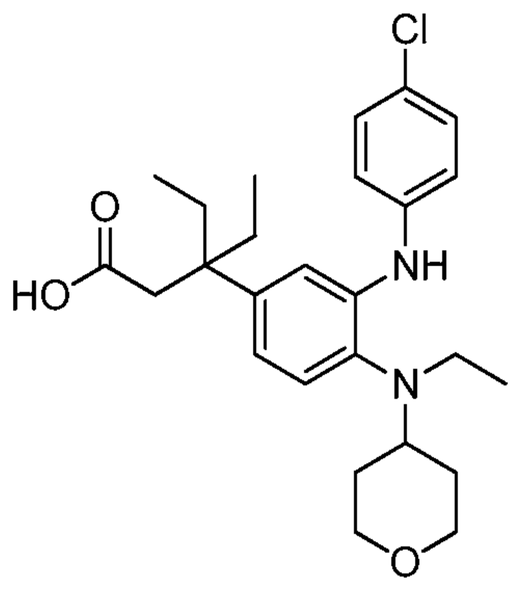
Compound 25A was prepared from 15F and 1-isocyanato-4-methylbenzene following the procedure described for the synthesis of 18A. LC-MS Anal. Calc'd. for $C_{29}H_{41}N_3O_5$ 511.3, found [M+H] 512.5, T_r = 1.53 min. (Method AY).

Example 25. 3-Methyl-3-(4-(propyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)butanoic acid

Example 25 was prepared from 25A following the procedure described for the synthesis of Example 15 from 15G. LC-MS Anal. Calc'd. for $C_{27}H_{37}N_3O_4$ 467.26, found [M+H] 468.3, T_r = 1.91 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.33 - 9.43 (m, 1H), 8.38 (s, 1H), 8.28 (m, 1H), 7.37 (m, 2H), 7.06 - 7.18 (m, 3H), 6.90 - 7.00 (m, 1H), 3.84 (m, 2H), 3.13 - 3.20 (m, 2H), 2.63 - 2.71 (m, 3H), 2.29 - 2.37 (m, 4H), 2.24 (s, 3H), 1.98 - 2.11 (m, 2H), 1.34 - 1.41 (m, 6H), 1.18 - 1.26 (m, 2H), 0.72 - 0.83 (t, *J*= 7.2 Hz, 3H).

Example 26

3-(3-((4-Chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-ethylpentanoic acid



26A. Diethyl 2-(pentan-3-ylidene)malonate

To a stirred solution of diethyl malonate (15.24 mL, 100 mmol), pentan-3-one (10.62 mL, 100 mmol) and pyridine (11.31 mL, 140 mmol) in tetrahydrofuran (480 mL) at 0 °C was added titanium tetrachloride (1M in DCM) (140 mL, 140 mmol) in dropwise (10 min) manner. The reaction mixture was allowed to rise to room temperature and stirred at room temperature for 24 h. Reaction mixture was quenched with water (150 mL). The mixture was extracted with diethyl ether (150 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (150 mL). The organic layers were combined, dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash silica gel column chromatography

gave 26A (yellow liquid, 5.8 g, 25.4 mmol, 25% yield). LC-MS Anal. Calc'd. for $C_{12}H_{20}O_4$ 228.1, found [M+H] 229.3, T_r = 1.43 min. (Method AY).

26B. Diethyl 2-(3-(4-fluorophenyl)pentan-3-yl)malonate

To a stirred solution of (4-fluorophenyl)magnesium bromide (89 mL, 89 mmol) in dry diethyl ether (76 mL), cooled to -10 °C, was added copper(I) chloride (2.2 g, 22.22 mmol). Then 26A (7.61 g, 33.3 mmol) in diethyl ether (7.6 mL) was added dropwise for 5 minutes. Reaction mixture was stirred for 20 minutes at room temperature and then refluxed for 12 h. LCMS indicated completion of reaction. Reaction mixture was cooled to 0 °C, quenched with ice cold 1 N HCl. Aqueous layer was extracted with ether (2 × 100 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash silica gel column chromatography gave 26B (yellow liquid, 7.5 g, 21.73 mmol, 98% yield). LC-MS Anal. Calc'd. for $C_{18}H_{25}FO_4$ 324.2, found [M+H] 325.3, T_r = 1.65 min. (Method AY).

26C. Ethyl 3-ethyl-3-(4-fluorophenyl)pentanoate

To a stirred solution of 26B (7.5 g, 23.12 mmol) in DMSO (75 mL), water (3.75 mL), was added lithium chloride (1.960 g, 46.2 mmol). The reaction mixture was heated at 180 °C for 12 h. TLC indicated completion of reaction. Reaction mixture was cooled to 0 °C and it was quenched with water (60 mL). It was extracted with ethyl acetate (2 × 60 mL). The combined organic layer was washed with brine (40 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash silica gel column chromatography gave 26C (yellow liquid, 4.7 g, 16.02 mmol, 69% yield). LC-MS Anal. Calc'd. for $C_{15}H_{21}FO_2$ 252.1, found [M+H] 253.3, T_r = 1.64 min. (Method AY).

26D. Ethyl 3-ethyl-3-(4-fluoro-3-nitrophenyl)pentanoate

To a stirred solution of 26C (4.7 g, 18.63 mmol) in H_2SO_4 (47 mL) at 0 °C was added potassium nitrate (1.883 g, 18.63 mmol). The reaction mixture was stirred at 0 °C for 15 min. TLC indicated completion of reaction. Reaction mixture was poured into ice and it was extracted with ethyl acetate (2 × 50 mL). The combined organic layer was

washed with brine (20 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash silica gel column chromatography gave 26D (yellow liquid, 2 g, 6.73 mmol, 36% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.64 (m, 1H), 7.29 (m, 1H), 4.05 (q, J = 7.2 Hz, 2H), 2.74 (s, 2H), 1.89 - 1.94 (m, 4H), 1.17 (t, J = 7.2 Hz, 3H), 0.82 (m, 6H).

26E. N-Ethyltetrahydro-2H-pyran-4-amine

Compound 26E was prepared from dihydro-2H-pyran-4(3H)-one and ethanamine following the procedure described for the synthesis of 15D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (m, 2H), 3.41 (m, 2H), 2.67 (m, 1H), 2.63 (m, 2H), 1.89 - 1.77 (m, 4H), 1.09 (t, J = 7.2 Hz, 3H).

26F. Ethyl 3-ethyl-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl) pentanoate

In a sealed tube 26D (2 g, 6.73 mmol) in N-methyl-2-pyrrolidinone (10 mL) were added DIPEA (3.52 mL, 20.18 mmol) and 26E (1.738 g, 13.45 mmol). The reaction mixture was stirred at 135 °C for 15 h. TLC indicated completion of reaction. Reaction mixture was cooled to room temperature, quenched with water (20 mL) and it was extracted with MTBE (3 × 30 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash silica gel column chromatography gave compound 26F (gummy liquid, 1.2 g, 2.83 mmol, 42% yield). LC-MS Anal. Calc'd. for $C_{22}H_{34}N_2O_5$ 406.2, found [M+H] 407.2, T_r = 1.64 min. (Method AY).

26G. Ethyl 3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-ethylpentanoate

The solution of 26F (1.2 g, 2.95 mmol) in ethyl acetate (12 mL) was charged to a sealable hydrogen flask. The solution was sequentially evacuated and purged with nitrogen gas. To this 10% Pd on carbon (0.157 g, 0.148 mmol) was added under nitrogen atmosphere. The reaction mixture was stirred under hydrogen atmosphere (40 psi). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through a CELITE® pad and the residue on the pad was thoroughly rinsed with

ethyl acetate (3 × 15 mL). The combined filtrate was concentrated under reduced pressure to get crude compound. Purification via flash chromatography gave 26G (yellow liquid, 900 mg, 2.271 mmol, 77% yield). LC-MS Anal. Calc'd. for $C_{22}H_{36}N_2O_3$ 376.3, found [M+H] 377.3, T_r = 1.65 min. (Method AY).

26H. Ethyl 3-(3-((4-chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)-3-ethylpentanoate

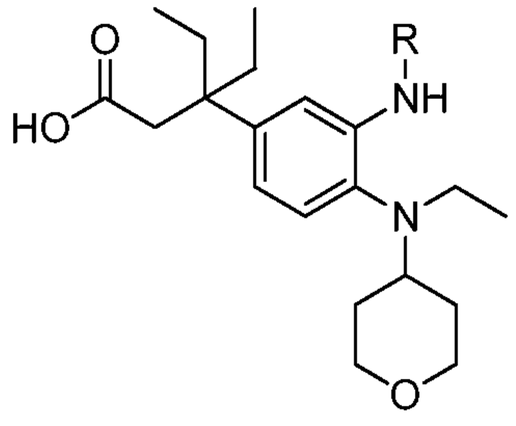
The mixture of 26G (0.050 g, 0.133 mmol), 1-bromo-4-chlorobenzene (0.031 g, 0.159 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (7.68 mg, 0.013 mmol) and Cs_2CO_3 (0.065 g, 0.199 mmol) in 1,4-dioxane (1.5 mL) was stirred. Argon gas was bubbled through the mixture for 5 min. Bis(dibenzylideneacetone)palladium (3.82 mg, 6.64 µmol) was added and argon gas was bubbled through the mixture for 5 min. The reaction mixture was sealed and placed in preheated oil bath at 110 °C for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford a residue. The residue was reconstituted in a mixture of ethyl acetate (15 mL) and water (15 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography gave 26H (gummy liquid, 50 mg, 0.050 mmol, 37% yield). LC-MS Anal. Calc'd. for $C_{28}H_{39}ClN_2O_3$ 486.3, found [M+H] 487.5, T_r = 2.31 min. (Method AY).

Example 26. 3-(3-((4-Chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)-3-ethylpentanoic acid

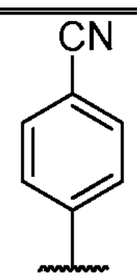
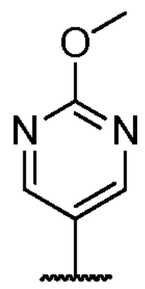
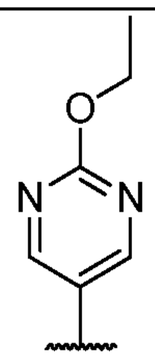
To a stirred solution of 26H (0.050 g, 0.103 mmol) in mixture of THF (1 mL), methanol (1 mL) and water (0.1 mL) was added $LiOH•H_2O$ (0.017 g, 0.411 mmol). The reaction mixture was stirred at 50 °C for 12 h. The reaction mixture was concentrated under reduced pressure. The aqueous residue so obtained was acidified with aqueous citric acid. The aqueous layer was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LCMS gave Example 26 (13.7

mg, 0.030 mmol, 28% yield). LC-MS Anal. Calc'd. for $C_{26}H_{35}ClN_2O_3$ 458.2, found [M+H] 459.1, T_r = 2.67 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36 (s, 1H), 7.20 - 7.29 (m, 2H), 7.06 - 7.17 (m, 4H), 6.85 (m, 1H), 3.79 (m, 2H), 3.11 - 3.23 (m, 2H), 2.91 - 3.04 (m, 3H), 2.56 (s, 2H), 1.69 - 1.81 (m, 4H), 1.64 (m, 2H), 1.41 (m, 2H), 0.80 (t, *J* = 7.2 Hz, 3H), 0.66 (m, 6H).

Examples 27 to 29

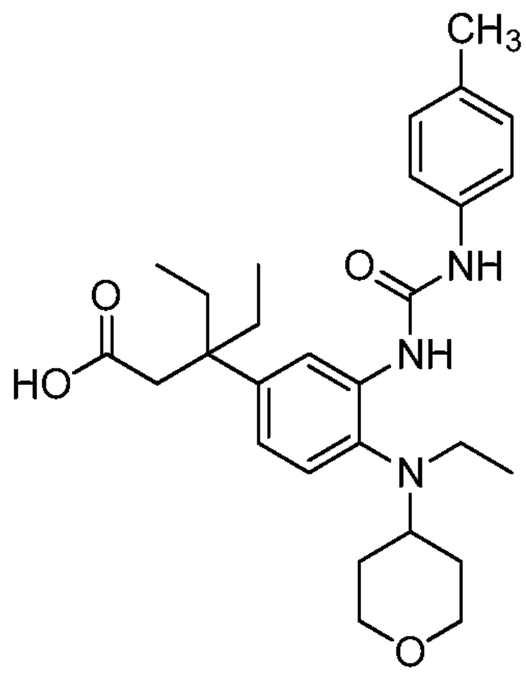


Examples 27 to 29 were prepared following the procedure for Example 26 by using the corresponding halides.

Ex. No.	Name	R	T_r (min) Method O	$[M+H]^+$
27	3-(3-((4-cyanophenyl)amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino) phenyl)-3-ethylpentanoic acid		2.267	450.1
28	3-ethyl-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methoxypyrimidin-5-yl)amino)phenyl) pentanoic acid		1.989	457.1
29	3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-ethylpentanoic acid		2.149	471.1

Example 30

3-Ethyl-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido) phenyl)pentanoic acid



30A. Ethyl 3-ethyl-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido) phenyl)pentanoate

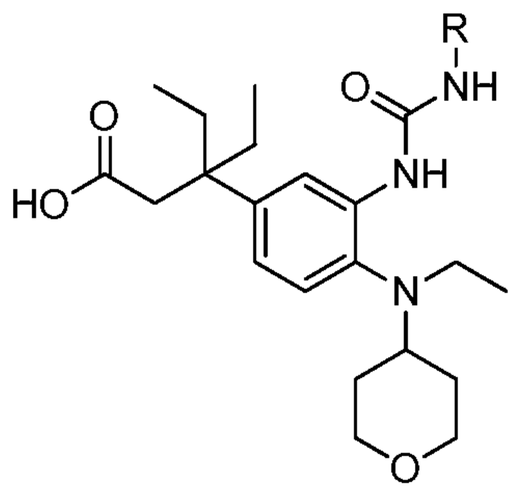
To a stirred solution of 26G (0.035 g, 0.093 mmol) in tetrahydrofuran (1 mL) was added 1-isocyanato-4-methylbenzene (0.015 g, 0.112 mmol). The reaction mixture was stirred at room temperature for 12 h. LCMS indicated completion of reaction. The reaction mixture was concentrated under reduced pressure to get 30A (gummy liquid, 45 mg, 0.071 mmol, 76% yield). LC-MS Anal. Calc'd. for $C_{30}H_{43}N_3O_4$ 509.32, found [M+H] 510.4. T_r = 1.74 min. (Method AY).

Example 30. 3-Ethyl-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido) phenyl)pentanoic acid

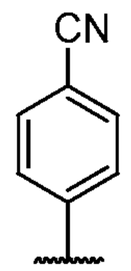
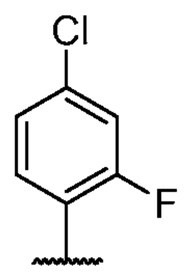
To a stirred solution of 30A (0.045 g, 0.088 mmol) in mixture of tetrahydrofuran (1 mL), methanol (1 mL) and water (0.1 mL), was added $LiOH•H_2O$ (0.015 g, 0.353 mmol). The reaction mixture was stirred at 50 °C for 12 h. The reaction mixture was concentrated under reduced pressure. The aqueous residue so obtained was acidified with aqueous citric acid. The aqueous layer was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LC/MS to afford Example 30 (25 mg, 0.051 mmol, 58% yield). LC-MS Anal. Calc'd. for $C_{28}H_{39}N_3O_4$ 481.2, found

[M+H] 482.2, T_r = 2.21 min. (Method R). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.43 (s, 1H), 8.45 - 8.56 (m, 1H), 8.15 - 8.30 (m, 1H), 7.31 - 7.45 (m, 2H), 7.16 (d, *J* = 8.2 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.79 - 6.93 (m, 1H), 3.83 (m, 2H), 3.13 - 3.31 (m, 2H), 2.87 - 3.05 (m, 3H), 2.59 (s, 2H), 2.25 (s, 3H), 1.63 - 1.86 (m, 6H), 1.39 (m, 2H), 0.79 (t, *J* = 7.2 Hz, 3H), 0.64 (m, 6H).

Examples 31 and 32



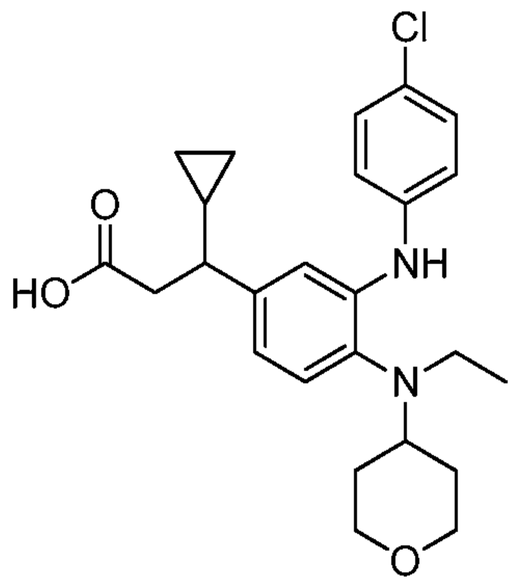
Examples 31 and 32 were prepared following the procedure for Example 30 by using the corresponding isocyanates.

Ex. No.	Name	R	T_r (min) Method O	$[M+H]^+$
31	3-(3-(3-(4-cyanophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-ethylpentanoic acid		2.04	493.1
32	3-(3-(3-(4-chloro-2-fluorophenyl) ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-ethylpentanoic acid		2.04	520.3

Example 33

(Enantiomer 1 and Enantiomer 2)

3-(3-((4-Chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-cyclopropylpropanoic acid



33A. N-(4-Bromo-2-nitrophenyl)-N-ethyltetrahydro-2H-pyran-4-amine

In a sealed tube containing 4-bromo-1-fluoro-2-nitrobenzene (5.6 g, 25.5 mmol) was added 26E. The reaction mixture was heated at 135 °C for 12 h. LCMS indicated completion of reaction. Purification via flash chromatography gave 33A (yellow liquid, 7.3 g, 21.73 mmol, 85% yield). LC-MS Anal. Calc'd. for $C_{13}H_{17}BrN_2O_3$ 328.0, found [M+2] 330.2, T_r = 3.10 min. (Method U).

33B. N-Ethyl-N-(2-nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) tetrahydro-2H-pyran-4-amine

To a stirred solution of 33A (2.6 g, 7.90 mmol), bis(pinacolato)diboron (3.01 g, 11.85 mmol) and potassium acetate (2.325 g, 23.69 mmol) in 1,4-dioxane (26 mL) was purged with argon for 10 min. To this $PdCl_2$ (dppf)•CH_2Cl_2 Adduct (0.322 g, 0.395 mmol) was added and purged with argon for 5 min. The reaction mixture was heated at 90 °C for 5 h. LCMS indicated completion of reaction. Reaction mixture was cooled to room temperature and quenched with water (30 mL). Aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash chromatography gave 33B (yellow solid, 2.8 g, 7.44 mmol, 91% yield). LC-MS Anal. Calc'd. for $C_{19}H_{29}BN_2O_5$ 376.2, found [M+H] 377.4, T_r = 3.63 min. (Method U).

33C. (E)-Methyl 3-cyclopropylacrylate

To a stirred suspension of lithium chloride (18.15 g, 428 mmol) in acetonitrile (80 mL) under nitrogen atmosphere was added trimethyl phosphonoacetate (55.4 mL, 342

mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (86 mL, 571 mmol) and followed by cyclopropanecarbaldehyde (21.32 mL, 285 mmol) at 0 °C. The reaction mixture was stirred for 12 h at room temperature. TLC indicated completion of reaction. Reaction mixture was quenched with water (300 mL) and it was extracted with ethyl acetate (300 mL). Aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layer was washed with 1N HCl (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash chromatography gave 33C (yellow liquid, 11 g, 87 mmol, 30% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 (m, 1H), 5.87 (m, 1H), 3.72 (s, 3H), 1.68 (m, 1H), 0.98 (m, 2H), 0.66 (m, 2H).

33D. Methyl 3-cyclopropyl-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl) propanoate

In a sealed tube, the suspension of 33B, 33C and sodium hydroxide (8.98 mL, 8.98 mmol) in 1,4-dioxane (37 mL) was purged with argon for 10 min. To this chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.242 g, 0.492 mmol) was added and purged with argon for 5 min. The reaction mixture was heated at 50 °C for 6 h. LCMS indicated completion of reaction. Reaction mixture was cooled to room temperature and quenched with acetic acid (0.563 mL) and it was stirred for 5 minutes before it was partitioned between ethyl acetate (40 mL) and water (20 mL). Aqueous layer was extracted with ethyl acetate (30 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash chromatography gave 33D (yellow solid, 2.1 g, 5.24 mmol, 53% yield). LC-MS Anal. Calc'd. for $C_{20}H_{28}N_2O_5$ 376.2, found [M+H] 377.4, T_r = 1.53 min. (Method AY).

33E. Methyl 3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-cyclopropylpropanoate

The solution of 33D (2.1 g, 5.58 mmol) in ethyl acetate (21 mL) was charged to a sealable hydrogen flask. The solution was sequentially evacuated and purged with nitrogen gas. To this 10% Pd on carbon (0.297 g, 0.279 mmol) was added under nitrogen atmosphere. The reaction mixture was stirred under hydrogen atmosphere (40 psi). The

reaction mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through a CELITE® pad and the residue on the pad was thoroughly rinsed with ethyl acetate (3 × 15 mL). The combined filtrate was concentrated under reduced pressure to get crude compound Racemate 33E (yellow solid, 1.5 g). LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_3$ 346.2, found [M+H] 347.2, T_r = 1.46 min. (Method AY).

Chiral separation of Racemate 33E (Method BK) gave Enantiomer 1 and Enantiomer 2 as single enantiomers. Enantiomer 1 T_r = 2.89 min (Method BK) and Enantiomer 2 T_r = 3.61 min (Method BK).

33E Enantiomer 1 (yellow liquid, 390 mg, 1.126 mmol, 20% yield): LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_3$ 346.2, found [M+H] 347.2, T_r = 2.17 min (Method BB).

33E Enantiomer 2 (yellow liquid, 440 mg, 1.245 mmol, 22% yield): LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_3$ 346.2, found [M+H] 347.2, T_r = 2.17 min (Method BB).

33F. Methyl 3-(3-((4-chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)-3-cyclopropylpropanoate

The mixture of 33E Enantiomer 1 (0.050 g, 0.144 mmol), 1-bromo-4-chlorobenzene (0.033 g, 0.173 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.042 g, 0.072 mmol) and Cs_2CO_3 (0.141 g, 0.433 mmol) in 1,4-dioxane (2 mL) was stirred at room temperature. Argon gas was bubbled through the mixture for 5 min. Bis(dibenzylideneacetone)palladium (8.30 mg, 0.014 mmol) was added and argon gas was bubbled through the mixture for 5 min. The reaction mixture was sealed and placed in preheated oil bath at 110 °C for 5 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford a residue. The residue was reconstituted in a mixture of ethyl acetate (15 mL) and water (15 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography to afford 33F (yellow liquid, 50 mg, 0.048 mmol, 33% yield). LC-MS Anal. Calc'd. for $C_{26}H_{33}ClN_2O_3$ 456.2, found [M+H] 457.4, T_r = 1.31 min. (Method AY).

Example 33 Enantiomer 1. 3-(3-((4-Chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-cyclopropylpropanoic acid

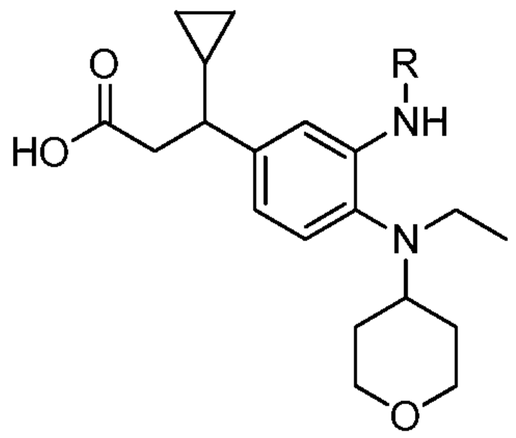
To a stirred solution of 33F (0.050 g, 0.109 mmol) in mixture of tetrahydrofuran (1 mL), methanol (1 mL) and water (0.2 mL) was added $LiOH•H_2O$ (0.018 g, 0.438 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure. The aqueous residue so obtained was acidified with aqueous citric acid The aqueous layer was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LCMS to afford Example 33 Enantiomer 1 (20.4 mg, 0.046 mmol, 41% yield). LC-MS Anal. Calc'd. for $C_{25}H_{31}ClN_2O_3$ 442.2, found [M+H] 443.2, T_r = 2.15 min. (Method O). ^1H NMR (400 MHz, DMSO-d_6) δ 7.40 (m, 1H), 7.04 - 7.20 (m, 2H), 7.08 - 7.18 (m, 4H), 6.95 (m, 1H), 3.79 (m, 2H), 3.10 - 3.22 (m, 2H), 2.98 (m, 3H), 2.57 - 2.72 (m, 2H), 2.33 (m, 1H), 1.63 (m, 2H), 1.43 (m, 2H), 0.94 - 1.08 (m, 1H), 0.83 (t, *J* = 7.2 Hz, 3H), 0.44 - 0.58 (m, 1H), 0.31 - 0.40 (m, 1H), 0.19 - 0.28 (m, 1H), 0.06 - 0.18 (m, 1H).

Example 33 Enantiomer 2. 3-(3-((4-Chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-cyclopropylpropanoic acid

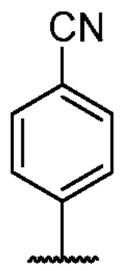
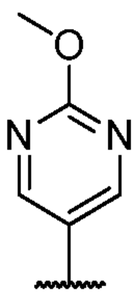
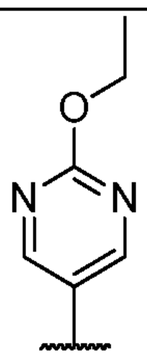
Example 33 Enantiomer 2 was prepared following the same procedure for Example 33 Enantiomer 1 by utilizing compound 33E Enantiomer 2. LC-MS Anal. Calc'd. for $C_{25}H_{31}ClN_2O_3$ 442.2, found [M+H] 443.1, T_r = 2.15 min. (Method O). ^1H NMR (400 MHz, DMSO-d_6) δ 7.35 - 7.43 (m, 1H), 7.22 - 7.28 (m, 2H), 7.08 - 7.18 (m, 4H), 6.71 - 6.87 (m, 1H), 3.79 (m, 2H), 3.10 - 3.22 (m, 2H), 2.91 - 3.05 (m, 3H), 2.56 - 2.70 (m, 2H), 2.17 - 2.26 (m, 1H), 1.65 (m, 2H), 1.32 - 1.47 (m, 2H), 0.95 - 1.06 (m, 1H), 0.83 (t, *J*=7.2 Hz, 3H), 0.45 - 0.55 (m, 1H), 0.30 - 0.40 (m, 1H), 0.22 (m, 1H), 0.06 - 0.18 (m, 1H).

Examples 34 to 36

(Enantiomer 1)

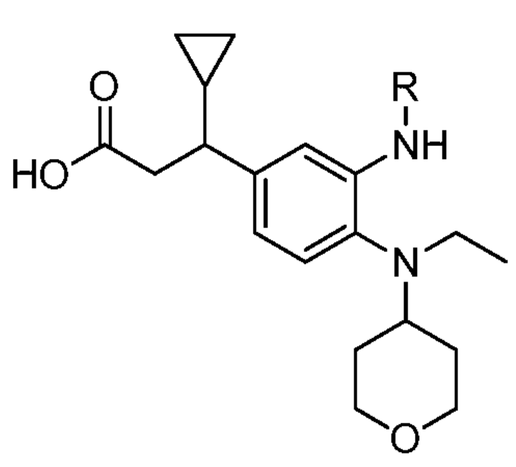


Examples 34 to 36 was prepared from 33E Enantiomer 1 and corresponding halides following the procedure described for the synthesis of Example 33 Enantiomer 1 (absolute stereochemistry unknown).

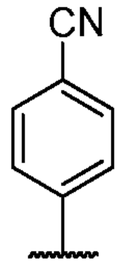
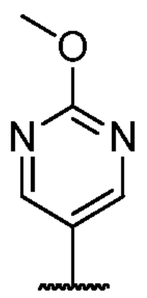
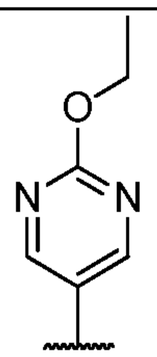
Ex. No.	Name	R	T_r (min)	$[M+H]^+$
34	3-(3-((4-cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-cyclopropylpropanoic acid		1.62 (Method O)	434.3
35	3-cyclopropyl-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methoxypyrimidin-5-yl)amino) phenyl)propanoic acid		1.34 (Method O)	441.3
36	3-cyclopropyl-3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)propanoic acid		1.15 (Method R)	455.3

Examples 37 to 39

(Enantiomer 2)



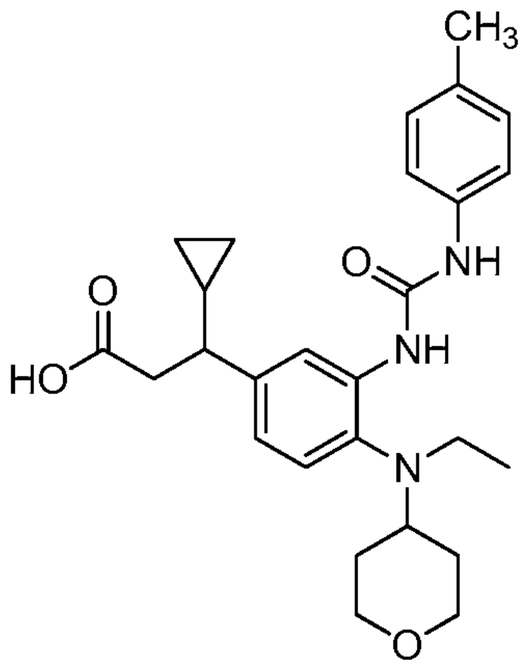
Examples 37 to 39 was prepared from 33E Enantiomer 2 and corresponding halides following the procedure described for the synthesis of Example 33 Enantiomer 1.

Ex. No.	Name	R	T_r (min)	$[M+H]^+$
37	3-(3-((4-cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-cyclopropylpropanoic acid		1.81 (Method O)	434.2
38	3-cyclopropyl-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methoxypyrimidin-5-yl)amino)phenyl) propanoic acid		1.55 (Method O)	441.2
39	3-cyclopropyl-3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)propanoic acid		1.15 (Method R)	455.4

Example 40

(Enantiomer 1 and Enantiomer 2)

3-Cyclopropyl-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)propanoic acid



40A. Methyl 3-cyclopropyl-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)propanoate

To a stirred solution of 33E Enantiomer 1 (0.035 g, 0.101 mmol) in tetrahydrofuran (1.5 mL) was added 1-isocyanato-4-methylbenzene (0.032 g, 0.242 mmol). The reaction mixture was stirred at room temperature for 12 h. LCMS indicated completion of reaction. The reaction mixture was concentrated under reduced pressure to get 40A (yellow liquid, 45 mg, 0.057 mmol, 56% yield). LC-MS Anal. Calc'd. for $C_{28}H_{37}N_3O_4$ 479.3, found [M+H] 480.4, T_r = 1.12 min. (Method AY).

Example 40 Enantiomer 1. 3-Cyclopropyl-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)propanoic acid

To a stirred solution of compound 40A (0.045 g, 0.094 mmol) in mixture of tetrahydrofuran (1.5 mL), methanol (1.5 mL) and water (0.5 mL) was added $LiOH•H_2O$ (0.016 g, 0.375 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure. The aqueous residue so obtained was acidified with aqueous citric acid. The aqueous layer was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LCMS to afford Example 40 Enantiomer 1 (22.5 mg, 0.047 mmol, 50% yield). LC-MS Anal. Calc'd. for $C_{27}H_{35}N_3O_4$ 465.2, found [M+H] 466.4, T_r = 1.54 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.63 - 9.73 (m, 1H), 8.67 - 8.80 (m, 1H), 8.34 - 8.42 (m, 1H), 7.58 - 7.68 (m, 2H), 7.30 - 7.43 (m, 3H), 6.85 (m, 1H), 4.08 (m, 2H), 3.39 - 3.55 (m, 2H), 3.24 (q, *J* = 6.4 Hz, 2H), 2.80 - 2.95 (m, 3H), 2.44 - 2.57 (m, 4H), 1.61 - 1.73 (m, 2H), 1.20 - 1.31 (m, 2H) 1.06 (t, *J* = 7.2 Hz, 1H), 0.82 (t, *J* = 7.2 Hz, 3H), 0.76 (t, *J* = 7.2 Hz, 1H), 0.55 - 0.68 (m, 1H), 0.49 (m, 1H), 0.38 (m, 1H).

Example 40 Enantiomer 2. 3-Cyclopropyl-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)propanoic acid

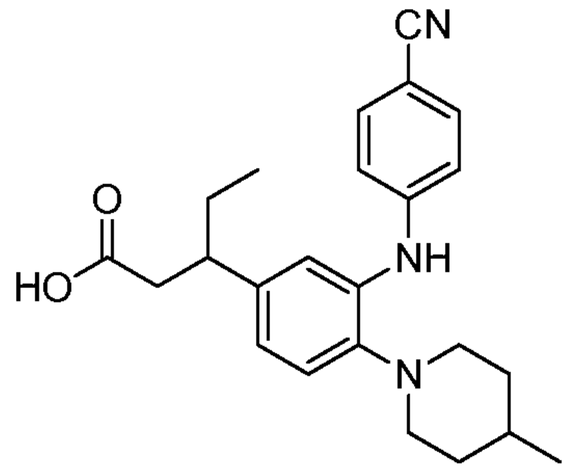
Example 40 Enantiomer 2 was prepared from 33E Enantiomer 2 following the procedure described for the synthesis of Example 40 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{27}H_{35}N_3O_4$ 465.2, found [M+H] 466.3, T_r = 1.75 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (s, 1H), 8.47 (s, 1H), 8.13 (m, 1H), 7.37 (m, 2H), 7.04 - 7.18 (m, 3H), 6.84 (m, 1H), 3.76 - 3.91 (m, 2H), 3.39 - 3.55 (m, 2H), 3.24 (q, *J* = 6.4 Hz, 2H),

2.89 - 3.03 (m, 3H), 2.63 - 2.74 (m, 4H), 1.64 - 1.77 (m, 2H), 1.33 - 1.45 (m, 2H), 0.92 - 1.02 (m, 1H), 0.73 - 0.85 (t, J = 7.2 Hz, 3H), 0.43 - 0.56 (m, 2H), 0.29 - 0.38 (m, 2H).

Example 41

(Enantiomer 1 and Enantiomer 2)

3-(3-((4-Cyanophenyl)amino)-4-(4-methylpiperidin-1-yl)phenyl)pentanoic acid



41A. 2-(4-Fluoro-3-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

To a stirred solution of 4-bromo-1-fluoro-2-nitrobenzene (10 g, 45.5 mmol), 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi(1,3,2-dioxaborolane) (16.16 g, 63.6 mmol), potassium acetate (13.38 g, 136 mmol) in dioxane (100 mL). The reaction mixture was purged with argon for 5 min. After 5 min, $PdCl_2$ (dppf)•CH_2Cl_2 Adduct (3.71 g, 4.55 mmol) was added to the reaction mixture under argon and heated to 108 °C for 12 h. The reaction mixture was allowed to cool to rt, filtered through CELITE® pad, washed with ethyl acetate (100 mL). The organic layer was washed with water (50 mL) and the aqueous layer was separated and re-extracted with ethyl acetate (2 × 100 mL). Combined the organic extracts were washed with brine, dried over sodium sulfate and solvent was removed under reduced pressure to give the crude product as a brown colored oil. The oily compound was purified by silica gel column chromatography eluting with pet ether / ethyl acetate to afford 41A (light yellow solid, 10.4 g, 38.9 mmol, 86% yield). LC-MS Anal. Calc'd. for $C_{12}H_{15}BFNO_4$ 267.108, found [M+NH_4] 285.2, T_r =1.07 (Method AY).

41B. Methyl 3-(4-fluoro-3-nitrophenyl)pentanoate

To a stirred solution of 41A (5 g, 18.72 mmol) in dioxane (80 mL), to this (E)-methyl pent-2-enoate (5.34 g, 46.8 mmol) was added followed by NaOH (1M) (16.85 mL, 16.85 mmol). The reaction mixture was purged with argon for 15 mins. To the above reaction mixture was charged with chloro(1,5-cyclooctadiene)rhodium(I) dimer

(0.462 g, 0.936 mmol) and the argon purge cycle was repeated. The reaction suspension was stirred at 50 °C for 6 h. The reaction mixture was allowed to cool to room temperature and quenched with AcOH (0.965 mL, 16.85 mmol) and it was stirred for 5 minutes before it was partitioned between ethyl acetate (100 mL) and water (80 mL). The aqueous layer was re-extracted with ethyl acetate (2 × 100 mL). Combined organic extracts was washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford a residue. The residue was purified by silica gel column chromatography using pet ether / ethyl acetate to afford 41B (brown oil, 4.0 g, 15.74 mmol,84% yield). LC-MS Anal. Calc'd. for $C_{12}H_{14}FNO_4$ 255.09, found $[M+NH_4]$ 273.0, T_r = 2.751 (Method U).

41C. Methyl 3-(4-(4-methylpiperidin-1-yl)-3-nitrophenyl)pentanoate

In a sealed tube 41B (1.5 g, 5.88 mmol) in N-methyl-2-pyrrolidinone (15 mL) were added DIPEA (3.08 mL, 17.63 mmol) and 4-methylpiperidine (1.166 g, 11.75 mmol). The reaction mixture was stirred at 135 °C for 12 h. TLC indicated completion of reaction. Reaction mixture was cooled to room temperature, quenched with water (20 mL) and it was extracted with MTBE (3 × 30 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash chromatography gave 41C (yellow liquid, 1.8 g, 5.38 mmol, 86% yield). LC-MS Anal. Calc'd. for $C_{18}H_{26}N_2O_4$ 334.2, found [M+2] 336.6, T_r = 1.69 min. (Method AY).

41D. Methyl 3-(3-amino-4-(4-methylpiperidin-1-yl)phenyl)pentanoate

The solution of 41C (1.8 g, 5.38 mmol) in ethyl acetate (18 mL) was charged to a sealable hydrogen flask. The solution was sequentially evacuated and purged with nitrogen gas. To this 10% Pd on carbon (0.286 g, 0.269 mmol) was added under nitrogen atmosphere. The reaction mixture was stirred under hydrogen atmosphere (40 psi). The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was filtered through a CELITE® pad and the residue on the pad was thoroughly rinsed with ethyl acetate (3 × 15 mL). The combined filtrate was concentrated under reduced pressure to get crude compound 41D (yellow solid, 1.2 g). LC-MS Anal. Calc'd. for $C_{18}H_{28}N_2O_2$ 3 304.2, found [M+H] 305.2, T_r = 1.67 min. (Method AY).

Chiral separation of Racemate 41D (Method BU) gave Enantiomer 1 and Enantiomer 2 as single enantiomers. 41D Enantiomer 1, T_r = 4.25 min (Method BU) and 41D Enantiomer 2, T_r = 5.4 min (Method BU).

41D Enantiomer 1 (yellow liquid, 350 mg, 1.138 mmol, 21% yield): LC-MS Anal. Calc'd. for $C_{18}H_{28}N_2O_2$ 304.2, found [M+H] 305.2. T_r = 3.54 min (Method BE).

41D Enantiomer 2 (yellow liquid, 350 mg, 1.138 mmol, 21% yield): LC-MS Anal. Calc'd. for $C_{18}H_{28}N_2O_2$ 304.2, found [M+H] 305.2. T_r = 3.53 min (Method BE).

41E. Methyl 3-(3-((4-cyanophenyl)amino)-4-(4-methylpiperidin-1-yl)phenyl)pentanoate

The mixture of 41D Enantiomer 1 (0.050 g, 0.164 mmol), 4-bromobenzonitrile (0.036 g, 0.197 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (9.50 mg, 0.016 mmol) and Cs_2CO_3 (0.080 g, 0.246 mmol) in 1,4-dioxane (1.5 mL) was stirred. Argon gas was bubbled through the mixture for 5 min. Bis(dibenzylideneacetone) palladium (4.72 mg, 8.21 μmol) was added and argon gas was bubbled through the mixture for 5 min. The reaction mixture was sealed and placed in preheated oil bath at 110 °C for 4 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford a residue. The residue was reconstituted in a mixture of ethyl acetate (15 mL) and water (15 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography (conditions: 50% ethyl acetate in pet ether) to afford 41E (yellow liquid, 50 mg, 0.112 mmol, 68% yield). LC-MS Anal. Calc'd. for $C_{25}H_{31}N_3O_2$ 405.2, found [M+H] 406.5, T_r = 1.85 min. (Method AY).

Example 41 Enantiomer 1. 3-(3-((4-Cyanophenyl)amino)-4-(4-methylpiperidin-1-yl)phenyl)pentanoic acid

To a stirred solution of 41E in mixture of tetrahydrofuran (1 mL), methanol (1 mL) and water (0.1 mL) was added $LiOH•H_2O$ (0.021 g, 0.493 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure. The aqueous residue so obtained was acidified with aqueous citric acid. The aqueous layer was diluted with water (10 mL) and extracted with ethyl

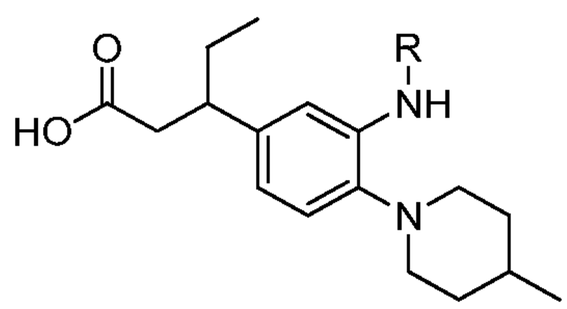
acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LC/MS to afford Example 41 Enantiomer 1 (16.7 mg, 0.036 mmol, 35% yield). LC-MS Anal. Calc'd. for $C_{24}H_{29}N_3O_2$ 391.2, found [M+H] 392.3. T_r = 1.97 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 - 8.06 (s, 1H), 7.47 - 7.58 (m, 2H), 6.98 (m, 5H), 3.17 (s, 1H), 3.04 (m, 4H), 2.81 (m, 1H), 2.28 - 2.42 (m, 1H), 1.46 - 1.68 (m, 5H), 1.17 - 1.34 (m, 2H), 0.88 (m, 3H), 0.73 (t, *J* = 7.2 Hz, 3H).

Example 41 Enantiomer 2. 3-(3-((4-Cyanophenyl)amino)-4-(4-methylpiperidin-1-yl)phenyl)pentanoic acid

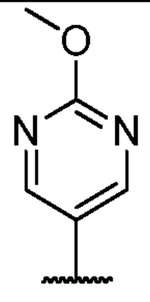
Example 41 Enantiomer 2 was prepared from 41D Enantiomer 2 following the procedure described for the synthesis of Example 41 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{24}H_{29}N_3O_2$ 391.2, found [M+H] 392.3. T_r = 1.98 min. (Method O).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 1H), 7.46 - 7.59 (m, 2H), 6.85 - 7.09 (m, 5H), 3.17 (s, 1H), 3.04 (m, 4H), 2.81 (m, 1H), 2.37 - 2.46 (m, 1H), 1.46 - 1.68 (m, 5H), 1.10 - 1.24 (m, 2H), 0.88 (m, 3H), 0.73 (t, *J* = 7.2 Hz, 3H).

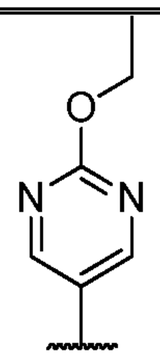
Examples 42 and 43

(Enantiomer 1)



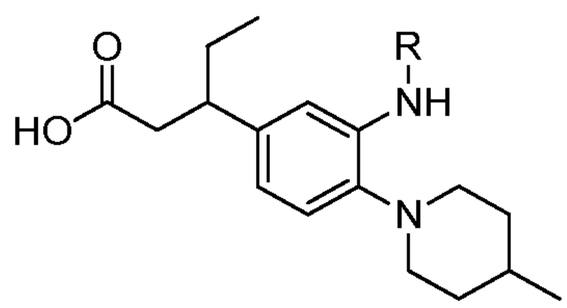
Examples 42 and 43 was prepared from 41D Enantiomer 1 and corresponding halides following the procedure described for the synthesis of Example 41 Enantiomer 1.

Ex. No.	Name	R	T_r (min)	$[M+H]^+$
42	3-(3-((2-methoxypyrimidin-5-yl)amino)-4-(4-methylpiperidin-1-yl)phenyl)pentanoic acid		1.68 (Method O)	399.3

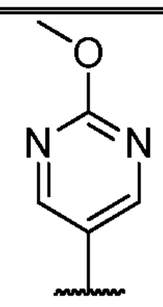
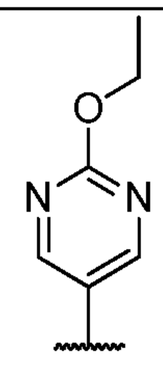
Ex. No.	Name	R	T_r (min)	$[M+H]^+$
43	3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(4-methylpiperidin-1-yl)phenyl) pentanoic acid		1.42 (Method R)	413.3

Examples 44 and 45

(Enantiomer 2)



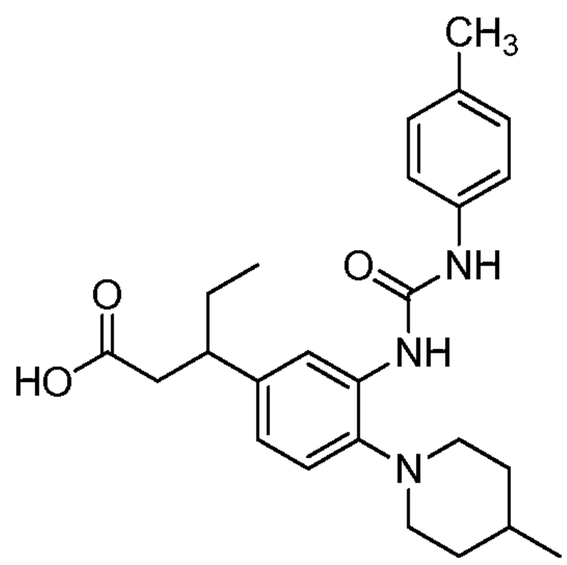
Examples 44 and 45 was prepared from 41D Enantiomer 2 and corresponding halides following the procedure described for the synthesis of Example 41 Enantiomer 1.

Ex. No.	Name	R	T_r (min) Method R	$[M+H]^+$
44	3-(3-((2-methoxypyrimidin-5-yl)amino)-4-(4-methylpiperidin-1-yl)phenyl) pentanoic acid		1.95	399.1
45	3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(4-methylpiperidin-1-yl)phenyl)pentanoic acid		1.41	413.3

Example 46

(Enantiomer 1 and Enantiomer 2)

3-(4-(4-Methylpiperidin-1-yl)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoic acid



46A. Methyl 3-(4-(4-methylpiperidin-1-yl)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoate

To a stirred solution of 41D Enantiomer 1 (0.035 g, 0.115 mmol) in tetrahydrofuran (1.5 mL) was added 1-isocyanato-4-methylbenzene (0.018 g, 0.138 mmol). The reaction mixture was stirred at room temperature for 12 h. LCMS indicated completion of reaction. The reaction mixture was concentrated under reduced pressure to get compound 46A (yellow liquid, 50 mg, 0.075 mmol, 65% yield). LC-MS Anal. Calc'd. for $C_{26}H_{35}N_3O_3$ 437.2, found [M+H] 438.5. T_r = 1.76 min. (Method AY).

Example 46 Enantiomer 1. 3-(4-(4-Methylpiperidin-1-yl)-3-(3-(*p*-tolyl)ureido)phenyl) pentanoic acid

To a stirred solution of 46A (0.050 g, 0.114 mmol) in mixture of tetrahydrofuran (1 mL), methanol (1 mL) and water (0.1 mL) was added $LiOH•H_2O$ (0.019 g, 0.457 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure. The aqueous residue so obtained was acidified with aqueous citric acid. The aqueous layer was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LC/MS to afford Example 46 Enantiomer 1 (13.3 mg, 0.031 mmol, 27% yield). LC-MS Anal. Calc'd. for $C_{25}H_{33}N_3O_3$ 423.3, found [M+H] 424.3. T_r = 2.24 min. (Method O). ^1H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, 1H), 7.87 - 8.04 (m, 2H), 7.37 (m, 2H), 7.01 - 7.18 (m, 3H), 6.67 - 6.85 (m, 1H), 2.87 - 2.96 (m, 3H), 2.56 - 2.64 (m, 2H), 2.36 - 2.45 (m, 1H),

2.14 - 2.29 (m, 4H), 1.58 - 1.77 (m, 3H), 1.36 - 1.54 (m, 4H), 0.99 (m, 3H), 0.73 (t, *J*=7.2 Hz, 3H).

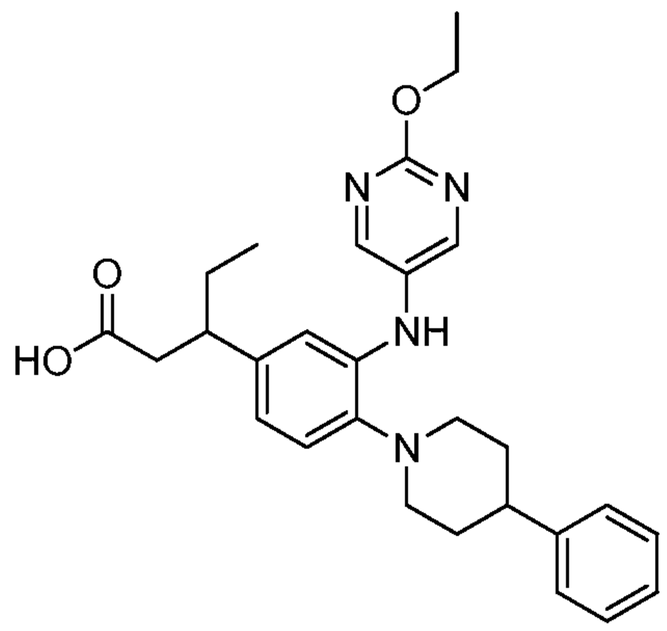
Example 46 Enantiomer 2. 3-(4-(4-Methylpiperidin-1-yl)-3-(3-(*p*-tolyl)ureido)phenyl) pentanoic acid

Example 46 Enantiomer 2 was prepared following the same procedure for Example 46 Enantiomer 1 by utilizing 41D Enantiomer 2. LC-MS Anal. Calc'd. for $C_{25}H_{33}N_3O_3$ 423.2, found [M+H] 424.3. T_r = 2.15 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, 1H), 7.84 - 8.04 (m, 2H), 7.31 - 7.46 (m, 2H), 6.98 - 7.17 (m, 3H), 6.77 (m, 1H), 2.75 - 2.96 (m, 3H), 2.54 - 2.67 (m, 2H), 2.35 - 2.45 (m, 1H), 2.19 - 2.30 (m, 4H), 1.56 - 1.77 (m, 3H), 1.34 - 1.53 (m, 4H), 0.99 (m, 3H), 0.73 (t, *J* = 7.2 Hz, 3H).

Example 47

(Enantiomer 1 and Enantiomer 2)

3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(4-phenylpiperidin-1-yl)phenyl)pentanoic acid



47A. Methyl 3-(3-nitro-4-(4-phenylpiperidin-1-yl)phenyl)pentanoate

Compound 47A was prepared from 41B and 4-phenylpiperidine following the procedure described for the synthesis of 41C. LC-MS Anal. Calc'd. for $C_{23}H_{28}N_2O_4$ 396.2, found [M+H] 397.4, T_r = 1.73 min. (Method AY).

47B. Methyl 3-(3-amino-4-(4-phenylpiperidin-1-yl)phenyl)pentanoate

Compound 47B was prepared from 47A following the procedure described for the synthesis of 41D. LC-MS Anal. Calc'd. for $C_{23}H_{30}N_2O_2$ 366.2, found [M+H] 367.2, T_r = 1.72 min (Method AY).

47C. Methyl 3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(4-phenylpiperidin-1-yl)phenyl) pentanoate

Compound 47C was prepared from 47B following the procedure described for the synthesis of 41E. LC-MS Anal. Calc'd. for $C_{29}H_{36}N_4O_3$ 488.3, found [M+H] 489.5, T_r = 1.83 min (Method AY).

Racemate Example 47. 3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(4-phenylpiperidin-1-yl)phenyl)pentanoic acid

Racemate Example 47 was prepared from 47C following the procedure described for the synthesis of Example 41 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{28}H_{34}N_4O_3$ 474.3, found [M+H] 475.5, T_r = 1.40 min (Method AY).

Chiral separation of Racemic Example 47 (Method BF) gave Enantiomer 1 and Enantiomer 2 as single enantiomers. Enantiomer 1, T_r = 5.22 min and Enantiomer 2, T_r = 6.76 min (Method BF).

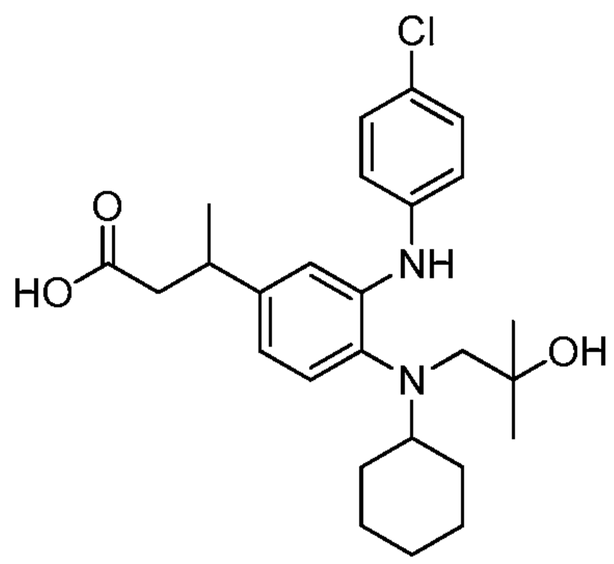
Example 47 Enantiomer 1: LC-MS Anal. Calc'd. for $C_{28}H_{34}N_4O_3$ 474.3, found [M+H] 475.4, T_r = 1.98 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 2H), 7.45 (s, 1H), 7.25 - 7.33 (m, 2H), 7.14 - 7.23 (m, 3H), 7.01 (m, 1H), 6.83 (m, 1H), 6.75 (m, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.12 - 3.26 (m, 3H), 2.73 - 2.85 (m, 1H), 2.61 - 2.71 (m, 2H), 2.37 - 2.46 (m, 2H), 1.65 - 1.80 (m, 2H), 1.42 - 1.62 (m, 4H), 1.34 (m, 3H), 0.61 - 0.77 (t, *J* = 7.2 Hz, 3H).

Example 47 Enantiomer 2: LC-MS Anal. Calc'd. for $C_{28}H_{34}N_4O_3$ 474.3, found [M+H] 475.4, T_r = 1.98 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 2H), 7.45 (s, 1H), 7.27 - 7.28 (m, 2H), 7.17 - 7.20 (m, 3H), 7.01 (m, 1H), 6.82 (m, 1H), 6.75 (m, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.12 - 3.26 (m, 3H), 2.79 - 2.85 (m, 1H), 2.61 - 2.71 (m, 2H), 2.37 - 2.46 (m, 2H), 1.65 - 1.80 (m, 2H), 1.56 - 1.62 (m, 4H), 1.34 (m, 3H), 0.72 (t, *J* = 7.2 Hz, 3H).

Example 48

(Enantiomer 1 and Enantiomer 2)

3-(3-((4-Chlorophenyl)amino)-4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino) phenyl)butanoic acid



48A. 1-(Cyclohexylamino)-2-methylpropan-2-ol

To a stirred solution of cyclohexanone (10.0 g, 102 mmol), 1-amino-2-methylpropan-2-ol (9.08 g, 102 mmol) in dry THF (100 mL), MeOH (100 mL), were added 3.0 g molecular sieves under nitrogen atmosphere. Reaction mixture was stirred at room temperature for 16 h. Reaction cooled to 0 °C and added $NaBH_4$ (11.56 g, 306 mmol) portionwise in 60 minutes. Reaction mixture was stirred at room temperature for 3 h. Reaction mixture was quenched with water (20 mL) at 0 °C. Concentrated under reduced pressure to remove methanol completely to get semi-solid and it was quenched with 10% sodium bicarbonate (100 mL). Aqueous layer extracted with ethyl acetate (2 × 100 mL). Organic layer separated and washed with brine (50 mL). Organic layer dried over sodium sulfate, concentrated under reduced pressure to get liquid compound. Purification via flash chromatography gave 48A (light yellow liquid, 13.5 g, 102 mmol, 78% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.10 (br. s., 1H), 2.40 (s, 2H), 2.33-2.30 (m, 1H), 1.90-1.20 (m, 11H), 1.16 (s, 6H).

48B. 1-((4-Bromo-2-nitrophenyl)(cyclohexyl)amino)-2-methylpropan-2-ol

To a stirred solution of NaH (2.182 g, 54.5 mmol) in dry DMF (60.0 mL), 48A (12.46 g, 72.7 mmol) was added at 0 °C and maintained for 30 minutes at same temperature. 4-Bromo-1-fluoro-2-nitrobenzene (8.0 g, 36.4 mmol) was added at 0 °C. Reaction stirred at room temperature for 4 h. Reaction mixture cooled to 0 °C and quenched with 3 mL water and stirred for 10 minutes at room temperature. Reaction mixture was diluted with ethyl acetate (20 mL) washed with water (10 mL), organic layer separated and aqueous layer extracted with ethyl acetate (2 × 20 mL). Organic layer combined together dried over sodium sulfate, concentrated under reduced pressure to get

orange liquid. Purification via flash chromatography gave 48B (orange liquid, 0.7 g, 1.65 mmol, 93% yield). LC-MS Anal. Calc'd. for $C_{16}H_{23}BrN_2O_3$ 370.2, found [M+2] 372.2, T_r = 3.58 min (Method N).

48C. 1-(Cyclohexyl(2-nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) amino)-2-methylpropan-2-ol

To a stirred solution of 48B (5.0 g, 13.47 mmol), 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi(1,3,2-dioxaborolane) (4.10 g, 16.16 mmol), potassium acetate (3.97 g, 40.4 mmol) in dry DMSO (50.0 mL) purged argon for 10 minutes added $PdCl_2$ (dppf)•CH_2Cl_2 Adduct (0.550 g, 0.673 mmol). Reaction placed on preheated oil bath at 80 °C and maintained for 2 h. Reaction mixture cooled to room temperature, diluted with ethyl acetate (50 mL) washed with water (25 mL) and organic layer separated, aqueous layer back extracted with ethyl acetate (2 × 50 mL). Organic layers mixed together dried over sodium sulfate, concentrated completely to get brown liquid. Purification via flash chromatography gave 48C (orange semi-solid, 4.5 g, 10.76 mmol, 80% yield). LC-MS Anal. Calc'd. for $C_{22}H_{35}BN_2O_5$ 418.2, found [M+H] 419.2, T_r = 4.00 min (Method N).

48D. Methyl 3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-nitrophenyl) butanoate

Compound 48D was prepared from methyl crotonate following the procedure described for the synthesis of 33D. LC-MS Anal. Calc'd. for $C_{21}H_{32}N_2O_5$ 392.2, found [M+H] 393.4, T_r = 3.66 min (Method N).

48E. Methyl 3-(3-amino-4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)phenyl) butanoate

The solution of 48D (1.8 g, 4.59 mmol) in ethyl acetate (30 mL) was charged to a sealable hydrogen flask. The solution was sequentially evacuated and purged with nitrogen gas. To this 10% Pd on carbon (0.332 g, 0.312 mmol) was added under nitrogen atmosphere. The reaction mixture was stirred under hydrogen atmosphere (40 psi). The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was filtered through a CELITE® pad and the residue on the pad was thoroughly rinsed with ethyl acetate (3 × 15 mL). The combined filtrate was concentrated under reduced pressure

to get crude compound Racemate 48E (yellow solid, 1.4 g). LC-MS Anal. Calc'd. for $C_{21}H_{34}N_2O_3$ 362.2, found [M+H] 363.3, T_r = 3.06 min (Method N).

Chiral separation of Racemate 48E (Method AE) to get Enantiomer 1 and Enantiomer 2 as single enantiomers (Method AE) Enantiomer 1, T_r = 3.15 min and Enantiomer 2, T_r = 5.12 min (Method AE).

48E Enantiomer 1 (yellow liquid, 450 mg, 1.241 mmol, 26% yield): LC-MS Anal. Calc'd. for $C_{21}H_{34}N_2O_3$ 362.2, found [M+H] 363.2. T_r = 3.18 min (Method BO).

48E Enantiomer 2 (yellow liquid, 450 mg, 1.241 mmol, 26% yield): LC-MS Anal. Calc'd. for $C_{21}H_{34}N_2O_3$ 362.2, found [M+H] 363.5. T_r = 3.81 min (Method U).

48F. Methyl 3-(3-((4-chlorophenyl)amino)-4-(cyclohexyl(2-hydroxy-2-methylpropyl) amino)phenyl)butanoate

The mixture of 48E Enantiomer 1 (0.050 g, 0.138 mmol), 1-bromo-4-chlorobenzene (0.032 g, 0.166 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.040 g, 0.069 mmol) and Cs_2CO_3 (0.135 g, 0.414 mmol) in 1,4-dioxane (1.5 mL) was stirred. Argon gas was bubbled through the mixture for 5 min. Bis(dibenzylideneacetone) palladium (7.93 mg, 0.014 mmol) was added and argon gas was bubbled through the mixture for 5 min. The reaction mixture was sealed and placed in preheated oil bath at 110 °C for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford a residue. The residue was reconstituted in a mixture of ethyl acetate (15 mL) and water (15 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography gave 48F (yellow liquid, 50 mg, 0.037 mmol, 26% yield). LC-MS Anal. Calc'd. for $C_{27}H_{37}ClN_2O_3$ 472.2, found [M+H] 473.5, T_r = 2.03 min. (Method AY).

Example 48 Enantiomer 1. 3-(3-((4-Chlorophenyl)amino)-4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)phenyl)butanoic acid

To a stirred solution of 48F (0.050 g, 0.106 mmol) in mixture of tetrahydrofuran (1 mL), methanol (1 mL) and water (0.1 mL) was added $LiOH•H_2O$ (0.018 g, 0.423

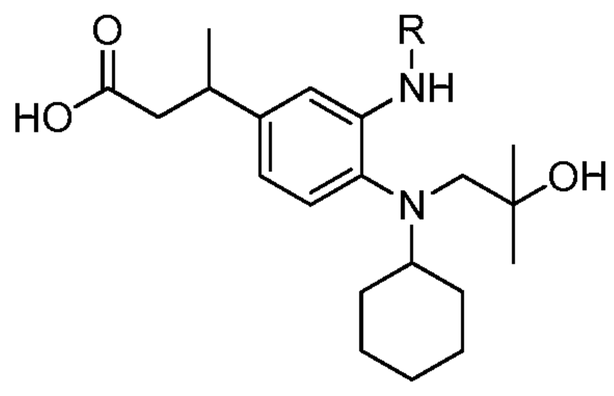
mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure. The aqueous residue so obtained was acidified with aqueous citric acid. The aqueous layer was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LC/MS gave Example 48 Enantiomer 1 (20.6 mg, 0.045 mmol, 42% yield). LC-MS Anal. Calc'd. for $C_{26}H_{35}ClN_2O_3$ 458.2, found [M+H] 459.3, T_r = 2.24 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 (s, 1H), 7.22 - 7.31 (m, 2H), 7.02 - 7.17 (m, 4H), 6.73 (m, 1H), 3.05 (m, 2H), 2.95 (br. s., 2H), 2.31 - 2.46 (m, 3H), 1.76 - 1.89 (m, 2H), 1.61 (m, 2H), 1.42 (m, 1H), 1.08 - 1.22 (m, 5H), 0.91 (m, 9H).

Example 48 Enantiomer 2. 3-(3-((4-Chlorophenyl)amino)-4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)phenyl)butanoic acid

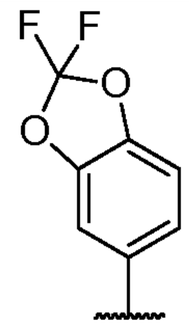
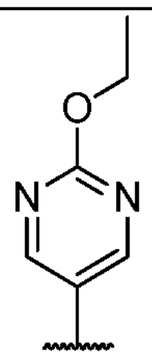
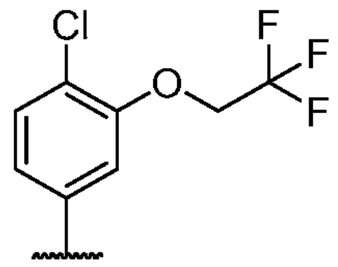
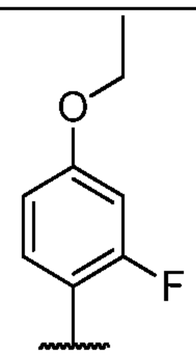
Example 48 Enantiomer 2 was prepared from 48E Enantiomer 2 following the procedure described for the synthesis of Example 48 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{26}H_{35}ClN_2O_3$ 458.2, found [M+H] 459.2, T_r = 2.24 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 (s, 1H), 7.26 (m, 2H), 7.10 - 7.17 (m, 3H), 7.01 - 7.09 (m, 1H), 6.73 (m, 1H), 3.05 - 3.18 (m, 2H), 2.95 (m, 2H), 2.49 (m, 3H), 1.97 - 2.10 (m, 2H), 1.62 (m, 2H), 1.43 (m, 1H), 1.06 - 1.26 (m, 5H), 0.90 (m, 9H).

Examples 49 to 52

(Enantiomer 1)

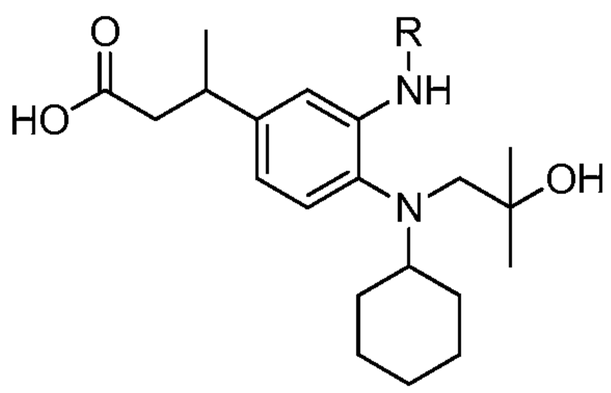


Examples 49 to 52 was prepared from 48E Enantiomer 1 and corresponding halides following the procedure described for the synthesis of Example 48 Enantiomer 1.

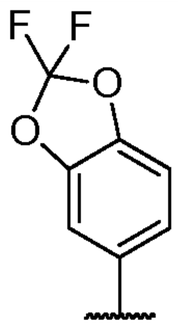
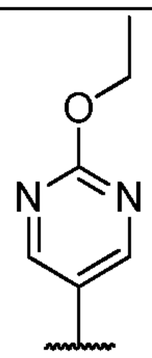
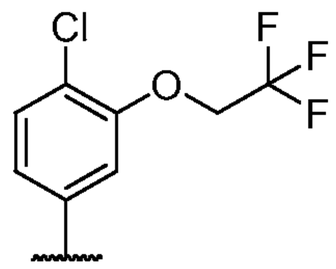
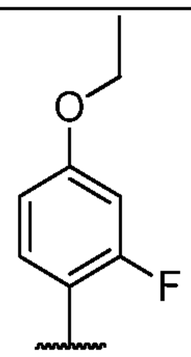
Ex. No.	Name	R	T_r (min) Method O	$[M+H]^+$
49	3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-((2,2-difluorobenzo[d][1,3]dioxol-5-yl)amino)phenyl)butanoic acid		2.32	505.3
50	3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-((2-ethoxypyrimidin-5-yl)amino) phenyl)butanoic acid		1.81	471.3
51	3-(3-((4-chloro-3-(2,2,2-trifluoroethoxy)phenyl)amino)-4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)phenyl) butanoic acid		2.40	557.3
52	3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-((4-ethoxy-2-fluorophenyl)amino) phenyl)butanoic acid		2.23	487.3

Examples 53 to 56

(Enantiomer 2)



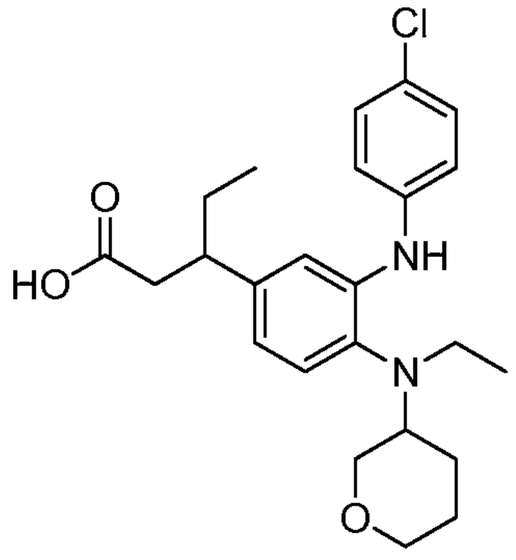
Examples 53 to 56 was prepared from 48E Enantiomer 2 and corresponding halides following the procedure described for the synthesis of Example 48 Enantiomer 1.

Ex. No.	Name	R	T_r (min) Method O	$[M+H]^+$
53	3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-((2,2-difluorobenzo[d][1,3]dioxol-5-yl)amino)phenyl)butanoic acid		2.35	505.3
54	3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-((2-ethoxypyrimidin-5-yl)amino) phenyl)butanoic acid		1.79	471.3
55	3-(3-((4-chloro-3-(2,2,2-trifluoroethoxy)phenyl)amino)-4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)phenyl) butanoic acid		2.42	557.2
56	3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-((4-ethoxy-2-fluorophenyl)amino) phenyl)butanoic acid		2.28	487.3

Example 59

(Diastereomer 1 and Diastereomer 2)

3-(3-((4-Chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino) phenyl)pentanoic acid



59A. N-Ethyltetrahydro-2H-pyran-3-amine

To a stirred solution of dihydro-2H-pyran-3(4H)-one (10 g, 100 mmol) in tetrahydrofuran (100 mL), methanol (100 mL) under nitrogen atmosphere was added ethanamine (2M in THF) (49.9 mL, 100 mmol), followed by 4A° molecular sieves (4 g). The reaction mixture was stirred for 12 h at room temperature. To this was added $NaBH_4$ (11.34 g, 300 mmol) portionwise at 0 °C and the reaction mixture was stirred at room temperature for 3 h. Reaction mixture was quenched with water (10 mL) and concentrated under reduced pressure to get semi-solid which was quenched with 10% sodium bicarbonate (500 mL). It was extracted with ethyl acetate (2 × 200 mL), washed with brine (100 mL). Organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to get 59A (yellow liquid, 11 g, 85 mmol, 85% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.74 - 3.65 (m, 4H), 2.70 (m, 1H), 2.67 (m, 2H), 1.98 - 1.57 (m, 4H), 1.02 (t, J = 7.2 Hz 3H).

59B. N-(4-Bromo-2-nitrophenyl)-N-ethyltetrahydro-2H-pyran-3-amine

In a sealed tube 4-bromo-1-fluoro-2-nitrobenzene (4 g, 18.18 mmol) was added 59A (3.52 g, 27.3 mmol). The reaction mixture was heated at 135 °C for 12 h. LCMS indicated completion of reaction. Purification via flash chromatography gave 59B (yellow liquid, 3.5 g, 10.63 mmol, 58% yield). LC-MS Anal. Calc'd. $C_{13}H_{17}BrN_2O_3$ 328.0, found [M+H] 329.2. T_r = 3.10 min. (Method U).

59C. 4-Bromo-N1-ethyl-N1-(tetrahydro-2H-pyran-3-yl)benzene-1,2-diamine

To a stirred solution of 59B (6.8 g, 20.66 mmol) in acetic acid (68 mL) under nitrogen atmosphere at 0 °C was added iron (4.61 g, 83 mmol). The reaction mixture was stirred at room temperature for 12 h. LCMS indicated completion of reaction. Reaction mixture was concentrated under reduced pressure to get residue which was basified to pH ~ 9 by using 10% sodium bicarbonate and it was extracted with ethyl acetate (4 × 50 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound 59C (yellow solid, 5 g). LC-MS Anal. Calc'd. for $C_{13}H_{19}BrN_2O$ 298.06, found [M+2] 301.3. T_r = 1.46 min (Method AY).

Chiral separation of Racemate 59C gave Enantiomer 1 and Enantiomer 2 as single enantiomers (Method AR). 59C Enantiomer 1, T_r = 4.27 min and 59C Enantiomer 2, T_r = 5.33 min (Method AR).

59C Enantiomer 1 (yellow liquid, 2 g, 6.68 mmol, 32% yield): LC-MS Anal. Calc'd. for $C_{13}H_{19}BrN_2O$ 298.06, found [M+H] 299.2, T_r = 2.874 min (Method U).

59C Enantiomer 2 (yellow liquid, 1.5 g, 5.01 mmol, 24% yield): LC-MS Anal. Calc'd. for $C_{13}H_{19}BrN_2O$ 298.06, found [M+H] 299.2, T_r = 2.876 min (Method U).

59D. N1-Ethyl-N1-(tetrahydro-2H-pyran-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene-1,2-diamine

To a stirred solution of 59C Enantiomer 1 (1.9 g, 6.35 mmol), bis(pinacolato) diboron (2.419 g, 9.53 mmol) and potassium acetate (1.870 g, 19.05 mmol) in 1,4-dioxane (19 mL) was purged with argon for 10 min. To this $PdCl_2$ (dppf)•CH_2Cl_2 Adduct (0.259 g, 0.318 mmol) was added and purged with argon for 5 min. The reaction mixture was heated at 90 °C for 5 h. LCMS indicated completion of reaction. Reaction mixture was cooled to room temperature and quenched with water (30 mL). Aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash chromatography gave 59D (yellow liquid, 2.0 g, 5.78 mmol, 91% yield). LC-MS Anal. Calc'd. for $C_{19}H_{31}BN_2O_3$ 346.2, found [M+H] 347.6, T_r = 1.56 min. (Method AY).

59E. Methyl 3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)phenyl)pentanoate

In a pressure tube equipped with Teflon cap, compound 59D (1g, 2.89 mmol), 1,4-dioxane (10 mL) were added followed by (E)-methyl pent-2-enoate (0.989 g, 8.66 mmol), (S)-(-)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (0.036 g, 0.058 mmol) and 1M solution of sodium hydroxide (2.60 mL, 2.60 mmol). Argon gas was bubbled through the mixture for 10 min and chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.014 g, 0.029 mmol) was added at room temperature. Argon gas was bubbled through the mixture for 5 min. The tube was then screw-capped and heated at 50 °C for 2 h. The reaction mixture was cooled to room temperature, quenched with acetic acid (0.165 mL) and was stirred for 5 minutes before it was diluted with water (15 mL). The aqueous layer was extracted

with ethyl acetate (3 × 20 mL). Combined organic layer was washed with water (15 mL), brine (15 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography to afford 59E (yellow solid, 800 mg). LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_3$ 334.2, found [M+H] 335.8, T_r = 1.48 min (Method AY).

Chiral separation of 59E (Method BY) gave 59E Diastereomer 1 T_r = 2.78 min (Method BY) and 59E Diastereomer 2 T_r = 3.51 min (Method BY)

59E Diastereomer 1 (yellow liquid, 240 mg): LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_3$ 334.2, found [M+H] 335.2, T_r = 3.26 min (Method U).

59E Diastereomer 2 (yellow liquid, 265 mg): LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_3$ 334.2, found [M+2] 335.2, T_r = 3.26 min (Method U).

59F. Methyl 3-(3-((4-chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino) phenyl)pentanoate

The mixture of 59E Diastereomer 1 (0.050 g, 0.149 mmol), 1-bromo-4-chlorobenzene (0.034 g, 0.179 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.043 g, 0.075 mmol) and Cs_2CO_3 (0.146 g, 0.448 mmol) in 1,4-dioxane (2 mL) was stirred. Argon gas was bubbled through the mixture for 5 min. Bis(dibenzylideneacetone) palladium (8.60 mg, 0.015 mmol) was added and argon gas was bubbled through the mixture for 5 min. The reaction mixture was sealed and placed in preheated oil bath at 110 °C for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford a residue. The residue was reconstituted in a mixture of ethyl acetate (15 mL) and water (15 mL). The combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography to afford 59F (yellow liquid, 60 mg, 0.082 mmol, 55% yield). LC-MS Anal. Calc'd. for $C_{25}H_{33}ClN_2O_3$ 444.2, found [M+H] 445.5, T_r = 2.06 min. (Method AY).

Example 59 Diastereomer 1. 3-(3-((4-Chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)phenyl)pentanoic acid

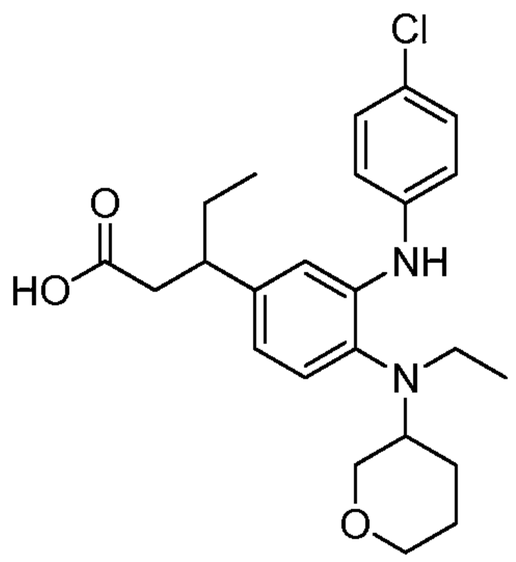
To a stirred solution of 59F (0.060 g, 0.135 mmol) in mixture of tetrahydrofuran (1 mL), methanol (1 mL) and water (0.2 mL) was added $LiOH•H_2O$ (0.023 g, 0.539 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure. The aqueous residue so obtained was acidified with aqueous citric acid. The aqueous layer was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LCMS to afford Example 59 Diastereomer 1 (16.3 mg, 0.037 mmol, 27% yield). LC-MS Anal. Calc'd. for $C_{24}H_{31}ClN_2O_3$ 430.2, found [M+H] 431.2, T_r = 2.33 min. (Method O). ^1H NMR (400 MHz, DMSO-d_6) δ 7.36 (s, 1H), 7.22 - 7.29 (m, 2H), 7.09 - 7.16 (m, 3H), 7.03 (m, 1H), 6.68 - 6.78 (m, 1H), 3.79 (m, 1H), 3.60 - 3.69 (m, 3H), 3.10 - 3.21 (m, 2H), 2.92 - 3.03 (m, 1H), 2.81 (m, 1H), 2.38 - 2.47 (m, 2H), 1.54 - 1.70 (m, 4H), 1.33 - 1.47 (m, 2H), 0.79 (t, *J*= 7.2 Hz, 3H), 0.73 (t, *J* = 7.2 Hz, 3H).

Example 59 Diastereomer 2. 3-(3-((4-Chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)phenyl)pentanoic acid

Example 59 Diastereomer 2 was prepared from 59E Diastereomer 2 following the procedure described for the synthesis of Example 59 Diastereomer 1. LC-MS Anal. Calc'd. for $C_{24}H_{31}ClN_2O_3$ 430.2, found [M+H] 431.2, T_r = 2.32 min. (Method O).^1H NMR (400 MHz, DMSO-d_6) δ 7.36 (s, 1H), 7.21 - 7.29 (m, 2H), 7.08 - 7.17 (m, 3H), 7.03 (m, 1H), 6.74 (m, 1H), 3.79 (m, 1H), 3.59 - 3.71 (m, 3H), 3.09 - 3.22 (m, 2H), 2.93 - 3.03 (m, 1H), 2.77 - 2.90 (m, 1H), 2.38 - 2.48 (m, 2H), 1.55 - 1.67 (m, 4H), 1.45 - 1.54 (m, 2H), 0.79 (t, *J* = 7.2 Hz, 3H), 0.73 (t, *J* = 7.2 Hz, 3H).

Example 60

3-(3-((4-Chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)phenyl) pentanoic acid (Diastereomer 3 and Diastereomer 4)



60A. N1-Ethyl-N1-(tetrahydro-2H-pyran-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene-1,2-diamine

To a stirred solution of 59C Enantiomer 2 (1.9 g, 6.35 mmol), bis(pinacolato) diboron (2.419 g, 9.53 mmol) and potassium acetate (1.870 g, 19.05 mmol) in 1,4-dioxane (19 mL) was purged with argon for 10 min. To this $PdCl_2$ (dppf)•CH_2Cl_2 Adduct (0.259 g, 0.318 mmol) was added and purged with argon for 5 min. The reaction mixture was heated at 90 °C for 5 h. LCMS indicated completion of reaction. Reaction mixture was cooled to room temperature and quenched with water (30 mL). Aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash chromatography gave 60A (yellow liquid, 1.5 g, 4.33 mmol, 93% yield). LC-MS Anal. Calc'd. for $C_{19}H_{31}BN_2O_3$ 346.2, found [M+H] 347.6, T_r = 1.56 min. (Method AY).

60B. Methyl 3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)phenyl)pentanoate

Compound 60B was prepared from 60A following the procedure described for the synthesis of 59E. LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_3$ 334.2, found [M+H] 335.8, T_r = 1.48 min (Method AY).

Chiral separation of 60B (Method DN) gave 60B Diastereomer 3 T_r = 2.3 min (Method DN) and 60B Diastereomer 4 T_r = 3.08 min (Method DN).

60B Diastereomer 3: LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_3$ 334.2, found [M+H] 335.2, T_r = 3.26 min (Method U).

60B Diastereomer 4: LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_3$ 334.2, found [M+2] 335.2, T_r = 3.42 min (Method U).

60C. Methyl 3-(3-((4-chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino) phenyl)pentanoate

The mixture of 60B Diastereomer 3 (0.050 g, 0.149 mmol), 1-bromo-4-chlorobenzene (0.034 g, 0.179 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.043 g, 0.075 mmol) and Cs_2CO_3 (0.146 g, 0.448 mmol) in 1,4-dioxane (2 mL) was stirred. Argon gas was bubbled through the mixture for 5 min. Bis(dibenzylideneacetone) palladium (8.60 mg, 0.015 mmol) was added and argon gas was bubbled through the mixture for 5 min. The reaction mixture was sealed and placed in preheated oil bath at 110 °C for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford a residue. The residue was reconstituted in a mixture of ethyl acetate (15 mL) and water (15 mL). The combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography to afford 60C (yellow liquid, 55 mg, 0.054 mmol, 36% yield). LC-MS Anal. Calc'd. for $C_{25}H_{33}ClN_2O_3$ 444.2, found [M+H] 445.4, T_r = 2.08 min. (Method AY).

Example 60 Diastereomer 3. 3-(3-((4-Chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)phenyl)pentanoic acid

To a stirred solution of 60C (0.060 g, 0.135 mmol) in mixture of tetrahydrofuran (1 mL), methanol (1 mL) and water (0.2 mL) was added $LiOH•H_2O$ (0.023 g, 0.539 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure. The aqueous residue so obtained was acidified with aqueous citric acid. The aqueous layer was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LCMS to afford Example 60 Diastereomer 3 (15 mg, 0.033 mmol, 26% yield). LC-MS Anal. Calc'd. for $C_{24}H_{31}ClN_2O_3$ 430.2, found [M+H] 431.2, T_r = 2.32 min. (Method O). ^1H NMR (400 MHz, DMSO-d_6) δ 7.36 (s, 1H), 7.25 (m, 2H), 7.09 - 7.18 (m, 3H), 6.98 - 7.06 (m, 1H), 6.74 (m, 1H), 3.77 - 3.84 (m, 1H), 3.62 - 3.70 (m, 3H), 3.10 - 3.23 (m, 2H), 2.98

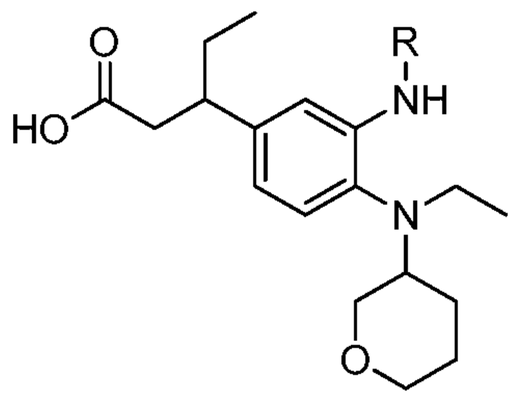
(m, 1H), 2.76 - 2.92 (m, 1H), 2.35 - 2.47 (m, 2H), 1.58 - 1.69 (m, 4H), 1.35 - 1.45 (m, 2H), 0.79 (t, J = 7.2 Hz, 3H), 0.73 (t, J = 7.2 Hz, 3H).

Example 60 Diastereomer 4. 3-(3-((4-Chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)phenyl)pentanoic acid

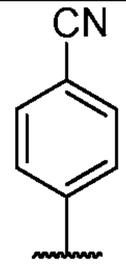
Example 60 Diastereomer 4 was prepared from 60B Diastereomer 4 following the procedure described for the synthesis of Example 60 Diastereomer 3. LC-MS Anal. Calc'd. for $C_{24}H_{31}ClN_2O_3$ 430.2, found [M+H] 431.2, T_r = 2.24 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 (s, 1H), 7.24 (d, J = 8.2 Hz, 2H), 7.00 - 7.17 (m, 4H), 6.67 - 6.88 (m, 1H), 3.79 (m, 1H), 3.60 - 3.69 (m, 3H), 3.10 - 3.21 (m, 2H), 2.92 - 3.03 (m, 1H), 2.81 (m, 1H), 2.38 - 2.47 (m, 2H), 1.54 - 1.70 (m, 4H), 1.33 - 1.47 (m, 2H), 0.79 (t, J = 7.2 Hz, 3H), 0.73 (t, J = 7.2 Hz, 3H).

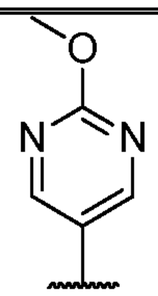
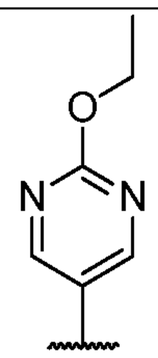
Examples 61 to 63

(Diastereomer 1)



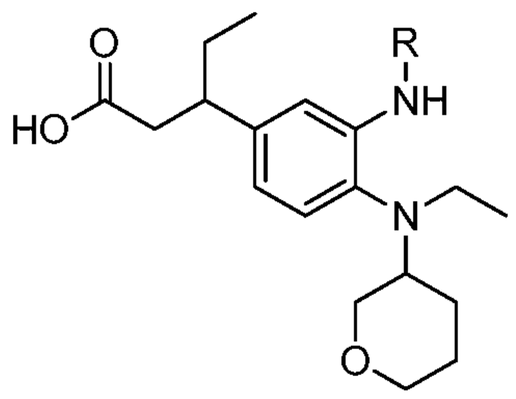
Examples 61 to 63 was prepared from 59E Diastereomer 1 and the corresponding halides following the procedure described for the synthesis of Example 59 Diastereomer 1.

Ex. No.	Name	R	T_r (min) Method O	$[M+H]^+$
61	3-(3-((4-cyanophenyl)amino)-4-(ethyl (tetrahydro-2H-pyran-3-yl)amino) phenyl)pentanoic acid		1.96	422.2

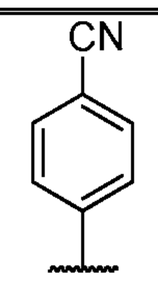
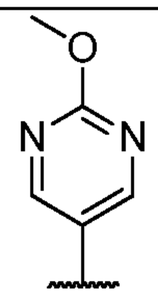
Ex. No.	Name	R	T_r (min) Method O	$[M+H]^+$
62	3-(4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)-3-((2-methoxypyrimidin-5-yl)amino)phenyl)pentanoic acid		1.67	429.2
63	3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino) phenyl)pentanoic acid		1.78	443.2

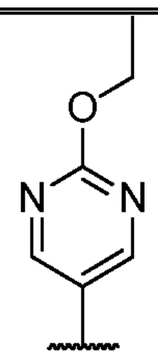
Examples 64 to 66

(Diastereomer 2)



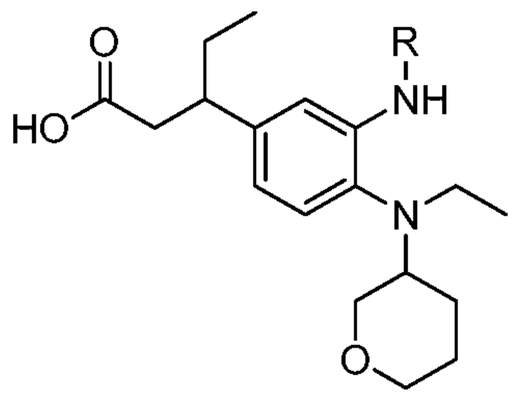
Examples 64 to 66 was prepared from 59E Diastereomer 2 and the corresponding halides following the procedure described for the synthesis of Example 59 Diastereomer 1.

Ex. No.	Name	R	T_r (min) Method O	$[M+H]^+$
64	3-(3-((4-cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino) phenyl)pentanoic acid		1.95	422.2
65	3-(4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)-3-((2-methoxypyrimidin-5-yl)amino)phenyl)pentanoic acid		1.68	429.2

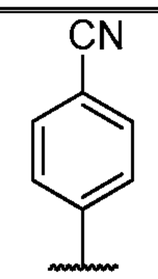
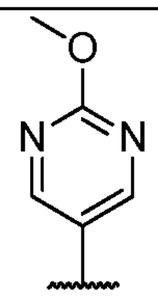
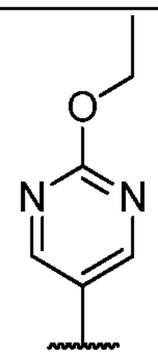
Ex. No.	Name	R	T_r (min) Method O	$[M+H]^+$
66	3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino) phenyl)pentanoic acid		1.78	443.2

Examples 67 to 69

(Diastereomer 3)

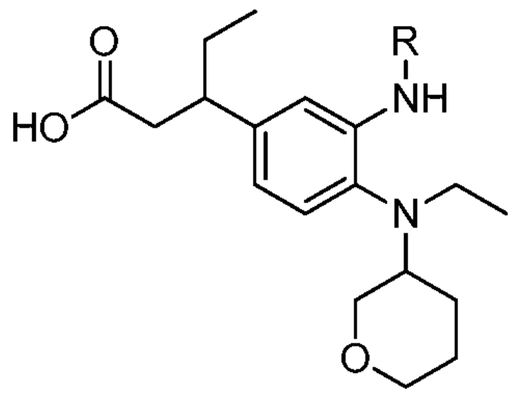


Examples 67 to 69 was prepared from 60B Diastereomer 3 and the corresponding halides following the procedure described for the synthesis of Example 60 Diastereomer 3.

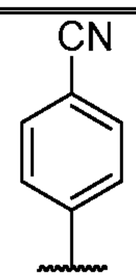
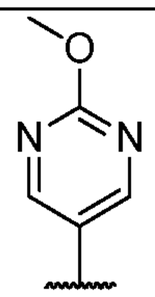
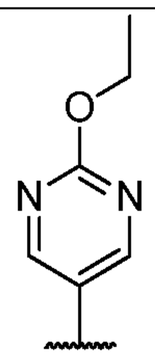
Ex. No.	Name	R	T_r (min) Method O	$[M+H]^+$
67	3-(3-((4-cyanophenyl)amino)-4-(ethyl (tetrahydro-2H-pyran-3-yl)amino) phenyl)pentanoic acid		1.95	422.2
68	3-(4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)-3-((2-methoxypyrimidin-5-yl)amino)phenyl)pentanoic acid		1.69	429.2
69	3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)phenyl)pentanoic acid		1.82	443.3

Examples 70 to 72

(Diastereomer 4)



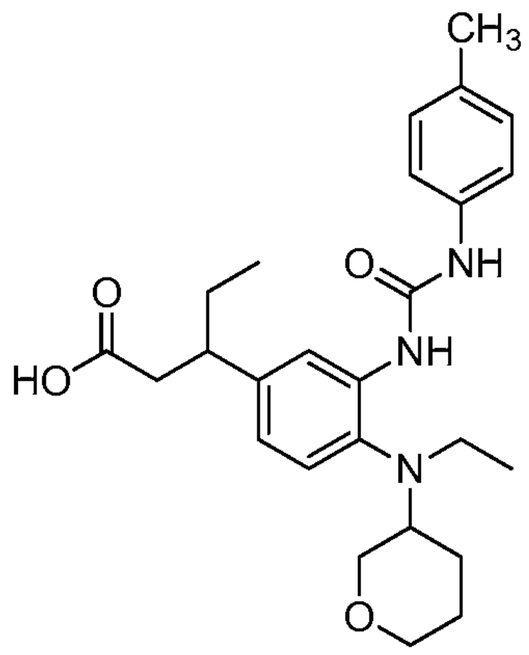
Examples 70 to 72 was prepared from 60B Diastereomer 4 and the corresponding halides following the procedure described for the synthesis of Example 60 Diastereomer 3.

Ex. No.	Name	R	T_r (min) Method O	$[M+H]^+$
70	3-(3-((4-cyanophenyl)amino)-4-(ethyl (tetrahydro-2H-pyran-3-yl)amino) phenyl)pentanoic acid		1.92	422.2
71	3-(4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)-3-((2-methoxypyrimidin-5-yl)amino)phenyl)pentanoic acid		1.62	429.3
72	3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)phenyl)pentanoic acid		1.79	443.2

Example 73

(Diastereomer 1, Diastereomer 2, Diastereomer 3, Diastereomer 4)

3-(4-(Ethyl(tetrahydro-2H-pyran-3-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoic acid



73A. Methyl 3-(4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl) pentanoate

To a stirred solution of 59E Diastereomer 1 (0.035 g, 0.105 mmol) in tetrahydrofuran (1.5 mL) was added 1-isocyanato-4-methylbenzene (0.017 g, 0.126 mmol). The reaction mixture was stirred at room temperature for 12 h. LCMS indicated completion of reaction. The reaction mixture was concentrated under reduced pressure to get 73A (yellow liquid, 45 mg, 0.069 mmol, 66% yield). LC-MS Anal. Calc'd. for $C_{27}H_{37}N_3O_4$ 467.3, found [M+H] 468.5. T_r = 1.63 min. (Method AY).

Example 73 Diastereomer 1. 3-(4-(Ethyl(tetrahydro-2H-pyran-3-yl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)pentanoic acid

To a stirred solution of 73A (0.045 g, 0.096 mmol) in mixture of tetrahydrofuran (1.5 mL), methanol (1.5 mL) and water (0.5 mL) was added $LiOH•H_2O$ (0.016 g, 0.385 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure. The aqueous residue so obtained was acidified with aqueous citric acid. The aqueous layer was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LC/MS to afford Example 73 Diastereomer 1 (25 mg, 0.056 mmol, 57% yield). LC-MS Anal. Calc'd. for $C_{26}H_{35}N_3O_4$ 453.2, found [M+H] 454.2, T_r = 1.85 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (s, 1H), 8.40 (s, 1H), 8.08 (s, 1H), 7.38 (m, 2H), 7.05 - 7.19 (m, 3H), 6.69 - 6.85 (m, 1H), 3.94 (m, 1H), 3.65 - 3.77 (m, 1H), 3.07 - 3.21 (m, 2H), 2.94

- 3.05 (m, 2H), 2.80 - 2.91 (m, 2H), 2.33 (m, 2H), 2.25 (s, 3H), 1.91 (m, 1H), 1.56 - 1.74 (m, 2H), 1.39 - 1.54 (m, 2H), 1.21 - 1.36 (m, 1H), 0.79 (t, J = 7.2 Hz, 3H), 0.63 - 0.74 (t, J = 7.2 Hz, 3H).

Example 73 Diastereomer 2. 3-(4-(Ethyl(tetrahydro-2H-pyran-3-yl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)pentanoic acid

Example 73 Diastereomer 2 was prepared from 59E Diastereomer 2 following the procedure described for the synthesis of Example 73 Diastereomer 1. LC-MS Anal. Calc'd. for $C_{26}H_{35}N_3O_4$ 453.2, found [M+H] 454.2, T_r = 1.85 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (s, 1H), 8.40 (s, 1H), 8.08 (s, 1H), 7.38 (m, 2H), 7.05 - 7.20 (m, 3H), 6.71 (s, 1H), 3.85 - 4.00 (m, 1H), 3.62 - 3.77 (m, 1H), 3.06 - 3.18 (m, 2H), 2.93 - 3.05 (m, 2H), 2.78 - 2.92 (m, 2H), 2.33 (m, 2H), 2.26 (s, 3H), 1.91 (m, 1H), 1.57 - 1.73 (m, 2H), 1.38 - 1.52 (m, 2H), 1.15 - 1.35 (m, 1H), 0.79 (t, J = 7.2 Hz, 3H), 0.63 - 0.74 (t, J = 7.2 Hz, 3H).

Example 73 Diastereomer 3. 3-(4-(Ethyl(tetrahydro-2H-pyran-3-yl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)pentanoic acid

Example 73 Diastereomer 3 was prepared from 60B Diastereomer 3 following the procedure described for the synthesis of Example 73 Diastereomer 1. LC-MS Anal. Calc'd. for $C_{26}H_{35}N_3O_4$ 453.2, found [M+H] 454.2. T_r = 1.84 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 - 9.46 (m, 1H), 8.36 - 8.45 (m, 1H), 8.02 - 8.12 (m, 1H), 7.34 - 7.44 (m, 2H), 7.16 (m, 1H), 7.03 - 7.12 (m, 2H), 6.80 (m, 1H), 3.88 - 3.98 (m, 1H), 3.71 (m, 1H), 3.06 - 3.20 (m, 2H), 2.94 - 3.03 (m, 2H), 2.80 - 2.92 (m, 2H), 2.33 (m, 2H), 2.24 (s, 3H), 1.91 (m, 1H), 1.56 - 1.71 (m, 2H), 1.39 - 1.54 (m, 2H), 1.20 - 1.34 (m, 1H), 0.79 (m, 3H), 0.62 - 0.75 (m, 3H).

Example 73 Diastereomer 4. 3-(4-(Ethyl(tetrahydro-2H-pyran-3-yl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)pentanoic acid

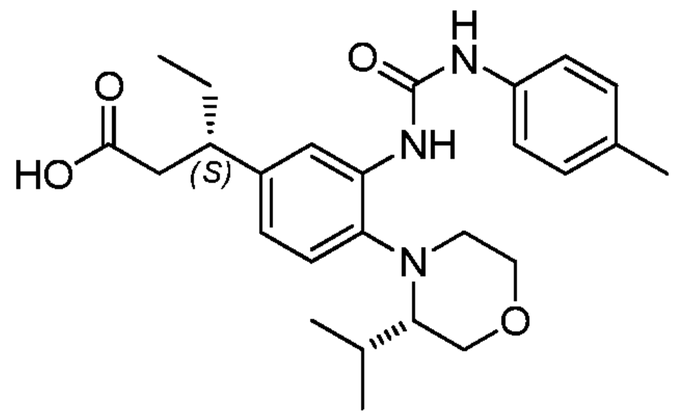
Example 73 Diastereomer 4 was prepared from 60B Diastereomer 4 following the procedure described for the synthesis of Example 73 Diastereomer 1. LC-MS Anal. Calc'd. for $C_{26}H_{35}N_3O_4$ 453.2, found [M+H] 454.3, T_r = 1.85 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (m, 1H), 8.36 - 8.51 (m, 1H), 8.01 - 8.15 (m, 1H), 7.38 (m,

2H), 7.16 (m, 1H), 7.10 (m, 2H), 6.73 - 6.85 (m, 1H), 3.94 (m, 1H), 3.64 - 3.80 (m, 1H), 3.07 - 3.20 (m, 2H), 2.94 - 3.05 (m, 2H), 2.79 - 2.92 (m, 2H), 2.34 (m, 2H), 2.26 (s, 3H), 1.84 - 1.98 (m, 1H), 1.56 - 1.74 (m, 2H), 1.38 - 1.54 (m, 2H), 1.29 (m, 1H), 0.79 (t, J = 7.2 Hz, 3H), 0.73 (t, J = 7.2 Hz, 3H).

Example 74

(Diastereomer 1)

(S)-3-(4-((S)-3-Isopropylmorpholino)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoic acid



74A. (S)-5-Isopropylmorpholin-3-one

To an ice cold suspension of 60% NaH (8.92 g, 223 mmol) in toluene (300 mL) was added L-Valinol (10 g, 97 mmol) in toluene (200 mL) in a dropwise manner. The reaction mixture was slowly warmed to room temperature and was added ethyl 2-chloroacetate (11.88 g, 97 mmol) in toluene (50 mL) in a dropwise manner. The reaction mixture was heated to reflux for 20 h. Reaction mass was cooled to room temperature, quenched with 20 mL of water and concentrated under reduced pressure. The crude was purified by flash chromatography (120 g silica gel column; 2% MeOH: $CHCl_3$) to afford 74A (off-white solid, 10 g, 69.8 mmol, 72.0% yield). LC-MS Anal. Calc'd. for $C_7H_{13}NO_2$ 143.1, found [M+H] 144.2, T_r = 0.6 min (Method U).

74B. (S)-3-Isopropylmorpholine

To a solution of $LiAlH_4$ (2.4 M in THF, 58.2 mL, 140 mmol) in THF (100 mL) cooled to 0 °C and was added 74A (10 g, 69.8 mmol) in THF (50 mL) in a dropwise manner. Then reaction mass was heated to reflux overnight. Reaction mass was cool to 0 °C, quenched with water (5 mL) followed by 2M NaOH solution (10 mL). Reaction mixture was stirred at room temperature for 1 h. The solids were filtered and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to afford 74B (brown

oil, 8.5 g, 65.8 mmol, 94% yield). LC-MS Anal. Calc'd. for $C_7H_{15}NO$ 129.2, found [M+H] 130.2, T_r = 0.33 min (Method U).

74C. (S)-4-(4-Bromo-2-nitrophenyl)-3-isopropylmorpholine

To a solution of 4-bromo-1-fluoro-2-nitrobenzene (9.02 g, 41.0 mmol) in NMP (30 mL) was added DIPEA (21.49 mL, 123 mmol), followed by 74B (5.3 g, 41.0 mmol) and heated to 120 °C overnight. Reaction mixture was diluted with water (100 mL) and extracted with MTBE (2 × 100 mL). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure to get crude which was purified by flash chromatography (5% EA:hexane; 40 g silica gel column) to afford 74C (brown gummy, 3.8 g, 11.43 mmol, 27.9% yield). LC-MS Anal. Calc'd. for $C_{13}H_{17}BrN_2O_3$ 328.04, found [M+H] 329.2, T_r = 3.23 min (Method U).

74D. (S)-4-(4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-2-nitrophenyl)-3-isopropylmorpholine

To a solution of 74C (1.1 g, 3.34 mmol) in DMSO (25 mL) were added 5,5,5′,5′-tetramethyl-2,2′-bi(1,3,2-dioxaborinane) (1.510 g, 6.68 mmol) and potassium acetate (1.476 g, 15.04 mmol). The reaction mixture was purged with nitrogen for 10 minutes. Then was added $PdCl_2$ (dppf)•CH_2Cl_2 Adduct (0.136 g, 0.167 mmol) and heated to 80 °C for 5 h. Reaction mixture was cooled to room temperature, diluted with ethyl acetate (50 mL) and washed with brine solution (10 × 50 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford 74D (brown solid, 1.4 g, 2.435 mmol, 72.9% yield). LC-MS Anal. Calc'd. for $C_{18}H_{27}BN_2O_5$ 362.2, found [M+H] 295.2 for parent boronic acid, T_r = 2.05 min (Method U).

74E. (S)-Methyl 3-(4-((S)-3-isopropylmorpholino)-3-nitrophenyl)pentanoate

To a solution of 74D (1.4 g, 3.86 mmol) in dioxane (20 mL) was added 1 N sodium hydroxide (3.48 mL, 3.48 mmol) and purged with nitrogen for 10 minutes. Then were added (E)-methyl pent-2-enoate (2.206 g, 19.32 mmol), (R)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (0.072 g, 0.116 mmol) and chlorobis(ethylene) rhodium(I) dimer (0.023 g, 0.058 mmol). Round bottomed flask was closed with septum and stirred at 35 °C for 2 h. Reaction mixture was cooled to room temperature, diluted

with ethyl acetate (50 mL) and washed with water (30 mL) followed by brine solution (2 × 30 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to get crude was purified by flash chromatography (15% EA:hexane; 24 g silica gel column) to afford 74E (brown gummy, 0.7 g, 1.748 mmol, 37% yield). LC-MS Anal. Calc'd. for $C_{19}H_{28}N_2O_5$ 364.2, found [M+H] 365.2, T_r = 3.08 min (Method U). (Absolute stereochemistry of the product assigned based on the expected product enantiomer from the use of (R)-BINAP in the conjugate addition)

74F. (S)-Methyl 3-(3-amino-4-((S)-3-isopropylmorpholino)phenyl)pentanoate

To a solution of 74E (0.65 g, 1.784 mmol) in ethyl acetate (10 mL) was added 10% Pd/C (0.15 g, 0.141 mmol) and stirred under hydrogen bladder pressure for 4 h. Reaction mixture was filtered through CELITE® and concentrated under reduced pressure to get crude which was purified by flash chromatography (15% EA:hexane; 40 g silica gel column) to afford Diastereomer mixture of 74F.

Chiral separation of diastereomer mixture (91:9) 74F yielded 74F Diastereomer 1 T_r = 6.9 min, 74F Diastereomer 2 T_r = 7.2 min (Method BK).

74F Diastereomer 1 (brown solid, 230 mg, 0.681 mmol, 38.2% yield): LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_3$ 334.2, found 335.2, T_r = 3.55 min (Method U).

74G. (S)-Methyl 3-(4-((S)-3-isopropylmorpholino)-3-(3-(*p*-tolyl)ureido)phenyl) pentanoate

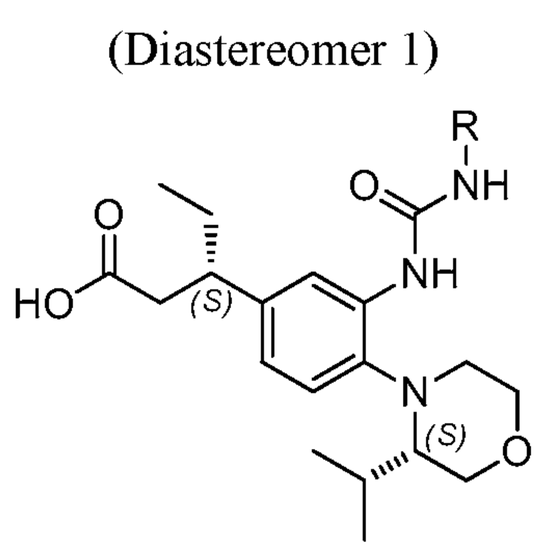
To a solution of 74F Diastereomer 1 (15 mg, 0.045 mmol) in THF (1 mL) was added 1-isocyanato-4-methylbenzene (11.94 mg, 0.090 mmol) and stirred at room temperature overnight. Reaction mass was diluted with ethyl acetate (10 mL) and washed with brine solution (2 × 10 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to get 74G (30 mg, 0.022 mmol, 50.1% yield) as white solid. LC-MS Anal. Calc'd. for $C_{27}H_{37}N_3O_4$ 467.2, found 468.2, T_r = 4.01 min (Method U).

Example 74. (S)-3-(4-((S)-3-Isopropylmorpholino)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoic acid

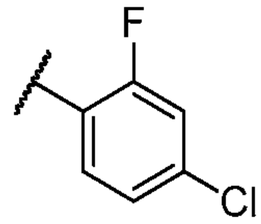
To a solution of 74G (30 mg, 0.064 mmol) in THF (2 mL) and MeOH (0.5 mL) was added $LiOH•H_2O$ (13.45 mg, 0.321 mmol) in water (1 mL) and stirred at room temperature overnight. Reaction mass was concentrated under reduced pressure. To that residue water (10 mL) was added and acidified (pH~4) with solid citric acid and extracted with ethyl acetate (2 × 25 mL). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure to get crude was purified by prep HPLC to obtain Example 74 (11.3 mg, 0.025 mmol, 38.4% yield). LC-MS Anal. Calc'd. for $C_{26}H_{35}N_3O_4$ 453.2, found 454.2, T_r = 4.01 min (Method O). ^1H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.38 (s, 1H), 8.10 (d, *J* = 2.0 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.79 (dd, *J* = 2.0, 8.0 Hz, 1H), 3.74 - 3.88 (m, 3H), 3.50 - 3.55 (m, 1H), 3.01 (d, *J* = 9.6 Hz, 1H), 2.81- 2.84 (m, 1H), 2.62 - 2.64 (m, 2H), 2.43-2.45 (m, 1H), 2.25 (s, 3H), 1.60-1.62 (m, 2H), 1.59-1.60 (m, 1H), 0.80 (d, *J* = 7.2 Hz, 3H), 0.67-0.74 (m, 6H) (Note: 1H buried under solvent peak).

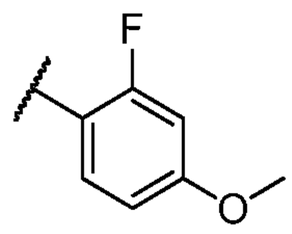
Examples 75 and 76

(Diastereomer 1)



Examples 75 and 76 was prepared from 74F Diastereomer 1 and corresponding isocyanates following the procedure described for the synthesis of Example 74.

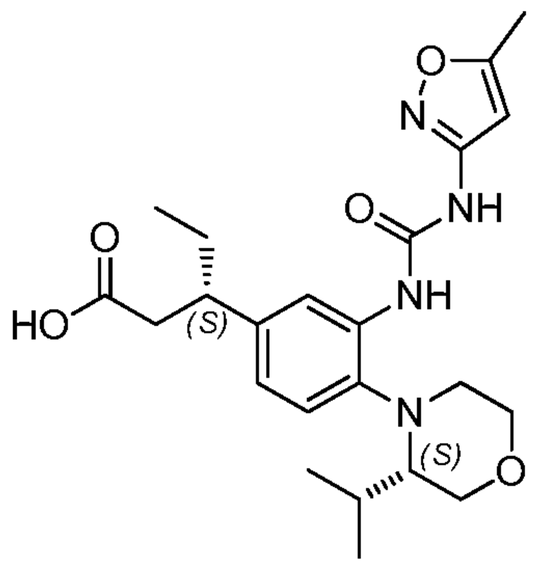
Ex. No.	Name	R	T_r min Method O	(M+H)
75	(S)-3-(3-(3-(4-chloro-2-fluorophenyl)ureido)-4-((S)-3-isopropylmorpholino)phenyl) pentanoic acid		1.85	492.2

Ex. No.	Name	R	T_r min Method O	(M+H)
76	(S)-3-(3-(3-(2-fluoro-4-methoxyphenyl)ureido)-4-((S)-3-isopropylmorpholino)phenyl) pentanoic acid		1.5	488.2

Example 77

(Diastereomer 1)

(S)-3-(4-((S)-3-Isopropylmorpholino)-3-(3-(5-methylisoxazol-3-yl)ureido) phenyl)pentanoic acid



77A. (S)-Methyl 3-(4-((S)-3-isopropylmorpholino)-3-(3-(5-methylisoxazol-3-yl)ureido) phenyl)pentanoate

To a solution of 74F Diastereomer 1 (15 mg, 0.045 mmol) in THF (2 mL) was added 4-nitrophenyl chloroformate (9.04 mg, 0.045 mmol) and stirred at room temperature for 2 h. To the reaction mass was added 5-methylisoxazol-3-amine (5.28 mg, 0.054 mmol) followed by pyridine (3.63 µl, 0.045 mmol), cat. amount of DMAP and stirred at 50 °C overnight. Reaction mass was diluted with ethyl acetate (20 mL) and washed with water (2 × 10 mL) followed by brine solution (2 × 15 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford 77A (brown gummy, 30 mg, 9.16 µmol, 20% yield). LC-MS Anal. Calc'd. for $C_{24}H_{34}N_4O_5$ 458.2, found 459.2 T_r = 1.49 min (Method AY).

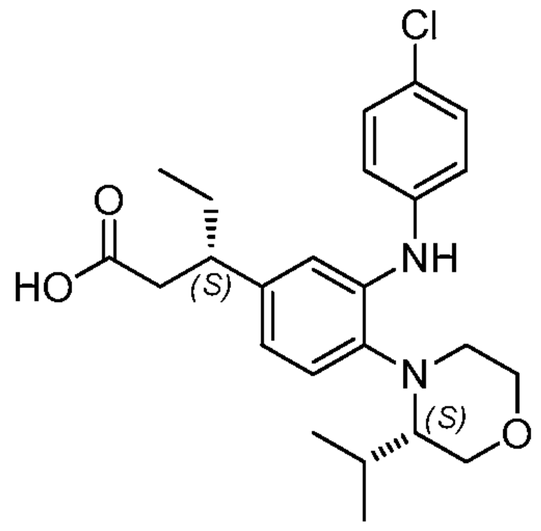
Example 77. (S)-3-(4-((S)-3-Isopropylmorpholino)-3-(3-(5-methylisoxazol-3-yl)ureido) phenyl)pentanoic acid

Example 77 was prepared from 77A following the procedure described for the synthesis of Example 74 from 74G. LC-MS Anal. Calc'd. for $C_{23}H_{32}N_4O_5$ 444.2, found 445.2, T_r = 1.42 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1H), 9.50 (s, 1H), 8.15 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.86 (dd, *J* = 2.00, 8.00 Hz, 1H), 6.38 (s, 1H), 3.87-3.89 (m, 2H), 3.72 (d, *J* = 10.40 Hz, 1H), 3.56-3.59 (m, 2H), 3.04 (d, *J* = 10.40 Hz, 1H), 2.79-2.84 (m, 1H), 2.62-2.65 (m, 1H), 2.51-2.54 (m, 1H), 2.43-2.46 (m, 1H), 2.37 (d, *J* = 0.80 Hz, 3H), 1.48-1.59 (m, 3H), 0.80 (d, *J* = 7.20 Hz, 3H), 0.72 (t, *J* = 7.60 Hz, 3H), 0.66 (d, *J* = 7.20 Hz, 3H).

Example 78

(Diastereomer 1)

(S)-3-(3-((4-Chlorophenyl)amino)-4-((S)-3-isopropylmorpholino)phenyl)pentanoic acid



78A. (S)-Methyl 3-(3-((4-chlorophenyl)amino)-4-((S)-3-isopropylmorpholino) phenyl)pentanoate

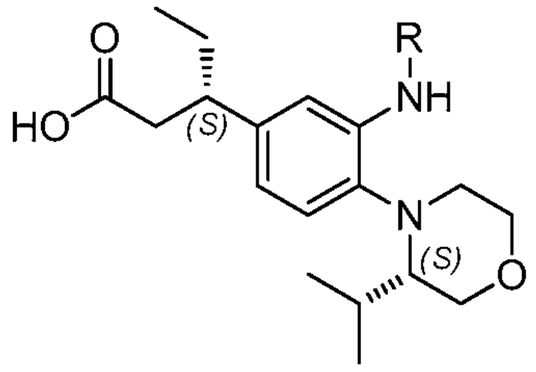
To a solution of 74F Diastereomer 1 (25 mg, 0.075 mmol) in 1,4-dioxane (2 mL) were added 1-bromo-4-chlorobenzene (17.17 mg, 0.090 mmol), Cs_2CO_3 (73.1 mg, 0.224 mmol). The reaction mixture was purged with nitrogen for 15 minutes. Then was added Xantphos (21.63 mg, 0.037 mmol) followed by bis(dibenzylideneacetone)palladium (4.30 mg, 7.47 µmol) and heated to 110 °C overnight. Reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (2 × 15 mL) followed by brine solution (2 × 15 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to obtained 78A (brown gummy, 45 mg, 0.029 mmol, 39.2% yield). LC-MS Anal. Calc'd. for $C_{25}H_{33}ClN_2O_3$ 444.2, found 445.2, T_r = 4.07 min (Method U).

Example 78. (S)-3-(3-((4-Chlorophenyl)amino)-4-((S)-3-isopropylmorpholino) phenyl)pentanoic acid

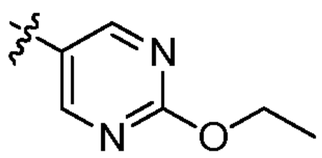
To a solution of 78A (40 mg, 0.090 mmol) in THF (2 mL) and MeOH (0.5 mL) was added $LiOH•H_2O$ (18.84 mg, 0.449 mmol) in water (1 mL) and stirred at rt overnight. Reaction mixture was concentrated under reduced pressure. To that residue water (10 mL) was added and acidified (pH~4) with solid citric acid and extracted with ethyl acetate (2 × 25 mL). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure to get crude was purified by prep HPLC to obtain Example 78 (5.8 mg, 0.013 mmol, 15% yield). LC-MS Anal. Calc'd. for $C_{24}H_{31}ClN_2O_3$ 430.2, found 431.2, T_r = 2.17 min (Method O). ^1H NMR (400 MHz, DMSO-d_6) δ 7.45 (s, 1H), 7.27 (d, *J* = 8.80 Hz, 2H), 7.14 (d, *J* = 8.80 Hz, 3H), 7.02 (s, 1H), 6.73 (d, *J* = 9.60 Hz, 1H), 3.69-3.76 (m, 3H), 3.46-3.49 (m, 1H), 3.01-3.04 (m, 1H), 2.67-2.72 (m, 3H), 2.52-2.55 (m, 1H), 2.41-2.44 (m, 1H), 1.70-1.73 (m, 1H), 1.58-1.62 (m, 1H), 1.46-1.52 (m, 1H), 0.71-0.78 (m, 6H), 0.66 (d, *J* = 7.20 Hz, 3H).

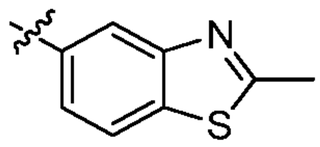
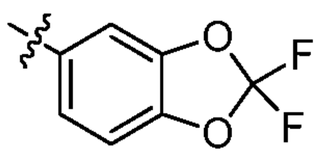
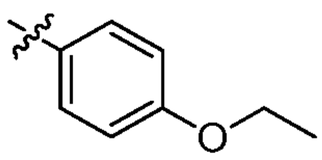
Examples 79 to 82

(Diastereomer 1)



Examples 79 to 82 were prepared from 74F Diastereomer 1 and corresponding aryl halides following the procedure described for the synthesis of Example 78.

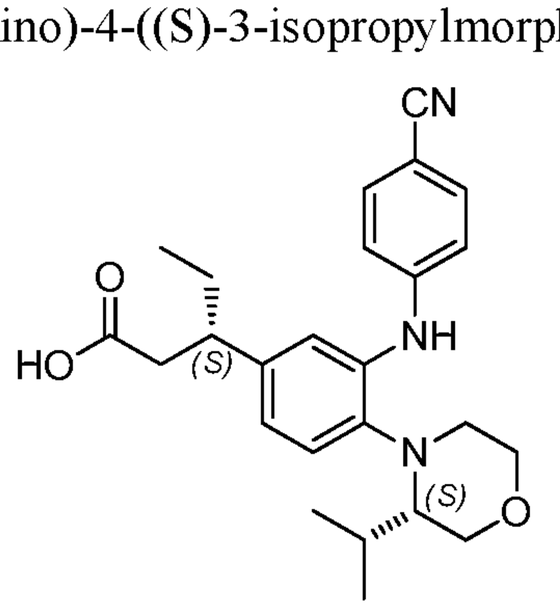
Ex. No.	Name	R	T_r min Method O	(M+H)
79	(S)-3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-((S)-3-isopropylmorpholino)phenyl) pentanoic acid		1.69	443.3

Ex. No.	Name	R	T_r min Method O	(M+H)
80	(S)-3-(4-((S)-3-isopropylmorpholino)-3-((2-methylbenzo[d]thiazol-6-yl)amino)phenyl)pentanoic acid		1.95	468.2
81	(S)-3-(3-((2,2-difluorobenzo[d][1,3]dioxol-5-yl)amino)-4-((S)-3-isopropylmorpholino)phenyl)pentanoic acid		2.26	477.2
82	(S)-3-(3-((4-ethoxyphenyl)amino)-4-((S)-3-isopropylmorpholino)phenyl)pentanoic acid		2.1	441.3

Example 83

(Diastereomer 1)

(S)-3-(3-((4-Cyanophenyl)amino)-4-((S)-3-isopropylmorpholino)phenyl)pentanoic acid



83A. (S)-Methyl 3-(3-((4-cyanophenyl)amino)-4-((S)-3-isopropylmorpholino)phenyl) pentanoate

Compound 83A was prepared from 74F Diastereomer 1 and 4-bromobenzonitrile following the procedure described for the synthesis of 78A. LC-MS Anal. Calc'd. for $C_{26}H_{33}N_3O_3$ 435.2, found 436.2 T_r = 3.58 min (Method U).

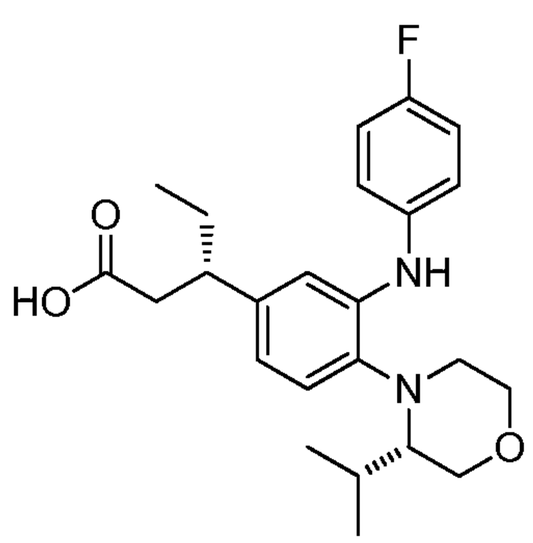
Example 83. (S)-3-(3-((4-Cyanophenyl)amino)-4-((S)-3-isopropylmorpholino)phenyl) pentanoic acid

To a solution of 83A (40 mg, 0.092 mmol) in THF (2 mL) and MeOH (0.5 mL) was added $LiOH•H_2O$ (19.25 mg, 0.459 mmol) and stirred at room temperature overnight. Reaction mixture was concentrated under reduced pressure. To that residue water (10 mL) was added and acidified (pH~4) with solid citric acid and extracted with ethyl acetate (2 × 25 mL). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure to get crude. The crude mixture was purified by prep HPLC to obtain Example 83 (8.4 mg, 0.020 mmol, 22% yield). LC-MS Anal. Calc'd. for $C_{25}H_{31}N_3O_3$ 421.2, found 422.2, T_r = 1.93 min (Method O). ^1H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 1H), 7.56 (d, *J* = 8.40 Hz, 2H), 7.15 (d, *J* = 8.00 Hz, 1H), 7.09 (d, *J* = 8.80 Hz, 3H), 6.89 (dd, *J* = 2.00, 8.20 Hz, 1H), 3.63-3.68 (m, 3H), 3.48-3.51 (m, 1H), 3.01-3.03 (m, 1H), 2.82-2.86 (m, 2H), 2.69-2.72 (m, 1H), 2.51-2.58 (m, 1H), 2.41-2.44 (m, 1H), 1.78-1.81 (m, 1H), 1.61-1.64 (m, 1H), 1.45-1.50 (m, 1H), 0.71-0.74 (m, 6H), 0.64 (d, *J* = 6.80 Hz, 3H).

Example 84

(Diastereomer 1)

(S)-3-(3-((4-Fluorophenyl)amino)-4-((S)-3-isopropylmorpholino)phenyl)pentanoic acid



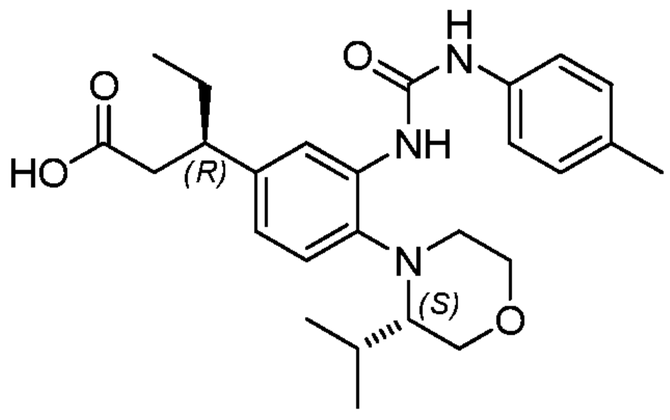
To a solution of 74F Diastereomer 1 (25 mg, 0.075 mmol) in 1,4-dioxane (2 mL) were added 1-bromo-4-fluorobenzene (15.70 mg, 0.090 mmol), sodium *tert*-butoxide (21.55 mg, 0.224 mmol). The reaction mixture was purged with nitrogen for 15 minutes. Then Xantphos (21.63 mg, 0.037 mmol) was added followed by bis(dibenzylideneacetone)palladium (4.30 mg, 7.47 µmol) and heated to 110 °C overnight. Reaction mass was cooled to room temperature and was concentrated under reduced pressure. To that residue water (10 mL) was added and acidified (pH~4) with solid citric acid. The reaction mixture was extracted with ethyl acetate (2 × 25 mL). The combined organic layer was dried over sodium sulfate and concentrated under reduced

pressure to get crude which was purified by prep HPLC to obtain Example 84 (pale yellow solid, 3.5 mg, 8.27 µmol, 11.07% yield). LC-MS Anal. Calc'd. for $C_{24}H_{31}FN_2O_3$ 414.2, found 415.2, T_r = 2.0 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 (s, 1H), 7.07-7.16 (m, 5H), 6.93 (d, *J* = 2.00 Hz, 1H), 6.66 (dd, *J* = 1.60, 8.00 Hz, 1H), 3.78-3.81 (m, 1H), 3.69-3.71 (m, 2H), 3.02-3.05 (m, 1H), 2.65-2.70 (m, 3H), 2.35-2.40 (m, 1H), 1.70-1.71 (m, 1H), 1.57-1.58 (m, 1H), 1.47-1.49 (m, 1H), 0.78 (d, *J* = 6.80 Hz, 3H), 0.65-0.73 (m, 6H), (1H buried under solvent peak and 1H buried under moisture peak).

Example 85

(Diastereomer 2)

(R)-3-(4-((S)-3-Isopropylmorpholino)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoic acid



85A. (R)-Methyl 3-(4-((S)-3-isopropylmorpholino)-3-nitrophenyl)pentanoate

To a solution of 74D (1.25 g, 3.45 mmol) in dioxane (20 mL) was added 1 N sodium hydroxide (3.11 mL, 3.11 mmol) and purged with nitrogen for 10 minutes. Then were added (E)-methyl pent-2-enoate (1.969 g, 17.25 mmol), (S)-(-)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (0.107 g, 0.173 mmol) and chlorobis(ethylene) rhodium(I) dimer (0.027 g, 0.069 mmol). The RB was closed with septum and stirred at 35 °C for 2 h. Reaction mixture was cooled to room temperature, diluted with ethyl acetate (50 mL) and washed with water (30 mL) followed by brine solution (2 × 30 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to get crude was purified by flash chromatography (15% EA:hexane; 24 g silica gel column) to afford 85A (brown gummy, 0.7 g, 1.748 mmol, 37.2% yield). LC-MS Anal. Calc'd. for $C_{19}H_{28}N_2O_5$ 364.2, found 365.2 T_r = 3.3 min (Method U). (Absolute stereochemistry of the product assigned based on the expected product enantiomer from the use of (S)-BINAP in the conjugate addition)

85B. (R)-Methyl 3-(3-amino-4-((S)-3-isopropylmorpholino)phenyl)pentanoate

Compound 85B (diastereomer mixture) was prepared from 85A following the procedure described for the synthesis of 74F.

Chiral separation of Diastereomer mixture (10:90) 85B yielded 85B Diastereomer 1, T_r = 6.9 min, 85B Diastereomer 2, T_r = 7.2 min (Method BK).

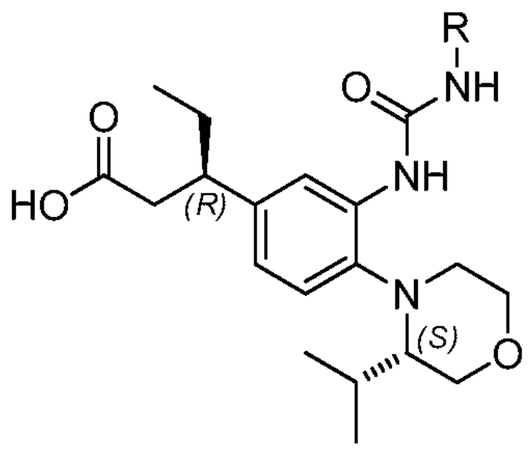
85B Diastereomer 2: LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_3$ 334.2, found 335.2 T_r = 3.55 min (Method U).

Example 85. (R)-3-(4-((S)-3-Isopropylmorpholino)-3-(3-(*p*-tolyl)ureido)phenyl) pentanoic acid

Example 85 was prepared from 85B Diastereomer 2 following the procedure described for the synthesis of Example 74. LC-MS Anal. Calc'd. for $C_{26}H_{35}N_3O_4$ 453.2, found 454.2, T_r = 1.7 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.38 (s, 1H), 8.10 (d, *J* = 2.00 Hz, 1H), 7.37 (d, *J* = 8.40 Hz, 2H), 7.16 (d, *J* = 8.40 Hz, 1H), 7.10 (d, *J* = 8.40 Hz, 2H), 6.79 (dd, *J* = 2.00, 8.00 Hz, 1H), 3.74-3.88 (m, 3H), 3.50-3.55 (m, 1H), 3.01 (d, *J* = 9.60 Hz, 1H), 2.81-2.84 (m, 1H), 2.62-2.64 (m, 2H), 2.43-2.45 (m, 1H), 2.25 (s, 3H), 1.60-1.62 (m, 2H), 1.59-1.60 (m, 1H), 0.80 (d, *J* = 7.20 Hz, 3H), 0.67-0.74 (m, 6H) (Note: 1H buried under solvent peak).

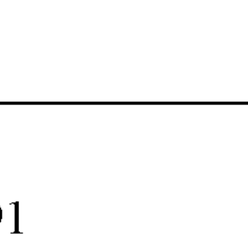
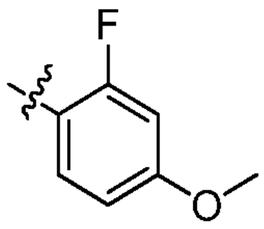
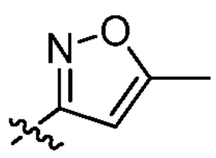
Examples 86 to 88

(Diastereomer 2)



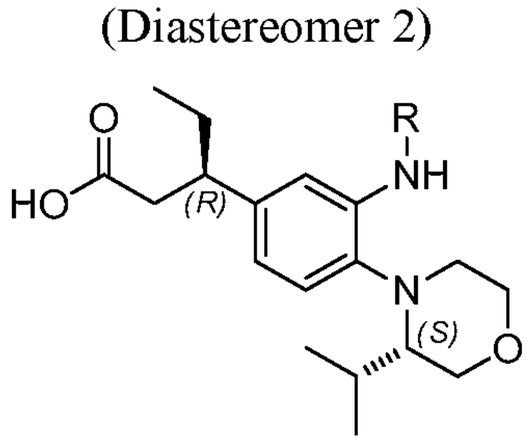
Examples 86 and 87 was prepared from 85B Diastereomer 2 and corresponding isocyanates following the procedure described for the synthesis of Example 85.

Example 88 was prepared from 85B Diastereomer 2 and corresponding amine following the procedure described for the synthesis of Example 77.

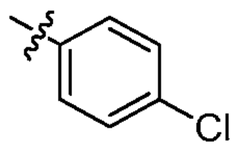
Ex. No.	Name	R	T_r min Method O	(M+H)
86	(R)-3-(3-(3-(4-chloro-2-fluorophenyl)ureido)-4-((S)-3-isopropylmorpholino)phenyl) pentanoic acid		1.85	492.2
87	(R)-3-(3-(3-(2-fluoro-4-methoxyphenyl)ureido)-4-((S)-3-isopropylmorpholino)phenyl) pentanoic acid		1.64	488.2
88	(R)-3-(4-((S)-3-isopropylmorpholino)-3-(3-(5-methylisoxazol-3-yl)ureido)phenyl) pentanoic acid		1.58	445.2

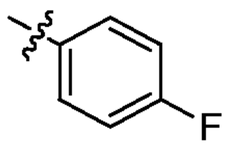
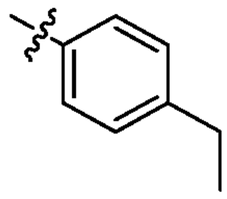
Examples 89 to 91

(Diastereomer 2)



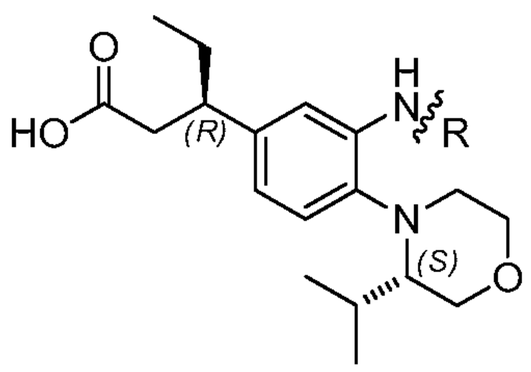
Examples 89 to 91 was prepared from 85B Diastereomer 2 and corresponding aryl halides following the procedure described for the synthesis of Example 84.

Ex. No.	Name	R	T_r min Method O	(M+H)
89	(R)-3-(3-((4-chlorophenyl)amino)-4-((S)-3-isopropylmorpholino)phenyl) pentanoic acid		2.18	431.2

Ex. No.	Name	R	T_r min Method O	(M+H)
90	(R)-3-(3-((4-fluorophenyl)amino)-4-((S)-3-isopropylmorpholino)phenyl) pentanoic acid		1.9	415.2
91	(R)-3-(3-((4-ethylphenyl)amino)-4-((S)-3-isopropylmorpholino)phenyl) pentanoic acid		2.31	425.3

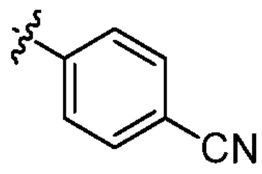
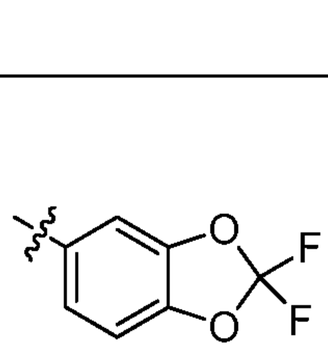
Examples 92 to 94

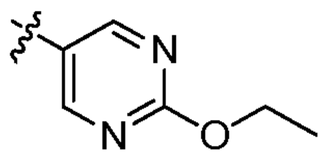
(Diastereomer 2)



Example 92 was prepared from 85B Diastereomer 2 and corresponding aryl halide following the procedure described for the synthesis of Example 83.

Examples 93 and 94 was prepared from 85B Diastereomer 2 and corresponding aryl halides following the procedure described for the synthesis of Example 78.

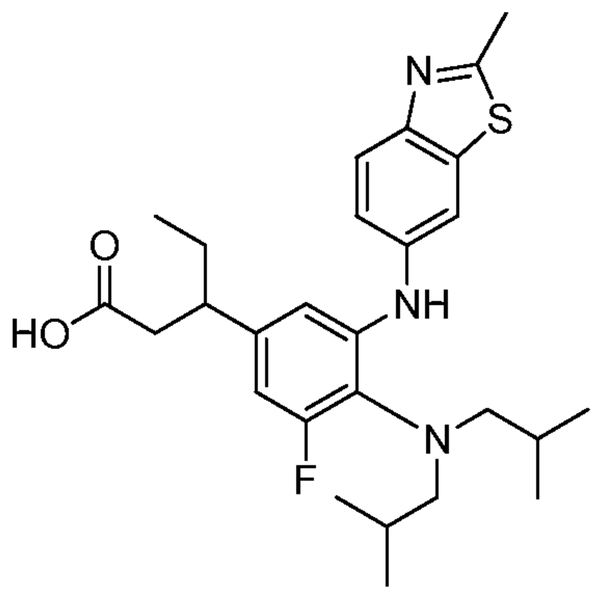
Ex. No.	Name	R	T_r min	Method	(M+H)
92	(R)-3-(3-((4-cyanophenyl) amino)-4-((S)-3-isopropylmorpholino) phenyl)pentanoic acid		2.32	R	422.2
93	(R)-3-(3-((2,2-difluorobenzo[d][1,3] dioxol-5-yl)amino)-4-((S)-3-isopropylmorpholino) phenyl)pentanoic acid		2.25	O	477.2

Ex. No.	Name	R	T_r min	Method	(M+H)
94	(R)-3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-((S)-3-isopropylmorpholino) phenyl)pentanoic acid		2.23	R	443.3

Example 95

(Enantiomer 1)

3-(4-(Diisobutylamino)-3-fluoro-5-((2-methylbenzo[d]thiazol-6-yl)amino) phenyl)pentanoic acid



95A. 4-Bromo-2-fluoro-N,N-diisobutyl-6-nitroaniline

A solution of 5-bromo-1,2-difluoro-3-nitrobenzene (1 g, 4.20 mmol) and diisobutylamine (1.629 g, 12.61 mmol) was placed under nitrogen and heated at 130 °C for 2 h. The reaction was diluted with ether and washed with 5% HOAc then brine. The org. phase was dried, stripped, and chromatographed on silica gel (EtOAc-hexane) to afford 95A (1.28 g, 83% yield) as an orange oil. MS(ES): *m/z* = 347 $[M+H]^+$, T_r = 1.34 min (Method A).

95B. 4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-2-fluoro-N,N-diisobutyl-6-nitroaniline

A solution of 5,5,5′,5′-tetramethyl-2,2′-bi(1,3,2-dioxaborinane) (1.015 g, 4.49 mmol) and 95A (1.2 g, 3.46 mmol) and potassium acetate (1.018 g, 10.37 mmol) in degassed DMSO (4.94 ml) was treated with 1,1′-bis(diphenylphosphino) ferrocenedichloro palladium(II) dichloromethane complex (0.126 g, 0.173 mmol). This

dark solution was placed under nitrogen and heated to 80 °C for 2 h then cooled to RT. The reaction was purified by flash chromatography (EtOAc-hexane). Concentration of the appropriate fractions afforded 95B (1.23 g, 89% yield) as an orange oil. MS(ES): *m/z* = 313 $[M+H]^+$ for parent boronic acid. T_r = 1.11 min (Method A).

95C. (+/-)-Methyl 3-(4-(diisobutylamino)-3-fluoro-5-nitrophenyl)pentanoate

A reaction vial was charged with 95B (1.2 g, 3.16 mmol). The SM was dissolved in dioxane (10 mL), and (E)-methyl pent-2-enoate (1.081 g, 9.47 mmol) was added followed by 1M aq. sodium hydroxide (2.84 mL, 2.84 mmol). The sample was degassed by freezing under vacuum then thawing under nitrogen twice. The reaction was charged with chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.078 g, 0.158 mmol), and the freeze/thaw purge cycle was repeated. The reaction was stirred 4.5 h at 50 °C, treated with acetic acid (0.361 mL, 6.31 mmol) then applied to a flash column and eluted with 5-15% EtOAc-hexane. Concentration of the appropriate fractions afforded 95C (0.81 g, 64% yield) as an orange oil. MS(ES): *m/z* = 383 $[M+H]^+$. T_r = 1.29 min (Method A).

95D. Methyl 3-(3-amino-4-(diisobutylamino)-5-fluorophenyl)pentanoate

Racemate 95D was prepared from 95C following the procedure described for the synthesis of 1H. MS(ES): *m/z* = 353 $[M+H]^+$. T_r = 1.22 min (Method A).

Chiral separation of Racemate 95D gave Enantiomer 1 T_r = 8.31 min and Enantiomer 2 T_r = 8.98 min (Method BG).

95D Enantiomer 1: LC-MS Anal. Calc'd. for $C_{20}H_{33}FN_2O_2$ 352.2, found [M+H] 353.4. T_r = 4.13 min (Method U).

95D Enantiomer 2: LC-MS Anal. Calc'd. for $C_{20}H_{33}FN_2O_2$ 352.2, found [M+H] 353.4. T_r = 4.12 min (Method U).

95E. Methyl 3-(4-(diisobutylamino)-3-fluoro-5-((2-methylbenzo[d]thiazol-6-yl)amino) phenyl)pentanoate

To a solution of methyl 95D Enantiomer 1 (50 mg, 0.142 mmol) in 1,4-dioxane (2 mL) were added 6-bromo-2-methylbenzo[d]thiazole (38.8 mg, 0.170 mmol), Cs_2CO_3 (139 mg, 0.426 mmol). The reaction mixture was purged with nitrogen for 15 minutes. Then was added Xantphos (41.0 mg, 0.071 mmol) followed by bis(dibenzylideneacetone)

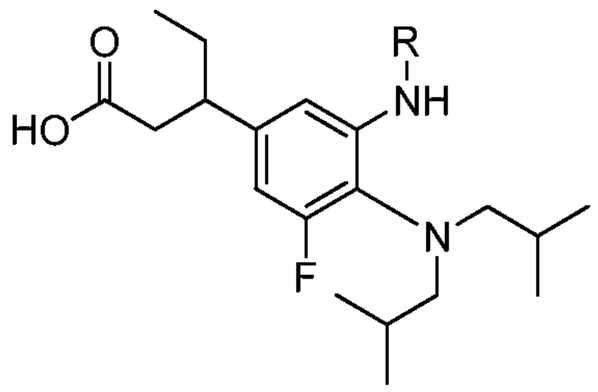
palladium (8.16 mg, 0.014 mmol) and heated to 110 °C overnight. Reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (2 × 15 mL) followed by brine solution (2 × 15 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure get crude was purified by flash chromatography (15% EA:hexane; 12g silica gel column) to afford 95E (brown gummy, 50 mg, 0.093 mmol, 65.6% yield). LC-MS Anal. Calc'd. for $C_{28}H_{38}FN_3O_2S$ 499.2, found 500.2, T_r = 4.67 min (Method U).

Example 95. 3-(4-(Diisobutylamino)-3-fluoro-5-((2-methylbenzo[d]thiazol-6-yl)amino) phenyl)pentanoic acid

Example 95 was prepared from 95E following the procedure described for the synthesis of Example 78. LC-MS Anal. Calc'd. for $C_{27}H_{36}FN_3O_2S$ 485.2, found 486.2, T_r = 2.65 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, *J* = 8.40 Hz, 1H), 7.77 (s, 1H), 7.53 (s, 1H), 7.19 (d, *J* = 10.40 Hz, 1H), 6.92 (s, 1H), 6.52 (d, *J* = 13.20 Hz, 1H), 2.67-2.86 (m, 8H), 2.55-2.57 (m, 1H), 2.39-2.45 (m, 1H), 1.45-1.67 (m, 4H), 0.87 (d, *J* = 6.40 Hz, 12H), 0.73 (t, *J* = 7.60 Hz, 3H).

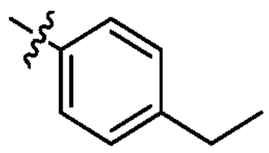
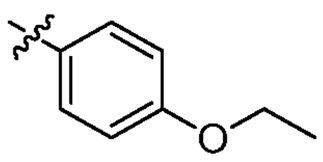
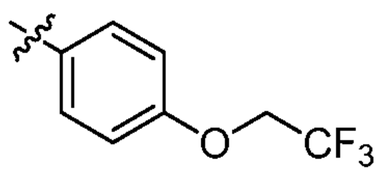
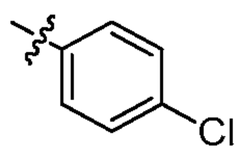
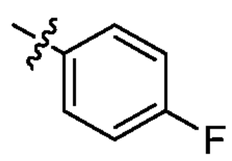
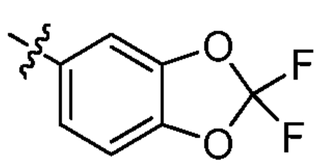
Examples 96 to 107

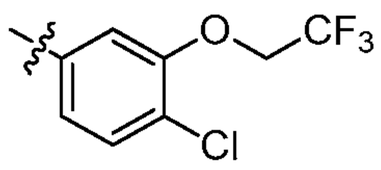
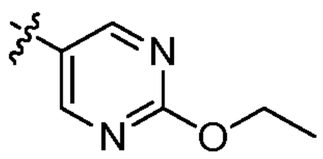
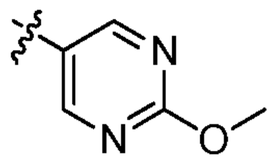
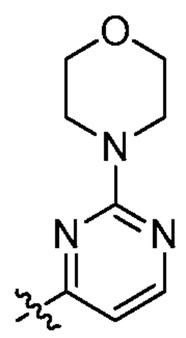
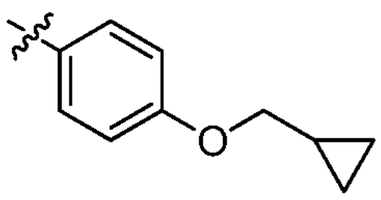
(Enantiomer 1)

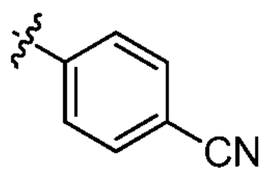


Examples 96 to 106 were prepared from Intermediate 95D Enantiomer 1 and corresponding halides following the procedure described for the synthesis of Example 95.

Example 107 was prepared from 95D Enantiomer 1 and corresponding halides following the procedure described for the synthesis of Example 83.

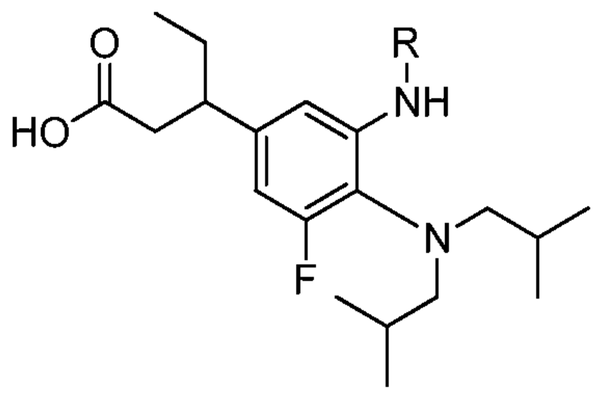
Ex. No.	Name	R	T_r min	Method	(M+H)
96	3-(4-(diisobutylamino)-3-((4-ethylphenyl) amino)-5-fluorophenyl) pentanoic acid		3.0	O	443.3
97	3-(4-(diisobutylamino)-3-((4-ethoxyphenyl) amino)-5-fluorophenyl) pentanoic acid		2.86	O	459.3
98	3-(4-(diisobutylamino)-3-fluoro-5-((4-(2,2,2-trifluoroethoxy)phenyl) amino)phenyl)pentanoic acid		2.86	O	513.3
99	3-(3-((4-chlorophenyl) amino)-4-(diisobutylamino)-5-fluorophenyl)pentanoic acid		2.95	O	449.2
100	3-(4-(diisobutylamino)-3-fluoro-5-((4-fluorophenyl)amino) phenyl)pentanoic acid		2.89	O	433.3
101	3-(3-((2,2-difluorobenzo [d][1,3]dioxol-5-yl)amino)-4-(diisobutylamino)-5-fluorophenyl)pentanoic acid		3.08	O	495.2

Ex. No.	Name	R	T_r min	Method	(M+H)
102	3-(3-((4-chloro-3-(2,2,2-trifluoroethoxy)phenyl) amino)-4-(diisobutylamino)-5-fluorophenyl)pentanoic acid		3.08	O	547.2
103	3-(4-(diisobutylamino)-3-((2-ethoxypyrimidin-5-yl)amino)-5-fluorophenyl)pentanoic acid		2.99	R	461.3
104	3-(4-(diisobutylamino)-3-fluoro-5-((2-methoxypyrimidin-5-yl)amino)phenyl) pentanoic acid		2.35	O	447.3
105	3-(4-(diisobutylamino)-3-fluoro-5-((2-morpholinopyrimidin-4-yl)amino)phenyl) pentanoic acid		2.46	O	502.3
106	3-(3-((4-(cyclopropylmethoxy) phenyl)amino)-4-(diisobutylamino)-5-fluorophenyl)pentanoic acid		2.97	O	485.3

Ex. No.	Name	R	T_r min	Method	(M+H)
107	3-(3-((4-cyanophenyl) amino)-4-(diisobutylamino)-5-fluorophenyl)pentanoic acid		2.66	O	440.3

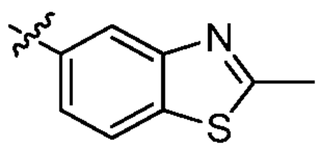
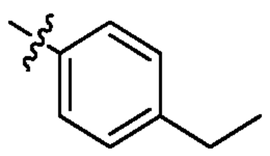
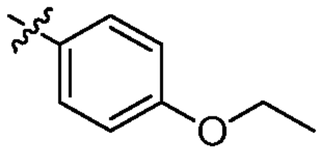
Examples 111 to 123

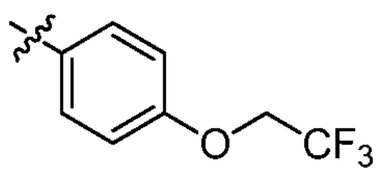
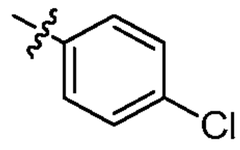
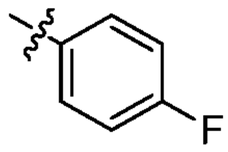
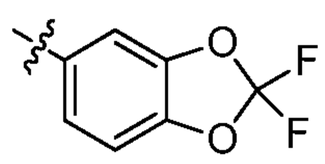
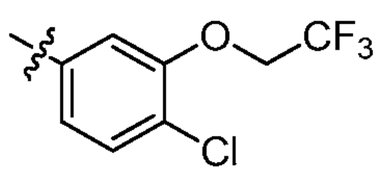
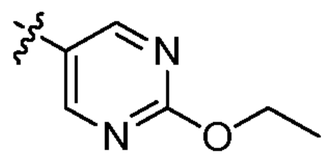
(Enantiomer 2)

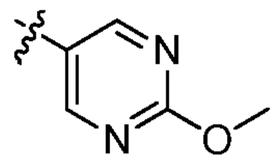
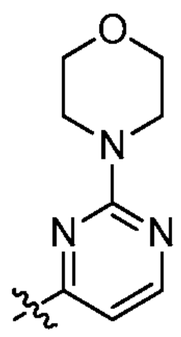
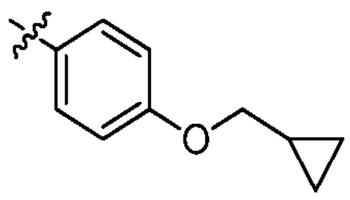
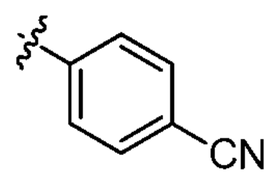


Examples 111 to 122 was prepared from 95D Enantiomer 2 and corresponding halides following the procedure described for the synthesis of Example 95.

Example 123 was prepared from 95D Enantiomer 2 and corresponding halides following the procedure described for the synthesis of Example 83.

Ex. No.	Name	R	T_r min	Method	(M+H)
111	3-(4-(diisobutylamino)-3-fluoro-5-((2-methylbenzo [d]thiazol-6-yl)amino) phenyl)pentanoic acid		2.65	O	486.2
112	3-(4-(diisobutylamino)-3-((4-ethylphenyl)amino)-5-fluorophenyl)pentanoic acid		3.0	O	443.3
113	3-(4-(diisobutylamino)-3-((4-ethoxyphenyl)amino)-5-fluorophenyl)pentanoic acid		2.86	O	459.3

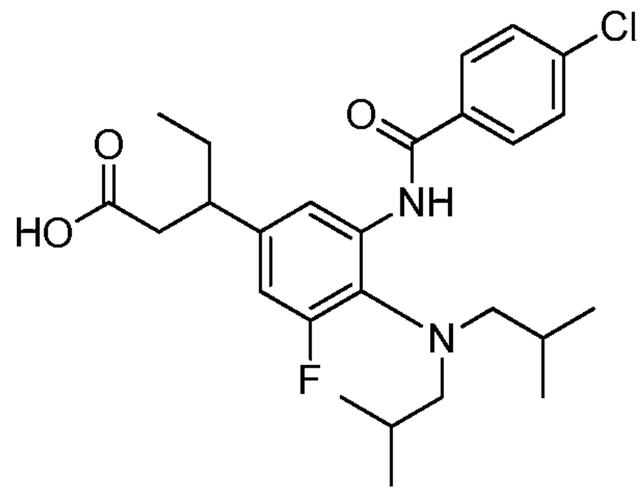
Ex. No.	Name	R	T_r min	Method	(M+H)
114	3-(4-(diisobutylamino)-3-fluoro-5-((4-(2,2,2-trifluoroethoxy)phenyl) amino)phenyl)pentanoic acid		2.85	O	513.3
115	3-(3-((4-chlorophenyl) amino)-4-(diisobutylamino)-5-fluorophenyl)pentanoic acid		2.95	O	449.2
116	3-(4-(diisobutylamino)-3-fluoro-5-((4-fluorophenyl) amino)phenyl)pentanoic acid		2.81	O	433.3
117	3-(3-((2,2-difluorobenzo [d][1,3]dioxol-5-yl)amino)-4-(diisobutylamino)-5-fluorophenyl)pentanoic acid		3.12	O	495.3
118	3-(3-((4-chloro-3-(2,2,2-trifluoroethoxy)phenyl) amino)-4-(diisobutylamino)-5-fluorophenyl)pentanoic acid		3.14	Q	547.2
119	3-(4-(diisobutylamino)-3-((2-ethoxypyrimidin-5-yl)amino)-5-fluorophenyl) pentanoic acid		2.65	O	461.3

Ex. No.	Name	R	T_r min	Method	(M+H)
120	3-(4-(diisobutylamino)-3-fluoro-5-((2-methoxypyrimidin-5-yl)amino)phenyl) pentanoic acid		2.34	O	447.3
121	3-(4-(diisobutylamino)-3-fluoro-5-((2-morpholinopyrimidin-4-yl)amino)phenyl) pentanoic acid		2.46	O	502.3
122	3-(3-((4-(cyclopropylmethoxy) phenyl)amino)-4-(diisobutylamino)-5-fluorophenyl)pentanoic acid		2.97	O	485.3
123	3-(3-((4-cyanophenyl) amino)-4-(diisobutylamino)-5-fluorophenyl)pentanoic acid		2.66	O	440.3

Example 127

(Enantiomer 1)

3-(3-(4-Chlorobenzamido)-4-(diisobutylamino)-5-fluorophenyl)pentanoic acid



127A. Methyl 3-(3-(4-chlorobenzamido)-4-(diisobutylamino)-5-fluorophenyl)pentanoate

To a solution of 4-chlorobenzoic acid (48.9 mg, 0.312 mmol) in DMF (1 mL) was added HATU (108 mg, 0.284 mmol) and DIPEA (0.149 mL, 0.851 mmol) stirred at rt for 30 minutes. Then was added 95D Enantiomer 1 (100 mg, 0.284 mmol) in DMF (1 mL) and stirred at room temperature overnight. Reaction mass was concentrated under reduced pressure. To that residue sodium bicarbonate (10%) solution (20 mL) was added and extracted with ethyl acetate (2 × 20 mL). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford 127A (brown gummy, 150 mg, 0.079 mmol, 28.0% yield). LC-MS Anal. Calc'd. for $C_{27}H_{36}ClFN_2O_3$ 490.2, found 491.2, T_r = 4.62 min (Method U).

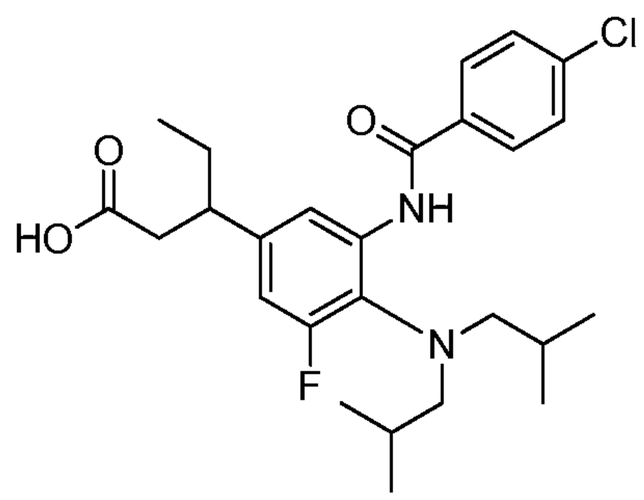
Example 127. 3-(3-(4-Chlorobenzamido)-4-(diisobutylamino)-5-fluorophenyl) pentanoic acid

Example 127 was prepared from 127A following the procedure described for the synthesis of Example 74. LC-MS Anal. Calc'd. for $C_{26}H_{34}ClFN_2O_3$ 476.2, found 477.2 T_r = 2.62 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 8.07 (s, 1H), 7.84 (d, *J* = 8.80 Hz, 2H), 7.66 (d, *J* = 8.40 Hz, 2H), 6.88 (d, *J* = 13.20 Hz, 1H), 2.88-2.90 (m, 1H), 2.73-2.75 (m, 4H), 2.55-2.58 (m, 1H), 2.44-2.49 (m, 1H), 1.50-1.67 (m, 4H), 0.82 (d, *J* = 6.40 Hz, 12H), 0.74 (t, *J* = 7.20 Hz, 3H).

Example 128

(Enantiomer 2)

3-(3-(4-Chlorobenzamido)-4-(diisobutylamino)-5-fluorophenyl)pentanoic acid



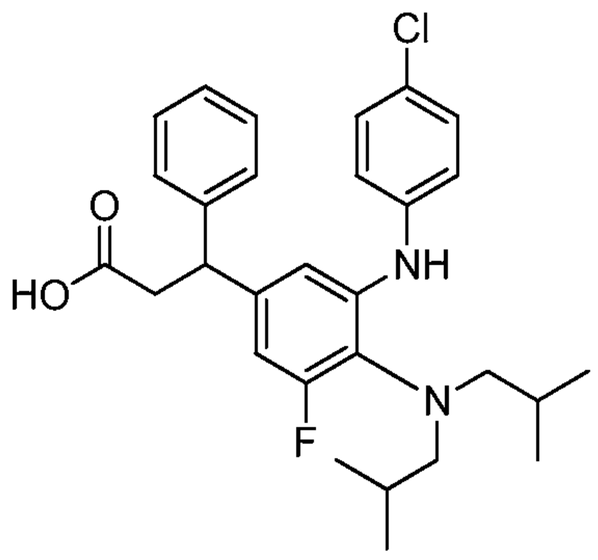
Example 128 was prepared from 95D Enantiomer 2 following the procedure described for the synthesis of Example 127. LC-MS Anal. Calc'd. for $C_{26}H_{34}ClFN_2O_3$

476.2, found 477.2, T_r = 2.62 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 8.07 (s, 1H), 7.84 (d, *J* = 8.80 Hz, 2H), 7.66 (d, *J* = 8.40 Hz, 2H), 6.88 (d, *J* = 13.20 Hz, 1H), 2.88-2.90 (m, 1H), 2.73-2.75 (m, 4H), 2.55-2.58 (m, 1H), 2.44-2.49 (m, 1H), 1.50-1.67 (m, 4H), 0.82 (d, *J* = 6.40 Hz, 12H), 0.74 (t, *J* = 7.20 Hz, 3H).

Example 129

(Enantiomer 1)

3-(3-((4-Chlorophenyl)amino)-4-(diisobutylamino)-5-fluorophenyl)-3-phenylpropanoic acid



129A. Methyl 3-(4-(diisobutylamino)-3-fluoro-5-nitrophenyl)-3-phenylpropanoate

To a solution of 95B (0.45 g, 1.183 mmol) in dioxane (15 mL) was added methyl cinnamate (0.384 g, 2.367 mmol) followed by 1M sodium hydroxide (1.065 mL, 1.065 mmol). The reaction mixture was purged with argon for 10 min, then was added chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.029 g, 0.059 mmol). Then reaction mixture was heated to 50 °C and stirred overnight. Reaction mass was cooled to room temperature, diluted with ethyl acetate (50 mL) and washed with water (2 × 50 mL) followed by brine solution (2 × 50 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to get crude which was purified by flash chromatography (5% EA:hexane; 40g silica gel column) to afford 129A (brown gummy, 0.4 g, 0.892 mmol, 75% yield). LC-MS Anal. Calc'd. for $C_{24}H_{31}FN_2O_4$ 430.2, found 431.2, T_r = 4.3 min (Method U).

129B. Methyl 3-(3-amino-4-(diisobutylamino)-5-fluorophenyl)-3-phenylpropanoate

To a solution of 129A (80 mg, 0.186 mmol) in ethyl acetate (2 mL) was added Pd/C (39.6 mg, 0.037 mmol) and stirred under hydrogen pressure at 40 psi in tiny clave

for 2.5 h. Reaction mass was filtered through CELITE® and concentrated under reduced pressure to get 129B (brown gummy, 0.07 g, 0.15 mmol, 80% yield). LC-MS Anal. Calc'd. for $C_{24}H_{33}FN_2O_2$ 400.2, found 401.2, T_r = 4.23 min (Method U).

Chiral separation of Racemate 129B gave Enantiomer 1, T_r = 4.5 min and Enantiomer 2, T_r = 5.0 min (Method BN).

129B Enantiomer 1 (0.02 g, 0.085 mmol, 27.1% yield): LC-MS Anal. Calc'd. for $C_{24}H_{33}FN_2O_2$ 400.2, found 401.2, T_r = 4.248 min (Method U).

129B Enantiomer 2 (0.02 g, 0.085 mmol, 27.1% yield): LC-MS Anal. Calc'd. for $C_{24}H_{33}FN_2O_2$ 400.2, found 401.2, T_r = 4.248 min (Method U).

129C. Methyl 3-(3-((4-chlorophenyl)amino)-4-(diisobutylamino)-5-fluorophenyl)-3-phenylpropanoate

To a solution of 129B Enantiomer 1 (40 mg, 0.100 mmol) in 1,4-dioxane (2 mL) were added 1-bromo-4-chlorobenzene (27.3 mg, 0.120 mmol), Cs_2CO_3 (98 mg, 0.300 mmol). The reaction mixture was purged with nitrogen for 15 minutes. Then was added Xantphos (28.9 mg, 0.050 mmol) followed by bis(dibenzylideneacetone)palladium (5.74 mg, 9.99 µmol) and heated to 110 °C overnight. Reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (2 × 15 mL) followed by brine solution (2 × 15 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford 129C (brown gummy, 50 mg, 0.030 mmol, 30.2% yield). LC-MS Anal. Calc'd. for $C_{30}H_{36}ClFN_2O_2$ 510.2, found 511.2, T_r = 4.79 min (Method U).

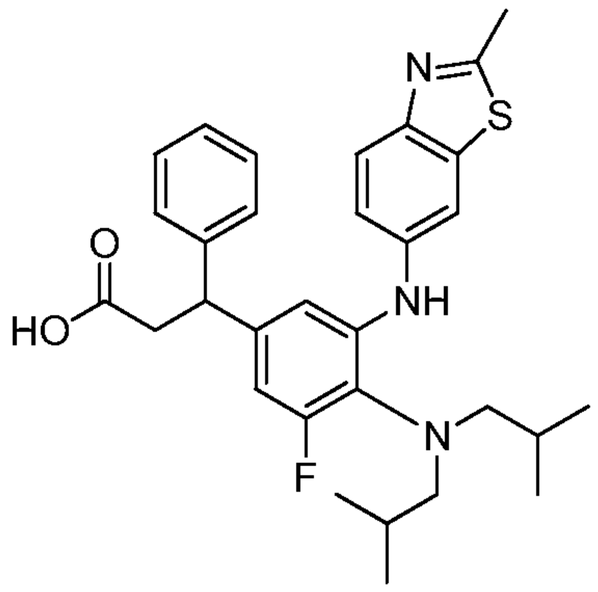
Example 129. 3-(3-((4-Chlorophenyl)amino)-4-(diisobutylamino)-5-fluorophenyl)-3-phenylpropanoic acid

Example 129 was prepared from 129C following the procedure described for the synthesis of Example 74 from 74G. LC-MS Anal. Calc'd. for $C_{29}H_{34}ClFN_2O_2$ 496.2, found 497.2 T_r = 2.99 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (s, 1H), 7.27-7.34 (m, 6H), 7.17-7.20 (m, 1H), 7.07-7.10 (m, 2H), 6.95 (s, 1H), 6.60 (dd, *J* = 1.60, 13.20 Hz, 1H), 4.35 (t, *J* = 8.00 Hz, 1H), 2.96-2.99 (m, 2H), 2.67-2.68 (m, 4H), 1.54-1.60 (m, 2H), 0.83 (d, *J* = 6.80 Hz, 12H).

Example 130

(Enantiomer 1)

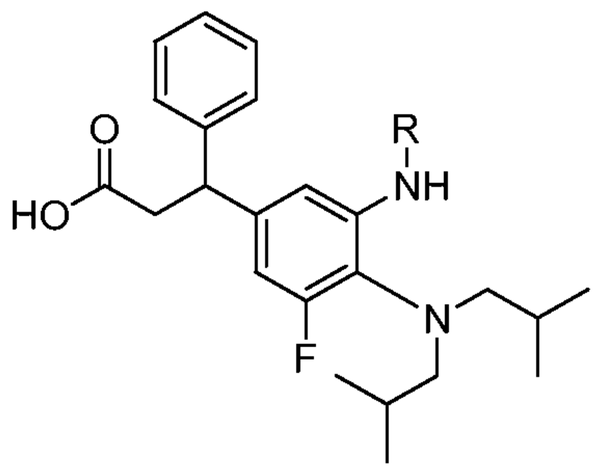
3-(4-(Diisobutylamino)-3-fluoro-5-((2-methylbenzo[d]thiazol-6-yl)amino)phenyl)-3-phenylpropanoic acid



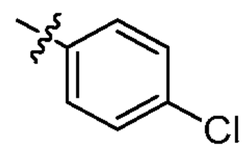
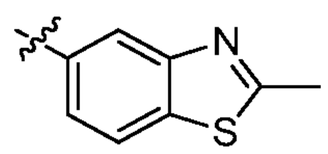
Example 130 was prepared from 129B Enantiomer 1 and 6-bromo-2-methylbenzo[d]thiazole following the procedure described for the synthesis of Example 129. LC-MS Anal. Calc'd. for $C_{31}H_{36}FN_3O_2S$ 533.2, found 534.2, T_r = 2.7 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ7.79 (d, *J* = 8.80 Hz, 1H), 7.68 (d, *J* = 2.40 Hz, 1H), 7.52 (s, 1H), 7.34 (d, *J* = 7.20 Hz, 2H), 7.29 (t, *J* = 7.60 Hz, 2H), 7.18-7.21 (m, 1H), 7.13 (dd, *J* = 2.40, 8.80 Hz, 1H), 7.01 (s, 1H), 6.60 (dd, *J* = 1.60, 13.20 Hz, 1H), 4.37 (t, *J* = 7.60 Hz, 1H), 2.97-3.00 (m, 2H), 2.75 (s, 3H), 2.67-2.70 (m, 4H), 1.56-1.63 (m, 2H), 0.85 (d, *J* = 6.80 Hz, 12H).

Examples 131 and 132

(Enantiomer 2)



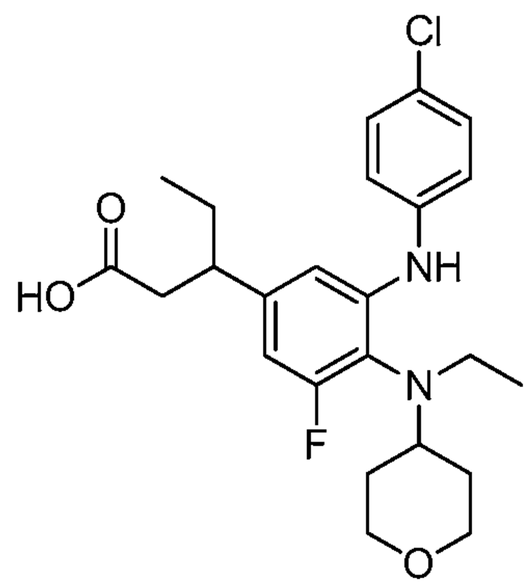
Examples 131 and 132 were prepared from 129B Enantiomer 2 and corresponding halide by following the procedure described for the synthesis of Example 129.

Ex. No.	Name	R	T_r min	Method	(M+H)
131	3-(3-((4-chlorophenyl) amino)-4-(diisobutylamino)-5-fluorophenyl)-3-phenylpropanoic acid		2.94	O	497.2
132	3-(4-(diisobutylamino)-3-fluoro-5-((2-methylbenzo[d] thiazol-6-yl)amino)phenyl)-3-phenylpropanoic acid		2.7	O	534.3

Example 133

(Enantiomer 1)

3-(3-((4-Chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-5-fluorophenyl)pentanoic acid



133A. N-(4-Bromo-2-fluoro-6-nitrophenyl)-N-ethyltetrahydro-2H-pyran-4-amine

Compound 133A was prepared from 5-bromo-1,2-difluoro-3-nitrobenzene and N-ethyltetrahydro-2H-pyran-4-amine following the procedure described for the synthesis of 74C. LC-MS Anal. Calc'd. for $C_{13}H_{16}BrFN_2O$ 346.03, found (M+2) 348.2, T_r = 3.28 (Method U). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (d, *J* = 1.60 Hz, 1H), 7.91 (dd, *J* = 2.00, 11.00 Hz, 1H), 3.82 (dd, *J* = 3.20, 11.20 Hz, 2H), 3.23 (t, *J* = 10.00 Hz, 2H), 3.11 - 3.17 (m, 1H), 3.01 - 3.06 (m, 2H), 1.58 (d, *J* = 8.00 Hz, 2H), 1.29 - 1.39 (m, 2H), 0.83 (t, *J* = 7.20 Hz, 3H).

133B. Methyl 3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-fluoro-5-nitrophenyl)pent-2-enoate

To a solution of 133A (2.1 g, 6.05 mmol) in DMF (40 mL) were added (E)-methyl pent-2-enoate (2.071 g, 18.15 mmol), TEA (2.53 mL, 18.15 mmol) followed by tetrabutylammonium bromide (0.390 g, 1.210 mmol). Then reaction mixture was purged with nitrogen for 10 minutes. Then was added dichlorobis(tri-o-tolylphosphine) palladium(II) (0.238 g, 0.302 mmol) and heated to 120 °C overnight. Reaction mixture was diluted with ethyl acetate (30 mL) and washed with water (20 mL) followed by brine solution (2 × 20 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to get crude which was purified by flash chromatography (15% EA:hexane; 40 g silica gel column) to afford 133B (brown gummy 420 mg, 0.773 mmol, 12.78% yield). LC-MS Anal. Calc'd. for $C_{19}H_{25}FN_2O_5$ 380.17, found 381.2, T_r = 3.41 min (Method U).

133C. Methyl 3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-5-fluorophenyl) pentanoate

To a solution of 133B (400 mg, 1.051 mmol) in ethyl acetate (10 mL) was added 10% Pd/C (224 mg, 0.210 mmol) and stirred at room temperature under hydrogen bladder pressure for 12 h. Reaction mixture was filtered through CELITE® and concentrated under reduced pressure to get crude which purified by flash chromatography to afford Racemate 133C. LC-MS Anal. Calc'd. for $C_{19}H_{29}FN_2O_3$ 352.21, found 353.2, T_r = 3.07 min (Method U).

Chiral separation of Racemate 133C gave Enantiomer 1 T_r = 11.56 min and Enantiomer 2 T_r = 16.43 min (Method BV).

133C Enantiomer 1 (brown gummy, 64 mg, 0.154 mmol, 14.67% yield): LC-MS Anal. Calc'd. for $C_{19}H_{29}FN_2O_3$ 352.21, found 353.2, T_r = 3.12 min (Method U).

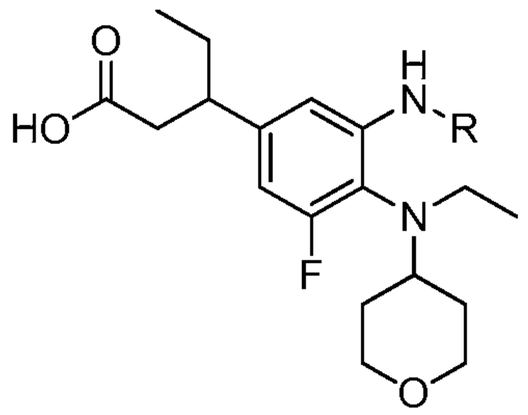
133C Enantiomer 2 (brown gummy, 57 mg, 0.145 mmol, 13.82% yield): LC-MS Anal. Calc'd. for $C_{19}H_{29}FN_2O_3$ 352.21, found 353.2, T_r = 3.06 min (Method U).

Example 133. 3-(3-((4-Chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-5-fluorophenyl)pentanoic acid

Example 133 was prepared from 133C Enantiomer 1 following the procedure described for the synthesis of Example 84. LC-MS Anal. Calc'd. for $C_{24}H_{30}ClFN_2O_3$ 448.19, found 449.2, T_r = 2.35 min (Method R). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.56 (s, 1H), 7.30 (dd, *J* = 2.00, 6.80 Hz, 2H), 7.20 (dd, *J* = 2.40, 6.80 Hz, 2H), 6.82 (d, *J* = 1.60 Hz, 1H), 6.51 (dd, *J* = 1.60, 12.80 Hz, 1H), 3.79 (s, 2H), 3.21-3.24 (m, 2H), 3.13-3.15 (m, 1H), 3.01-3.04 (m, 2H), 2.73-2.75 (m, 1H), 2.66-2.68 (m, 1H), 2.40-2.44 (m, 1H), 1.14-1.60 (m, 6H), 0.84 (t, *J* = 7.44 Hz, 3H), 0.72 (t, *J* = 7.20 Hz, 3H).

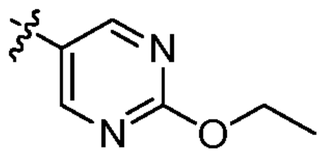
Examples 134 to 138

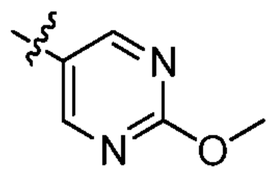
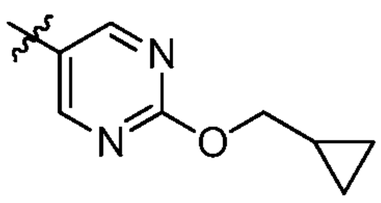
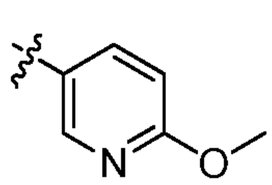
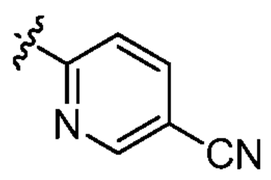
(Enantiomer 1)



Examples 134 to 137 were prepared from 133C Enantiomer 1 and corresponding aryl halides following the procedure described for the synthesis of Example 78.

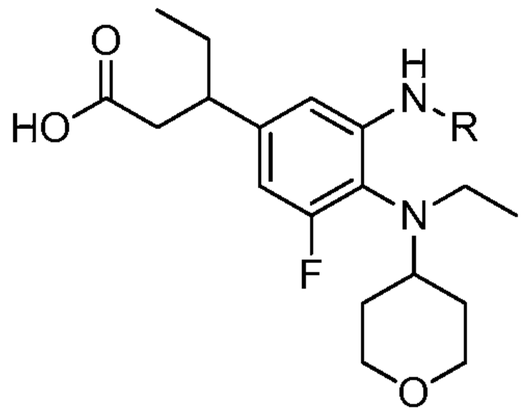
Example 138 was prepared from 133C Enantiomer 1 and corresponding aryl halides following the procedure described for the synthesis of Example 83.

Ex. No.	Name	R	T_r min	Method	(M+H)
134	3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-5-fluorophenyl)pentanoic acid		1.55	O	461.4

Ex. No.	Name	R	T_r min	Method	(M+H)
135	3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-fluoro-5-((2-methoxypyrimidin-5-yl)amino)phenyl) pentanoic acid		1.42	O	447.3
136	3-(3-((2-(cyclopropylmethoxy) pyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-5-fluorophenyl)pentanoic acid		1.93	O	487.4
137	3-(3-((6-methoxypyridin-3-yl)amino)phenyl) pentanoic acid		1.61	O	446.3
138	3-(3-((5-cyanopyridin-2-yl)amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-5-fluorophenyl)pentanoic acid		1.79	O	441.3

Examples 139 to 144

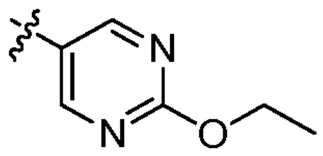
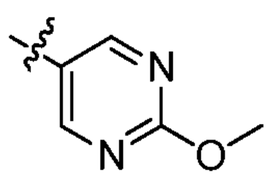
(Enantiomer 2)

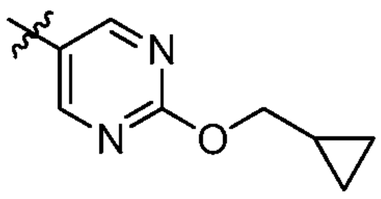
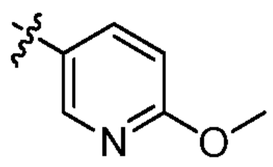
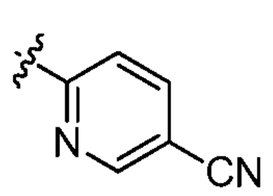
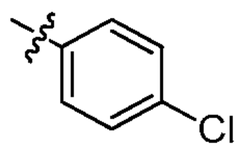


Examples 139 to 142 were prepared from 133C Enantiomer 2 and corresponding aryl halide following the procedure described for the synthesis of Example 78.

Example 143 was prepared from 133C Enantiomer 2 and corresponding aryl halide following the procedure described for the synthesis of Example 83.

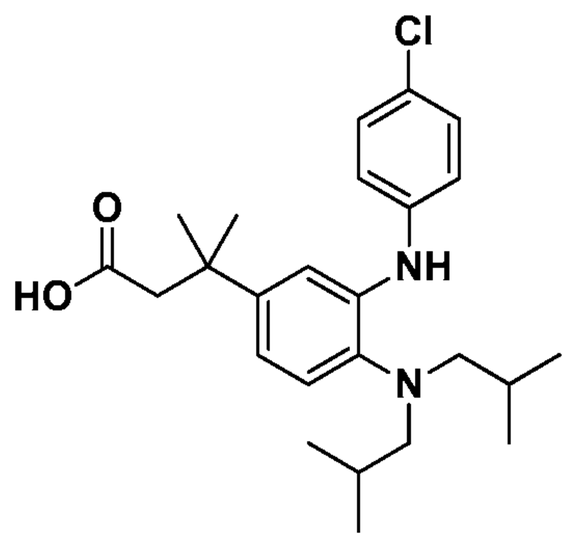
Example 144 was prepared from 133C Enantiomer 2 and corresponding aryl halide following the procedure described for the synthesis of Example 133.

Ex. No.	Name	R	T_r min	Method	(M+H)
139	3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-5-fluorophenyl)pentanoic acid		1.95	R	461.3
140	3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-fluoro-5-((2-methoxypyrimidin-5-yl)amino)phenyl) pentanoic acid		1.39	O	447.3

Ex. No.	Name	R	T_r min	Method	(M+H)
141	3-(3-((2-(cyclopropylmethoxy) pyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-5-fluorophenyl)pentanoic acid		1.71	O	487.4
142	3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-fluoro-5-((6-methoxypyridin-3-yl)amino)phenyl) pentanoic acid		1.59	O	446.4
143	3-(3-((5-cyanopyridin-2-yl)amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-5-fluorophenyl)pentanoic acid		1.54	O	441.3
144	3-(3-((4-chlorophenyl) amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-5-fluorophenyl)pentanoic acid		1.97	O	449.3

Example 145

3-(3-((4-Chlorophenyl)amino)-4-(diisobutylamino)phenyl)-3-methylbutanoic acid



145A. Diethyl 2-(2-(4-fluorophenyl) propan-2-yl) malonate

To a stirred solution of magnesium (0.139 g, 5.71 mmol) in dry diethyl ether (5.0 mL), 1-bromo-4-fluorobenzene (0.500 g, 2.86 mmol) and pinch of iodine was added at room temperature. Reaction mixture was stirred for 30 minutes at room temperature. Reaction mixture was cooled to -10 °C and diethyl isopropylidenemalonate (1.144 g, 5.71 mmol) was added in dropwise over 2 minutes and stirred for 20 minutes at room temperature. The reaction mixture was then refluxed for 3 h. Reaction mixture was quenched with ice cold 1 N HCl (5 mL). Organic layer separated and aqueous layer extracted with diethyl ether (2 × 10 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, and the solvent was evaporated to give 145A (light yellow liquid, 550 mg, 1.856 mmol, 65% yield). LC-MS Anal. Calc'd. for $C_{16}H_{21}FO_4$ 296.14, found [M+H] 297.2, T_r = 1.47 min (Method BA).

145B. Ethyl 3-(4-fluorophenyl)-3-methylbutanoate

To a stirred solution of 145A (0.500 g, 1.687 mmol), in DMSO (5.0 mL), water (0.15 mL) mixture lithium chloride (0.143 g, 3.37 mmol) was added. Reaction mixture was heated to 180 °C and stirred for 12 h. Reaction mixture was cooled to room temperature, partitioned between diethyl ether (50 mL) and water (25 mL). Aqueous layer was extracted with ether (2 × 25 mL). The combined organic layer was washed with brine (25 mL). The organic phase were dried over anhydrous Na_2SO_4, filtered and concentrated to give crude compound. Purification via flash chromatography gave 145B (light yellow liquid, 255 mg, 1.137 mmol, 67% yield). LC-MS Anal. Calc'd. for $C_{13}H_{17}FO_2$ 224.12, found [M+H] 225.2, T_r = 2.87 min (Method N).

145C. Ethyl 3-(4-fluoro-3-nitrophenyl)-3-methylbutanoate

To a 25 mL round bottomed flask at 0 °C was charged with 145B (0.200 g, 0.892 mmol) in H_2SO_4 (2.0 mL). Nitric acid (0.092 mL, 1.338 mmol) was added under nitrogen atmosphere and maintained at same temperature for 1 h. Reaction mixture was added to the ice and extracted with DCM (2 × 10 mL). The organic phase were dried over anhydrous Na_2SO_4, filtered and concentrated to give crude compound. Purification via flash chromatography gave 145C (colorless liquid, 210 mg, 0.780 mmol, 87% yield). LC-MS Anal. Calc'd. for $C_{13}H_{16}FNO_4$ 269.10, found [M+H] 270.2, T_r = 1.02 min (Method BC).

145D. Ethyl 3-(4-(diisobutylamino)-3-nitrophenyl)-3-methylbutanoate

To a 5 mL pressure tube was charged with 145C (200 mg, 0.743 mmol), diisobutylamine (192 mg, 1.486 mmol) and heated to 130 °C temperature for 12 h. Reaction mixture was concentrated completely under reduced pressure to get crude reaction mixture. Purification via flash chromatography gave 145D (orange liquid, 255 mg, 0.674 mmol, 91% yield). LC-MS Anal. Calc'd. for $C_{21}H_{34}N_2O_4$ 378.2, found [M+H] 379.2, T_r = 4.29 min (Method N).

145E. Ethyl 3-(3-amino-4-(diisobutylamino) phenyl)-3-methylbutanoate

The solution of 145D (255 mg, 0.674 mmol) in ethyl acetate (15 mL) was charged to a sealable hydrogen flask. The solution was sequentially evacuated and purged with nitrogen gas. To this 10% Pd/C (25 mg, 0.023 mmol) was charged under flow of nitrogen. The resulting mixture was sequentially evacuated then purged with nitrogen before the flask was pressured to 40 psi of hydrogen pressure and stirred at ambient temperature for 4 h. The reaction mixture was filtered through a pad of CELITE® which was then thoroughly rinsed with ethyl acetate (2 × 20 mL). The combined filtrates were concentrated under reduced pressure to afford 145E (230 mg, 0.660 mmol, 98% yield). LC-MS Anal. Calc'd. for $C_{21}H_{36}N_2O_2$ 348.2, found [M+H] 349.2, T_r = 4.22 min (Method N).

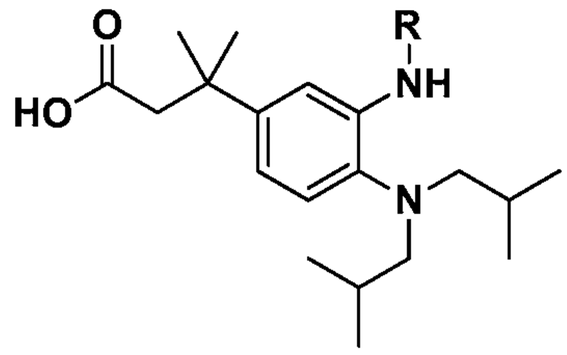
145F. Ethyl 3-(3-((4-chlorophenyl)amino)-4-(diisobutylamino)phenyl)-3-methylbutanoate

To a stirred solution of 145E (0.040 g, 0.115 mmol) in dry dioxane (2.0 mL), 1-bromo-4-chlorobenzene (0.022 g, 0.115 mmol), cesium carbonate (0.112 g, 0.344 mmol) was added and argon was purged for 10 minutes. 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (0.013 g, 0.023 mmol), and bis(dibenzylideneacetone)palladium (6.60 mg, 0.011 mmol) was added under argon atmosphere. The lid of tube was closed and placed on parallel synthesizer at 100 °C temperature for 16 h. The reaction mixture was filtered through pad of CELITE®, washed with EtOAc (2 × 10 mL). The filtrate was concentrated under reduced pressure to get crude reaction mixture. Purification via flash chromatography gave 145F (off-white solid, 42 mg, 0.091 mmol, 80% yield). LC-MS Anal. Calc'd. for $C_{27}H_{39}ClN_2O_2$ 458.2, found [M+H] 459.1, T_r = 1.71 min (Method BC).

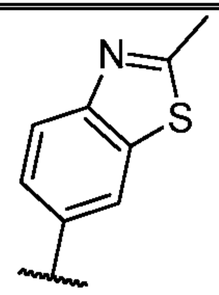
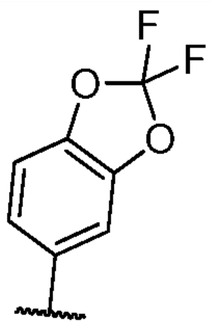
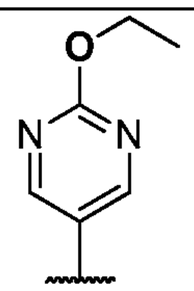
Example 145. 3-(3-((4-Chlorophenyl)amino)-4-(diisobutylamino)phenyl)-3-methylbutanoic acid

To a solution of 145F (0.040 g, 0.087 mmol) in THF (1.0 mL), MeOH (1.0 mL), water (0.5 mL) mixture LiOH (10.43 mg, 0.436 mmol) was added and was stirred at RT for 12 h. Solvent was concentrated under reduced pressure and the crude pH was adjusted to ~2 with 1.5 (N) HCl solution. The aqueous layer was extracted with dichloromethane (2 × 25 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification via preparative LC/MS gave Example 145 (36.4 mg, 0.083 mmol, 95% yield). LC-MS Anal. Calc'd. for $C_{25}H_{35}ClN_2O_2$ 430.2, found [M+H] 431.2. T_r = 3.09 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (br. s., 1H), 7.27 - 7.20 (m, 2H), 7.14 - 7.12 (m, 1H), 7.05 - 7.04 (m, 2H), 7.03 - 7.02 (m, 2H), 6.93 - 6.90 (m, 1H), 2.67 - 2.50 (m, 4H), 1.69 - 1.61 (m, 2H), 1.34 (s, 6H), 0.83 (m, 12H) (Note: one multiplet CH_2 buried under solvent peak).

Examples 146 to 148

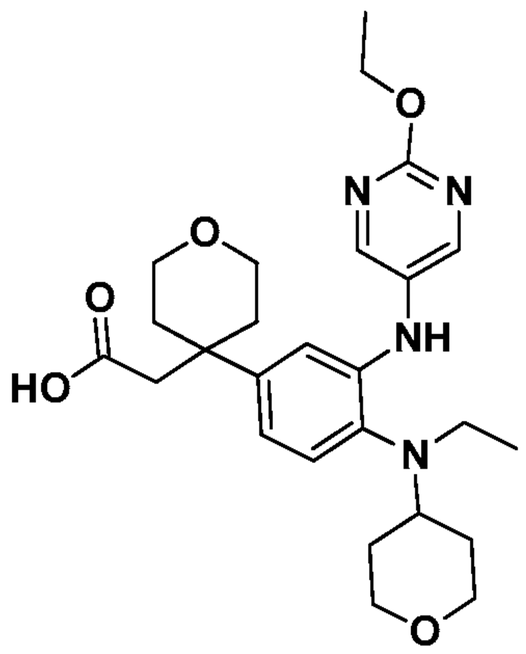


Examples 146 to 148 were prepared from 145E and corresponding aryl halides following the procedure described for the synthesis of Example 145.

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
146	3-(4-(diisobutylamino)-3-((2-methylbenzo[d]thiazol-6-yl)amino) phenyl)-3-methylbutanoic acid		2.807	468.3
147	3-(3-((2,2-difluorobenzo[d][1,3] dioxol-5-yl)amino)-4-(diisobutylamino)phenyl)-3-methylbutanoic acid		3.138	477.3
148	3-(4-(diisobutylamino)-3-((2-ethoxypyrimidin-5-yl)amino) phenyl)-3-methyl butanoic acid		2.624	443.4

Example 153

2-(4-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)tetrahydro-2H-pyran-4-yl)acetic acid



153A. Ethyl 2-cyano-2-(dihydro-2H-pyran-4(3H)-ylidene)acetate

To a stirred solution of dihydro-2H-pyran-4(3H)-one (5.0 g, 49.9 mmol), ethyl 2-cyanoacetate (5.65 g, 49.9 mmol) in dry toluene (50.0 mL), ammonium acetate (0.770 g, 9.99 mmol), acetic acid (2.45 ml, 42.8 mmol) and piperidine (0.00494 mL, 0.050 mmol)

were added at room temperature. Reaction mixture was heated to reflux at 110 °C for 3 h. Reaction mixture cooled to room temperature and toluene was evaporated under reduced pressure to get brown liquid. Above liquid was diluted with ethyl acetate (300 mL) and washed with water (100 mL), saturated bicarbonate solution (100 mL) and brine (100 mL). The organic phases were combined and the solvent was dried over anhydrous sodium sulfate, concentrated under reduced pressure to give off-white semi-solid. Purification by flash chromatography gave 153A (off-white solid, 7.65g, 39.2 mmol, 78% yield). LC-MS Anal. Calc'd. for $C_{10}H_{13}NO_3$ 195.2, found [M-H] 194.2, T_r = 0.96 min (Method BA).

153B. Ethyl 2-cyano-2-(4-(4-fluorophenyl)tetrahydro-2H-pyran-4-yl)acetate

To a stirred solution of 153A (2.5 g, 12.87 mmol), in dry diethyl ether (60 mL), (4-fluorophenyl)magnesium bromide (15.45 mL, 15.45 mmol) was added slowly in 20 min under nitrogen atmosphere at room temperature. A thick suspension of resulting mixture was refluxed at 40 °C for 5 h. Reaction mixture cooled to 0 °C and quenched with 1N HCl (25 mL). Aqueous layer extract with diethyl ether (2 × 50 mL). The organic phases were combined and the solvent was evaporated under reduced pressure to give brown liquid. Purification by flash chromatography gave 153B (light yellow liquid, 3.0 g, 10.30 mmol, 80% yield). LC-MS Anal. Calc'd. for $C_{16}H_{18}FNO_3$ 291.12, found [M-H] 290.4, T_r = 1.15 min (Method BA).

153C. 2-(4-(4-Fluorophenyl)tetrahydro-2H-pyran-4-yl)acetic acid

To a stirred solution of 153B (2.9 g, 9.95 mmol) in ethylene glycol (50 mL), KOH (4.55 g, 81 mmol) and water (10.0 mL, 555 mmol) were added. Reaction mixture was heated to 180 °C and maintained for 16 h. Reaction mixture cooled to room temperature, diluted with water (100 mL) and pH was adjusted about to 3 with con. HCl. Aqueous layer extracted with dichloromethane (3 × 50 mL). The organic phases were combined and the solvent dried over sodium sulfate, concentrated under reduced pressure to give 153C (light yellow liquid, 2.1 g, 8.81 mmol, 89.0% yield). LC-MS Anal. Calc'd. for $C_{13}H_{15}FO_3$ 238.1, found [M+H] 239.2, T_r = 0.48 min (Method U).

153D. Methyl 2-(4-(4-fluorophenyl)tetrahydro-2H-pyran-4-yl)acetate

To a stirred solution of 153C in MeOH (20.0 mL), H_2SO_4 (0.045 mL, 0.839 mmol) was added at room temperature. Reaction mixture was heated to reflux for 6 h. Reaction mixture was cooled to room temperature, concentrated under reduced pressure to get light yellow liquid. Purification by flash chromatography gave 153D (light yellow liquid, 1.25 g, 4.95 mmol, 59.0% yield). LC-MS Anal. Calc'd. for $C_{14}H_{17}FO_3$ 252.1, found [M+H] 253.2, T_r = 1.89 min (Method BE).

153E. Methyl 2-(4-(4-fluoro-3-nitrophenyl)tetrahydro-2H-pyran-4-yl)acetate

In a 50 mL round bottomed flask with 153D (0.750 g, 2.97 mmol) at 0 °C, H_2SO_4 (3.0 ml, 56.3 mmol) was slowly added, followed by potassium nitrate (0.301 g, 2.97 mmol) under nitrogen atmosphere. The reaction mixture was stirred at same temperature for 15 min. Reaction mixture was poured in ice slowly for 20 minutes. Aqueous layer was extracted with ethyl acetate (2 × 10 mL). The organic phases were combined, dried over sodium sulfate and concentrated under reduced pressure to give light yellow liquid. Purification by flash chromatography gave 153E (light yellow liquid, 785 mg, 2.64 mmol, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 - 7.99 (m, 1H), 7.61 - 7.57 (m, 1H), 7.33 - 7.26 (m, 1H), 3.83 - 3.64 (m, 4H), 3.46 (s, 3H), 2.69 (s, 2H), 2.23 - 2.04 (m, 4H).

153F. Methyl 2-(4-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)tetrahydro-2H-pyran-4-yl)acetate

To a stirred solution of 153E (1.0 g, 3.36 mmol), N-ethyltetrahydro-2H-pyran-4-amine (0.652 g, 5.05 mmol) in NMP (10.0 mL), DIPEA (1.763 mL, 10.09 mmol) was added and heated to 135 °C for 36 h. Reaction mixture was cooled to room temperature, diluted with MTBE (50.0 mL). Organic layer was washed with water (2 × 25 mL). Aqueous layer was extracted with MTBE (2 × 30 mL). The organic phases were combined and the solvent was dried over sodium sulfate concentrated to give light yellow liquid. Purification by flash chromatography gave 153F (light orange liquid, 1.1 g, 2.71 mmol, 80% yield). LC-MS Anal. Calc'd. for $C_{21}H_{30}N_2O_6$ 406.2, found [M+H] 407.2, T_r = 2.64 min (Method N).

153G. Methyl 2-(4-(3-amino-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) tetrahydro-2H-pyran-4-yl)acetate

To a stirred solution of 153F (1.0 g, 2.460 mmol), in dry ethyl acetate (7.5 mL), 10% Pd/C (0.100 g, 0.094 mmol) was added under nitrogen atmosphere. The resulting mixture was sequentially evacuated then purged with nitrogen before the flask was pressured to 40 psi of hydrogen and stirred at ambient temperature for 16 h. The reaction mixture was filtered through a pad of CELITE® which was then thoroughly rinsed with ethyl acetate. The combined filtrates were concentrated under reduced pressure to afford 153G (light yellow liquid, 900 mg, 2.391 mmol, 97% yield). LC-MS Anal. Calc'd. for $C_{21}H_{32}N_2O_4$ 376.2, found [M+H] 377.3, T_r = 2.79 min (Method N).

153H. Methyl 2-(4-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)tetrahydro-2H-pyran-4-yl)acetate

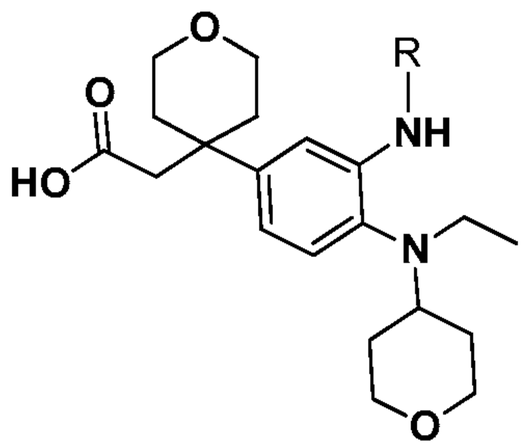
To a degassed solution of 153G (0.075 g, 0.199 mmol), 5-bromo-2-ethoxypyrimidine (0.040 g, 0.199 mmol), cesium carbonate (0.097 g, 0.299 mmol) in dry dioxane (2.0 mL) purged argon for 15 minutes. 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (0.012 g, 0.020 mmol), bis(dibenzylideneacetone)palladium (5.73 mg, 9.96 µmol) was added, the pressure tube lid was closed and placed on an oil bath. Reaction mixture was heated to 110 °C temperature and maintained for 4 h. The reaction mixture was filtered through pad of CELITE®, washed with EtOAc (2 × 10 mL). The filtrate was concentrated under reduced pressure. Purification via flash chromatography gave 153H (off-white solid, 78 mg, 0.156 mmol, 79% yield). LC-MS Anal. Calc'd. for $C_{27}H_{38}N_4O_5$ 498.2, found [M+H] 499.4. T_r = 2.75 min (Method N).

Example 153. 2-(4-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)tetrahydro-2H-pyran-4-yl)acetic acid

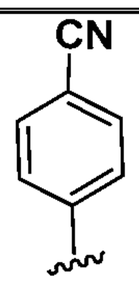
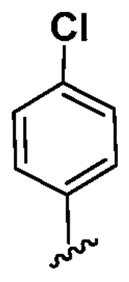
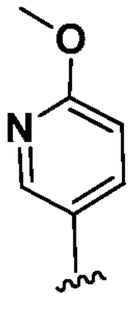
Example 153 was prepared from 153H following the procedure described for the synthesis of Example 145 from 145F. LC-MS Anal. Calc'd. for $C_{26}H_{36}N_4O_5$ 484.2, found [M+H] 485.1, T_r =1.51 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.9 (br. s., 1H), 8.41 (s, 2H), 7.28 (s, 1H), 7.15 - 7.12 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 2.0 Hz, 1H), 6.84 - 6.82 (m, 1H), 4.29 - 4.27 (m, 2H), 3.80 - 3.76 (m, 2H), 3.64 - 3.63 (m, 2H), 3.49 -

3.47 (m, 2H), 3.23 - 3.16 (m, 3H), 3.00 -2.96 (m, 2H), 2.53 - 2.49 (m, 2H), 2.06 - 1.92 (m, 4H), 1.68 - 1.65 (m, 2H), 1.42 - 1.40 (m, 2H), 1.33 (m, 3H), 0.82 (t, J = 7.2 Hz, 3H).

Examples 154 to 156

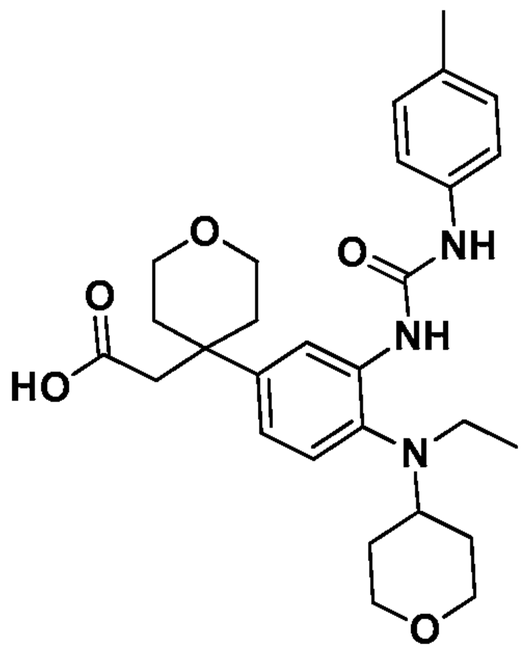


Examples 154 to 156 were prepared from 153G and corresponding aryl halides following the procedure described for the synthesis of Example 153.

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
154	2-(4-(3-((4-cyanophenyl)amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)phenyl) tetrahydro-2H-pyran-4-yl)acetic acid		1.659	464.1
155	2-(4-(3-((4-chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)tetrahydro-2H-pyran-4-yl)acetic acid		1.991	473.1
156	2-(4-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((6-methoxypyridin-3-yl)amino)phenyl)tetrahydro-2H-pyran-4-yl)acetic acid		1.592	470.1

Example 157

2-(4-(4-(Ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)tetrahydro-2H-pyran-4-yl)acetic acid



157A. Methyl 2-(4-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido) phenyl)tetrahydro-2H-pyran-4-yl)acetate

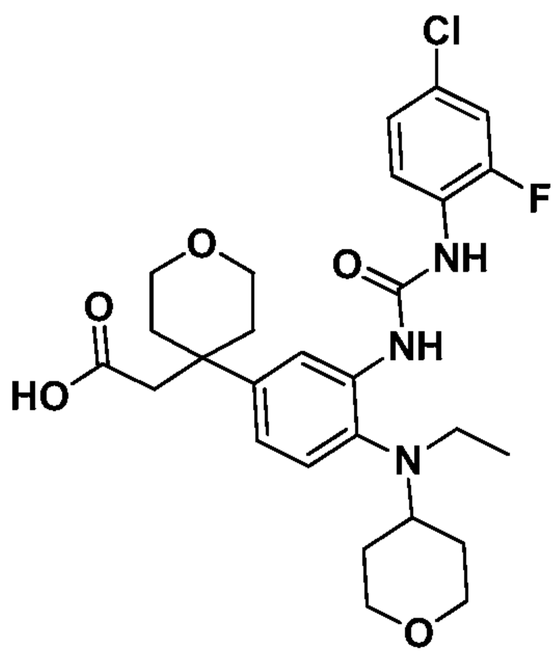
Compound 157A was prepared from 153G and 1-isocyanato-4-methylbenzene following the procedure described for the synthesis of 5A. LC-MS Anal. Calc'd. for $C_{29}H_{39}N_3O_5$ 509.2, found [M+H] 510.5, T_r = 1.36 min (Method BA).

Example 157. 2-(4-(4-(Ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido) phenyl)tetrahydro-2H-pyran-4-yl)acetic acid

Example 157 was prepared from 157A following the procedure described for the synthesis of Example 145 from 145F. LC-MS Anal. Calc'd. for $C_{28}H_{37}N_3O_5$ 495.2, found [M+H] 496.1, T_r = 1.59 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (s, 1H), 8.48 (s, 1H), 8.28 (s, 1H), 7.38 - 7.36 (d, *J* = 8.4 Hz, 2H), 7.18 - 7.16 (m, 1H), 7.10 - 7.08 (m, 2H), 6.95 - 6.93 (m, 1H), 3.90 - 3.82 (m, 2H), 3.71 - 3.68 (m, 2H), 3.52 - 3.50 (m, 2H), 3.34 - 3.17 (m, 4H), 3.00 -2.96 (m, 3H), 2.25 (s, 3H), 2.07 - 1.99 (m, 4H), 1.72 - 1.69 (m, 2H), 1.39 - 1.38 (m, 2H), 0.80 (t, *J* = 6.8 Hz, 3H).

Example 158

2-(4-(3-(3-(4-Chloro-2-fluorophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)tetrahydro-2H-pyran-4-yl)acetic acid



158A. Methyl 2-(4-(3-(3-(4-chloro-2-fluorophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)tetrahydro-2H-pyran-4-yl)acetate

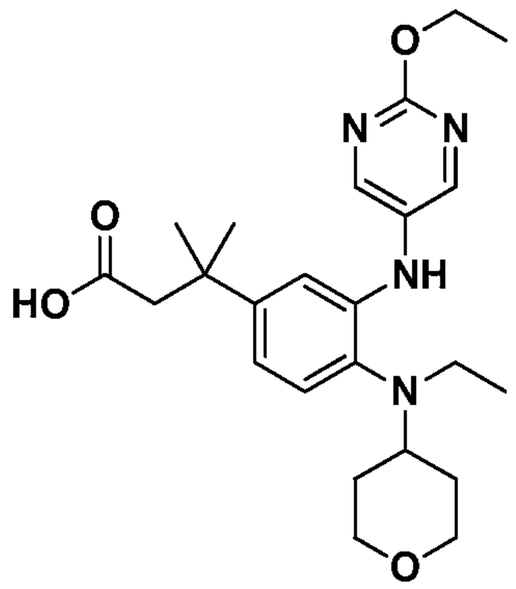
Compound 158A was prepared from 153G and 4-chloro-2-fluoro-1-isocyanatobenzene following the procedure described for the synthesis of 5A. LC-MS Anal. Calc'd. for $C_{28}H_{35}ClFN_3O_5$ 547.2, found [M+H] 548.4, T_r = 1.44 min (Method BA).

Example 158. 2-(4-(3-(3-(4-Chloro-2-fluorophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)tetrahydro-2H-pyran-4-yl)acetic acid

Example 158 was prepared from 158A following the procedure described for the synthesis of Example 145 from 145F. LC-MS Anal. Calc'd. for $C_{27}H_{33}ClFN_3O_5$ 533.2, found [M+H] 534.0, T_r = 1.71 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.86 (s, 1H), 8.23 (d, *J* = 2.0 Hz, 1H), 8.16 - 8.11 (m, 1H), 7.45 - 7.24 (dd, *J* = 2.4 Hz, 2.4 Hz, 1H), 7.22 - 7.16 (m, 2H), 6.98 - 6.96 (dd, *J* = 2.0 Hz, 2.0 Hz, 1H), 3.89 - 3.82 (m, 2H), 3.68 - 3.66 (m, 2H), 3.50 -3.46 (m, 2H), 3.34 - 3.17 (m, 2H), 3.00 - 2.96 (m, 3H), 2.53 - 2.50 (m, 2H), 2.07 - 1.90 (m, 4H), 1.72 - 1.69 (m, 2H), 1.41 - 1.38 (m, 2H), 0.80 (t, *J* = 7.2 Hz, 3H).

Example 159

3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoic acid



159A. Ethyl 3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)-3-methylbutanoate

To a stirred solution of 145C (2.0 g, 7.43 mmol) and N-ethyltetrahydro-2H-pyran-4-amine (1.439 g, 11.14 mmol) in NMP (5.0 mL) solvent, DIPEA (3.89 mL, 22.28 mmol) was added. Reaction mixture was heated to 135 °C for 16 h. Reaction mixture cooled to room temperature, diluted with MTBE (20 mL), washed with water (10 mL). Organic layer was separated and aqueous layer was back extracted with MTBE (2 × 20 mL). The organic phases were combined, dried over sodium sulfate and concentrated under reduced pressure to give light yellow liquid. Purification by flash chromatography gave 159A (520 mg, 1.374 mmol, 18.50% yield). LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_5$ 378.2, found [M+H] 379.2, T_r = 3.374 min (Method N).

159B. Ethyl 3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoate

159B was prepared from 159A following the procedure described for the synthesis of 145E. LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_3$ 348.2, found [M+H] 349.2 T_r = 3.05 min (Method N).

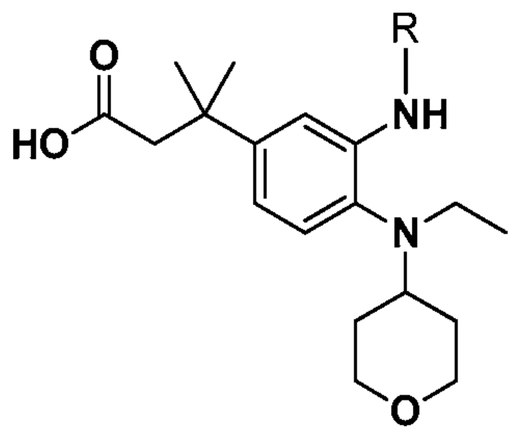
159C. Ethyl 3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoate

Compound 159C was prepared from 159B and 5-bromo-2-ethoxypyrimidine following the procedure described for the synthesis of 145F. LC-MS Anal. Calc'd. for $C_{26}H_{38}N_4O_4$ 470.2, found [M+H] 471.2, T_r = 3.684 min (Method N).

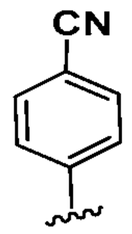
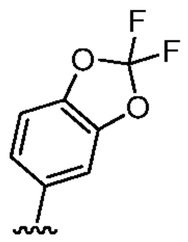
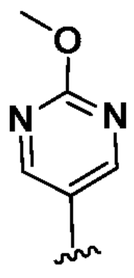
Example 159. 3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoic acid

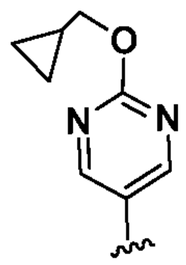
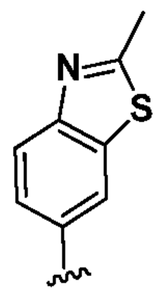
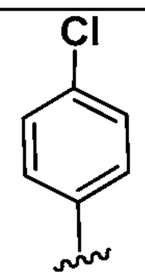
Example 159 was prepared from 159C following the procedure described for the synthesis of Example 145 from 145F. LC-MS Anal. Calc'd. for $C_{24}H_{34}N_4O_4$ 442.2, found [M+H] 443.4, T_r = 2.39 min. (Method N). ^{1}H NMR(400 MHz, DMSO-d_6) δ 11.90 (br. s., 1H), 8.43 (s, 2H), 7.29 (s, 1H), 7.11 (d, *J* = 8.40 Hz, 1H), 7.02 (m, 1H), 6.86 (m, 1H), 4.27 (m, 2H), 3.83 - 3.80 (m, 2H), 3.25 - 2.97 (m, 4H), 2.99 - 2.98 (m, 3H), 1.51 - 1.50 (m, 2H), 1.48 (m, 2H), 1.44 (m, 9H), 0.77 -0.82 (m, 3H).

Examples 160 to 165



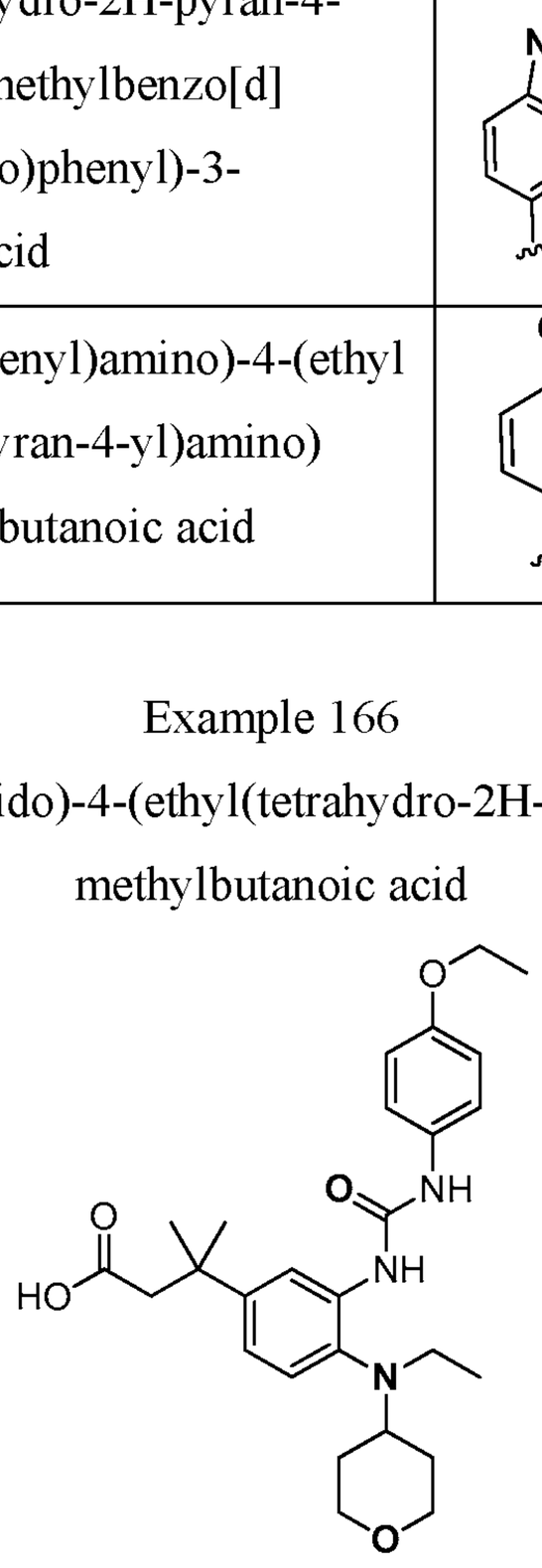
Examples 160 to 165 were prepared from 159B and the corresponding aryl halides following the procedure described for the synthesis of Example 145.

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
160	3-(3-((4-cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoic acid		1.814	422.3
161	3-(3-((2,2-difluorobenzo[d][1,3]dioxol-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoic acid		1.814	477.2
162	3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methoxypyrimidin-5-yl)amino)phenyl)-3-methylbutanoic acid		1.51	429.2

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
163	3-(3-((2-(cyclopropylmethoxy) pyrimidin-5-yl)amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino) phenyl)-3-methylbutanoic acid		1.98	469.3
164	3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methylbenzo[d] thiazol-6-yl)amino)phenyl)-3-methylbutanoic acid		2.00	468.2
165	3-(3-((4-chlorophenyl)amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino) phenyl)-3-methylbutanoic acid		2.32	431.2

Example 166

3-(3-(3-(4-Ethoxyphenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoic acid



166A. Ethyl 3-(3-(3-(4-ethoxyphenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)-3-methylbutanoate

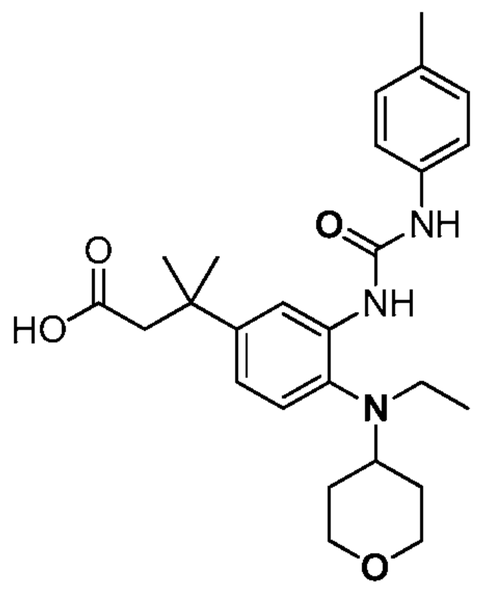
Compound 166A was prepared from 159B and 1-ethoxy-4-isocyanatobenzene following the procedure described for the synthesis of 5A. LC-MS Anal. Calc'd. for $C_{29}H_{41}N_3O_5$ 511.305, found [M+H] 512.6, T_r = 1.20 min (Method BC).

Example 166. 3-(3-(3-(4-Ethoxyphenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-methylbutanoic acid

Example 166 was prepared from 166A following the procedure described for the synthesis of Example 145 from 145F. LC-MS Anal. Calc'd. $C_{27}H_{37}N_3O_5$ for 483.2, found [M+H] 484.3, T_r = 1.64 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H), 8.32 - 8.31 (m, 2H), 7.36 - 7.34 (d, *J* = 8.8 Hz, 1H), 7.14 - 7.12 (d, *J* = 8.0 Hz, 2H), 6.97 - 6.94 (m, 1H), 6.86 - 6.84 (m, 2H), 4.03 - 3.95 (m, 2H), 3.45 - 2.90 (m, 7H), 2.18 - 2.15 (m, 2H), 1.87 - 1.85 (m, 2H), 1.36 -1.32 (m, 9H), 0.79 (t, *J* = 6.8 Hz, 3H) (Note: one -CH_2 peak buried under solvent peak).

Example 167

3-(4-(Ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)-3-methylbutanoic acid



167A. Ethyl 3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)-3-methylbutanoate

Compound 167A was prepared from 159B and 1-isocyanato-4-methylbenzene following the procedure described for the synthesis of 5A. LC-MS Anal. Calc'd. for $C_{28}H_{39}N_3O_4$ 481.294, found [M+H] 482.5, T_r = 1.23 min (Method CI).

Example 167. 3-(4-(Ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)-3-methylbutanoic acid

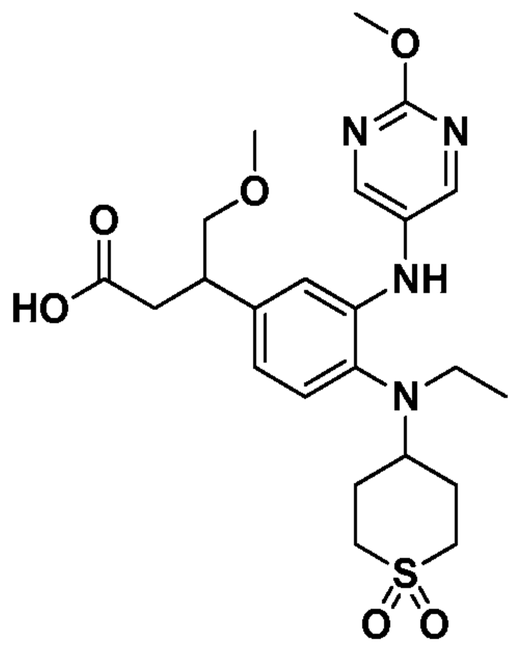
Example 167 was prepared from 167A following the procedure described for the synthesis of Example 145 from 145F. LC-MS Anal. Calc'd. $C_{26}H_{35}N_3O_4$ for 453.263, found [M+H] 454.3, T_r = 1.806 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.8

(br. s., 1H), 9.4 (s, 1H), 8.46 (s, 1H), 8.31 (d, *J* = 2.0 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.14 - 7.08 (m, 3H), 6.97 - 6.76 (m, 1H), 3.83 - 3.81 (m, 2H), 3.37 - 3.23 (m, 4H), 2.99 - 2.94 (m, 3H), 2.25 (s, 3H), 1.72 - 1.69 (m, 2H), 1.41-1.37 (m, 8H), 0.79 (t, *J* = 6.8 Hz, 3H).

Example 168

(Enantiomer 1 and Enantiomer 2)

3-(4-((1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((2-methoxy pyrimidin-5-yl)amino)phenyl)-4-methoxybutanoic acid



168A. (E)-Methyl 4-methoxybut-2-enoate

To stirred solution of (E)-methyl 4-bromobut-2-enoate (3 g, 16.76 mmol) in methanol (1.5 mL), silver oxide (3.11 g, 13.41 mmol) was added and stirred at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate (30 mL) filtered through CELITE® bed and washed with ethyl acetate (2 × 30 mL). The filtrate was evaporated to dryness under reduced pressure to get crude. Purification via flash chromatography gave 168A (yellow liquid, 0.7 g, 5.00 mmol, 29.8% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.93 - 6.85 (m, 1H), 6.02 - 5.95 (m, 1H), 4.08 - 4.06 (m, 2H), 3.66 (s, 3H), 3.29 (s, 3H).

168B. 2-(4-Fluorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane

To a stirred solution of 1-bromo-4-fluorobenzene (20 g, 114 mmol), bis(neopentyl glycolato)diboron (31.0 g, 137 mmol) and potassium acetate (33.6 g, 343 mmol) in toluene (200 mL) was purged argon for 20 min. $PdCl_2$ (dppf)•CH_2Cl_2 Adduct (2.80 g, 3.43 mmol) was added and purged argon for 5 min. The reaction mixture was heated to

80 °C and maintained for 2 h. Reaction mixture was cooled to room temperature and it was concentrated under reduced pressure. The crude was dissolved in EtOAc (300 mL), filtered through a pad of CELITE® and rinsed with EtOAc (100 mL), filtrate was washed with water (200 mL) followed by brine (100 mL). The organic layers were mixed and dried over anhydrous sodium sulfate. Organic layer was concentrated under reduced pressure. Purification via flash chromatography gave 168B (off-white solid, 21 g, 96 mmol, 84% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 - 7.71 (m, 2H), 7.18 - 7.13 (m, 2H), 3.75 (s, 4H), 0.95 (s, 6H).

168C. Methyl 3-(4-fluorophenyl)-4-methoxybutanoate

In a sealed tube 168B (1.877 g, 14.42 mmol), 168A (1.877 g, 14.42 mmol) and sodium hydroxide solution (8.65 mL, 8.65 mmol) in 1,4-dioxane (20.0 mL) was purged argon for 30 min. To this chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.237 g, 0.481 mmol) was added and purged argon for 10 min. The reaction mixture was heated at 50 °C for 2 h. Reaction mixture was cooled to room temperature and quenched with acetic acid (0.495 mL, 8.65 mmol) and it was stirred for 5 minutes. Reaction mixture was partitioned between ethyl acetate (50 mL) and water (20 mL). Aqueous layer was extracted with ethyl acetate (2 × 25 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash chromatography gave Racemate 168C (light yellow liquid, 1.25 g, 5.53 mmol, 57.5% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 - 7.16 (m, 2H), 7.00 - 6.95 (m, 2H), 3.59 (s, 3H), 3.51 - 3.38 (m, 3H), 3.31 (s, 3H), 2.84 - 2.60 (m, 1H), 2.60 - 2.52 (m, 1H).

168D. Methyl 3-(4-fluoro-3-nitrophenyl)-4-methoxybutanoate

Compound 168D was prepared from 168C following the procedure described for the synthesis of 145C. LC-MS Anal. Calc'd. for $C_{12}H_{14}FNO_5$ 271.1, found [M+H] 272.2, T_r = 2.28 min (Method U).

168E. N-Ethyltetrahydro-2H-thiopyran-4-amine

To a stirred solution of dihydro-2H-thiopyran-4(3H)-one (6.0 g, 51.6 mmol) in dry MeOH (50 mL), ethanamine (28.4 mL, 56.8 mmol) was added. Then molecular sieves

(5.0 g) were added to the reaction mixture and stirred at room temperature overnight. Reaction mixture was cooled to 0 °C and $NaBH_4$ (3.91 g, 103 mmol) was added portionwise in 10 minutes. Reaction mixture was stirred at room temperature for 3 h. Reaction mixture was concentrated under reduced pressure to get semi-solid. To this was added sat. aq. $NaHCO_3$ (200 mL) and was stirred overnight. Mixture was extracted with EtOAc (2 × 200 mL). Combined organic layer was washed with water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get 168E (light yellow liquid, 6.4 g, 44.1 mmol, 85% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 2.69 - 2.59 (m, 6H), 2.49 - 2.43 (m, 1H), 2.21 - 2.15 (m, 2H), 1.55 - 1.41 (m, 2H), 1.10 (t, J = 7.2 Hz, 3H).

168F. Methyl 3-(4-(ethyl(tetrahydro-2H-thiopyran-4-yl)amino)-3-nitrophenyl)-4-methoxybutanoate

Compound 168F was prepared from 168D and 168E following the procedure described for the synthesis of 153F. LC-MS Anal. Calc'd. for $C_{19}H_{28}N_2O_5S$ 396.17, found [M+H] 397.2, T_r = 3.108 min (Method U).

168G. Methyl 3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-nitrophenyl)-4-methoxybutanoate

To a stirred solution of 168F (0.7 g, 1.765 mmol) in acetonitrile (7.0 mL), water (5.38 mL) mixture OXONE® (2.71 g, 4.41 mmol), sodium bicarbonate (1.483 g, 17.65 mmol) was added at 0 °C. The reaction mixture was stirred at the same temperature for 20 minutes and continued at ambient temperature for 1 h. The resulting precipitates was diluted with acetonitrile and filtered through a pad of CELITE®. The filtrate was concentrated under reduced pressure and dilute with ethyl acetate (25 mL) washed with water (10 mL). Organic layer separated and dried over sodium sulfate, concentrated under reduced pressure to get orange liquid. Purification via flash chromatography gave Racemic 168G (orange liquid, 0.7 g, 1.65 mmol, 93% yield). LC-MS Anal. Calc'd. for $C_{19}H_{28}N_2O_7S$ 428.1, found [M+H] 429.1, T_r = 2.58 min (Method U).

168H. Methyl 3-(3-amino-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl)-4-methoxybutanoate

168H was prepared from 168G following the procedure described for the synthesis of 145E. LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_5S$ 398.1, found [M+H] 399.2, T_r = 1.94 min (Method U).

Chiral separation of Racemic 168H (Method Z) gave 168H Enantiomer 1 T_r = 4.24 min (Method Z) and 168H Enantiomer 2 T_r = 2.91 min (Method Z) as single enantiomers.

168H Enantiomer 1 (brown semi-solid, 0.15 g, 0.376 mmol, 23% yield): LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_5S$ 398.1, found [M+H] 399.2, T_r = 1.94 min (Method N).

168H Enantiomer 2 (brown semi-solid, 0.15 g, 0.376 mmol, 23% yield): LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_5S$ 398.1, found [M+H] 399.2, T_r = 1.94 min (Method N).

168I Enantiomer 1. Methyl 3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl) amino)-3-((2-methoxypyrimidin-5-yl)amino)phenyl)-4-methoxybutanoate

168I Enantiomer 1 was prepared from 168H Enantiomer 1 and 5-bromo-2-methoxypyrimidine following the procedure described for the synthesis of 145F. LC-MS Anal. Calc'd. for $C_{24}H_{34}N_4O_6S$ 506.2 found [M+H] 507.4, T_r = 1.13 min (Method BA).

Example 168 Enantiomer 1. 3-(4-((1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl) amino)-3-((2-methoxypyrimidin-5-yl)amino)phenyl)-4-methoxybutanoic acid

Example 168 Enantiomer 1 was prepared from 168I Enantiomer 1 following the procedure described for the synthesis of Example 145 from 145F. LC-MS Anal. Calc'd. for $C_{23}H_{32}N_4O_6S$ 492.2 found [M+H] 493.2, T_r = 1.13 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 2H), 7.34 (s, 1H), 7.11 - 7.09 (d, *J* = 8.0Hz, 1H), 6.84 (m, 1H), 6.71 - 6.68 (dd, *J* = 1.6, 2.0Hz, 1H), 3.89 (s, 3H), 3.30 (s, 3H), 3.28 - 3.15 (m, 5H), 3.10 - 2.94 (m, 5H), 2.60 - 2.40 (m, 2H), 2.13 - 1.96 (m, 4H), 0.87 - 0.83 (t, *J* = 6.80 Hz, 3H).

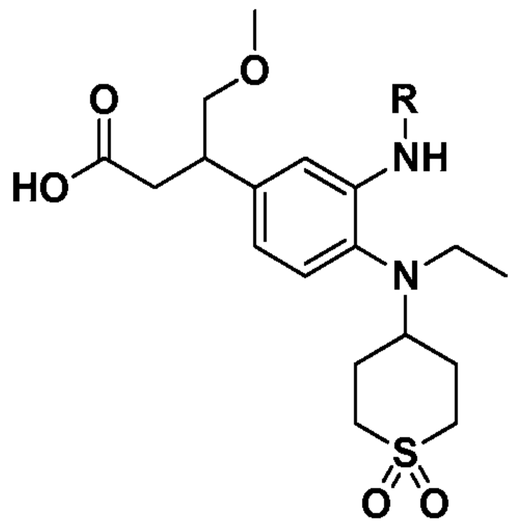
Example 168 Enantiomer 2. 3-(4-((1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl) amino)-3-((2-methoxypyrimidin-5-yl)amino)phenyl)-4-methoxybutanoic acid

Example 168 Enantiomer 2 was prepared from 168H Enantiomer 2 following the procedure described for the synthesis of Example 168 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{23}H_{32}N_4O_6S$ 492.2 found [M+H] 493.2, T_r = 1.13 min (Method O). ^{1}H NMR

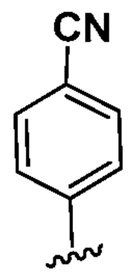
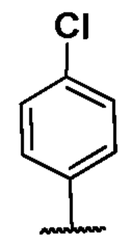
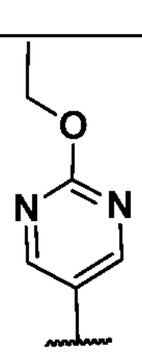
(400 MHz, DMSO-d_6) δ 8.45 (s, 2H), 7.34 (s, 1H), 7.11 - 7.09 (d, J = 8.0Hz, 1H), 6.84 (m, 1H), 6.71 - 6.68 (dd, J = 1.6, 2.0Hz, 1H), 3.89 (s, 3H), 3.30 (s, 3H), 3.28 - 3.15 (m, 5H), 3.10 - 2.94 (m, 5H), 2.60 - 2.40 (m, 2H), 2.13 - 1.96 (m, 4H), 0.87 - 0.83 (t, J = 6.80 Hz, 3H).

Examples 169 to 172

(Enantiomer 1)



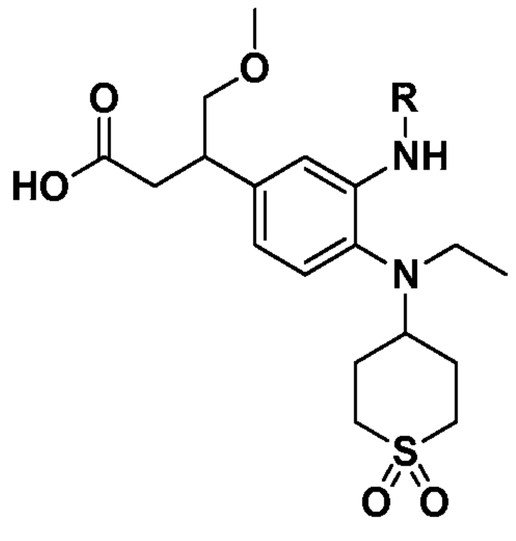
Examples 169 to 172 were prepared from 168H Enantiomer 1 and the corresponding aryl halides following the procedure described for the synthesis of Example 168 Enantiomer 1.

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
169	3-(3-((4-cyanophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl)-4-methoxybutanoic acid		1.341	486.2
170	3-(3-((4-chlorophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl)-4-methoxybutanoic acid		1.580	495.2
171	3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl)-4-methoxybutanoic acid		1.06	507.3

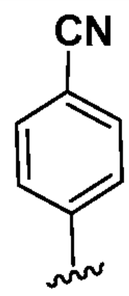
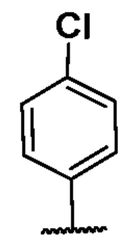
Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
172	3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((4-fluorophenyl)amino)phenyl)-4-methoxybutanoic acid		1.393	479.0

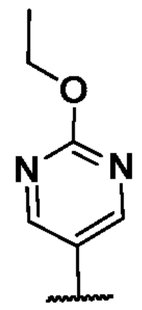
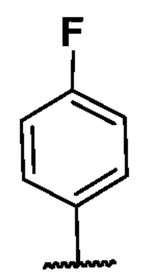
Examples 173 to 176

(Enantiomer 2)



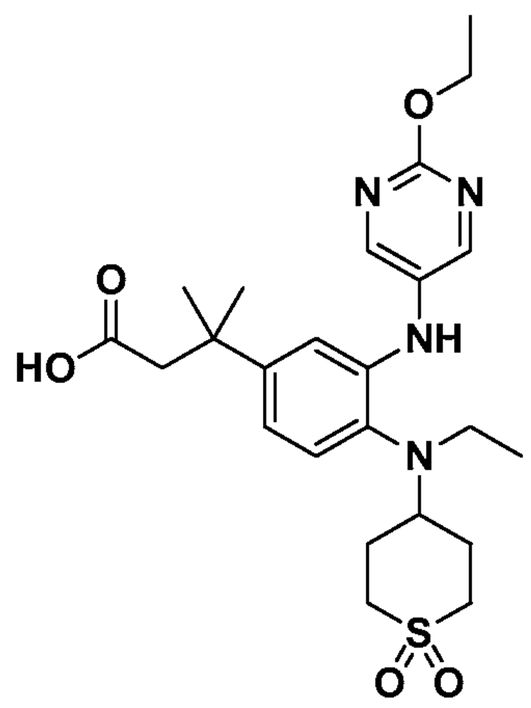
Examples 173 to 176 were prepared from 168H Enantiomer 2 and the corresponding aryl halides following the procedure described for the synthesis of Example 168 Enantiomer 1.

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
173	3-(3-((4-cyanophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl)-4-methoxybutanoic acid		1.333	486.2
174	3-(3-((4-chlorophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl)-4-methoxybutanoic acid		1.369	495.3

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
175	3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl)-4-methoxybutanoic acid		1.063	507.3
176	3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((4-fluorophenyl)amino)phenyl)-4-methoxybutanoic acid		1.389	479.1

Example 177

3-(4-((1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl)-3-methylbutanoic acid



177A. N-Ethyltetrahydro-2H-thiopyran-4-amine

To a stirred solution of dihydro-2H-thiopyran-4(3H)-one (6.0 g, 51.6 mmol) in dry MeOH (50 mL), ethanamine (28.4 mL, 56.8 mmol) was added. Then molecular sieves (5.0 g) were added to the reaction mixture and were stirred at RT overnight. Reaction mixture was cooled to 0 °C and $NaBH_4$ (3.91 g, 103 mmol) was added portionwise in 10 minutes. It was stirred at room temperature for 3 h. Reaction mixture was concentrated under reduced pressure to get semi-solid. To this was added sat. aq. $NaHCO_3$ (200 mL) and was stirred overnight. Mixture was extracted with EtOAc (2 × 200 mL). Combined

organic layer was washed with water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get 177A (light yellow liquid, 6.4 g, 44.1 mmol, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 - 2.59 (m, 6H), 2.49 - 2.43 (m, 1H), 2.21 - 2.15 (m, 2H), 1.55 - 1.41 (m, 2H), 1.10 (t, J = 7.2 Hz, 3H).

177B. Ethyl 3-(4-(ethyl(tetrahydro-2H-thiopyran-4-yl)amino)-3-nitrophenyl)-3-methylbutanoate

Compound 177B was prepared from 145C and 177A following the procedure described for the synthesis of 159A. LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_4S$ 394.2 found [M+H] 395.2, T_r = 3.67 min (Method N).

177C. Ethyl 3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-nitrophenyl)-3-methylbutanoate

Compound 177C was prepared from 177B following the procedure described for the synthesis of 168G. LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_6S$ 426.2 found [M+H] 427.2, T_r = 2.945 min (Method N).

177D. Ethyl 3-(3-amino-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino) phenyl)-3-methylbutanoate

Compound 177D was prepared from 177C following the procedure described for the synthesis of 145E. LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_4S$ 396.2 found [M+H] 397.4, T_r = 2.669 min (Method N).

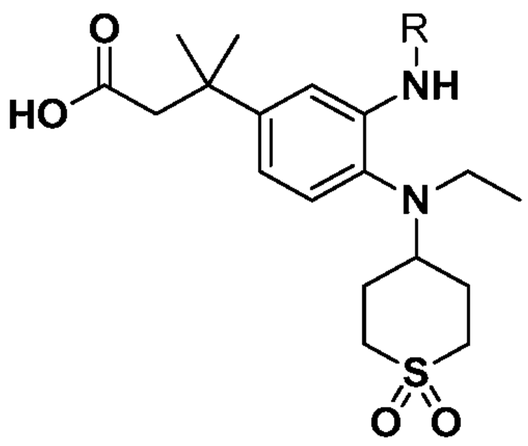
177E. Ethyl 3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl)-3-methylbutanoate

Compound 177E was prepared from 177D and 5-bromo-2-ethoxypyrimidine following the procedure described for the synthesis of 145F. LC-MS Anal. Calc'd. for $C_{26}H_{38}N_4O_5S$ 518.2 found [M+H] 519.5, T_r = 1.43 min (Method BC).

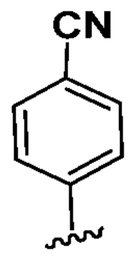
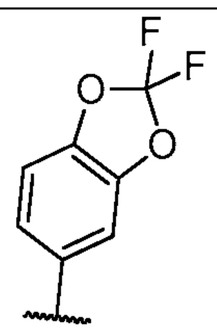
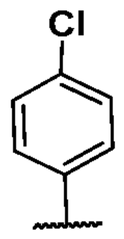
Example 177. 3-(4-((1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl)-3-methylbutanoic acid

Example 177 was prepared from 177E following the procedure described for the synthesis of Example 145 from 145F. LC-MS Anal. Calc'd. for $C_{24}H_{34}N_4O_5S$ 490.2 found [M+H] 491.2, T_r = 2.104 min (Method N). ^{1}H NMR(400 MHz, DMSO-d_6) δ 11.72 (br. s., 1H) 8.43 (s, 2H) 7.31 (m, 1H), 7.11 - 7.08 (m, 1H), 6.95 (m, 1H), 6.84 - 6.81 (m, 1H) 4.27 (m, 2H), 3.33 - 3.05 (m, 2H), 3.00 - 2.95 (m, 2H), 2.90 (m, 2H), 2.50 (m, 3H), 1.95 - 2.10 (m, 4H), 1.50 - 1.51 (m, 9H), 0.87 (m, 3H).

Examples 178 to 180

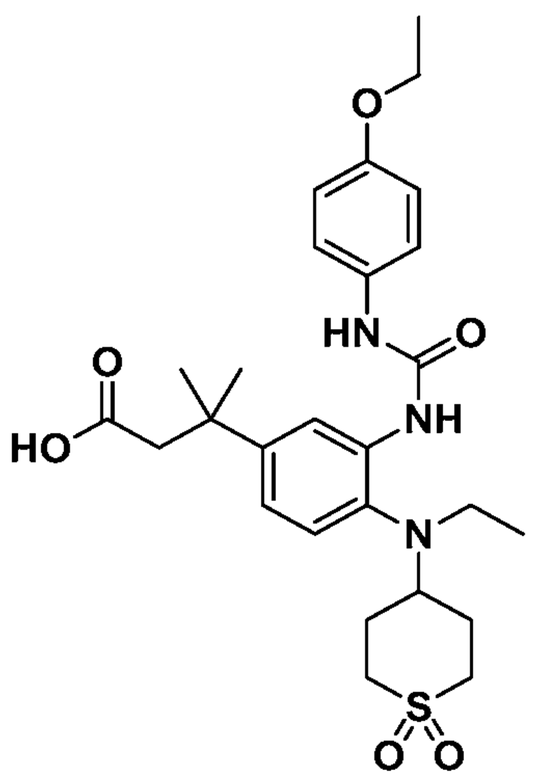


Examples 178 to 180 were prepared from 177D and the corresponding aryl halides following the procedure described for the synthesis of Example 177.

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
178	3-(3-((4-cyanophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl)-3-methylbutanoic acid		1.679	470.2
179	3-(3-((2,2-difluorobenzo[d][1,3] dioxol-5-yl)amino)-4-((1,1-dioxido tetrahydro-2H-thiopyran-4-yl)(ethyl) amino)phenyl)-3-methylbutanoic acid		2.067	525.2
180	3-(3-((4-chlorophenyl)amino)-4-((1,1-dioxido tetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl)-3-methylbutanoic acid		1.971	479.2

Example 181

3-(4-((1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-(3-(4-ethoxyphenyl)ureido)phenyl)-3-methylbutanoic acid



181A. Ethyl 3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-(3-(4-ethoxyphenyl)ureido)phenyl)-3-methylbutanoate

Compound 181A was prepared from 177D and 1-ethoxy-4-isocyanatobenzene following the procedure described for the synthesis of 5A. LC-MS Anal. Calc'd. for $C_{29}H_{41}N_3O_6S$ 559.2, found [M+H] 560.2, T_r = 0.95 min (Method BC).

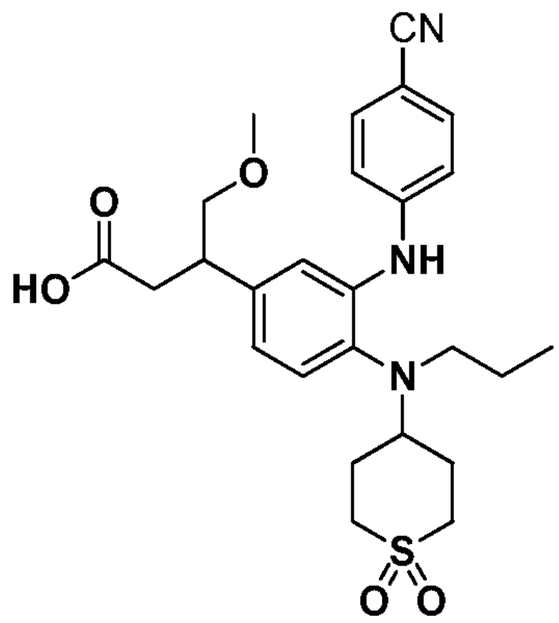
Example 181. 3-(4-((1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-(3-(4-ethoxyphenyl)ureido)phenyl)-3-methylbutanoic acid

Example 181 was prepared from 181A following the procedure described for the synthesis of Example 145 from 145F. LC-MS Anal. Calc'd. for $C_{27}H_{37}N_3O_6S$ 531.2, found [M+H] 532.3, T_r = 1.49 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (s 1H), 8.32 - 8.31 (m, 2H), 7.36 - 7.34 (d, *J* = 8.8 Hz, 2H), 7.14 - 7.12 (d, *J* = 8.8 Hz, 1H), 6.97 - 6.94 (m, 1H), 6.86 - 6.84 (m, 2H), 4.00 - 3.95 (m, 2H), 3.37 - 2.96 (s, 9H), 2.18 - 2.16 (m, 2H), 1.88 -1.85 (m, 2H), 1.36 (s, 6H), 1.32 -1.28 (m, 3H), 0.83 - 0.79 (m, 3H).

Example 182

(Enantiomer 1 and Enantiomer 2)

3-(3-((4-Cyanophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)phenyl)-4-methoxybutanoic acid



182A. N-Propyltetrahydro-2H-thiopyran-4-amine

To a stirred solution of dihydro-2H-thiopyran-4(3H)-one (5.0 g, 43.0 mmol) in dry MeOH (80 mL), propan-1-amine (2.80 g, 47.3 mmol) was added. Then molecular sieves (5.0 g) was added to the reaction mixture. Reaction mixture was stirred at RT overnight. Reaction mixture was cooled to 0 °C and added $NaBH_4$ (3.26 g, 86 mmol) portionwise in 10 minutes. It was stirred at room temperature for 3 h. Reaction mixture was concentrated under reduced pressure to get semi-solid. To this was added sat. aq. $NaHCO_3$ (200 mL) and was stirred overnight. Mixture was extracted with EtOAc (400 mL), washed with water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get 182A (light yellow liquid, 5.5 g, 34.5 mmol, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.74 - 2.51 (m, 6H), 2.49 - 2.35 (m, 1H), 2.21 - 2.1 (m, 2H), 1.56 - 1.41 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H).

182B. N-(4-Bromo-2-nitrophenyl)-N-propyltetrahydro-2H-thiopyran-4-amine

To a solution of 4-bromo-1-fluoro-2-nitrobenzene (2.0 g, 9.09 mmol) in NMP (15 mL) was added DIPEA (4.76 mL, 27.3 mmol), followed by 182A (2.172 g, 13.64 mmol). Reaction mixture was heated to 135 °C and was stirred overnight. Reaction mixture was cooled to RT and was diluted with EtOAc (100 mL), washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get crude compound as yellow liquid. The residue was purified via flash silica gel column chromatography to afford 182B (yellow liquid, 2.8 g, 7.79 mmol, 86% yield). LC-MS Anal. Calc'd. for $C_{14}H_{19}BrN_2O_2S$ 358.035, found [M+H] 359.2, T_r = 3.75 min (Method U).

182C. N-(4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-2-nitrophenyl)-N-propyltetrahydro-2H-thiopyran-4-amine

Compound 182C was prepared from 182B following the procedure described for the synthesis of 168B. LC-MS Anal. Calc'd. for $C_{19}H_{29}BN_2O_4S$ 392.2, found [M+H] 325.2 for parent boronic acid. T_r = 2.74 min (Method N).

182D. Methyl 4-methoxy-3-(3-nitro-4-(propyl(tetrahydro-2H-thiopyran-4-yl)amino) phenyl)butanoate

Compound 182D was prepared from 182C and (E)-methyl 4-methoxybut-2-enoate following the procedure described for the synthesis of 168C. LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_5S$ 410.2, found [M+H] 411.2, T_r = 3.40 min (Method BD).

182E. Methyl 3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)-3-nitrophenyl)-4-methoxybutanoate

Compound 182E was prepared from 182D following the procedure described for the synthesis of 168G. LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_7S$ 442.2, found [M+H] 443.2, T_r = 2.17 min (Method BD).

182F. Methyl 3-(3-amino-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino) phenyl)-4-methoxybutanoate

Compound 182F was prepared from 182E following the procedure described for the synthesis of 145E. LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_5S$ 412.2, found [M+H] 413.2, T_r = 0.78 min (Method BC).

Chiral separation of racemic Example 182F (Method Z) gave 182F Enantiomer 1 T_r = 3.14 min (Method Z) and 182F Enantiomer 2 T_r = 5.85 min (Method Z) as single enantiomers.

182F Enantiomer 1 (brown semi-solid, 0.060 g, 0145 mmol, 6.44% yield): LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_5S$ 412.2, found [M+H] 413.2, T_r = 0.78 min (Method BC).

182F Enantiomer 2 (brown semi-solid, 0.050 g, 0121 mmol, 5.36% yield): LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_5S$ 412.2, found [M+H] 413.2, T_r = 0.78 min (Method BC).

182G Enantiomer 1. Methyl 3-(3-((4-cyanophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)phenyl)-4-methoxybutanoate

182G Enantiomer 1 was prepared from 182F Enantiomer 1 and 4-bromobenzonitrile following the procedure described for the synthesis of 145F. LC-MS Anal. Calc'd. for $C_{27}H_{35}N_3O_5S$ 513.2 found [M+H] 514.3, T_r = 1.29 min (Method BA).

Example 182 Enantiomer 1. 3-(3-((4-Cyanophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)phenyl)-4-methoxybutanoic acid

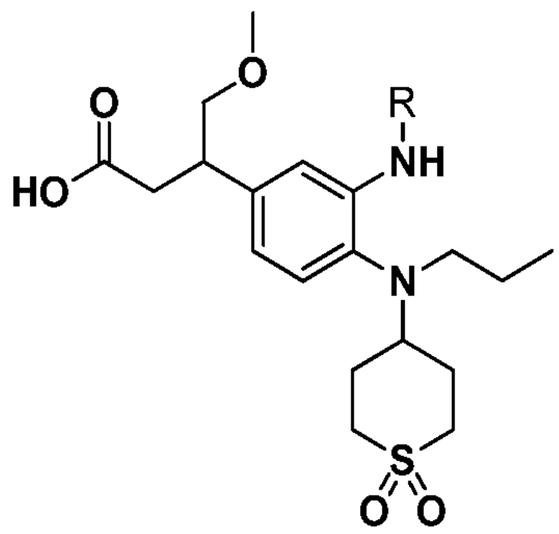
Example 182 Enantiomer 1 was prepared from 182G Enantiomer 1 following the procedure described for the synthesis of Example 145 from 145F. LC-MS Anal. Calc'd. for $C_{26}H_{33}N_3O_5S$ 499.2, found [M+H] 500.1, T_r =1.48 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.57 - 7.52 (m, 2H), 7.18 - 7.14 (m, 2H), 7.06 - 7.04 (d, *J* = 8.8Hz, 2H), 6.97 - 6.94 (m, 1H), 3.40 - 3.23 (m, 6H), 3.19 - 3.10 (m, 4H), 3.05 - 2.90 (m, 2H), 2.85 - 2.36 (m, 3H), 2.07 - 1.90 (m, 4H), 1.25 - 1.21 (m, 2H), 0.81(t, *J* = 7.2 Hz, 3H).

Example 182 Enantiomer 2. 3-(3-((4-Cyanophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)phenyl)-4-methoxybutanoic acid

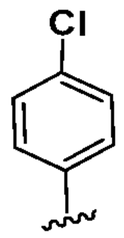
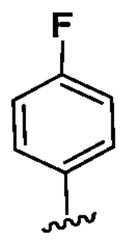
Example 182 Enantiomer 2 was prepared from 182F Enantiomer 2 following the procedure described for the synthesis of Example 182 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{26}H_{33}N_3O_5S$ 499.2, found [M+H] 500.1, T_r =1.47 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.58 - 7.55 (m, 2H), 7.18 - 7.15 (m, 2H), 7.06 - 7.04 (d, *J* = 8.8Hz, 2H), 6.98 - 6.95 (m, 1H), 3.43 - 3.21 (m, 6H), 3.17 - 3.10 (m, 4H), 3.05 - 2.90 (m, 2H), 2.88 - 2.36 (m, 3H), 2.07 - 1.90 (m, 4H), 1.25 - 1.21 (m, 2H), 0.75 (t, *J* = 7.2 Hz, 3H).

Examples 183 and 184

(Enantiomer 1)

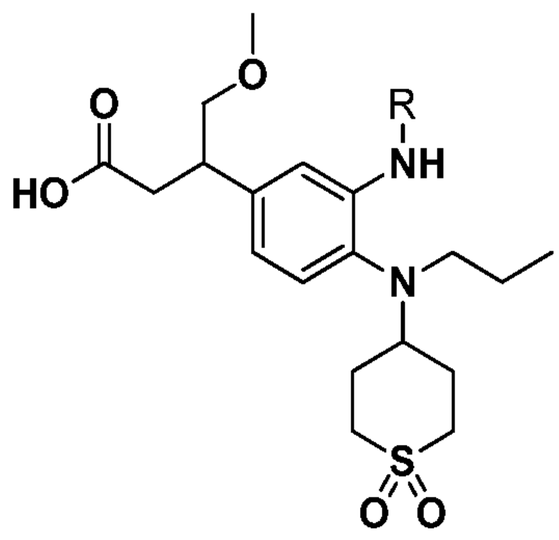


Examples 183 and 184 were prepared from 182F Enantiomer 1 and the corresponding aryl halides following the procedure described for the synthesis of Example 182 Enantiomer 1.

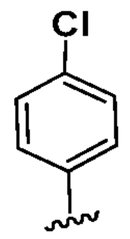
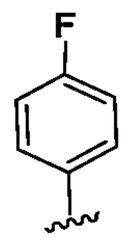
Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
183	3-(3-((4-chlorophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)phenyl)-4-methoxybutanoic acid		1.663	509.0
184	3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)-3-((4-fluorophenyl)amino)phenyl)-4-methoxybutanoic acid		1.530	493.0

Examples 185 and 186

(Enantiomer 2)

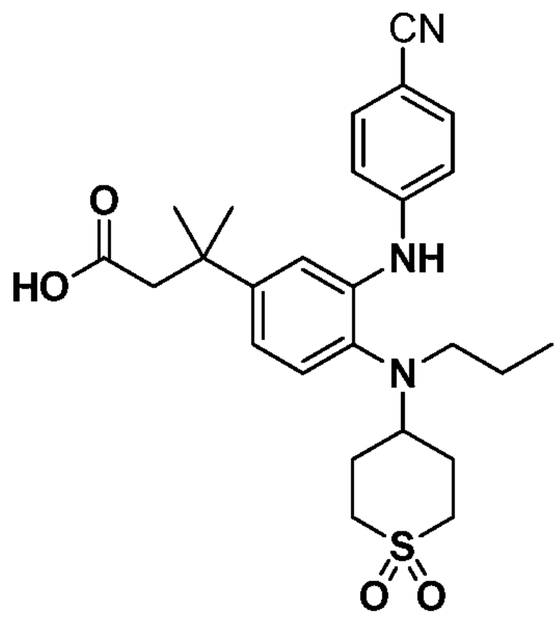


Examples 185 and 186 were prepared from 182F Enantiomer 2 and the corresponding aryl halides following the procedure described for the synthesis of Example 182 Enantiomer 1.

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
185	3-(3-((4-chlorophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)phenyl)-4-methoxybutanoic acid		1.652	509.0
186	3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)-3-((4-fluorophenyl)amino)phenyl)-4-methoxybutanoic acid		1.53	493.3

Example 187

3-(3-((4-Cyanophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)phenyl)-3-methylbutanoic acid



187A. N-Propyltetrahydro-2H-thiopyran-4-amine

To a stirred solution of dihydro-2H-thiopyran-4(3H)-one (5.0 g, 43.0 mmol) in dry MeOH (80 mL), propan-1-amine (2.80 g, 47.3 mmol) was added. Then molecular sieves (5.0 g) were added to the reaction mixture. Reaction mixture was stirred at RT overnight. Reaction mixture was cooled to 0 °C and added $NaBH_4$ (3.26 g, 86 mmol) portionwise in 10 minutes. It was stirred at room temperature for 3 h. Reaction mixture was concentrated

under reduced pressure to get semi-solid. To this was added sat. aq. $NaHCO_3$ (200 mL) and was stirred overnight. Reaction mixture was extracted with EtOAc (400 mL), washed with water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get 187A (light yellow liquid, 5.5 g, 34.5 mmol, 80% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 2.74 - 2.51 (m, 6H), 2.49 - 2.35 (m, 1H), 2.21 - 2.1 (m, 2H), 1.56 - 1.41 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H).

187B. Ethyl 3-methyl-3-(3-nitro-4-(propyl(tetrahydro-2H-thiopyran-4-yl)amino)phenyl) butanoate

Compound 187B was prepared from 145C and 187A following the procedure described for the synthesis of 159A. LC-MS Anal. Calc'd. for $C_{21}H_{32}N_2O_4S$ 408.2, found [M+H] 409.2, T_r = 4.108 min (Method N).

187C. Ethyl 3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)-3-nitrophenyl)-3-methylbutanoate

Compound 187C was prepared from 187B following the procedure described for the synthesis of 168G. LC-MS Anal. Calc'd. for $C_{21}H_{32}N_2O_6S$ 440.2, found [M+H] 441.2, T_r = 3.672 min (Method N).

187D. Ethyl 3-(3-amino-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino) phenyl)-3-methylbutanoate

187D was prepared from 187C following the procedure described for the synthesis of 145E. LC-MS Anal. Calc'd. for $C_{21}H_{34}N_2O_4S$ 410.2, found [M+H] 411.2, T_r = 3.48 min (Method N).

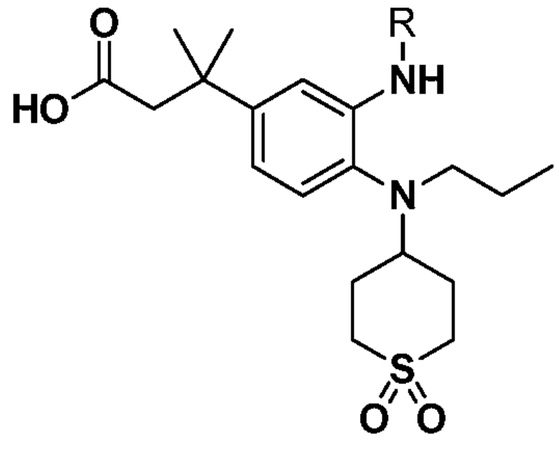
187E. Ethyl 3-(3-((4-cyanophenyl) amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)phenyl)-3-methylbutanoate

Compound 187E was prepared from 187D and 4-bromobenzonitrile following the procedure described for the synthesis of 145F. LC-MS Anal. Calc'd. for $C_{28}H_{37}N_3O_4S$ 511.2, found [M+H] 512.3, T_r = 1.47 min (Method BA).

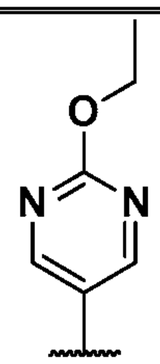
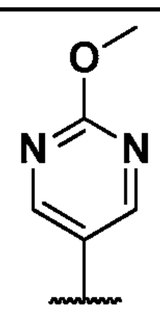
Example 187. 3-(3-((4-Cyanophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)phenyl)-3-methylbutanoic acid

Example 187 was prepared from 187E following the procedure described for the synthesis of Example 145 from 145F. LC-MS Anal. Calc'd. for $C_{26}H_{33}N_3O_4S$ 483.2, found [M+H] 484.0, T_r = 1.72 min (Method O). ^{1}H NMR (400MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.55 - 7.52 (d, *J*= 8.8 Hz, 2H), 7.25 - 7.20 (m, 1H), 7.16 - 7.10 (m, 2H), 7.08 - 7.00 (m, 2H), 3.17 -3.02 (m, 2H), 2.99 - 2.87 (m, 5H), 2.53 - 2.51 (m, 2H), 1.97-1.91 (m, 4H), 1.33 (s, 6H), 1.19 (m, 2H), 0.75 (m, 3H).

Examples 188 and 189

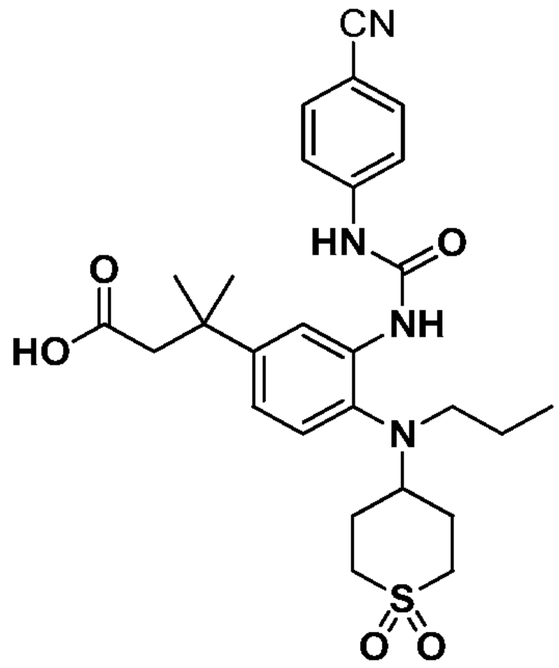


Examples 188 and 189 were prepared from 187D and the corresponding aryl halides following the procedure described for the synthesis of Example 187.

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
188	3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl)-3-methylbutanoic acid		1.619	505.1
189	3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)-3-((2-methoxypyrimidin-5-yl)amino)phenyl)-3-methylbutanoic acid		1.482	491.1

Example 190

3-(3-(3-(4-Cyanophenyl)ureido)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)phenyl)-3-methylbutanoic acid



190A. Ethyl 3-(3-(3-(4-cyanophenyl)ureido)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)phenyl)-3-methylbutanoate

190A was prepared from 187D and 4-isocyanatobenzonitrile following the procedure described for the synthesis of 5A. LC-MS Anal. Calc'd. for $C_{29}H_{38}N_4O_5S$ 554.25, found [M+H] 555.3, T_r = 1.39 min (Method BC).

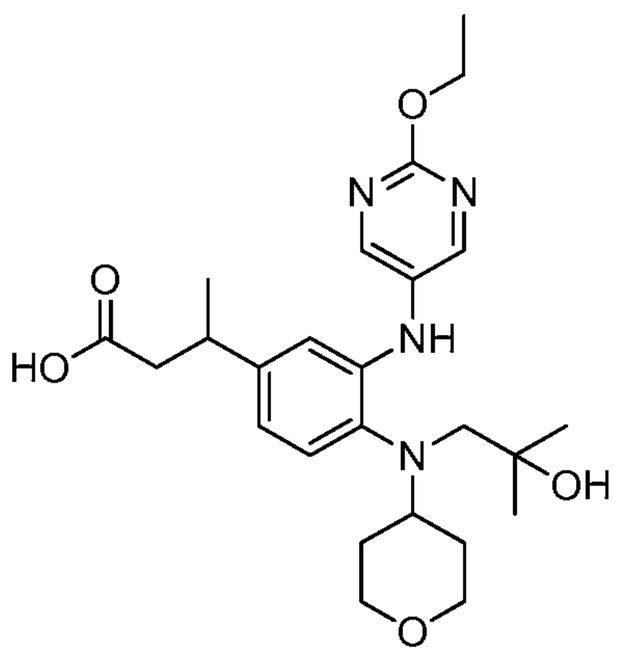
Example 190. 3-(3-(3-(4-Cyanophenyl)ureido)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(propyl)amino)phenyl)-3-methylbutanoic acid

Example 190 was prepared from 190A following the procedure described for the synthesis of Example 145 for 145F. LC-MS Anal. Calc'd. for $C_{27}H_{34}N_4O_5S$ 526.2, found [M+H] 527.1, T_r = 1.66 min (Method O). ^{1}H NMR (400MHz, DMSO-d_6) δ 10.02 (s, 1H), 8.50 (s, 1H), 8.30 (d, *J* = 2.0 Hz, 1H), 7.76 -7.63 (m, 5H), 7.20 - 7.18 (m, 1H), 7.03 - 6.98 (m, 1H), 3.20 - 2.95 (m, 7H), 2.50 - 2.40 (m, 2H), 2.24 - 2.21 (m, 2H), 1.92 - 1.86 (m, 2H), 1.37 (s, 6H), 1.20 - 1.19 (m, 2H), 0.81(t, *J* = 7.60 Hz, 3H).

Example 191

(Enantiomer 1)

3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)butanoic acid



191A. 2-Methyl-1-((tetrahydro-2H-pyran-4-yl)amino)propan-2-ol

Compound 191A was prepared from dihydro-2H-pyran-4(3H)-one and 1-amino-2-methylpropan-2-ol following the procedure described for the synthesis of 168E. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 - 3.80 (m, 2H), 3.45 - 3.30 (m, 2H), 2.55 - 2.50 (m, 1H), 2.40 (m, 2H), 1.90 - 1.83 (m, 2H), 1.45 - 1.30 (m, 2H), 1.14 (s, 6H).

191B. 1-((4-Bromo-2-nitrophenyl)(tetrahydro-2H-pyran-4-yl)amino)-2-methyl propan-2-ol

To a stirred solution of NaH (0.818 g, 20.45 mmol) in dry DMF (20.0 mL), 191A (4.73 g, 27.3 mmol) was added at 0 °C and stirred for 30 minutes at same temperature. 4-Bromo-1-fluoro-2-nitrobenzene (3.0 g, 13.64 mmol) was added at 0 °C. Reaction stirred at room temperature for 4 h. Reaction mixture quenched with 3 mL water at 0 °C and was diluted with ethyl acetate (50 mL). Organic layer washed with water (10 mL) and aqueous layer extract with ethyl acetate (2 × 20 mL). Organic layer dried over sodium sulfate, concentrated under reduced pressure to get orange liquid. Purification via flash chromatography gave 191B (orange semi-solid, 3.5 g, 9.38 mmol, 69% yield). LC-MS Anal. Calc'd. for $C_{15}H_{21}BrN_2O_4$ 372.06, found [M+H] 373.4.1, T_r = 1.31 min (Method BA).

191C. 1-((4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-2-nitrophenyl)(tetrahydro-2H-pyran-4-yl)amino)-2-methylpropan-2-ol

Compound 191C was prepared from 191B following the procedure described for the synthesis of 168B. LC-MS Anal. Calc'd. for $C_{20}H_{31}BN_2O_6$ 406.2, found [M+H] 339.0 for parent boronic acid, T_r = 0.50 min (Method BA).

191D. Methyl 3-(4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)butanoate

191D was prepared from 191C and methyl but-2-enoate following the procedure described for the synthesis of 168C. LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_6$ 394.20, found [M+H] 395.5, T_r = 1.22 min (Method BC).

191E. Methyl 3-(3-amino-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)butanoate

191E was prepared from 191D following the procedure described for the synthesis of 145E. LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_4$ 364.20, found [M+H] 365.5, T_r = 1.14 min (Method BC).

Chiral separation of racemic 191E (Method AM) gave 191E Enantiomer 1 T_r = 4.24 min (Method AM) and 191E Enantiomer 2 T_r = 9.14 min (Method AM) as single enantiomers.

191E Enantiomer 1 (light yellow semi-solid, 0.350 g, 0145 mmol, 18.4% yield): LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_4$ 364.2, found [M+H] 365.2, T_r = 2.09 min (Method N).

191E Enantiomer 2 (light yellow semi-solid, 0.350 g, 0145 mmol, 18.4% yield): LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_4$ 364.2, found [M+H] 365.2, T_r = 2.10 min (Method N).

191F Enantiomer 1. Methyl 3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)butanoate

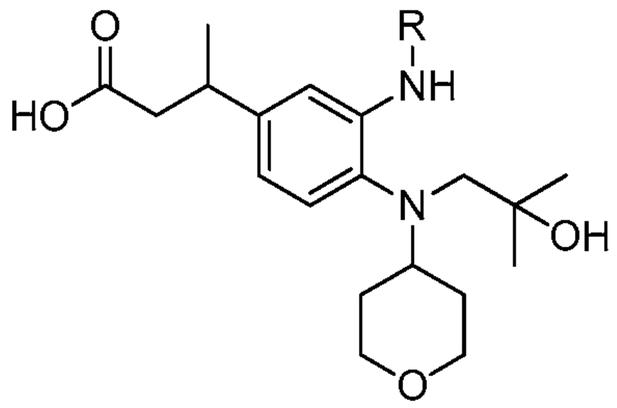
191F Enantiomer 1 was prepared from 191E Enantiomer 1 and 5-bromo-2-ethoxypyrimidine following the procedure described for the synthesis of 145F. LC-MS Anal. Calc'd. for $C_{26}H_{38}N_4O_5$ 486.2 found [M+H] 487.6, T_r = 1.09 min (Method BC).

Example 191 Enantiomer 1. 3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)butanoic acid

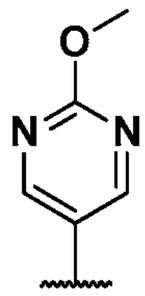
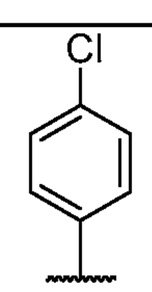
Example 191 Enantiomer 1 was prepared from 191F Enantiomer 1 and 5-bromo-2-ethoxypyrimidine following the procedure described for the synthesis of Example 145 from 145F. LC-MS Anal. Calc'd. for $C_{25}H_{36}N_4O_5$ 472.2, found [M+H] 473.4, T_r = 1.08 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 2H), 7.44 (br. s., 1H) 7.21 - 7.13 (m, 1H), 6.95 (m, 1H), 6.69 - 6.67 (m, 1H), 4.35 - 4.30 (m, 2H), 3.84 - 3.80 (m, 4H), 3.15 - 2.90 (m, 5H), 2.99 (m, 1H), 2.44 (m, 1H), 1.77 (m, 2H), 1.50 (m, 2H), 1.36 - 1.32 (t, *J* = 7.20 Hz, 3H), 1.16 - 1.15 (d, *J* = 6.80Hz, 3H), 0.96 (m, 6H).

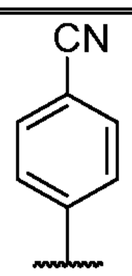
Examples 192 to 194

(Enantiomer 1)



Examples 192 to 194 were prepared from 191E Enantiomer 1 and the corresponding aryl halides following the procedure described for the synthesis of Example 191 Enantiomer 1.

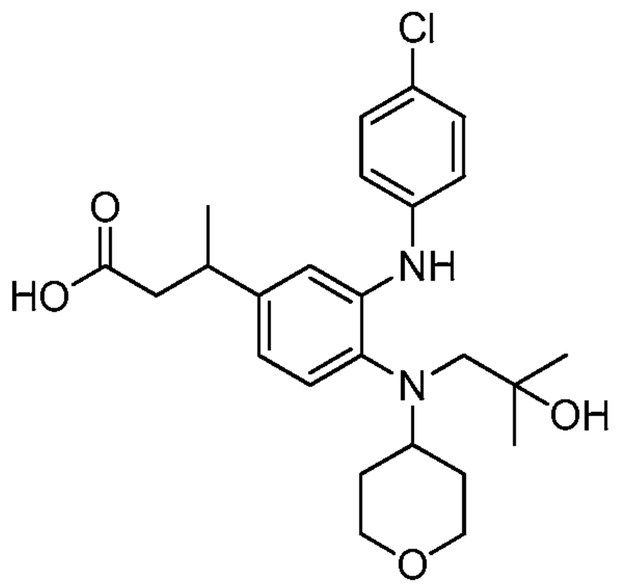
Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
192	3-(4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methoxypyrimidin-5-yl)amino)phenyl) butanoic acid		1.202	459.4
193	3-(3-((4-chlorophenyl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)butanoic acid		1.420	461.3

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
194	3-(3-((4-cyanophenyl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)butanoic acid		1.17	452.3

Example 195

(Enantiomer 2)

3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)butanoic acid



195A. Methyl 3-(3-((4-chlorophenyl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)butanoate

195A was prepared from 191E Enantiomer 2 and 1-bromo-4-chlorobenzene following the procedure described for the synthesis of 145F. LC-MS Anal. Calc'd. for $C_{26}H_{35}ClN_2O_4$ 474.2 found [M+H] 475.6, T_r = 1.38 min (Method BC).

Example 195 Enantiomer 2. 3-(3-((4-Chlorophenyl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)butanoic acid

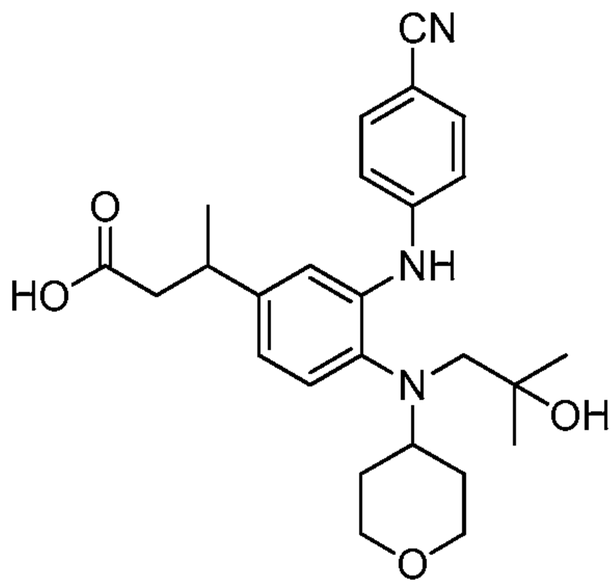
Example 195 Enantiomer 2 was prepared from 195A following the procedure described for the synthesis of Example 145 from 145F. LC-MS Anal. Calc'd. for $C_{25}H_{33}ClN_2O_4$ 460.2 found [M+H] 461.3, T_r = 1.43 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (br. s., 1H), 7.61 (s, 1H) 7.29 -7.26 (m, 2H), 7.17 -7.11 (m, 4H), 7.07 -7.06 (m, 1H), 6.76 - 6.73 (dd, *J* = 2.0, 2.0 Hz, 1H), 3.09 - 2.90 (m, 3H), 2.68 - 2.54

(m, 3H), 2.52 - 2.30 (m, 2H), 1.71 (m, 2H), 1.46 (m, 2H), 1.16 - 1.15 (d, *J* = 6.80Hz, 3H), 0.93 (m, 6H) (Note: 2 proton buried under solvent peak).

Example 196

(Enantiomer 2)

3-(3-((4-Cyanophenyl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)butanoic acid



196A. Methyl 3-(3-((4-cyanophenyl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)butanoate

196A was prepared from 191E Enantiomer 2 and 4-bromobenzonitrile following the procedure described for the synthesis of 145F. LC-MS Anal. Calc'd. for $C_{27}H_{35}N_3O_4$ 465.2 found [M+H] 466.6, T_r = 1.25 min (Method BC).

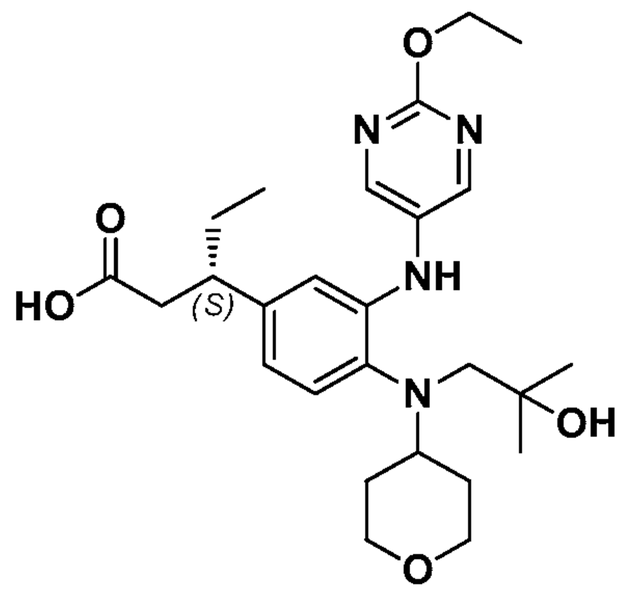
Example 196 Enantiomer 2. 3-(3-((4-Cyanophenyl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)butanoic acid

Example 196 Enantiomer 2 was prepared from 196A following the procedure described for the synthesis of Example 145 for 145F. LC-MS Anal. Calc'd. for $C_{26}H_{33}N_3O_4$ 451.2 found [M+H] 452.3, T_r = 1.19 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (br. s., 1H), 8.15 (s, 1H) 7.62 -7.59 (m, 2H), 7.24 -7.19 (m, 2H), 7.13 - 7.08 (m, 2H), 6.95 - 6.90 (dd, *J* = 2.0, 2.0 Hz, 1H), 3.10 - 2.90 (m, 5H), 2.68 - 2.54 (m, 4H), 1.63 (m, 2H), 1.46 (m, 2H), 1.22 - 1.15 (m, 3H), 0.94 (m, 6H) (Note: 2 proton buried under solvent peak).

Example 197

(Enantiomer 1)

(S)-3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid



197A. (S)-Methyl 3-(4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)pentanoate

197A was prepared from 191C, chlorobis(ethylene)rhodium(I) dimer and (R)-BINAP following the procedure described for the synthesis of 9B. LC-MS Anal. Calc'd. for $C_{21}H_{32}N_2O_6$ 408.2, found [M+H] 409.2, T_r = 2.55 min (Method N). (Absolute stereochemistry of the product assigned based on the expected product enantiomer from the use of (R)-BINAP in the conjugate addition)

197B. (S)-Methyl 3-(3-amino-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

197B was prepared from 197A following the procedure described for the synthesis of 145E. LC-MS Anal. Calc'd. for $C_{21}H_{34}N_2O_4$ 378.2, found [M+H] 379.2, T_r = 2.20 min (Method N). Analytical chiral HPLC; Chiral Purity, ee = 100%, T_r = 2.92 min. (Method AM).

197C. (S)-Methyl 3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

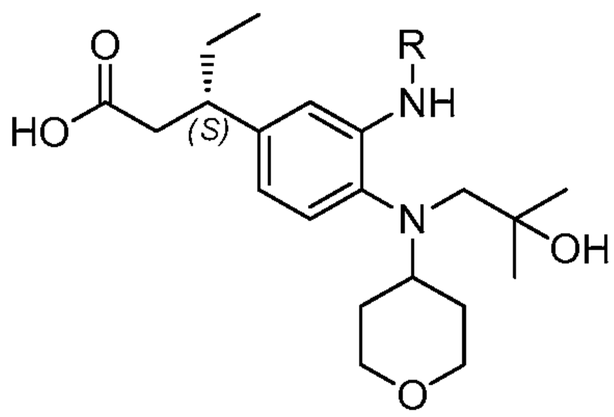
197C was prepared from 197B and 5-bromo-2-ethoxypyrimidine following the procedure described for the synthesis of 145F. LC-MS Anal. Calc'd. for $C_{27}H_{40}N_4O_5$ 500.3, found [M+H] 501.6, T_r = 1.39 min (Method AY).

Example 197. (S)-3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid

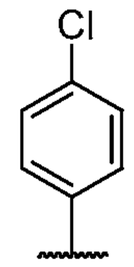
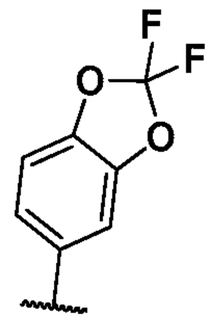
Example 197 was prepared from 197C following the procedure described for the synthesis of Example 145 from 145F. LC-MS Anal. Calc'd. for $C_{26}H_{38}N_4O_5$ 486.2 found [M+H] 487.3, T_r = 1.320 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (br. s., 1H), 8.42 (s, 2H) 7.42 (s, 1H), 7.15 -7.13 (d, *J* = 8.0 Hz, 1H), 6.75 (m, 1H), 6.64 - 6.62 (dd, *J* = 2.0, 2.0 Hz, 1H), 4.39 - 4.30 (m, 2H), 3.82 - 3.78 (m, 2H), 3.15 (m, 2H), 2.98 (m, 2H), 2.68 - 2.54 (m, 3H), 2.52 - 2.40 (m, 2H), 1.71 (m, 2H), 1.62 - 1.45 (m, 4H), 1.34 - 1.31 (m, 3H), 0.98 (s, 6H). 0.69 - 0.65 (d, *J* = 8.0 Hz, 3H).

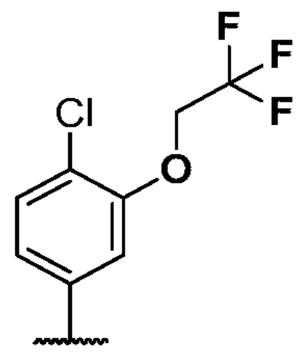
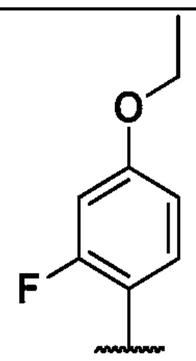
Examples 198 to 201

(Enantiomer 1)



Examples 198 to 201 was prepared from 197B and the corresponding aryl halides following the procedure described for the synthesis of Example 197.

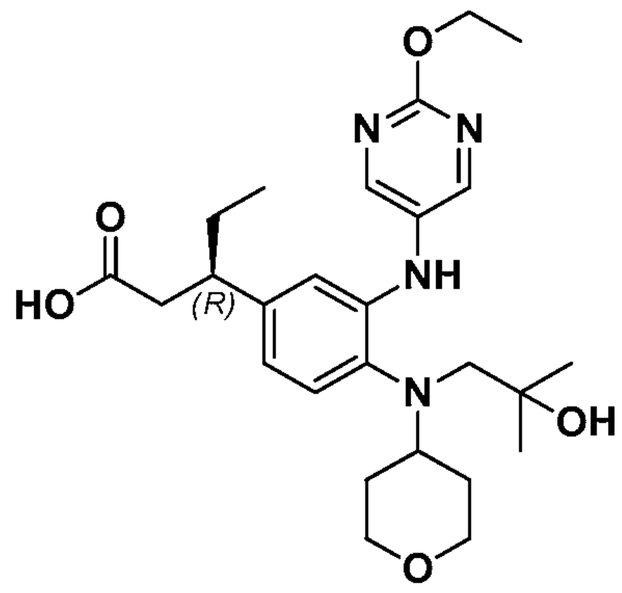
Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
198	(S)-3-(3-((4-chlorophenyl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		2.014	475.2
199	(S)-3-(3-((2,2-difluorobenzo[d][1,3]dioxol-5-yl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		2.140	521.2

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
200	(S)-3-(3-((4-chloro-3-(2,2,2-trifluoroethoxy)phenyl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		2.267	573.3
201	(S)-3-(3-((4-ethoxy-2-fluorophenyl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.810	503.3

Example 202

(Enantiomer 2)

(R)-3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid



202A. (R)-Methyl 3-(4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)pentanoate

202A was prepared from 191C, chlorobis(ethylene)rhodium(I) dimer and (S)-BINAP following the procedure described for the synthesis of 9B. LC-MS Anal. Calc'd. for $C_{21}H_{32}N_2O_6$ 408.2, found [M+H] 409.2, T_r = 2.55 min (Method N). (Absolute stereochemistry of the product assigned based on the expected product enantiomer from the use of (S)-BINAP in the conjugate addition)

202B. (R)-Methyl 3-(3-amino-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

202B was prepared from 202A following the procedure described for the synthesis of 145E. LC-MS Anal. Calc'd. for $C_{21}H_{34}N_2O_4$ 378.2, found [M+H] 379.4, T_r = 2.18 min (Method N). Chiral purity T_r = 4.53 min with 99% ee (Method AN) as single enantiomer.

202C. (R)-Methyl 3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

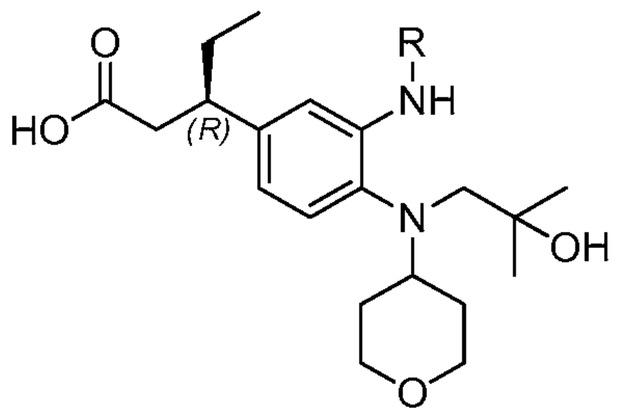
202C was prepared from 202B and 5-bromo-2-ethoxypyrimidine following the procedure described for the synthesis of 145F. LC-MS Anal. Calc'd. for $C_{27}H_{40}N_4O_5$ 500.3, found [M+H] 501.6, T_r = 1.39 min (Method AY).

Example 202. (R)-3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid

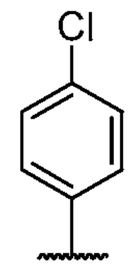
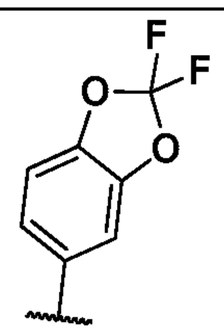
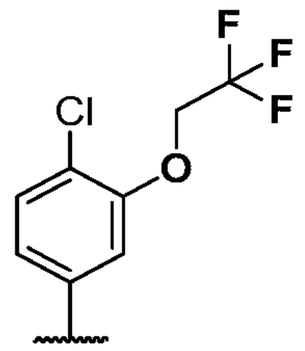
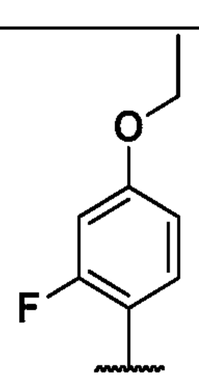
Example 202 was prepared from 202C following the procedure described for the synthesis of Example 145 from 145F. LC-MS Anal. Calc'd. for $C_{26}H_{38}N_4O_5$ 486.2 found [M+H] 487.3, T_r = 1.32 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (br. s., 1H), 8.42 (s, 2H) 7.42 (s, 1H), 7.15 -7.13 (d, *J* = 8.0 Hz, 1H), 6.75 (m, 1H), 6.64 - 6.62 (dd, *J* = 2.0, 2.0 Hz, 1H), 4.39 - 4.30 (m, 2H), 3.82 - 3.78 (m, 2H), 3.15 (m, 2H), 2.98 (m, 2H), 2.68 - 2.54 (m, 3H), 2.52 - 2.40 (m, 2H), 1.71 (m, 2H), 1.62 - 1.45 (m, 4H), 1.34 - 1.31 (m, 3H), 0.98 (s, 6H). 0.69 - 0.65 (d, *J* = 8.0 Hz, 3H).

Examples 203 to 206

(Enantiomer 2)



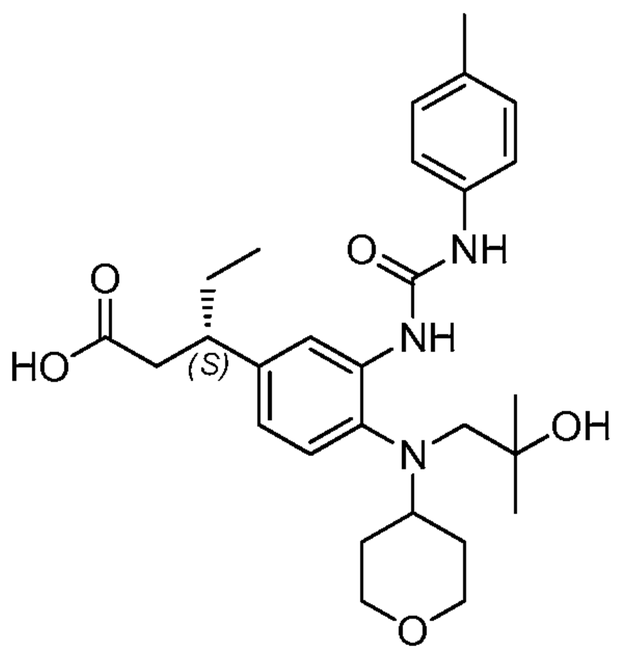
Examples 203 to 206 were prepared from 202B and the corresponding aryl halides following the procedure described for the synthesis of Example 202.

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
203	(R)-3-(3-((4-chlorophenyl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		2.00	475.3
204	(R)-3-(3-((2,2-difluorobenzo[d][1,3]dioxol-5-yl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		2.139	521.2
205	(R)-3-(3-((4-chloro-3-(2,2,2-trifluoroethoxy)phenyl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		2.274	573.3
206	(R)-3-(3-((4-ethoxy-2-fluorophenyl)amino)-4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		2.105	503.3

Example 207

(Enantiomer 1)

(S)-3-(4-((2-Hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoic acid



207A. (S)-Methyl 3-(4-((2-hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoate

207A was prepared from 197B and 1-isocyanato-4-methylbenzene following the procedure described for the synthesis of 5A. LC-MS Anal. Calc'd. for $C_{29}H_{41}N_3O_5$ 511.65, found [M+H] 512.4, T_r = 2.78 min (Method Q).

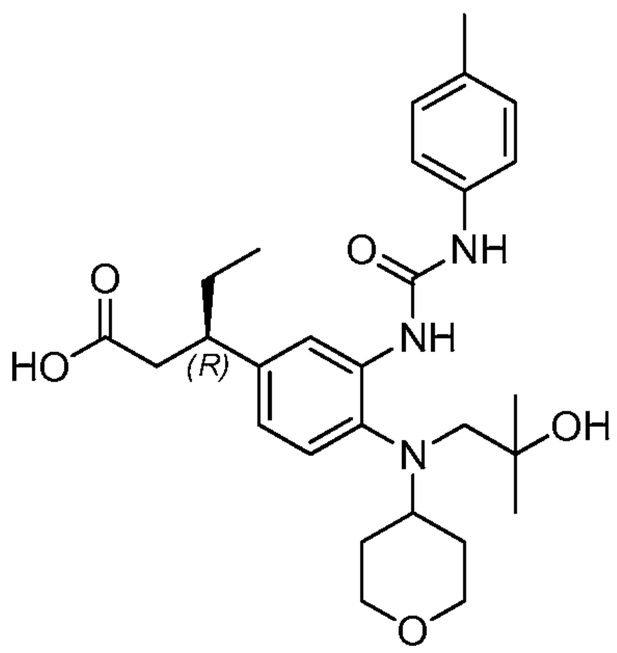
Example 207. (S)-3-(4-((2-Hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoic acid

Example 207 was prepared from 207A following the procedure described for the synthesis of Example 145 from 145F. LC-MS Anal. Calc'd. for $C_{28}H_{39}N_3O_5$ 497.6, found [M+H] 498.3 T_r = 1.49 min (Method O). ^{1}H NMR (400MHz, DMSO-d_6) δ 11.90 (br. s., 1H), 9.25 (s, 1H), 8.14 (s, 1H), 8.00 (s, 1H), 7.38 -7.35 (m, 2H), 7.20 - 7.08 (m, 3H), 6.79 - 6.77 (m, 1H), 3.98 - 3.95 (m, 2H), 3.10 - 3.05 (m, 2H), 2.95 - 2.80 (m, 3H), 2.54 - 2.41 (m, 2H), 2.31 (s, 3H), 1.82 - 1.76 (m, 4H), 1.65 - 1.45 (m, 3H), 1.20 - 1.19 (m, 1H), 0.89 (s, 6H), 0.70 (t, *J* = 7.20 Hz, 3H).

Example 208

(Enantiomer 2)

(R)-3-(4-((2-Hydroxy-2-methylpropyl)(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoic acid

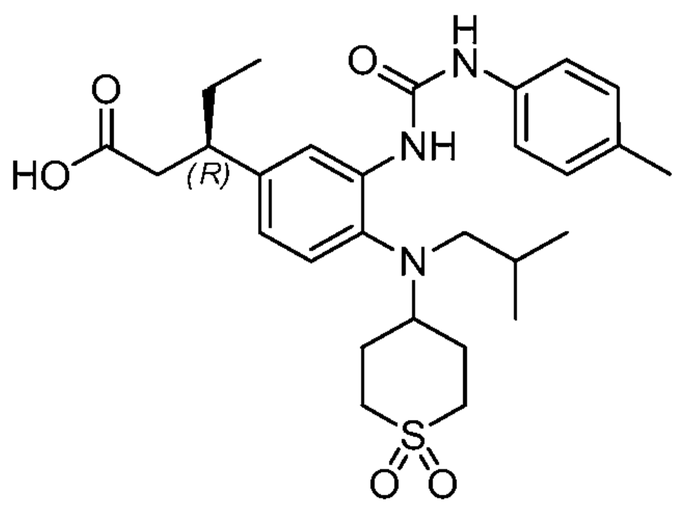


Example 208 was prepared from 202B and 1-isocyanato-4-methylbenzene following the procedure described for the synthesis of Example 207. LC-MS Anal. Calc'd. for $C_{28}H_{39}N_3O_5$ 497.6, found [M+H] 498.3 T_r = 1.49 min (Method O). ^{1}H NMR (400MHz, DMSO-d_6) δ 11.90 (br. s., 1H), 9.25 (s, 1H), 8.15 (s, 1H), 8.00 (s, 1H), 7.38 - 7.36 (m, 2H), 7.19 - 7.09 (m, 3H), 6.80 - 6.78 (m, 1H), 3.98 - 3.95 (m, 2H), 3.16 - 3.05 (m, 2H), 2.95 - 2.80 (m, 4H), 2.54 - 2.41 (m, 2H), 2.31 (s, 3H), 1.82 - 1.76 (m, 4H), 1.65 - 1.45 (m, 3H), 1.20 - 1.19 (m, 1H), 0.89 (s, 6H), 0.70 (t, *J* = 7.20 Hz, 3H).

Example 209

(Enantiomer 1)

(R)-3-(4-((1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)pentanoic acid



209A. N-Isobutyltetrahydro-2H-thiopyran-4-amine.HCl

To a stirred solution of dihydro-2H-thiopyran-4(3H)-one (10.0 g, 86 mmol), isobutylamine (9.36 mL, 95 mmol) in dry THF (100 mL), MeOH (100 mL) mixture under nitrogen atmosphere molecular sieves (3.0 g) was added to the reaction mixture and was stirred at RT overnight. Reaction mixture was cooled to 0 °C and $NaBH_4$ (3.91 g, 103

mmol) was added portionwise in 10 minutes. It was stirred at room temperature for 3 h. Reaction mixture was concentrated under reduced pressure to get semi-solid. To this was added sat. aq. $NaHCO_3$ (200 mL) and was stirred overnight. Mixture was extracted with EtOAc (2 × 200 mL). Combined organic layer was washed with water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get light yellow liquid. Above liquid dissolved in ether and acidified by using 4N HCl in dioxane to make HCl salt. Solid was filtered and dried under reduced pressure to give 209A (off-white solid, 14.5 g, 69.1 mmol, 80% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (br. s., 1H), 3.10 (m, 1H), 2.90 - 2.70 (m, 5H), 2.52 - 2.43 (m, 2H), 2.05 - 1.90 (m, 1H), 1.73 -1.68 (m, 2H), 1.10 - 0.90 (m, 6H).

209B. N-(4-Bromo-2-nitrophenyl)-N-isobutyltetrahydro-2H-thiopyran-4-amine

209B was prepared from 209A and 4-bromo-1-fluoro-2-nitrobenzene following the procedure described for the synthesis of 153F. LC-MS Anal. Calc'd. for $C_{15}H_{21}BrN_2O_2S$ 372.0, found [M+2] 374.4, T_r = 1.69 min (Method AP).

209C. N-(4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-2-nitrophenyl)-N-isobutyltetrahydro-2H-thiopyran-4-amine

209C was prepared from 209B following the procedure described for the synthesis of 168B. LC-MS Anal. Calc'd. for $C_{20}H_{31}BN_2O_4S$ 406.2, found [M+H] 339.2 for parent boronic acid. T_r = 2.91 min (Method N).

209D. (R)-Methyl 3-(4-(isobutyl(tetrahydro-2H-thiopyran-4-yl)amino)-3-nitrophenyl) pentanoate

209D was prepared from 209C and (S)-BINAP following the procedure described for the synthesis of 197A. LC-MS Anal. Calc'd. for $C_{21}H_{32}N_2O_4S$ 408.2, found [M+H] 409.6, T_r = 1.33 min (Method BC). (Absolute stereochemistry of the product assigned based on the expected product enantiomer from the use of (S)-BINAP in the conjugate addition)

209E. (R)-Methyl 3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl)amino)-3-nitrophenyl)pentanoate

209E was prepared from 209D following the procedure described for the synthesis of 168G. LC-MS Anal. Calc'd. for $C_{21}H_{32}N_2O_6S$ 440.2, found [M+H] 441.5, T_r = 1.40 min (Method BA). Chiral purity T_r = 2.92 min with 87% ee (Method BS).

209F. (R)-Methyl 3-(3-amino-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl) amino)phenyl)pentanoate

209F was prepared from 209E following the procedure described for the synthesis of 145E. LC-MS Anal. Calc'd. for $C_{21}H_{32}N_2O_6S$ 410.2, found [M+H] 411.2, T_r = 2.87 min (Method N).

209G. (R)-Methyl 3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoate

209G was prepared from 209F and 1-isocyanato-4-methylbenzene following the procedure described for the synthesis of 5A. LC-MS Anal. Calc'd. for $C_{29}H_{41}N_3O_5S$ 543.2, found [M+H] 544.6, T_r = 1.14 min (Method BC).

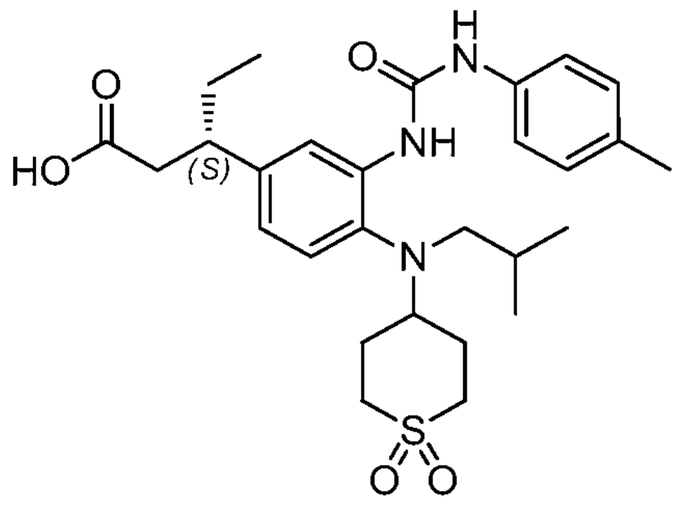
Example 209. (R)-3-(4-((1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoic acid

Example 209 was prepared from 209G following the procedure described for the synthesis of Example 145 for 145F. LC-MS Anal. Calc'd. for $C_{28}H_{39}N_3O_5S$ 529.2, found [M+H] 530.3, T_r = 1.79 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (s, 1H) 8.05 - 7.98 (m, 2H), 7.37 - 7.35 (d, *J* = 8.4 Hz, 2H), 7.14 - 7.08 (m, 3H), 6.79 (m, 1H), 3.33 - 3.10 (m, 4H), 3.05 - 2.95 (m, 2H), 2.60 - 2.50 (m, 3H), 2.40 (m, 1H). 2.32 (s, 3H), 2.22 - 2.15 (m, 2H), 1.92 - 1.85 (m, 2H), 1.74 - 1.21 (m, 3H), 0.82 (m, 6H). 0.72 - 0.69 (t, *J* = 7.2 Hz, 3H).

Example 210

(Enantiomer 2)

(S)-3-(4-((1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)pentanoic acid



210A. (S)-Methyl 3-(4-(isobutyl(tetrahydro-2H-thiopyran-4-yl)amino)-3-nitrophenyl) pentanoate

210A was prepared from 209C and R(+) BINAP following the procedure described for the synthesis of 9B. LC-MS Anal. Calc'd. for $C_{21}H_{32}N_2O_4S$ 408.2, found [M+H] 409.2, T_r = 1.33 min (Method BC). (Absolute stereochemistry of the product assigned based on the expected product enantiomer from the use of (R)-BINAP in the conjugate addition)

210B. (S)-Methyl 3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl)amino)-3-nitrophenyl)pentanoate

210B was prepared from 210A following the procedure described for the synthesis of 168G. LC-MS Anal. Calc'd. for $C_{21}H_{32}N_2O_6S$ 440.2, found [M+H] 441.2, T_r = 1.40 min (Method BA). Chiral purity T_r = 2.92 min with 98% ee (Method BS).

210C. (S)-Methyl 3-(3-amino-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl) amino)phenyl)pentanoate

210C was prepared from 210B following the procedure described for the synthesis of 145E. LC-MS Anal. Calc'd. for $C_{21}H_{34}N_2O_6S$ 410.2, found [M+H] 411.2, T_r = 2.87 min (Method N).

210D. (S)-Methyl 3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoate

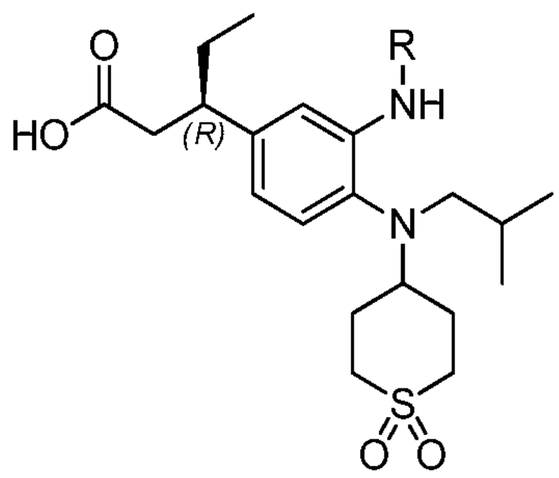
210D was prepared from 210C and 1-isocyanato-4-methylbenzene following the procedure described for the synthesis of 5A. LC-MS Anal. Calc'd. for $C_{29}H_{41}N_3O_5S$ 543.2, found [M+H] 544.5, T_r = 1.48 min (Method BC).

Example 210. (S)-3-(4-((1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoic acid

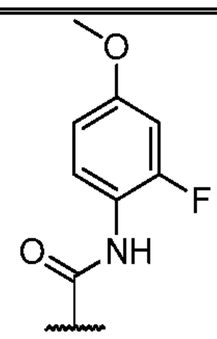
Example 210 was prepared from 210D following the procedure described for the synthesis of Example 145 for 145F. LC-MS Anal. Calc'd. for $C_{28}H_{39}N_3O_5S$ 529.2, found [M+H] 530.3, T_r = 1.79 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (s, 1H) 8.05 - 7.98 (m, 2H), 7.37 - 7.35 (d, *J* = 8.4 Hz, 2H), 7.14 - 7.08 (m, 3H), 6.79 (m, 1H), 3.33 - 3.10 (m, 4H), 3.05 - 2.95 (m, 2H), 2.60 - 2.50 (m, 3H), 2.40 (m, 1H). 2.32 (s, 3H), 2.22 - 2.15 (m, 2H), 1.92 - 1.85 (m, 2H), 1.74 - 1.21 (m, 3H), 0.82 (m, 6H). 0.72 - 0.69 (t, *J* = 7.2 Hz, 3H).

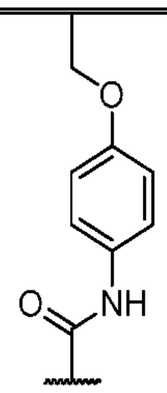
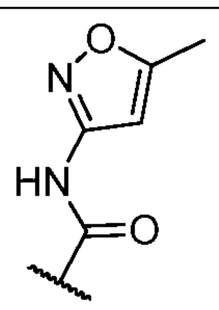
Examples 211 to 213

(Enantiomer 1)



Examples 211 to 213 were prepared from 209F and the corresponding isocyanates following the procedure described for the synthesis of Example 210.

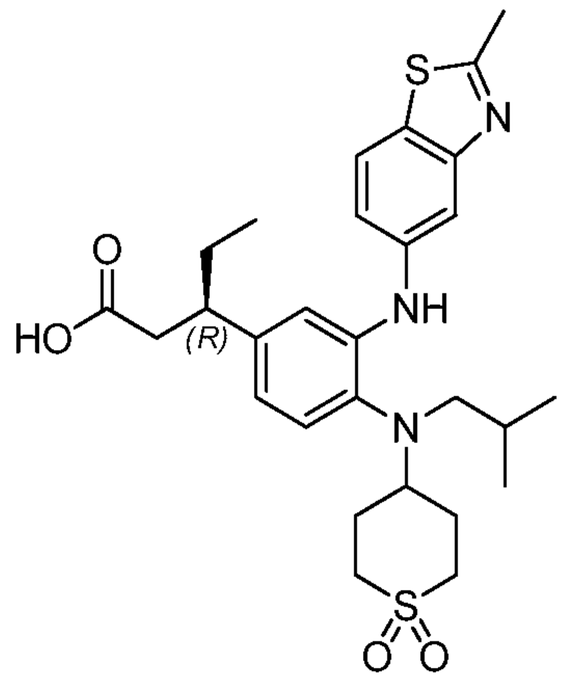
Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
211	(R)-3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl)amino)-3-(3-(2-fluoro-4-methoxyphenyl)ureido)phenyl) pentanoic acid		1.798	564.4

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
212	(R)-3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl)amino)-3-(3-(4-ethoxyphenyl)ureido)phenyl)pentanoic acid		1.895	560.4
213	(R)-3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl)amino)-3-(3-(5-methylisoxazol-3-yl)ureido)phenyl) pentanoic acid		521.4	1.347

Example 214

(Enantiomer 1)

3-(4-((1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl)amino)-3-((2-methylbenzo[d] thiazol-5-yl)amino)phenyl)pentanoic acid

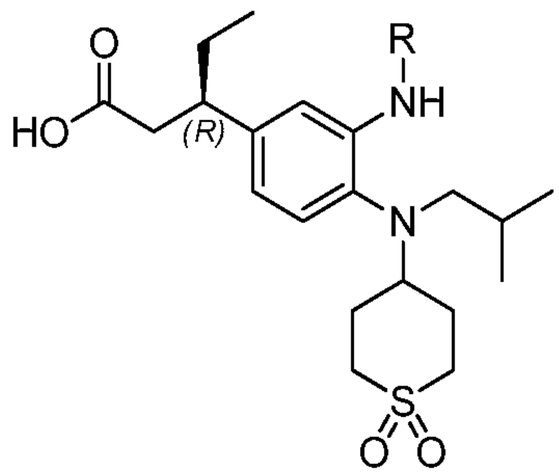


To a vial containing 209F (20 mg, 0.049 mmol), cesium carbonate (31.7 mg, 0.097 mmol), and 5-bromo-2-methylbenzo[d]thiazole (12 mg, 0.073 mmol), was added 1,4-dioxane (1 mL). The mixture was degasified with nitrogen for 10 minutes. Xantphos (6.88 mg, 0.012 mmol) and bis(dibenzylideneacetone)palladium (1.401 mg, 2.436 µmol) were added and the reaction mixture was stirred to 110 °C for 6 h. The solvent was removed under reduced pressure. The crude residue was dissolved with DCM (0.5 mL) and treated with 1.5 N HCl until pH is acidic. The aqueous layer was extracted with DCM (1 × 20 mL) and concentrated under reduced pressure to get crude. To this LiOH (11.67

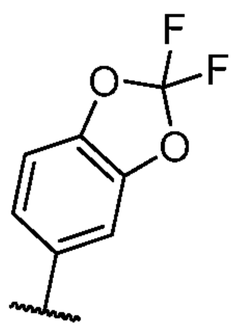
mg, 0.487 mmol) and MeOH (1 mL) were added. Reaction mixture was stirred at RT overnight. Purified by reverse phase prep HPLC to give Example 214 (off-white solid, 12 mg, 0.048 mmol, 42% yield). LC-MS Anal. Calc'd. for $C_{28}H_{37}N_3O_4S_2$ 543.7, found [M+H] 544.4, T_r = 1.95 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 9.34 (s, 1H), 8.07 - 7.98 (m, 2H), 7.37 - 7.35 (m, 2H), 7.15 - 7.08 (m, 2H), 6.80 - 6.70 (m, 1H), 3.33 - 3.10 (m, 2H), 3.05 - 2.95 (m, 3H), 2.60 - 2.50 (m, 3H), 2.40 (m, 1H), 2.32 (s, 3H), 2.22 - 2.15 (m, 2H), 1.92 - 1.85 (m, 2H), 1.74 - 1.21 (m, 3H), 0.82 (m, 6H). 0.72 - 0.69 (t, J = 7.2 Hz, 3H).

Example 215

(Enantiomer 1)

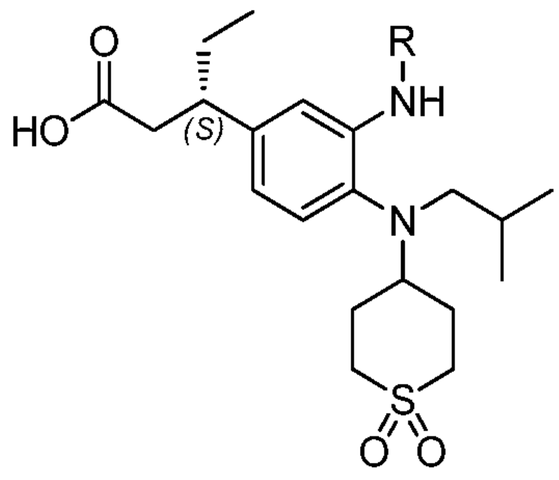


Example 215 was prepared from 209F and 5-bromo-2,2-difluorobenzo[d][1,3] dioxole following the procedure described for the synthesis of Example 214.

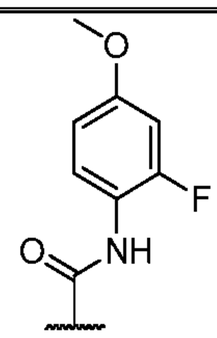
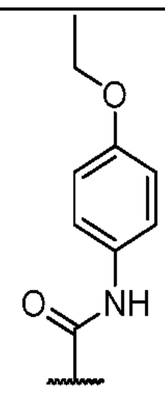
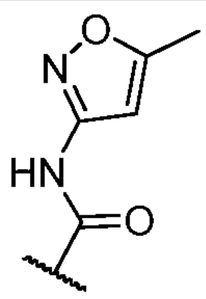
Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
215	(R)-3-(3-((2,2-difluorobenzo[d][1,3] dioxol-5-yl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl)amino)phenyl)pentanoic acid		1.961	553.3

Examples 216 to 218

(Enantiomer 2)

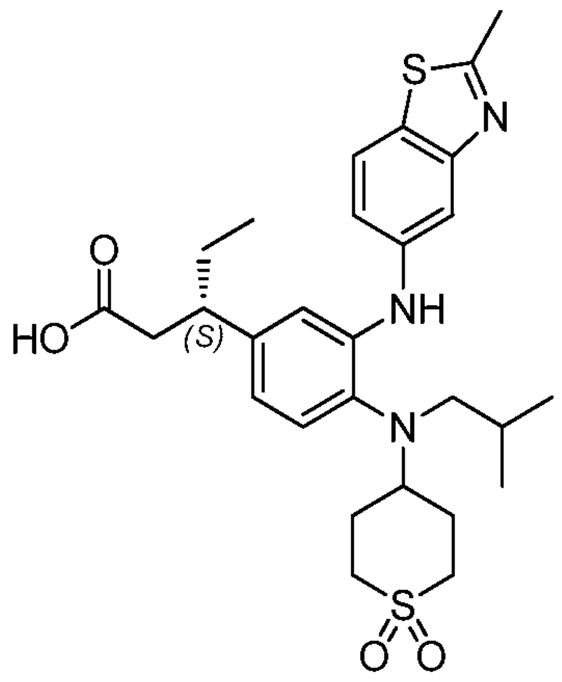


Examples 216 to 218 were prepared from 210C and the corresponding isocyanates following the procedure described for the synthesis of Example 210.

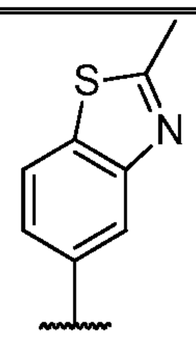
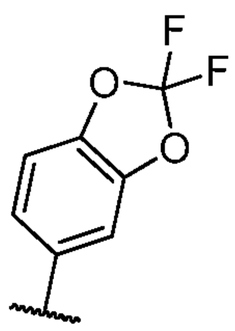
Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
216	(S)-3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl)amino)-3-(3-(2-fluoro-4-methoxyphenyl)ureido)phenyl) pentanoic acid		1.603	564.2
217	(S)-3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl)amino)-3-(3-(4-ethoxyphenyl)ureido)phenyl)pentanoic acid		1.698	560.4
218	(S)-3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl)amino)-3-(3-(5-methylisoxazol-3-yl)ureido)phenyl) pentanoic acid		1.538	521.4

Examples 219 and 220

(Enantiomer 2)



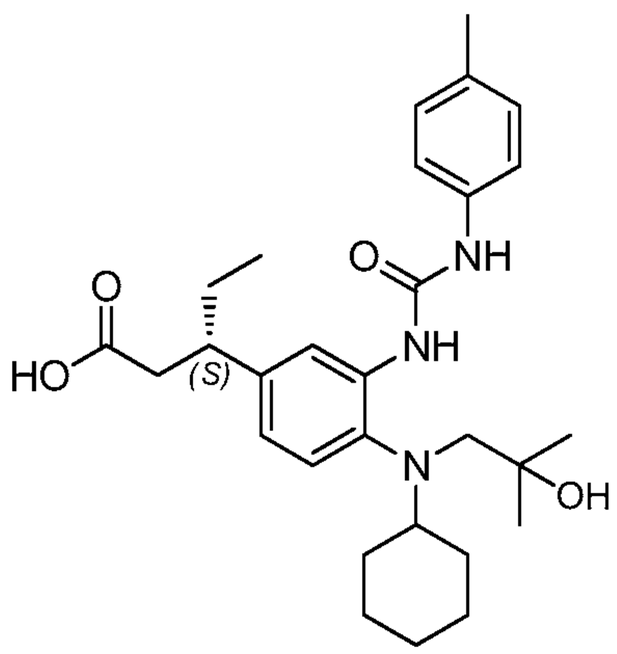
Examples 219 and 220 were prepared from 210C the corresponding aryl halides following the procedure described for the synthesis of Example 214.

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
219	(S)-3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl)amino)-3-((2-methylbenzo[d]thiazol-5-yl)amino) phenyl)pentanoic acid		1.804	544.4
220	(S)-3-(3-((2,2-difluorobenzo[d][1,3] dioxol-5-yl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(isobutyl)amino)phenyl)pentanoic acid		2.117	553.3

Example 221

(Enantiomer 1)

(S)-3-(4-(Cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-(3-(*p*-tolyl)ureido) phenyl)pentanoic acid



221A. 1-(Cyclohexylamino)-2-methylpropan-2-ol

To a stirred solution of cyclohexanone (10.0 g, 102 mmol), 1-amino-2-methylpropan-2-ol (9.08 g, 102 mmol) in dry THF (100 mL), MeOH (100 mL), added 3.0 g molecular sieves under nitrogen atmosphere. Reaction mixture was stirred at room temperature for 16 h. Reaction cooled to 0 °C and added $NaBH_4$ (11.56 g, 306 mmol) portionwise in 60 minutes. Reaction mixture was stirred at room temperature for 3 h. Reaction mixture was quenched with water (20 mL) at 0 °C. Concentrated under reduced pressure to remove methanol completely to get semi-solid and it was quenched with 10% sodium bicarbonate (100 mL). Aqueous layer extracted with ethyl acetate (2 × 100 mL). Organic layer separated and washed with brine (50 mL). Organic layer dried over sodium sulfate, concentrated under reduced pressure to get liquid compound. Purification via flash chromatography gave 221A (light yellow liquid, 13.5 g, 102 mmol, 78% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.10 (br. s., 1H), 2.40 (s, 2H), 2.33 - 2.30 (m, 1H), 1.90 - 1.20 (m, 9H), 1.16 (s, 6H).

221B. 1-((4-Bromo-2-nitrophenyl)(cyclohexyl)amino)-2-methylpropan-2-ol

To a stirred solution of NaH (2.182 g, 54.5 mmol) in dry DMF (60.0 mL), 221A (12.46 g, 72.7 mmol) was added at 0 °C and maintained for 30 minutes at same temperature. 4-Bromo-1-fluoro-2-nitrobenzene (8.0 g, 36.4 mmol) was added at 0 °C. Reaction stirred at room temperature for 4 h. Reaction mixture was cooled to 0 °C and quenched with 3 mL water and stirred for 10 minutes at room temperature. Reaction mixture dilute with ethyl acetate (20 mL) washed with water (10 mL), organic layer separated and aqueous layer extract with ethyl acetate (2 × 20 mL). Organic layer

combined together dried over sodium sulfate, concentrated under reduced pressure to get orange liquid. Purification via flash chromatography gave 221B (orange liquid, 0.7 g, 1.65 mmol, 93% yield). LC-MS Anal. Calc'd. for $C_{16}H_{23}BrN_2O_3$ 370.2, found [M+2] 372.2, T_r = 3.58 min (Method N).

221C. 1-(Cyclohexyl(2-nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) amino)-2-methylpropan-2-ol

To a stirred solution of 221B (5.0 g, 13.47 mmol), 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi(1,3,2-dioxaborolane) (4.10 g, 16.16 mmol), potassium acetate (3.97 g, 40.4 mmol) in dry DMSO (50.0 mL) purged argon for 10 minutes added $PdCl_2$ (dppf)•CH_2Cl_2 Adduct (0.550 g, 0.673 mmol). Reaction placed on preheated oil bath at 80 °C and maintained for 2 h. Reaction mixture was cooled to room temperature, diluted with ethyl acetate (50 mL) washed with water (25 mL) and organic layer separated, aqueous layer back extracted with ethyl acetate (2 × 50 mL). Organic layers mixed together dried over sodium sulfate, concentrated completely to get brown liquid. Purification via flash chromatography gave 221C (orange semi-solid, 4.5 g, 10.76 mmol, 80% yield). LC-MS Anal. Calc'd. for $C_{22}H_{35}BN_2O_5$ 418.2, found [M+H] 419.2, T_r = 4.00 min (Method N).

221D. (S)-Methyl 3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-nitrophenyl) pentanoate

In a 100 mL round bottom flask 1,4-dioxane (50.0 mL), chlorobis(ethylene) rhodium(I) dimer (0.021 g, 0.054 mmol), (R)-BINAP (0.049 g, 0.079 mmol) bubbled with argon for 10 minutes, 221C (1.5 g, 3.59 mmol) and methyl pent-2-enoate (0.491 g, 4.30 mmol), sodium hydroxide (1 molar solution) (3.27 mL, 3.27 mmol) were added respectively and bubbled argon for another 5 minutes. The reaction mixture was heated at 50 °C for 1 h. Reaction mixture was cooled to room temperature and quenched with acetic acid (0.185 mL, 3.23 mmol) and it was stirred for 5 minutes. Reaction mixture was partitioned between ethyl acetate (25 mL) and water (25 mL). Aqueous layer was back extracted with ethyl acetate (2 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash chromatography gave 221D (orange semi-solid, 0.9 g, 2.214 mmol, 62% yield). LC-MS Anal. Calc'd. for $C_{22}H_{34}N_2O_5$ 406.2, found

[M+H] 407.2, T_r = 3.58 min (Method N). (Absolute stereochemistry of the product assigned based on the expected product enantiomer from the use of (R)-BINAP in the conjugate addition)

221E. (S)-Methyl 3-(3-amino-4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)phenyl) pentanoate

To sealable hydrogen stirring flask, 221D (0.900 g, 2.214 mmol), Pd/C (0.160 g, 0.151 mmol) charged in dry ethyl acetate (20.0 mL) under flow of nitrogen. The resulting mixture was sequentially evacuated then purged with nitrogen before the flask was pressured to 40 psi of hydrogen and stirred at ambient temperature for 4 hours. The reaction mixture was filtered through a pad of CELITE® which was then thoroughly rinsed with ethyl acetate (10 mL). The combined filtrates were concentrated *in vacuo* to afford orange semi-solid. Purification via flash chromatography gave 221E (orange semi-solid, 0.9 g, 2.214 mmol, 62% yield). LC-MS Anal. Calc'd. for $C_{22}H_{36}N_2O_3$ 376.2, found [M+H] 377.2, T_r = 3.38 min (Method N). Chiral purity = 94% ee, T_r = 31.48 min (Method DA).

221F. (S)-Methyl 3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)pentanoate

To a stirred solution of 221E (0.025 g, 0.066 mmol) in dry THF (1.0 mL) 1-isocyanato-4-methylbenzene (8.84 mg, 0.066 mmol) was added and stirred for 1 h at room temperature. Purification via flash chromatography gave 221F. LC-MS Anal. Calc'd. for $C_{30}H_{43}N_3O_4$ 509.3, found [M+H] 510.6, T_r = 1.11 min (Method BC).

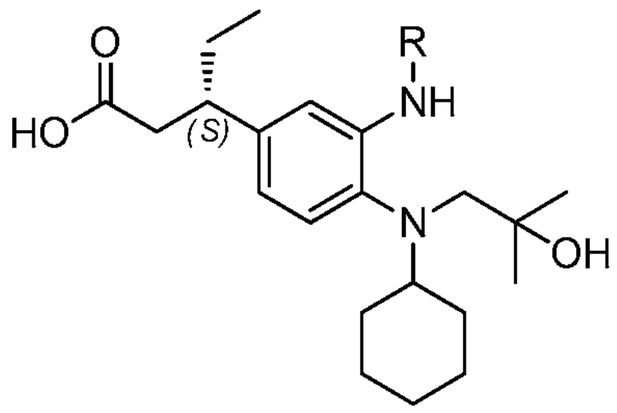
Example 221. (S)-3-(4-(Cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)pentanoic acid

To a stirred solution of 221F (0.034 g, 0.067 mmol) in THF (1.0 mL), MeOH (0.667 mL), water (0.333 mL) mixture $LiOH•H_2O$ (7.99 mg, 0.334 mmol) was added and stirred for 16 h at room temperature. Reaction mixture was concentrated under reduced pressure to get crude material. The crude pH was adjusted to ~2 with 1.5 N HCl solution and the aqueous layer was extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced

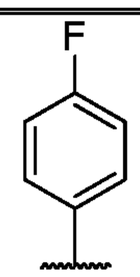
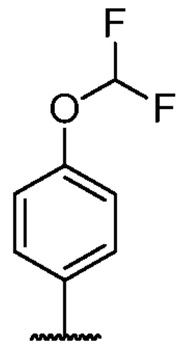
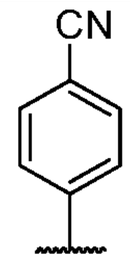
pressure to get crude product. Purification via preparative LC/MS gave Example 221 (off-white solid, 25.7 mg, 0.048 mmol, 72% yield). LC-MS Anal. Calc'd. for $C_{29}H_{41}N_3O_4$ 495.3, found [M+H] 496.3, T_r = 1.72 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.24 (m, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 7.39 - 7.35 (m, 2H), 7.17 -7.04 (m, 3H), 6.77 - 6.75 (m, 1H), 4.10 (br. s., 1H), 3.08 -2.90 (m, 2H), 2.88 - 2.08 (m, 1H), 2.49 - 2.40 (m, 2H), 2.25 (s, 3H), 1.98 - 1.80 (m, 2H), 1.75 - 1.60 (m, 4H), 1.58 - 1.40 (m, 2H), 1.20 - 1.05 (m, 6H), 0.88 (m, 6H), 0.69 (t, J = 8.00 Hz, 3H).

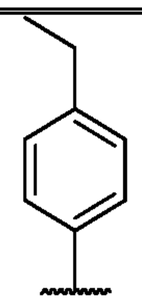
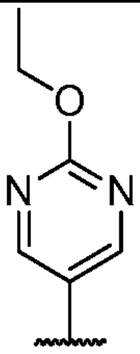
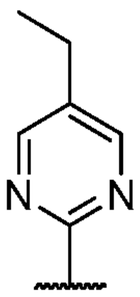
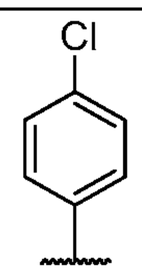
Examples 225 to 231

(Enantiomer 1)



Examples 225 to 231 were prepared from 221E and corresponding aryl halides following the procedure described for the synthesis of Example 214.

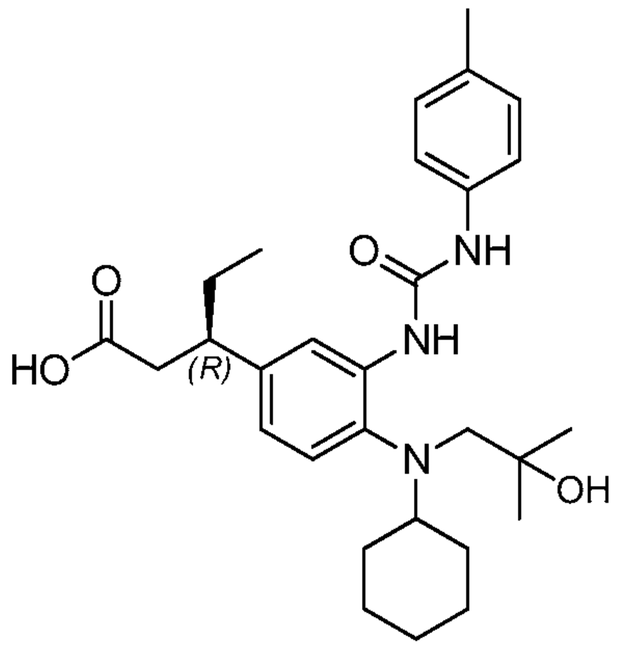
Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
225	(S)-3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-((4-fluorophenyl) amino)phenyl)pentanoic acid		1.633	457.4
226	(S)-3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-((4-(difluoromethoxy)phenyl)amino)phenyl) pentanoic acid		1.698	505.4
227	(S)-3-(3-((4-cyanophenyl)amino)-4-(cyclohexyl(2-hydroxy-2-methylpropyl) amino)phenyl)pentanoic acid		1.720	464.4

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
228	(S)-3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-((4-ethylphenyl) amino)phenyl)pentanoic acid		2.199	467.5
229	(S)-3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl) pentanoic acid		1.617	485.4
230	(S)-3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-((5-ethylpyrimidin-2-yl)amino)phenyl) pentanoic acid		1.723	469.4
231	(S)-3-(3-((4-chlorophenyl)amino)-4-(cyclohexyl(2-hydroxy-2-methylpropyl) amino)phenyl)pentanoic acid		2.080	473.4

Example 232

(Enantiomer 2)

(R)-3-(4-(Cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-(3-(*p*-tolyl)ureido) phenyl)pentanoic acid



232A. (R)-Methyl 3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-nitrophenyl) pentanoate

232A was prepared from 221C and (S)-BINAP following the procedure described for the synthesis of 221D. LC-MS Anal. Calc'd. for $C_{22}H_{34}N_2O_5$ 406.2, found [M+H] 407.4, T_r = 3.742 min (Method N). (Absolute stereochemistry of the product assigned based on the expected product enantiomer from the use of (S)-BINAP in the conjugate addition)

232B. (R)-Methyl 3-(3-amino-4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)phenyl) pentanoate

232B was prepared from 232A following the procedure described for the synthesis of 221E. LC-MS Anal. Calc'd. for $C_{22}H_{36}N_2O_3$ 376.2, found [M+H] 377.2, T_r = 3.38 min (Method N). Chiral purity 83% ee, T_r = 29.39 min (Method DA).

232C. Methyl 3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-(3-(*p*-tolyl)ureido) phenyl)pentanoate

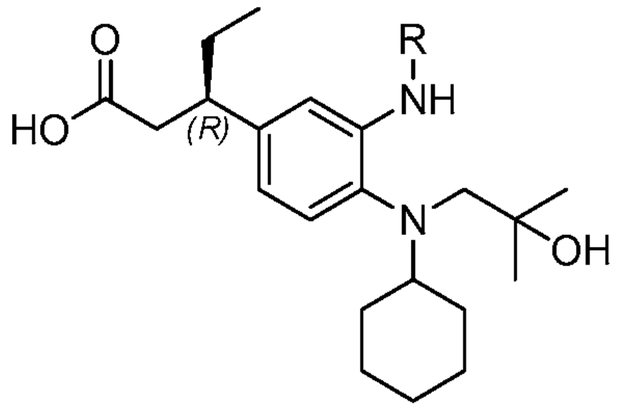
232C was prepared from 232B and 1-isocyanato-4-methylbenzene following the procedure described for the synthesis of 221F. LC-MS Anal. Calc'd. for $C_{30}H_{43}N_3O_4$ 509.3, found [M+H] 510.6, T_r = 1.11 min (Method BC).

Example 232. (R)-3-(4-(Cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)pentanoic acid

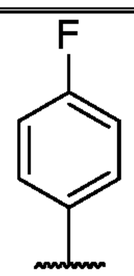
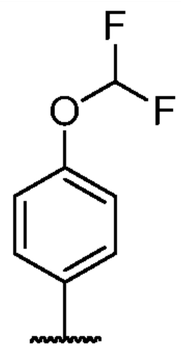
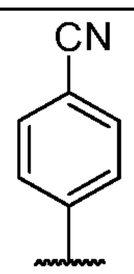
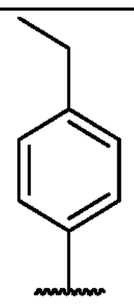
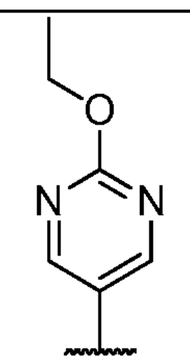
Example 232 was prepared from 232C following the procedure described for the synthesis of Example 221 for 221F. LC-MS Anal. Calc'd. for $C_{29}H_{41}N_3O_4$ 495.3, found [M+H] 496.3, T_r = 1.72 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.24 (m, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 7.39 - 7.35 (m, 2H), 7.17 -7.04 (m, 3H), 6.77 - 6.75 (m, 1H), 4.10 (br. s., 1H), 3.08 -2.90 (m, 2H), 2.88 - 2.08 (m, 1H), 2.49 - 2.40 (m, 2H), 2.25 (s, 3H), 1.98 - 1.80 (m, 2H), 1.75 - 1.60 (m, 4H), 1.58 - 1.40 (m, 2H), 1.20 - 1.05 (m, 6H), 0.88 (m, 6H), 0.69 (t, *J* = 8.00 Hz, 3H).

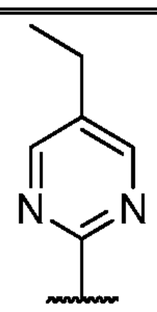
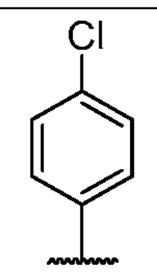
Examples 236 to 242

(Enantiomer 2)



Examples 236 to 242 were prepared from 232B and corresponding aryl halides following the procedure described for the synthesis of Example 214.

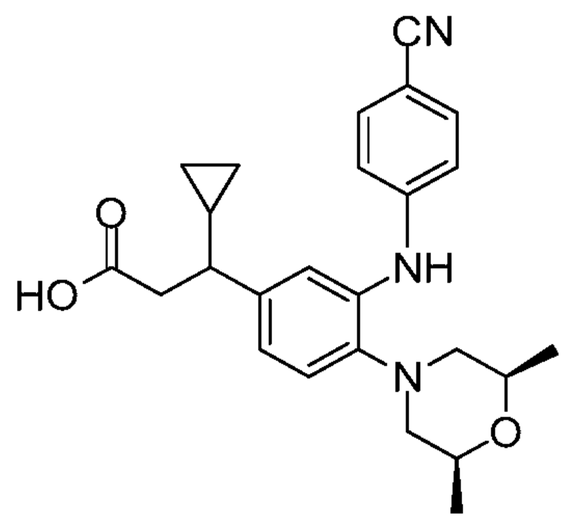
Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
236	(R)-3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-((4-fluorophenyl)amino)phenyl)pentanoic acid		1.944	457.4
237	(R)-3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-((4-(difluoromethoxy)phenyl)amino)phenyl)pentanoic acid		2.022	505.4
238	(R)-3-(3-((4-cyanophenyl)amino)-4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)phenyl)pentanoic acid		1.787	464.4
239	(R)-3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-((4-ethylphenyl)amino)phenyl)pentanoic acid		2.241	467.5
240	(R)-3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl)pentanoic acid		1.676	485.4

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
241	(R)-3-(4-(cyclohexyl(2-hydroxy-2-methylpropyl)amino)-3-((5-ethylpyrimidin-2-yl)amino)phenyl) pentanoic acid		1.786	469.4
242	(R)-3-(3-((4-chlorophenyl)amino)-4-(cyclohexyl(2-hydroxy-2-methylpropyl) amino)phenyl)pentanoic acid		1.828	473.4

Example 243

(Enantiomer 1)

3-(3-((4-Cyanophenyl)amino)-4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-3-cyclopropylpropanoic acid



243A. (2S,6R)-4-(4-Bromo-2-nitrophenyl)-2,6-dimethylmorpholine

To a solution of 4-bromo-1-fluoro-2-nitrobenzene (2.8 g, 12.73 mmol) and (2R,6S)-2,6-dimethylmorpholine (1.466 g, 12.73 mmol) in NMP (10 mL) was added DIPEA (6.67 mL, 38.2 mmol). Reaction mixture heated to 135 °C for 16 h. The reaction mixture was cooled to RT and diluted with diethyl ether. The organic layer was washed with 10% aq. AcOH solution followed by 10% $NaHCO_3$ solution and brine solution. Organic layer dried over Na_2SO_4 and concentrated under reduced pressure to give crude sample. Purification via flash chromatography gave 243A (orange liquid, 3.5 g, 10.47 mmol, 82% yield). LC-MS Anal. Calc'd. for $C_{12}H_{15}BrN_2O_3$ 315.163, found [M+2] 317.0. T_r = 3.191 min (Method N).

243B. (2S,6R)-4-(4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-2-nitrophenyl)-2,6-dimethylmorpholine

The mixture of 243A (2.5 g, 7.93 mmol), bis(neopentyl glycolato)diboron (2.365 g, 10.47 mmol) and potassium acetate (2.336 g, 23.80 mmol) in dioxane (30 mL) was stirred at room temperature. Argon gas was bubbled through the mixture for 5 min. $PdCl_2$(dppf)•CH_2Cl_2 Adduct (0.194 g, 0.238 mmol) was added and argon gas was bubbled through the mixture for 5 min. The reaction mixture was heated at 80 °C for 6 h. The reaction mixture was cooled to room temperature and diluted with dichloromethane (100 mL). The organic layer was washed with water (50 m), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification via flash chromatography gave 243B (yellow solid, 2.4 g, 6.76 mmol, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 1.60 Hz, 1H), 7.83 (dd, J = 1.60, 8.40 Hz, 1H), 7.02 (d, J = 8.40 Hz, 1H), 3.82-3.87 (m, 2H), 3.75 (s, 4H), 3.09 (dd, J = 2.00, 9.60 Hz, 2H), 2.60 (dd, J = 10.40, 12.00 Hz, 2H), 1.19 (d, J = 6.00 Hz, 6H), 1.01 (s, 6H).

243C. Methyl 3-cyclopropyl-3-(4-((2S,6R)-2,6-dimethylmorpholino)-3-nitrophenyl) propanoate

In a pressure tube equipped with Teflon cap, 243B (2.0 g, 5.74 mmol), 1,4-dioxane (40 mL) were added followed by (E)-methyl 3-cyclopropylacrylate (0.870 g, 6.89 mmol), sodium hydroxide (5.17 mL, 5.17 mmol). Argon gas was bubbled through the mixture for 10 min and chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.042 g, 0.086 mmol) was added at room temperature. Argon gas was bubbled through the mixture for 5 min. The tube was then screw-capped and heated at 50 °C for 1 h. The reaction mixture was cooled to room temperature, quenched with acetic acid (0.2 mL) and was stirred for 5 minutes before it was diluted with water (50 mL). The aqueous layer was extracted with ethyl acetate (3 × 100 mL). Combined organic layer were washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to get crude product. Purification via flash chromatography gave 243C (yellow liquid, 2.0 g, 5.13 mmol, 89% yield). LC-MS Anal. Calc'd. for $C_{19}H_{26}N_2O_5$ 362.420, found [M+H] 363.0. T_r = 1.47 min (Method BA).

243D. Methyl 3-(3-amino-4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-3-cyclopropylpropanoate

The solution of 243C (2.4 g, 6.62 mmol) in ethyl acetate (100 mL) was charged to a sealable hydrogen flask. The solution was sequentially evacuated and purged with nitrogen gas. To this 10% Pd on carbon (0.352 g, 0.331 mmol) was added under nitrogen atmosphere. The reaction mixture was stirred under hydrogen atmosphere (40 psi). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through a CELITE® pad and the residue on the pad was thoroughly rinsed with MeOH (3 × 100 mL). The combined filtrate was concentrated under reduced pressure. Purification via flash chromatography gave 243D. LC-MS Anal. Calc'd. for $C_{19}H_{28}N_2O_3$ 332.437, found [M+H] 333.3. T_r = 1.33 min (Method BA).

Chiral separation of Racemate 243D (Method BZ) 243D Enantiomer 1, T_r = 3.46 min (Method BZ), 243D Enantiomer 2, T_r = 4.13 min (Method BZ).

243D Enantiomer 1: (brown semi-solid, 0.65 g, 1.955 mmol, 29.5% yield). LC-MS Anal. Calc'd. for $C_{19}H_{28}N_2O_3$ 332.437, found [M+H] 333.3. T_r = 3.38 min (Method N).

243D Enantiomer 2: (brown semi-solid 0.7 g, 2.069 mmol, 31.2% yield). LC-MS Anal. Calc'd. for $C_{19}H_{28}N_2O_3$ 332.437, found [M+H] 333.3. T_r = 3.37 min (Method N).

243E. Methyl 3-(3-((4-cyanophenyl)amino)-4-((2R,6S)-2,6-dimethylmorpholino) phenyl)-3-cyclopropylpropanoate

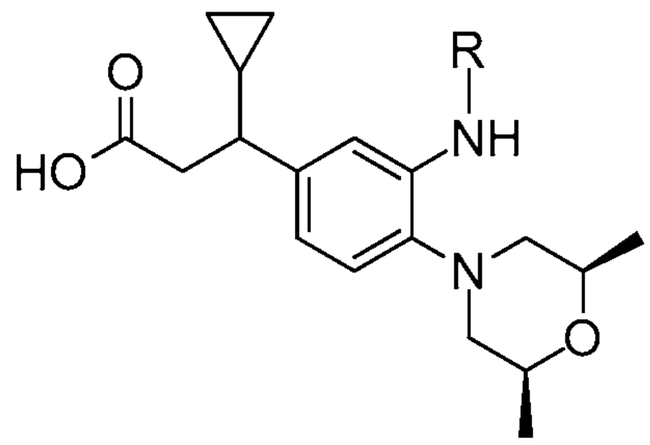
To degassed solution of 243D Enantiomer 1 and 4-bromobenzonitrile (0.027 g, 0.150 mmol), cesium carbonate (0.074 g, 0.226 mmol) in dry dioxane (2.0 mL) purged argon for 15 minutes.4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (8.70 mg, 0.015 mmol). Bis(dibenzylideneacetone)palladium (4.32 mg, 7.52 µmol). Reaction heated to 110 °C temperature and maintained for 4 h. The reaction mixture was filtered through pad of CELITE®, washed with EtOAc. The filtrate was concentrated under reduced pressure. Purification via flash chromatography gave 243E (brown semi-solid, 52 mg, 0.120 mmol, 80% yield). LC-MS Anal. Calc'd. for $C_{26}H_{31}N_3O_3$ 433.2, found [M+H] 434.4. T_r = 1.53 min (Method BA).

Example 243. 3-(3-((4-Cyanophenyl)amino)-4-((2R,6S)-2,6-dimethylmorpholino) phenyl)-3-cyclopropylpropanoic acid

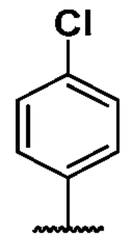
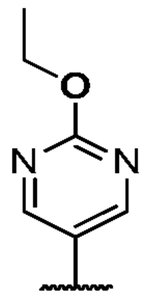
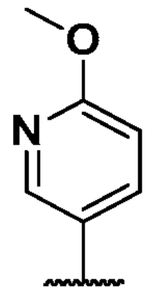
To stirred solution of 243E (0.050 g, 0.115 mmol) in dry THF (1.0 mL), MeOH (1.0 mL) mixture lithium hydroxide monohydrate (0.024 g, 0.577 mmol) was added at room temperature. Reaction mixture was stirred at room temperature for 16 h. Reaction mixture concentrated under reduced pressure, added water (2 mL) washed with diethyl ether (5 mL). Aqueous layer separated and acidified with saturated citric acid. Aqueous layer extract with DCM (3 × 5 mL). Combined organic layers were dried over sodium sulfate and concentrated to get semi-solid product. Purification via preparative LCMS method gave Example 243 (off-white solid, 18.2 mg, 0.042 mmol, 36% yield). LC-MS Anal. Calc'd. for $C_{25}H_{29}N_3O_3$ 419.2, found [M+H] 420.3, T_r = 1.50 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 1H) 7.53-7.51 (d, *J* = 8.8Hz, 2H), 7.09 (m, 1H), 7.01-6.99 (m, 2H), 6.98 - 6.96 (d, *J* = 8.4Hz, 2H), 3.51 - 3.45 (m, 2H), 2.99 - 2.97 (m, 2H), 2.64 -2.59 (m, 2H), 2.26 - 2.22 (m, 3H), 1.10 - 0.99 (m, 7H), 0.49 - 0.47 (m, 1H), 0.35 - 0.33 (m, 1H), 0.23 - 0.21 (m, 1H), 0.14 - 0.12 (m, 1H).

Examples 244 to 246

(Enantiomer 1)



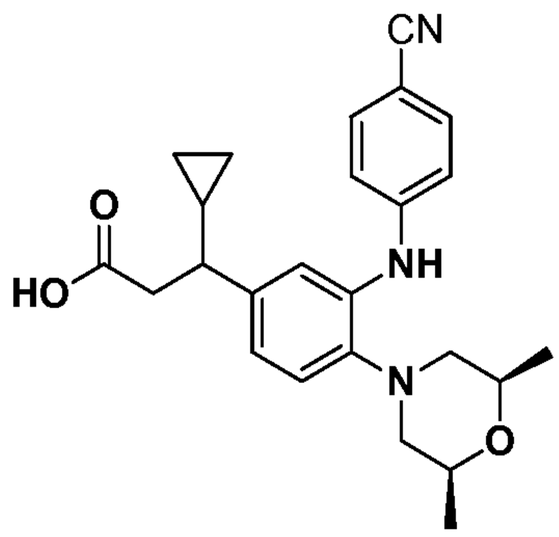
Examples 244 to 246 were prepared from 243D Enantiomer 1 and the corresponding aryl halides by following the procedure described for the synthesis of Example 243.

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
244	3-(3-((4-chlorophenyl)amino)-4-((2R,6S)-2,6-dimethylmorpholino) phenyl)-3-cyclopropylpropanoic acid		2.194	429.2
245	3-cyclopropyl-3-(4-((2R,6S)-2,6-dimethylmorpholino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl) propanoic acid		1.344	441.3
246	3-cyclopropyl-3-(4-((2R,6S)-2,6-dimethylmorpholino)-3-((6-methoxypyridin-3-yl)amino)phenyl) propanoic acid		1.454	426.3

Example 247

(Enantiomer 2)

3-(3-((4-Cyanophenyl)amino)-4-((2R,6S)-2,6-dimethylmorpholino)phenyl)-3-cyclopropylpropanoic acid



247A. Methyl 3-(3-((4-cyanophenyl)amino)-4-((2R,6S)-2,6-dimethylmorpholino) phenyl)-3-cyclopropylpropanoate

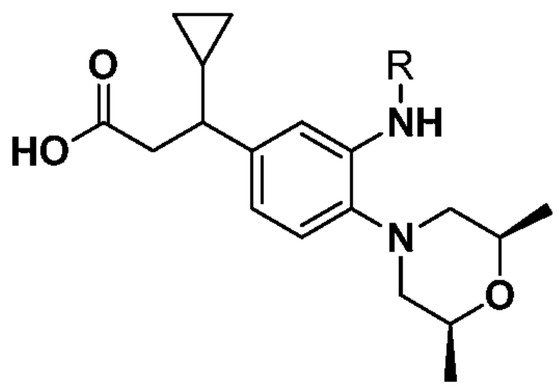
247A was prepared from 243D Enantiomer 2 and 4-bromobenzonitrile following the procedure described for the synthesis of 145F. LC-MS Anal. Calc'd. for $C_{26}H_{31}N_3O_3$ 433.2, found [M+H] 434.5. T_r = 1.53 min (Method BA).

Example 247. 3-(3-((4-Cyanophenyl) amino)-4-((2R,6S)-2,6-dimethylmorpholino) phenyl)-3-cyclopropylpropanoic acid

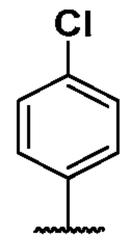
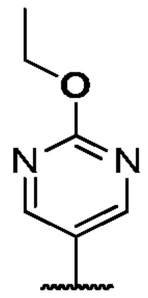
Example 247 was prepared from 247A following the procedure described for the synthesis of Example 145 for 145F. LC-MS Anal. Calc'd. for $C_{25}H_{29}N_3O_3$ 419.2, found [M+H] 420.3, T_r = 1.52 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 1H) 7.53-7.51 (d, *J* = 8.8Hz, 2H), 7.09 (m, 1H), 7.01-6.99 (m, 2H), 6.98 - 6.96 (d, *J* = 8.4Hz, 2H), 2.99 - 2.97 (m, 2H), 2.64 -2.59 (m, 2H), 2.26 - 2.22 (m, 3H), 1.10 - 0.99 (m, 7H), 0.49 - 0.47 (m, 1H), 0.35 - 0.33 (m, 1H), 0.23 - 0.21 (m, 1H), 0.14 - 0.12 (m, 1H) (Note: 2 proton buried under solvent peak).

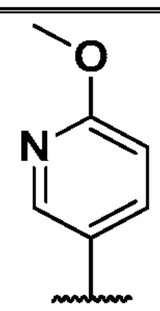
Examples 248 to 250

(Enantiomer 2)



Examples 248 to 250 were prepared from 243D Enantiomer 2 and the corresponding aryl halides following the procedure described for the synthesis of Example 243.

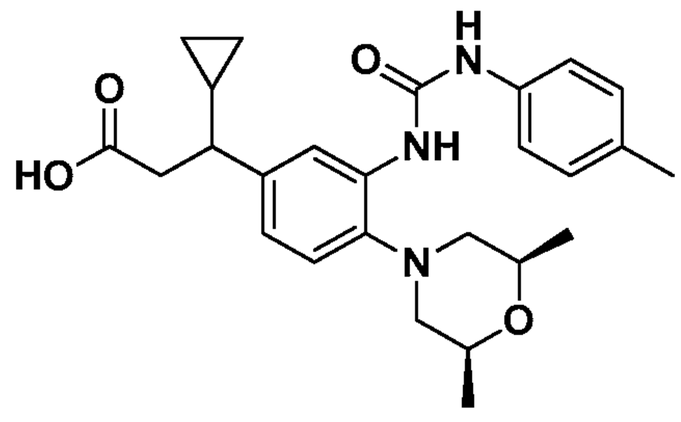
Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
248	3-(3-((4-chlorophenyl)amino)-4-((2R,6S)-2,6-dimethylmorpholino) phenyl)-3-cyclopropylpropanoic acid		1.87	429.3
249	3-cyclopropyl-3-(4-((2R,6S)-2,6-dimethylmorpholino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl) propanoic acid		1.357	441.3

Ex. No.	Name	R	T_r (min) Method O	$(M+H)^+$
250	3-cyclopropyl-3-(4-((2R,6S)-2,6-dimethylmorpholino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl) propanoic acid		1.453	426.3

Example 251

(Enantiomer 1 and Enantiomer 2)

3-Cyclopropyl-3-(4-((2R,6S)-2,6-dimethylmorpholino)-3-(3-(*p*-tolyl)ureido)phenyl) propanoic acid



251A. Methyl 3-cyclopropyl-3-(4-((2R,6S)-2,6-dimethylmorpholino)-3-(3-(*p*-tolyl) ureido)phenyl)propanoate

251A was prepared from 243D Enantiomer 1 and 1-isocyanato-4-methylbenzene following the procedure described for the synthesis of 5A. LC-MS Anal. Calc'd. for $C_{27}H_{35}N_3O_4$ 465.2, found [M+H] 466.4. T_r = 1.49 min (Method BA).

Example 251 Enantiomer 1. 3-Cyclopropyl-3-(4-((2R,6S)-2,6-dimethylmorpholino)-3-(3-(*p*-tolyl)ureido)phenyl)propanoic acid

Example 251 Enantiomer 1 was prepared from 251A following the procedure described for the synthesis of Example 145 from 145F (absolute stereochemistry unknown). LC-MS Anal. Calc'd. for $C_{26}H_{33}N_3O_4$ 451.2, found [M+H] 452.3, T_r = 1.76 min (Method O).^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.09 (s, 1H), 8.01 (d, *J* = 1.6Hz, 1H), 7.36 (m, 1H), 7.34 (m, 1H), 7.10 - 7.05 (m, 3H), 6.84 - 6.82 (m, 1H), 3.91 - 3.88 (m, 2H), 2.76 - 2.60 (m, 2H), 2.49 - 2.35 (m, 2H), 2.33 - 2.30 (m, 2H), 2.23 - 2.15

(s, 3H), 2.10 - 2.05 (m, 1H), 1.09 - 1.07 (d, *J* = 6.0 Hz, 6H), 0.93 - 0.08 (m, 1H), 0.49 - 0.47 (m, 1H), 0.32 - 0.30 (m, 1H), 0.23 - 0.19 (m, 1H), 0.09 - 0.05 (m, 1H).

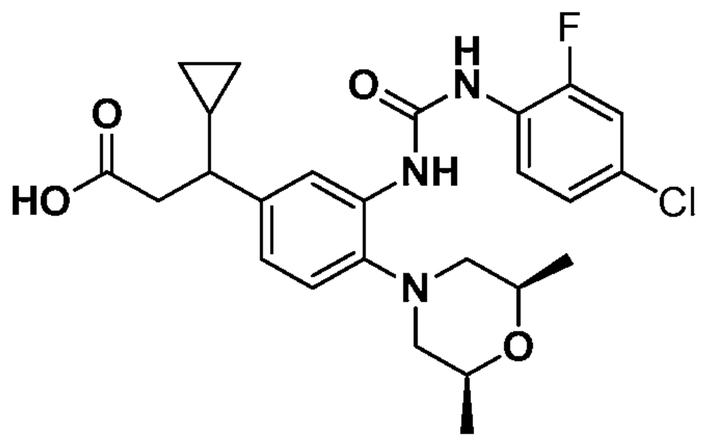
Example 251 Enantiomer 2. 3-Cyclopropyl-3-(4-((2R,6S)-2,6-dimethylmorpholino)-3-(3-(*p*-tolyl)ureido)phenyl)propanoic acid

Example 251 Enantiomer 2 was prepared from 243D Enantiomer 2 and 1-isocyanato-4-methylbenzene following the procedures described for the synthesis of Example 251 Enantiomer 1 (absolute stereochemistry unknown). LC-MS Anal. Calc'd. for $C_{26}H_{33}N_3O_4$ 451.2, found [M+H] 452.3, T_r = 1.45 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.09 (s, 1H), 8.01 (d, *J* = 1.6Hz, 1H), 7.36 (m, 1H), 7.34 (m, 1H), 7.10 - 7.05 (m, 3H), 6.84 - 6.82 (m, 1H), 3.91 - 3.88 (m, 2H), 2.76 - 2.60 (m, 2H), 2.49 - 2.35 (m, 2H), 2.33 - 2.30 (m, 2H), 2.23 - 2.15 (s, 3H), 2.10 - 2.05 (m, 1H), 1.09 - 1.07 (d, *J* = 6.0 Hz, 6H), 0.93 - 0.08 (m, 1H), 0.49 - 0.47 (m, 1H), 0.32 - 0.30 (m, 1H), 0.23 - 0.19 (m, 1H), 0.09 - 0.05 (m, 1H).

Example 252

(Enantiomer 1)

3-(3-(3-(4-Chloro-2-fluorophenyl)ureido)-4-((2R,6S)-2,6-dimethylmorpholino)phenyl)-3-cyclopropylpropanoic acid



252A. Methyl 3-(3-(3-(4-chloro-2-fluorophenyl)ureido)-4-((2R,6S)-2,6-dimethylmorpholino)phenyl)-3-cyclopropylpropanoate

252A was prepared from 243D Enantiomer 1 and 4-chloro-2-fluoro-1-isocyanatobenzene following the procedure described for the synthesis of 5A. LC-MS Anal. Calc'd. for $C_{26}H_{31}ClFN_3O_4$ 503.19, found [M+H] 504.4, T_r = 1.57 min (Method BA).

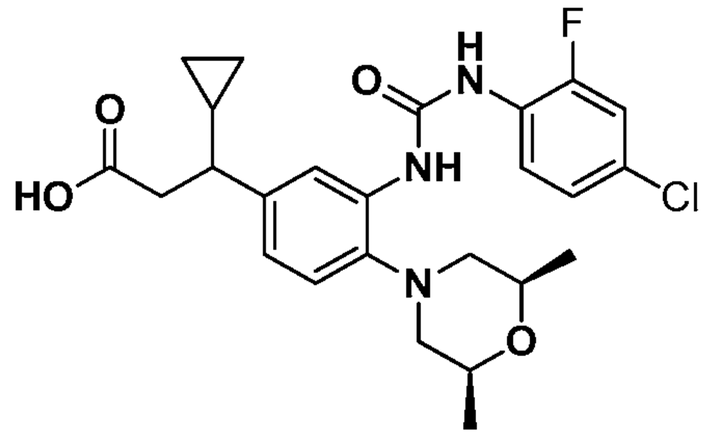
Example 252 Enantiomer 1. 3-(3-(3-(4-Chloro-2-fluorophenyl)ureido)-4-((2R,6S)-2,6-dimethylmorpholino)phenyl)-3-cyclopropylpropanoic acid

Example 252 Enantiomer 1 was prepared from 252A following the procedure described for the synthesis of Example 145 from 145F (absolute stereochemistry unknown). LC-MS Anal. Calc'd. for $C_{25}H_{29}ClFN_3O_4$ 489.18, found [M+H] 490.3, T_r = 1.59 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1H), 8.50 (s, 1H), 8.15-8.10 (t, *J* = 8.8Hz, 1H), 7.94-7.93 (m, 1H), 7.47 - 7.44 (m, 1H), 7.25 - 7.22 (m, 1H), 7.08 - 7.06 (d, *J* = 8.4Hz, 1H), 6.89 - 6.87 (m, 1H), 3.94 - 3.89 (m, 2H), 2.81 - 2.76 (m, 2H), 2.59 - 2.51 (m, 2H), 2.36 - 2.31 (m, 2H), 2.22 - 2.20 (m, 1H), 1.09-1.07 (d, *J* = 6.0Hz, 6H), 0.94 - 0.93 (m, 1H), 0.49 - 0.47 (m, 1H), 0.32 - 0.30 (m, 1H), 0.23 - 0.19 (m, 1H), 0.09 - 0.05 (m, 1H).

Example 253

(Enantiomer 2)

3-(3-(3-(4-Chloro-2-fluorophenyl)ureido)-4-((2R,6S)-2,6-dimethylmorpholino)phenyl)-3-cyclopropylpropanoic acid



253A. Methyl 3-(3-(3-(4-chloro-2-fluorophenyl)ureido)-4-((2R,6S)-2,6-dimethylmorpholino)phenyl)-3-cyclopropylpropanoate

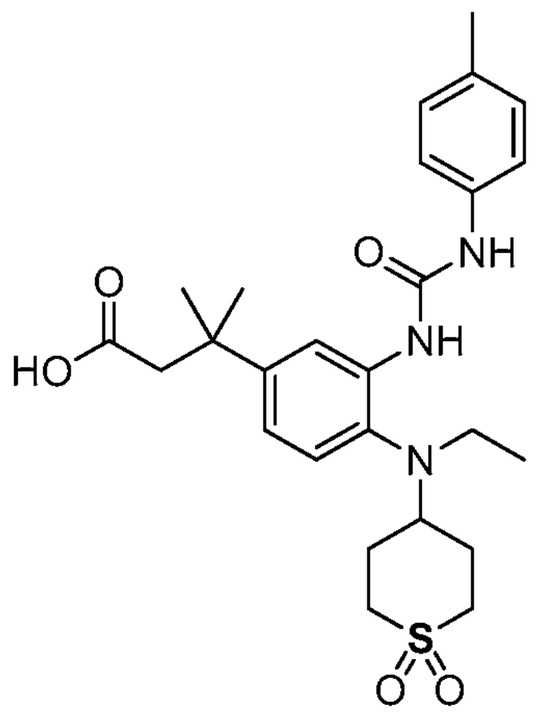
253A was prepared from 243D Enantiomer 2 and 4-chloro-2-fluoro-1-isocyanatobenzene following the procedure described for the synthesis of 5A. LC-MS Anal. Calc'd. for $C_{26}H_{31}ClFN_3O_4$ 503.19, found [M+H] 504.4, T_r = 1.57 min (Method BA).

Example 253 Enantiomer 2. 3-(3-(3-(4-Chloro-2-fluorophenyl)ureido)-4-((2R,6S)-2,6-dimethylmorpholino)phenyl)-3-cyclopropylpropanoic acid

Example 253 Enantiomer 2 was prepared from 253A following the procedure for Example 145 from 145F (absolute stereochemistry unknown). LC-MS Anal. Calc'd. for $C_{25}H_{29}ClFN_3O_4$ 489.18, found [M+H] 490.3, T_r = 1.59 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1H), 8.50 (s, 1H), 8.15-8.10 (t, *J* = 8.8Hz, 1H), 7.94-7.93 (m, 1H), 7.47 - 7.44 (m, 1H), 7.25 - 7.22 (m, 1H), 7.08 - 7.06 (d, *J* = 8.4Hz, 1H), 6.89 - 6.87 (m, 1H), 3.94 - 3.89 (m, 2H), 2.81 - 2.76 (m, 2H), 2.59 - 2.51 (m, 2H), 2.36 - 2.31 (m, 2H), 2.22 - 2.20 (m, 1H), 1.09-1.07 (d, *J* = 6.0Hz, 6H), 0.94 - 0.93 (m, 1H), 0.49 - 0.47 (m, 1H), 0.32 - 0.30 (m, 1H), 0.23 - 0.19 (m, 1H), 0.09 - 0.05 (m, 1H).

Example 254

3-(4-((1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)-3-methylbutanoic acid



254A. Ethyl 3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)-3-methylbutanoate

Compound 254A was prepared from 177D and 1-isocyanato-4-methylbenzene following the procedure described for the synthesis of 5A. LC-MS Anal. Calc'd. for $C_{28}H_{39}N_3O_5S$ 529.2, found [M+H] 530.2, T_r = 0.97 min (Method BC).

Example 254. 3-(4-((1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)-3-methylbutanoic acid

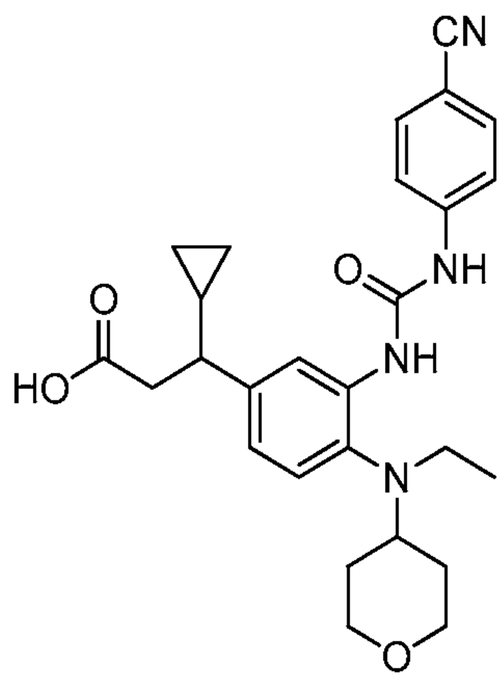
Example 254 was prepared from 254A following the procedure described for the synthesis of Example 145 from 145F. LC-MS Anal. Calc'd. for $C_{26}H_{35}N_3O_5S$ 501.2, found [M+H] 502.3, T_r = 1.50 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39

(s, 1H), 8.36 - 8.33 (m, 2H), 7.37 - 7.35 (d, J = 8.4 Hz, 2H), 7.22 - 7.07 (m, 3H), 6.98 - 6.95 (m, 1H), 3.42 - 2.97 (m, 6H), 2.24 (s, 3H), 2.20 - 2.16 (m, 2H), 1.88 -1.85 (m, 2H), 1.36 (s, 6H), 1.27 - 1.20 (m, 1H), 0.83 - 0.80 (m, 3H) (Note: one multiplet CH_2 buried under solvent peak).

Example 255

(Enantiomer 1 and Enantiomer 2)

3-(3-(3-(4-Cyanophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-cyclopropylpropanoic acid



255A. Methyl 3-(3-(3-(4-cyanophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)-3-cyclopropylpropanoate

To a stirred solution of 33E Enantiomer 1 (0.035 g, 0.101 mmol) in tetrahydrofuran (1.5 mL) was added 4-isocyanatobenzonitrile (0.017 g, 0.121 mmol). The reaction mixture was stirred at room temperature for 12 h. LCMS indicated completion of reaction. The reaction mixture was concentrated under reduced pressure to afford 255A (yellow liquid, 45 mg, 0.076 mmol, 75% yield). LC-MS Anal. Calc'd. for $C_{28}H_{34}N_4O_4$ 490.25, found [M+H] 491.4. T_r = 1.41 min. (Method AY).

Example 255 Enantiomer 1. 3-(3-(3-(4-Cyanophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-cyclopropylpropanoic acid

To a stirred solution of compound 255A (0.045 g, 0.076 mmol) in mixture of tetrahydrofuran (1.5 mL), methanol (1.5 mL) and water (0.5 mL) was added $LiOH•H_2O$ (0.015 g, 0.367 mmol). The reaction mixture was stirred at room temperature for 12 h.

The reaction mixture was concentrated under reduced pressure. The aqueous residue so obtained was acidified with aqueous citric acid to pH ~ 2. The aqueous layer was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LCMS to afford Example 255 Enantiomer 1 (absolute stereochemistry unknown) (26 mg, 0.056 mmol, 60% yield). LC-MS Anal. Calc'd. for $C_{27}H_{32}N_4O_4$ 476.2, found [M+H] 477.1. T_r = 1.60 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 - 8.92 (m, 1H), 8.02 - 8.32 (m, 1H), 7.55 - 7.87 (m, 5H), 7.05 - 7.28 (m, 1H), 6.68 - 6.97 (m, 1H), 3.82 (m, 4H), 3.08 - 3.23 (m, 2H), 2.84 - 3.05 (m, 1H), 2.67 (m, 1H), 2.25 - 2.41 (m, 2H), 1.87 - 2.15 (m, 4H), 0.82 (t, *J*=7.2 Hz, 3H), 0.54 - 0.79 (m, 5H).

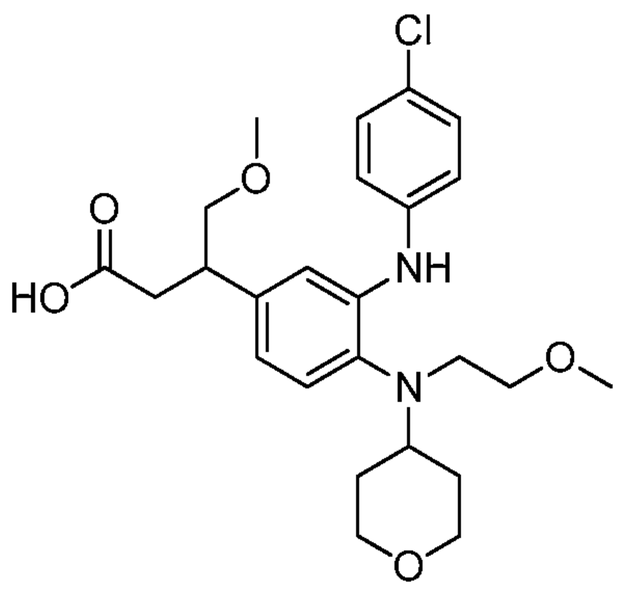
Example 255 Enantiomer 2. 3-(3-(3-(4-Cyanophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-cyclopropylpropanoic acid

Example 255 Enantiomer 2 was prepared following the same procedure for Example 255 Enantiomer 1 by utilizing 33E Enantiomer 2 (absolute stereochemistry unknown). LC-MS Anal. Calc'd. for $C_{27}H_{32}N_4O_4$ 476.2, found [M+H] 477.0. T_r = 1.58 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 - 8.92 (m, 1H), 8.02 - 8.32 (m, 1H), 7.55 - 7.87 (m, 5H), 7.05 - 7.28 (m, 1H), 6.68 - 6.97 (m, 1H), 3.82 (m, 4H), 3.08 - 3.23 (m, 2H), 2.84 - 3.05 (m, 1H), 2.67 (m, 1H), 2.25 - 2.41 (m, 2H), 1.87 - 2.15 (m, 4H), 0.82 (t, *J*=7.2 Hz, 3H), 0.54 - 0.79 (m, 5H).

Example 256

(Enantiomer 1 and Enantiomer 2)

3-(3-((4-Chlorophenyl)amino)-4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid



256A. N-(2-Methoxyethyl)tetrahydro-2H-pyran-4-amine

Compound 256A was prepared from 2-methoxyethanamine following the procedure described for the synthesis of 15D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.89 - 3.55 (m, 6H), 3.37 (s, 3H), 2.86 (m, 2H), 2.68 (m, 1H), 1.98 - 1.61 (m, 4H).

256B. N-(4-Bromo-2-nitrophenyl)-N-(2-methoxyethyl)tetrahydro-2H-pyran-4-amine

256B was prepared from 256A following the procedure described for the synthesis of 15E. LC-MS Anal. Calc'd. for $C_{14}H_{19}BrN_2O_4$ 358.05, found [M+H] 361.2. T_r = 1.37 min. (Method AY).

256C. N-(4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-2-nitrophenyl)-N-(2-methoxyethyl) tetrahydro-2H-pyran-4-amine

Compound 256C was prepared from 256B following the procedure described for the synthesis of 41A. LC-MS Anal. Calc'd. for $C_{19}H_{29}BN_2O_6$ 392.21, found MS(ES): *m/z* = 325.3 $[M+H]^+$ for parent boronic acid. T_r = 0.91 min. (Method AY).

256D. (E)-Ethyl 4-methoxybut-2-enoate

To a solution of ethyl but-2-ynoate (70 g, 624 mmol) in dry toluene (350 mL) then was added methanol (30.3 mL, 749 mmol), triphenylphosphine (8.19 g, 31.2 mmol), catalytic amount of acetic acid (7.15 mL, 125 mmol) was added at RT, and the reaction mixture allowed to stir for 10 minutes. Reaction mixture was heated at 110 °C for 20 h. Reaction mixture was cooled to room temperature, then added water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was dried over sodium sulfate and concentrated to give yellow oil. Above oil was purified via flash silica

gel column chromatography gave 256D (35 g, 243 mmol, 38.9% yield) as light yellow liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.84-6.91 (m, 1H), 5.94-5.99 (m, 1H), 4.07-4.15 (m, 4H), 3.29 (s, 3H), 1.22 (t, *J*=7.2 Hz, 3H).

256E. Ethyl 4-methoxy-3-(4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)butanoate

Compound 256E was prepared from 256C and 256D following the procedure described for the synthesis of 59E. LC-MS Anal. Calc'd. for $C_{21}H_{32}N_2O_7$ 424.2, found [M+H] 425.4. T_r = 1.29 min (Method AY).

256F. Ethyl 3-(3-amino-4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoate

Compound 256F was prepared from 256E following the procedure described for the synthesis of 33E. LC-MS Anal. Calc'd. for $C_{21}H_{34}N_2O_3$ 394.2, found [M+H] 395.4. T_r = 1.17 min (Method AY).

Chiral separation of 256F (Method CK) to get Enantiomer 1 and Enantiomer 2 as single enantiomers (Method CK) Enantiomer 1 T_r = 7.6 min and Enantiomer 2 T_r = 8.8 min (Method CK).

256F Enantiomer 1 (yellow liquid, 110 mg, 0.279 mmol, 39% yield): LC-MS Anal. Calc'd. for $C_{21}H_{34}N_2O_3$ 394.2, found [M+H] 395.2. T_r = 1.80 min (Method BB).

256F Enantiomer 2 (yellow liquid, 110 mg, 0.279 mmol, 39% yield): LC-MS Anal. Calc'd. for $C_{21}H_{34}N_2O_3$ 394.2, found [M+H] 395.2. T_r = 1.80 min (Method BB).

256G. Ethyl 3-(3-((4-chlorophenyl)amino)-4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoate

Compound 256G was prepared from 256F Enantiomer 1 following the procedure described for the synthesis of 33F. LC-MS Anal. Calc'd. for $C_{27}H_{37}ClN_2O_5$ 504.2, found [M+H] 505.2. T_r = 1.65 min (Method AY).

Example 256 Enantiomer 1. 3-(3-((4-Chlorophenyl)amino)-4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid

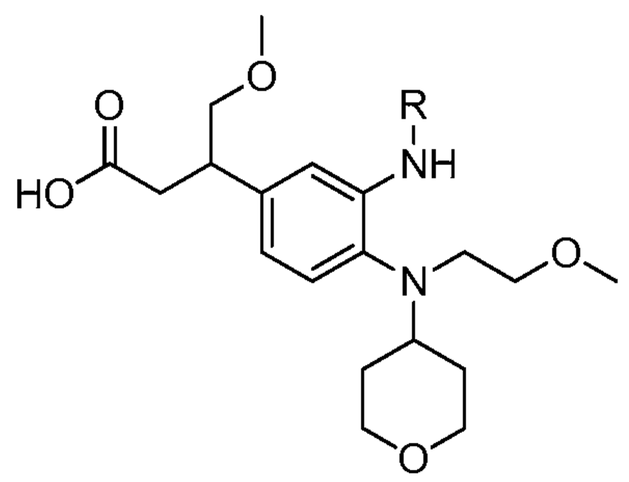
Example 256 Enantiomer 1 was prepared from 256G following the procedure described for the synthesis of Example 1 from 1I (absolute stereochemistry unknown). LC-MS Anal. Calc'd. for $C_{25}H_{33}ClN_2O_5$ 476.2, found [M+H] 477.1. T_r = 1.60 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (s, 1H), 7.27 (d, *J*=8.80 Hz, 2H), 7.18 (d, *J*=8.0 Hz, 1H), 7.04 - 7.13 (m, 3H), 6.70 - 6.85 (m, 1H), 3.78 (m, 4H), 3.42 - 3.51 (m, 6H), 3.05 - 3.23 (m, 7H), 2.97 (m, 1H), 2.59 - 2.71 (m, 2H), 1.66 (m, 2H), 1.27 - 1.47 (m, 2H).

Example 256 Enantiomer 2. 3-(3-((4-Chlorophenyl)amino)-4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid

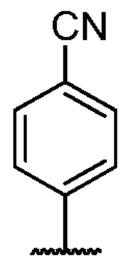
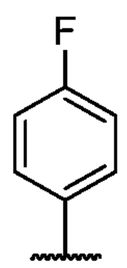
Example 256 Enantiomer 2 was prepared from 256F Enantiomer 2 following the procedure described for the synthesis of Example 256 Enantiomer 1 from 256F Enantiomer 1 (absolute stereochemistry unknown). LC-MS Anal. Calc'd. for $C_{25}H_{33}ClN_2O_5$ 476.2, found [M+H] 477.1. T_r = 1.60 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (s, 1H), 7.32 (m, 2H), 7.18 (m, 1H), 7.13 (m, 3H), 6.77 (m, 1H), 3.78 (m, 4H), 3.42 - 3.51 (m, 6H), 3.05 - 3.23 (m, 7H), 2.97 (m, 1H), 2.65 (m, 2H), 1.65 (m, 2H), 1.24 - 1.47 (m, 2H).

Examples 257 and 258

(Enantiomer 1)

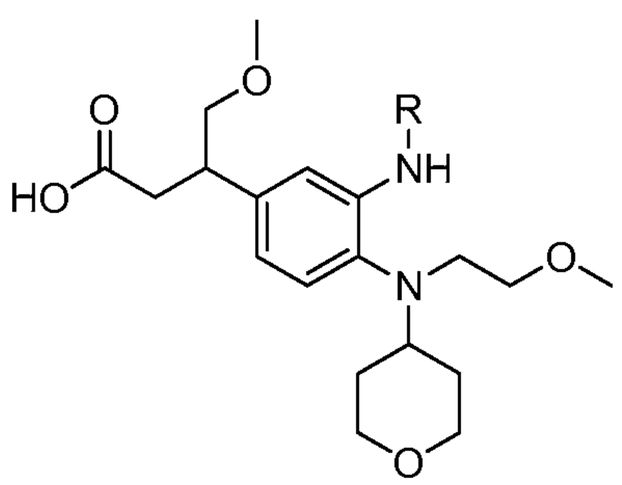


Examples 257 and 258 were prepared from 256F Enantiomer 1 and corresponding halides following the procedure described for the synthesis of Example 256 Enantiomer 1 (absolute stereochemistry unknown).

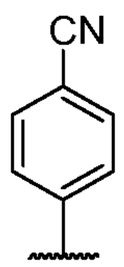
Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
257	3-(3-((4-cyanophenyl)amino)-4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.23	468.3
258	3-(3-((4-fluorophenyl)amino)-4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.51	461.2

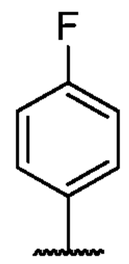
Examples 259 and 260

(Enantiomer 2)



Examples 259 and 260 was prepared from 256F Enantiomer 2 and corresponding halides following the procedure described for the synthesis of Example 256 Enantiomer 1 (absolute stereochemistry unknown).

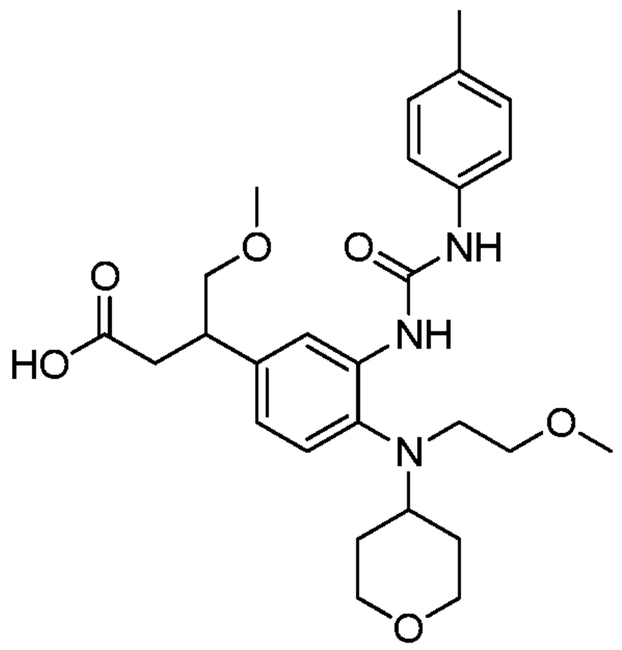
Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
259	3-(3-((4-cyanophenyl)amino)-4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.23	468.3

Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
260	3-(3-((4-fluorophenyl)amino)-4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.51	461.2

Example 261

(Enantiomer 1 and Enantiomer 2)

4-Methoxy-3-(4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)butanoic acid



261A. Ethyl 4-methoxy-3-(4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)butanoate

To a stirred solution of 256F Enantiomer 1 (0.025 g, 0.063 mmol) in tetrahydrofuran (1 mL) was added 1-isocyanato-4-methylbenzene (10.13 mg, 0.076 mmol). The reaction mixture was stirred at room temperature for 12 h. LCMS indicated completion of reaction. The reaction mixture was concentrated under reduced pressure to get 261A (yellow liquid, 30 mg, 0.044 mmol, 77% yield). LC-MS Anal. Calc'd. for $C_{29}H_{41}N_3O_6$ 527.3, found [M+H] 528.0. T_r = 1.41 min. (Method AY).

Example 261 Enantiomer 1. Ethyl 4-methoxy-3-(4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)butanoate

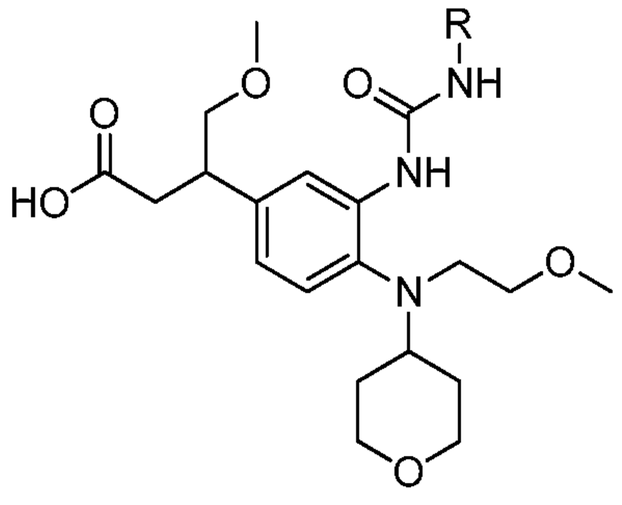
To a stirred solution of compound 261A (0.030 g, 0.057 mmol) in mixture of tetrahydrofuran (1.5 mL), methanol (1.5 mL) and water (0.5 mL) was added $LiOH•H_2O$ (9.54 mg, 0.227 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure. The aqueous residue so obtained was acidified with aqueous citric acid to pH ~ 2. The aqueous layer was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LCMS to afford Example 261 Enantiomer 1 (absolute stereochemistry unknown) (7.3 mg, 0.014 mmol, 25% yield). LC-MS Anal. Calc'd. for $C_{27}H_{37}N_3O_6$ 499.2, found [M+H] 500.1. T_r = 1.37 min (Method O). ^1H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 1H), 8.41 (s, 1H), 8.04 - 8.13 (m, 1H), 7.38 (m, 2H), 7.18 (m, 1H), 7.04 - 7.13 (m, 2H), 6.78 - 6.88 (m, 1H), 3.83 (m, 4H), 3.20 - 3.28 (m, 6H), 3.68 - 3.71 (m, 7H), 2.58 - 2.72 (m, 1H), 2.37 - 2.45 (m, 2H), 2.25 (s, 3H), 1.64 - 1.80 (m, 2H), 1.31 - 1.46 (m, 2H).

Example 261 Enantiomer 2. Ethyl 4-methoxy-3-(4-((2-methoxyethyl)(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)butanoate

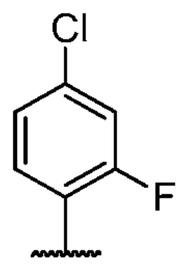
Example 261 Enantiomer 2 was prepared from 256F Enantiomer 2 following the procedure described for the synthesis of Example 261 Enantiomer 1 (absolute stereochemistry unknown). LC-MS Anal. Calc'd. for $C_{27}H_{37}N_3O_6$ 499.2, found [M+H] 500.1. T_r = 1.37 min (Method O). ^1H NMR (400 MHz, DMSO-d_6) δ 9.31 - 9.44 (m, 1H), 8.41 (s, 1H), 8.10 (m, 1H), 7.38 (m, 2H), 7.19 (m, 1H), 7.10 (m, 2H), 6.71 - 6.88 (m, 1H), 3.83 (m, 4H), 3.21 - 3.30 (m, 6H), 3.68 - 3.71 (m, 7H), 2.66 (m, 1H), 2.47 (m, 2H), 2.25 (s, 3H), 1.70 (m, 2H), 1.32 - 1.48 (m, 2H).

Example 262

(Enantiomer 1)

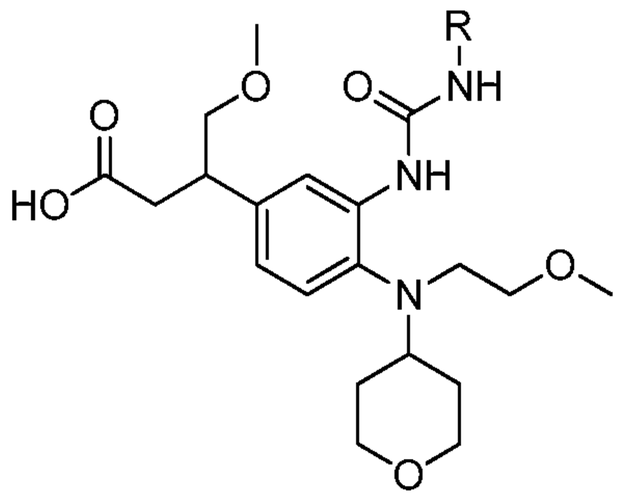


Example 262 was prepared from 256F Enantiomer 1 and corresponding isocyanate following the procedure described for the synthesis of Example 261 Enantiomer 1 (absolute stereochemistry unknown).

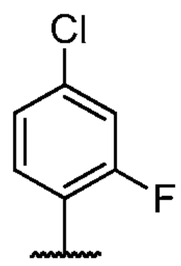
Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
262	3-(3-(3-(4-chloro-2-fluorophenyl) ureido)-4-((2-methoxyethyl) (tetrahydro-2H-pyran-4-yl)amino) phenyl)-4-methoxybutanoic acid		1.35	538.3

Example 263

(Enantiomer 2)



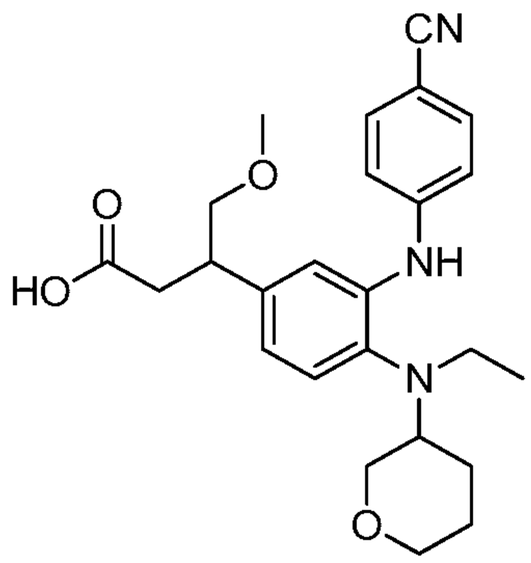
Example 263 was prepared from 256F Enantiomer 2 following the procedure described for the synthesis of Example 261 Enantiomer 1 (absolute stereochemistry unknown).

Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
263	3-(3-(3-(4-chloro-2-fluorophenyl) ureido)-4-((2-methoxyethyl) (tetrahydro-2H-pyran-4-yl)amino) phenyl)-4-methoxybutanoic acid		1.36	538.3

Example 264

(Diastereomer 1 and Diastereomer 2)

3-(3-((4-Cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)phenyl)-4-methoxybutanoic acid



264A. Ethyl 3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)phenyl)-4-methoxybutanoate

Compound 264A was prepared from (E)-ethyl 4-methoxybut-2-enoate and 59D following the procedure described for the synthesis of 59E. LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_4$ 364.2, found [M+H] 365.3. T_r = 1.31 min (Method AY).

Chiral separation of 264A (Method CL) gave 264A Diastereomer 1 T_r = 2.09 min (Method CL), and 264A Diastereomer 2 T_r = 2.85 min (Method CL).

264A Diastereomer 1 (yellow liquid, 100 mg, 32%) : LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_4$ 364.2, found [M+H] 365.3. T_r = 2.42 min (Method BB).

264A Diastereomer 2 (yellow liquid, 100 mg, 32%) : LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_4$ 364.2, found [M+H] 365.3. T_r = 2.43 min (Method BB).

264B. Ethyl 3-(3-((4-cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino) phenyl)-4-methoxybutanoate

The mixture of 264A Diastereomer 1 (0.050 g, 0.137 mmol), 4-bromobenzonitrile (0.030 g, 0.165 mmol), Cs_2CO_3 (0.067 g, 0.206 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (7.94 mg, 0.014 mmol) in 1,4-dioxane (2 mL) was stirred. Argon gas was bubbled through the mixture for 5 min. Bis(dibenzylideneacetone)palladium (3.94 mg, 6.86 µmol) was added and argon gas was bubbled through the mixture for 5 min. The reaction mixture was sealed and placed in preheated oil bath at 110 °C for 3 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford a residue. The residue was reconstituted in a mixture of ethyl acetate (15 mL) and water (15 mL). The combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography to afford 264B (yellow liquid, 60 mg, 0.108 mmol, 79% yield). LC-MS Anal. Calc'd. for $C_{27}H_{35}N_3O_4$ 465.2, found [M+H] 466.3. T_r = 2.06 min. (Method AY).

Example 264 Diastereomer 1. 3-(3-((4-Cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)phenyl)-4-methoxybutanoic acid

To a stirred solution of 264B (0.060 g, 0.135 mmol) in mixture of tetrahydrofuran (1 mL), methanol (1 mL) and water (0.2 mL) was added $LiOH•H_2O$ (0.023 g, 0.539 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure. The aqueous residue so obtained was acidified with aqueous citric acid to pH ~ 2. The aqueous layer was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LCMS to afford Example 264 Diastereomer 1 (absolute and relative stereochemistry unknown) (20.2 mg, 0.046 mmol, 35% yield). LC-MS Anal. Calc'd. for $C_{25}H_{31}N_3O_4$ 437.2, found [M+H] 438.1. T_r = 1.56 min. (Method O). ^1H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1H), 7.56 (d, *J* = 8.74 Hz, 2H), 7.06 - 7.21 (m, 4H), 6.93 (m, 1H), 3.73 - 3.90 (m, 4H), 3.20 - 3.28 (s, 3H), 3.09 - 3.18 (m, 4H), 3.00 (m, 1H), 2.79 - 2.91 (m, 1H), 2.60 (m,

1H), 2.46 (m, 1H), 1.73 - 1.82 (m, 1H), 1.51 - 1.62 (m, 1H), 1.38 - 1.47 (m, 1H), 1.27 - 1.36 (m, 1H), 0.81 (t, *J*=6.8 Hz, 3H).

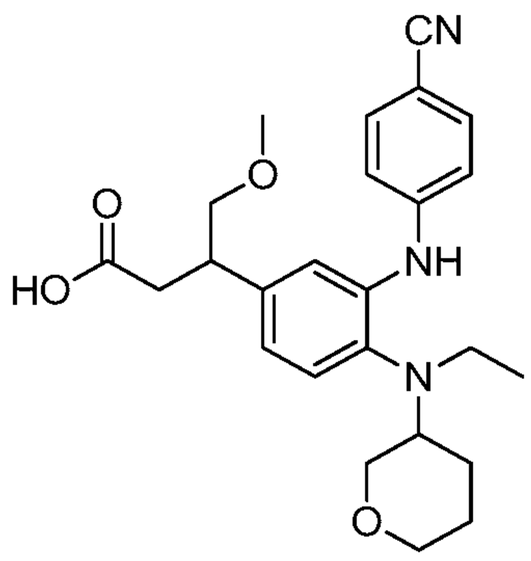
Example 264 Diastereomer 2. 3-(3-((4-Cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)phenyl)-4-methoxybutanoic acid

Example 264 Diastereomer 2 was prepared from 264A Diastereomer 2 following the procedure described for the synthesis of Example 264 Diastereomer 1 (absolute and relative stereochemistry unknown). LC-MS Anal. Calc'd. for $C_{25}H_{31}N_3O_4$ 437.2, found [M+H] 438.1. T_r = 1.61 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.56 (m, 2H), 7.04 - 7.14 (m, 4H), 6.87 - 7.01 (m, 1H), 3.74 (m, 4H), 3.20 - 3.28 (s, 3H), 3.03 - 3.19 (m, 4H), 3.00 (m, 1H), 2.79 - 2.91 (m, 1H), 2.60 (m, 1H), 2.28 - 2.39 (m, 1H), 1.73 - 1.82 (m, 1H), 1.57 (m, 1H), 1.40 - 1.49 (m, 1H), 1.28 - 1.38 (m, 1H), 0.82 (t, *J*=7.2 Hz, 3 H).

Example 265

(Diastereomer 3 and Diastereomer 4)

3-(3-((4-Cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)phenyl)-4-methoxybutanoic acid



265A. N1-Ethyl-N1-(tetrahydro-2H-pyran-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene-1,2-diamine

To a stirred solution of 59C Enantiomer 2 (800 mg, 2.67 mmol), bis(pinacolato) diboron (1.018 g, 4.01 mmol) and potassium acetate (0.787 g, 8.02 mmol) in 1,4-dioxane (8 mL) was purged with argon for 10 min. To this $PdCl_2$ (dppf)•CH_2Cl_2 Adduct (0.109 g, 0.134 mmol) was added and purged with argon for 5 min. The reaction mixture was heated at 90 °C for 5 h. LCMS indicated completion of reaction. Reaction mixture was

cooled to room temperature and quenched with water (30 mL). Aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash chromatography gave 265A (yellow liquid, 0.410 g, 1.184 mmol, 44% yield). LC-MS Anal. Calc'd. for $C_{19}H_{31}BN_2O_3$ 346.2, found [M+H] 347.0. T_r = 1.52 min. (Method AY).

265B. Ethyl 3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)phenyl)-4-methoxybutanoate

Compound 265B was prepared from 265A and *E*-4-methoxybut-2-enoate following the procedure described for the synthesis of 59E. LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_4$ 364.2, found [M+H] 365.3. T_r = 1.43 min (Method AY).

Chiral separation of 265B (Method CM) gave 265B Diastereomer 3 T_r = 1.62 min (Method CM), and 265B diastereomer 4 T_r = 2.09 min (Method CM).

265B Diastereomer 3 (yellow liquid, 100 mg, 44%): LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_4$ 364.2, found [M+H] 365.3. T_r = 1.43 min (Method BB).

265B Diastereomer 4 (yellow liquid, 100 mg, 44%): LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_4$ 364.2, found [M+H] 365.3. T_r = 1.43 min (Method BB).

265C. Ethyl 3-(3-((4-cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)phenyl)-4-methoxybutanoate

The mixture of 265B Diastereomer 3 (0.050 g, 0.137 mmol), 4-bromobenzonitrile (0.030 g, 0.165 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (7.94 mg, 0.014 mmol) and Cs_2CO_3 (0.067 g, 0.206 mmol) in 1,4-dioxane (2 mL) was stirred. Argon gas was bubbled through the mixture for 5 min. Bis(dibenzylideneacetone) palladium (3.94 mg, 6.86 μmol) was added and argon gas was bubbled through the mixture for 5 min. The reaction mixture was sealed and placed in preheated oil bath at 110 °C for 3 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford a residue. The residue was reconstituted in a mixture of ethyl acetate (15 mL) and water (15 mL). The combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel

column chromatography to afford 265C (yellow liquid, 60 mg, 0.104 mmol, 76% yield). LC-MS Anal. Calc'd. for $C_{27}H_{35}N_3O_4$ 465.2, found [M+H] 466.3. T_r = 1.56 min. (Method AY).

Example 265 Diastereomer 3. 3-(3-((4-Cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)phenyl)-4-methoxybutanoic acid

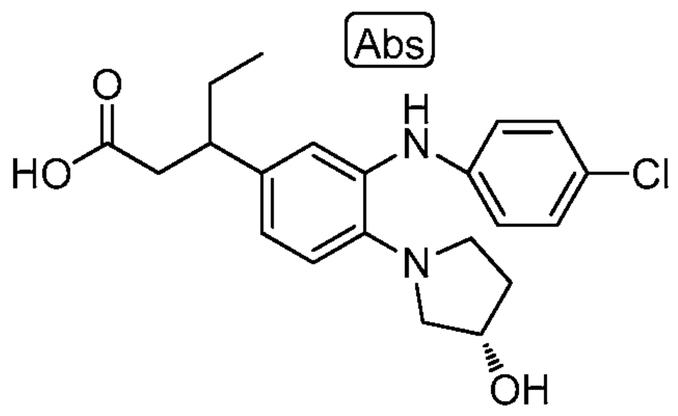
To a stirred solution of 265C (0.060 g, 0.129 mmol) in mixture of tetrahydrofuran (1 mL), methanol (1 mL) and water (0.2 mL) was added $LiOH•H_2O$ (0.022 g, 0.515 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure. The aqueous residue so obtained was acidified with aqueous citric acid to pH ~ 2. The aqueous layer was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LCMS to afford Example 265 Diastereomer 3 (absolute and relative stereochemistry unknown) (15 mg, 0.034 mmol, 26% yield). LC-MS Anal. Calc'd. for $C_{25}H_{31}N_3O_4$ 437.2, found [M+H] 438.1. T_r = 1.56 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1H), 7.50 - 7.64 (m, 2H), 7.05 - 7.22 (m, 4H), 6.82 - 6.99 (m, 1H), 3.69 - 3.78 (m, 4H), 3.20 - 3.26 (m, 3H), 3.10 - 3.18 (m, 4H), 2.94 - 3.05 (m, 1H), 2.81 - 2.91 (m, 1H), 2.60 (m, 1H), 2.46 (m, 1H), 1.73 - 1.82 (m, 1H), 1.54 - 1.65 (m, 1H), 1.40 - 1.49 (m, 1H), 1.27 - 1.38 (m, 1H), 0.81 (t, *J*=7.2 Hz, 3H).

Example 265 Diastereomer 4. 3-(3-((4-Cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-3-yl)amino)phenyl)-4-methoxybutanoic acid

Example 265 Diastereomer 4 was prepared from 265B Diastereomer 4 following the procedure described for the synthesis of Example 265 Diastereomer 3 (absolute stereochemistry unknown). LC-MS Anal. Calc'd. for $C_{25}H_{31}N_3O_4$ 437.2, found [M+H] 438.1. T_r = 1.56 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1H), 7.56 (d, *J*=8.74 Hz, 2H), 7.06 - 7.22 (m, 4H), 6.83 - 7.00 (m, 1H), 3.72 (m, 4H), 3.20 - 3.28 (s, 3H), 3.08 - 3.17 (m, 4H), 2.94 - 3.05 (m, 1H), 2.86 (m, 1H), 2.65 (m, 1H), 2.46 (d, *J*=8.68 Hz, 1H), 1.73 - 1.82 (m, 1H), 1.51 - 1.60 (m, 1H), 1.38 - 1.49 (m, 1H), 1.27 - 1.38 (m, 1H), 0.81 (t, *J*=7.2 Hz, 3H).

Example 266

3-(3-((4-Chlorophenyl)amino)-4-((S)-3-hydroxypyrrolidin-1-yl)phenyl)pentanoic acid



266A. 2-(4-Fluorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane

A stirred solution of 1-bromo-4-fluorobenzene (10 g, 57.1 mmol), bis(pinacolato) diboron (19.36 g, 86 mmol) and potassium acetate (16.82 g, 171 mmol) in toluene (100 mL) was purged with argon for 10 min. To this $PdCl_2$ (dppf)•CH_2Cl_2 Adduct (1.400 g, 1.714 mmol) was added and purged with argon for 5 min. The reaction mixture was heated at 80 °C for 2 h. LCMS indicated completion of reaction. Reaction mixture was cooled to room temperature and quenched with water (30 mL). Aqueous layer was extracted with DCM (3 × 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to get crude compound. Purification via flash chromatography gave 266A (off-white solid, 10 g, 48.1 mmol, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 - 7.76 (m, 2H), 7.05 - 6.99 (m, 2H), 3.76 (s, 4H), 1.02 (s, 6H).

266B. Methyl 3-(4-fluorophenyl)pentanoate

In a pressure tube equipped with Teflon cap, compound 266A (1g, 2.89 mmol), 1,4-dioxane (10 mL) were added followed by (E)-methyl pent-2-enoate (0.549 g, 4.81 mmol), (R)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (0.066 g, 0.106 mmol) and 1M solution of sodium hydroxide (4.33 mL, 4.33 mmol). Argon gas was bubbled through the mixture for 10 min and chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.028 g, 0.072 mmol) was added at room temperature. Argon gas was bubbled through the mixture for 5 min. The tube was then screw-capped and heated at 50 °C for 4 h. The reaction mixture was cooled to room temperature, quenched with acetic acid (0.2 mL) and was stirred for 5 minutes before it was diluted with water (15 mL). The aqueous layer was extracted with

ethyl acetate (3 × 20 mL). Combined organic layer was washed with water (15 mL), brine (15 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography to afford 266B (liquid, 0.8 g, 3.81 mmol, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 - 7.10 (m, 2H), 6.99 - 6.95 (m, 2H), 3.57 (s, 3H), 3.05 - 2.95 (m, 1H), 2.65 - 2.52 (m, 2H), 1.75 - 1.52 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H).

266C. Methyl 3-(4-fluoro-3-nitrophenyl)pentanoate

To a stirred solution of 266B (0.1 g, 0.476 mmol) in H_2SO_4 (3 mL, 56.3 mmol) at 0 °C, nitric acid (0.031 mL, 0.476 mmol) was slowly added under nitrogen atmosphere and maintained at same temperature for 1 h. Reaction mixture quenched with ice and extracted with ethyl acetate (2 × 50 mL). Organic layer dried over sodium sulfate and concentrated under reduced pressure to get light yellow liquid. Purification via flash chromatography gave 266C (yellow liquid, 0.07 g, 0.274 mmol, 57.7% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 - 7.86 (m, 1H), 7.48 - 7.45 (m, 1H), 7.26 - 7.19 (m, 1H), 3.57 (s, 3H), 3.15 - 3.05 (m, 1H), 2.71 - 2.52 (m, 2H), 1.81 - 1.52 (m, 2H), 0.82 (t, J = 7.2 Hz, 3H).

266D. Methyl 3-(4-((S)-3-hydroxypyrrolidin-1-yl)-3-nitrophenyl)pentanoate

Compound 266D was prepared from 266C and (S)-pyrrolidin-3-ol following the procedure described for the synthesis of 1G. LC-MS Anal. Calc'd. $C_{16}H_{22}N_2O_5$ for 322.2, found [M+H] 323.2., T_r = 3.012 min (Method U).

266E. Methyl 3-(3-amino-4-((S)-3-hydroxypyrrolidin-1-yl)phenyl)pentanoate

Compound 266E was prepared from 266D following the procedure described for the synthesis of 1H. LC-MS Anal. Calc'd. $C_{16}H_{24}N_2O_3$ for 292.2, found [M+H] 293.2, T_r = 1.892 min (Method U).

266F. Methyl 3-(3-((4-chlorophenyl)amino)-4-((S)-3-hydroxypyrrolidin-1-yl)phenyl) pentanoate

Compound 266F was prepared from 266E and 1-bromo-4-chlorobenzene following the procedure described for the synthesis of 1I. LC-MS Anal. Calc'd. $C_{22}H_{27}ClN_2O_3$ for 402.2, found [M+H] 403.5, T_r = 1.55 min (Method T).

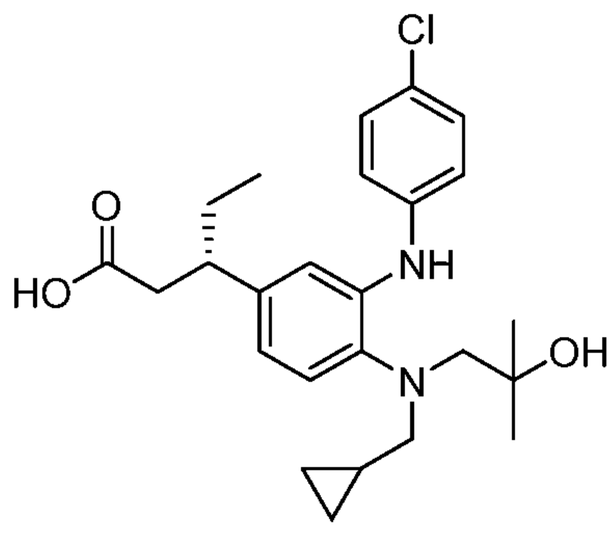
Example 266. 3-(3-((4-Chlorophenyl)amino)-4-((S)-3-hydroxypyrrolidin-1-yl)phenyl) pentanoic acid

Example 266 was prepared from 266F following the procedure described for the synthesis of Example 1 from 1I (homochiral, stereochemistry at the benzylic position unknown) LC-MS Anal. Calc'd. $C_{21}H_{25}ClN_2O_3$ for 388.2, found [M+H] 389.2, T_r = 1.560 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (s, 1H), 7.11 (d, *J* = 8.8 Hz, 2H), 6.88 - 6.76 (m, 3H), 6.67 (d, *J* = 8.8 Hz, 2H), 4.79 (d, *J* = 4.0 Hz, 1H), 4.25 - 4.15 (m, 1H), 3.37 - 3.16 (m, 2H), 3.07 - 3.06 (m, 1H), 2.68 - 2.53 (m, 2H), 2.40 - 2.33 (m, 2H), 1.95 - 1.85 (m, 1H), 1.75 - 1.35 (m, 3H), 0.72 (t, *J* = 7.2 Hz, 3H).

Example 267

(Enantiomer 1)

(S)-3-(3-((4-Chlorophenyl)amino)-4-((cyclopropylmethyl)(2-hydroxy-2-methylpropyl)amino)phenyl)pentanoic acid



267A. 1-((Cyclopropylmethyl)amino)-2-methylpropan-2-ol

To a stirred solution of cyclopropanecarbaldehyde (5 g, 71.3 mmol) in methanol (50 mL) under nitrogen was added 1-amino-2-methylpropan-2-ol (6.36 g, 71.3 mmol), followed by 4A° molecular sieves (4 g). The reaction mixture was stirred for 12 h at RT. To the above mixture $NaBH_4$ (8.10 g, 214 mmol) was added portionwise at 0 °C. The reaction mixture was stirred at RT for 3 h. Then quenched with ice water and removed volatiles under reduced pressure. The aqueous was diluted with 10% $NaHCO_3$ solution,

extracted with EtOAc (2 × 200 mL). The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford 267A (pale yellow oil, 6 g, 37.7 mmol, 52.9% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.18 (s, 1H), 2.40 - 2.27 (m, 4H), 1.08 (s, 6H), 0.87 - 0.85 (m, 1H), 0.41 - 0.37 (m, 2H), 0.09 - 0.07 (m, 2H).

267B. 1-((4-Bromo-2-nitrophenyl)(cyclopropylmethyl)amino)-2-methylpropan-2-ol

To a solution of 4-bromo-1-fluoro-2-nitrobenzene (5 g, 22.73 mmol) in NMP (20 mL) was added 267A (3.26 g, 22.73 mmol) followed by DIPEA (9.92 mL, 56.8 mmol). Then the reaction mixture was heated to 120 °C for 5 h. The reaction mixture was cooled to RT and poured into water extracted with EtOAc (2 × 100 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purified via flash chromatography to afford 267B (red color oil, 7.5 g, 19.67 mmol, 87% yield). LC-MS Analysis Calc'd. for $C_{14}H_{19}BrN_2O_3$ 343.2, found [M+2H] 345.1, T_r = 1.12 min (Method BC).

267C. 1-((Cyclopropylmethyl)(4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2-nitrophenyl) amino)-2-methylpropan-2-ol

A mixture of 267B (7.5 g, 21.85 mmol), bis(neopentyl glycolato)diboron (6.42 g, 28.4 mmol) and potassium acetate (6.43 g, 65.6 mmol) in 1,4-dioxane (30 mL), at room temperature in a sealable flask, was purged with argon for 20 minutes before $PdCl_2$ (dppf)•CH_2Cl_2 Adduct (0.535 g, 0.656 mmol) was added, the flask was sealed and the reaction heated at 80 °C for 6 h. The reaction mixture was cooled to RT and poured into water, extracted with EtOAc (2 × 150 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude sample was purified via flash chromatography to afford 267C (red color oil, 7 g, 17.67 mmol, 81% yield). LC-MS Analysis Calc'd. for $C_{19}H_{29}BN_2O_5$ 376.2, found [M-68] 309.1 for parent boronic acid, T_r = 0.81 min (Method BC).

267D. Methyl (S)-3-(3-((4-chlorophenyl)amino)-4-((cyclopropylmethyl)(2-hydroxy-2-methylpropyl)amino)phenyl)pentanoate

To a stirring and argon bubbling solution of 267C (2 g, 5.32 mmol) and (E)-methyl pent-2-enoate (1.820 g, 15.95 mmol) in 1,4-dioxane (20 mL) was added sodium hydroxide (1.0 molar) (4.85 mL, 4.85 mmol) and (R)-BINAP (0.073 g, 0.117 mmol), bubbling continued, then chlorobis(ethylene)rhodium(I) dimer (0.031 g, 0.080 mmol) was added and bubbled argon for another 5 minutes. The reaction mixture was heated at 50 °C for 1 h in sealed tube. Reaction mixture was cooled to room temperature and quenched with acetic acid (0.274 mL, 4.78 mmol) and it was stirred for 5 minutes before partitioned between ethyl acetate and water. Aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure. The crude sample was purified via flash chromatography to afford 267D (pale yellow oil, 0.85 g, 2.134 mmol, 40.1% yield). LC-MS Analysis Calc'd. for $C_{20}H_{30}N_2O_5$ 378.2, found [M+H] 379.2, T_r = 1.01 min (Method BC).

267E. Methyl (S)-3-(3-amino-4-((cyclopropylmethyl)(2-hydroxy-2-methylpropyl) amino)phenyl)pentanoate

To a stirred solution of 267D (0.8 g, 2.114 mmol) in MeOH (15 mL) was carefully added Pd/C (10%) (0.112 g, 0.106 mmol). The flask was sequentially evacuated then purged with nitrogen before being pressurized to 15 psi of hydrogen for 6 h. The reaction mixture was filtered through a CELITE® bed, and the filtrate was concentrated under reduced pressure to afford 267E.

Chiral separation of 267E Enantiomeric mixture (93:7) yielded 267E Enantiomer 1 T_r = 3.6 min, 267E Enantiomer 2 T_r = 4.86 min (Method CX).

267E Enantiomer 1: (pale yellow oil, 0.45 g, 1.227 mmol, 58.0% yield). LC-MS Analysis Calc'd. for $C_{20}H_{32}N_2O_3$ 348.2, found [M+H] 349.5, T_r = 1.45 min (Method AY).

267F. Methyl (S)-3-(3-((4-chlorophenyl)amino)-4-((cyclopropylmethyl)(2-hydroxy-2-methylpropyl)amino)phenyl)pentanoate

To a degassing solution of 267E Enantiomer 1 (0.03 g, 0.086 mmol) in 1,4-dioxane (2 mL) was added 1-bromo-4-chlorobenzene (0.020 g, 0.103 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (9.96 mg, 0.017 mmol), cesium carbonate (0.084 g, 0.258 mmol) then bis(dibenzylideneacetone)palladium (4.95 mg, 8.61 μmol).

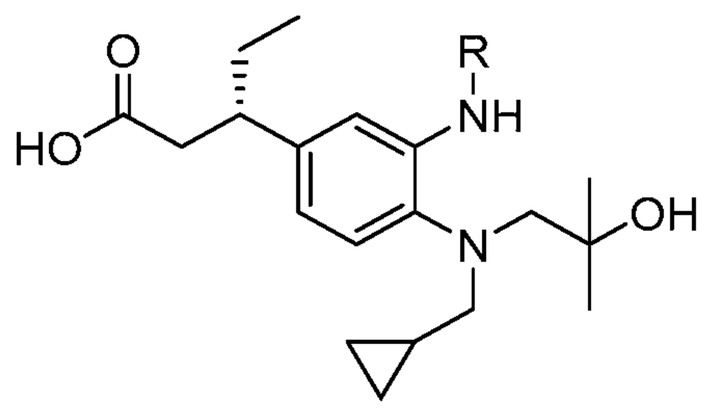
Then the reaction temperature was raised to 110 °C for 5 h in a sealed tube. The reaction mixture was filtered through a CELITE® plug and the plug was washed with EtOAc. The filtrate was concentrated under reduced pressure to afford 267F (0.035 g, 0.076 mmol, 89% yield) as crude. The crude was taken further without purification. LC-MS Analysis Calc'd. for $C_{26}H_{35}ClN_2O_3$ 458.2, found [M+H] 459.2, T_r = 0.93 min (Method BC).

Example 267 Enantiomer 1. (S)-3-(3-((4-Chlorophenyl)amino)-4-((cyclopropylmethyl)(2-hydroxy-2-methylpropyl)amino)phenyl)pentanoic acid

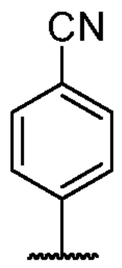
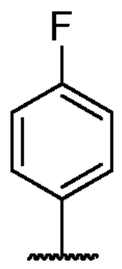
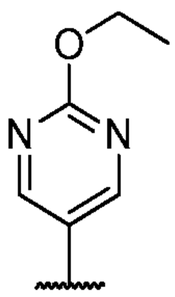
To a solution of 267F (0.04 g, 0.052 mmol) in mixture of THF (1 mL), MeOH (1 mL) and water (1 mL) was added $LiOH•H_2O$ (5.01 mg, 0.209 mmol) at RT and stirred for 5 h. Removed the volatiles under reduced pressure. The crude pH was adjusted to ~2 with 1.5N HCl solution. Aqueous solution was extracted with DCM (2 × 10 mL). The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude was purified via prep HPLC to afford Example 267 Enantiomer 1 (off-white solid, 0.006 g, 0.013 mmol, 26% yield). LC-MS Analysis Calc'd. for $C_{25}H_{33}ClN_2O_3$ 444.2, found [M+H] 445.2, T_r = 2.134 min (Method O). ^{1}H NMR (400 MHz, MeOD) δ 7.25 - 7.21 (m, 3H), 7.15 - 7.11 (m, 2H), 7.08 (d, *J* = 2.00 Hz, 1H), 6.75 (dd, *J* = 2.00, 7.60 Hz, 1H), 3.13 (s, 2H), 2.92-2.85 (m, 1H), 2.82 (d, *J* = 6.80 Hz, 2H), 2.66 - 2.60 (m, 1H), 2.54 - 2.51 (m, 1H), 1.75 - 1.55 (m, 2H), 1.12 (s, 6H), 0.84 - 0.80 (m, 4H), 0.31 - 0.28 (m, 2H), -0.07 - -0.88 (m, 2H).

Examples 268 to 270

(Enantiomer 1)



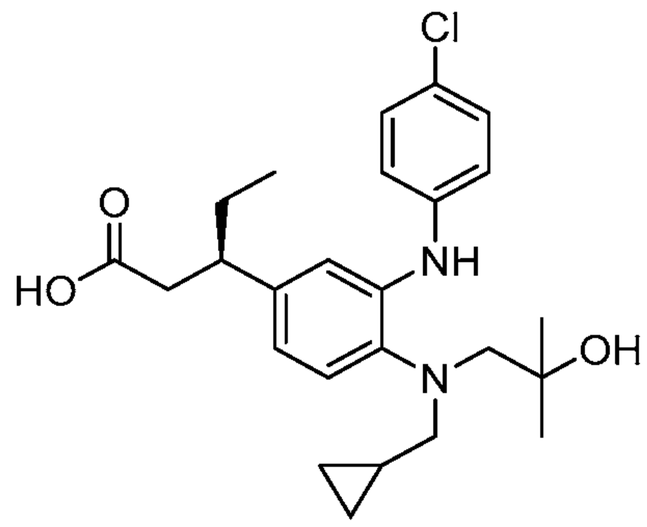
Examples 268 to 270 were prepared from 267E Enantiomer 1 and corresponding halides following the procedures described for the synthesis of Example 267.

Ex. No.	Name	R	T_r min	Method	(M+H)
268	(S)-3-(3-((4-cyanophenyl)amino)-4-((cyclopropylmethyl)(2-hydroxy-2-methylpropyl)amino)phenyl) pentanoic acid		1.827	O	436.2
269	(S)-3-(4-((cyclopropylmethyl)(2-hydroxy-2-methylpropyl)amino)-3-((4-fluorophenyl)amino)phenyl) pentanoic acid		1.986	O	429.3
270	(S)-3-(4-((cyclopropylmethyl)(2-hydroxy-2-methylpropyl)amino)-3-((2-ethoxypyrimidin-5-yl)amino) phenyl)pentanoic acid		1.724	O	457.3

Example 271

(Enantiomer 2)

(R)-3-(3-((4-Chlorophenyl)amino)-4-((cyclopropylmethyl)(2-hydroxy-2-methylpropyl) amino)phenyl)pentanoic acid



271A. Methyl (R)-3-(3-((4-chlorophenyl)amino)-4-((cyclopropylmethyl)(2-hydroxy-2-methylpropyl)amino)phenyl)pentanoate

271A was prepared using S-BINAP and 267C following the procedure described for the synthesis of 267D. LC-MS Analysis Calc'd. for $C_{20}H_{30}N_2O_5$ 378.2, found [M+H] 379.2, T_r = 1.06 min (Method BC).

271B. Methyl (R)-3-(3-amino-4-((cyclopropylmethyl)(2-hydroxy-2-methylpropyl) amino)phenyl)pentanoate

271B was prepared using 271A following the procedure described for the synthesis of 267E.

Chiral separation of 271B Enantiomeric mixture (9:91) yielded 271B Enantiomer 1 T_r = 3.6 min, 271B Enantiomer 2 T_r = 4.8 min (Method CX).

271B Enantiomer 2: (pale yellow oil, 0.45 g, 1.227 mmol, 58.0% yield). LC-MS Analysis Calc'd. for $C_{20}H_{32}N_2O_3$ 348.2, found [M+H] 349.5, T_r = 1.45 min (Method AY).

271C. Methyl (R)-3-(3-((4-chlorophenyl)amino)-4-((cyclopropylmethyl)(2-hydroxy-2-methylpropyl)amino)phenyl)pentanoate

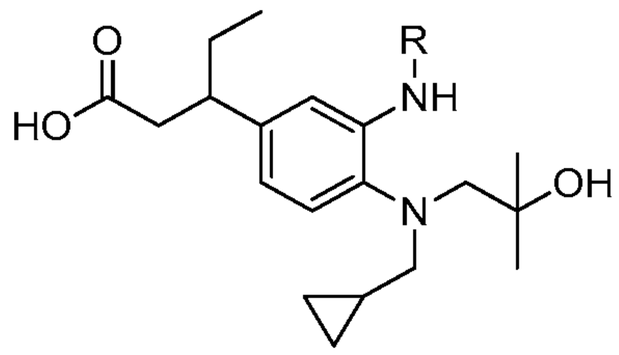
271C was prepared using 271B Enantiomer 2 and 1-bromo-4-chlorobenzene following the procedure described for the synthesis of 267F. LC-MS Analysis Calc'd. for $C_{26}H_{35}ClN_2O_3$ 458.2 found [M+H] 459.2. T_r = 0.93 min (Method BC).

Example 271 Enantiomer 2. (R)-3-(3-((4-Chlorophenyl)amino)-4-((cyclopropylmethyl) (2-hydroxy-2-methylpropyl)amino)phenyl)pentanoic acid

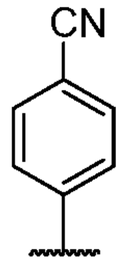
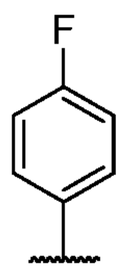
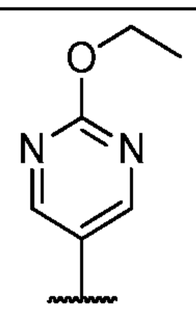
Example 271 Enantiomer 2 was prepared using the 271C following the procedure described for the synthesis of Example 267 Enantiomer 1. LC-MS Analysis Calc'd. for $C_{25}H_{33}ClN_2O_3$ 444.2, found [M+H] 445.2, T_r = 2.136 min (Method O). ^{1}H NMR (400 MHz, MeOD) δ 7.25 - 7.21 (m, 3H), 7.15 - 7.11 (m, 2H), 7.08 (d, *J* = 2.00 Hz, 1H), 6.75 (dd, *J* = 2.00, 7.60 Hz, 1H), 3.13 (s, 2H), 2.92 - 2.85 (m, 1H), 2.82 (d, *J* = 6.80 Hz, 2H), 2.66 - 2.60 (m, 1H), 2.54 - 2.51 (m, 1H), 1.75 - 1.55 (m, 2H), 1.12 (s, 6H), 0.84 - 0.80 (m, 4H), 0.31 - 0.28 (m, 2H), -0.07 - -0.88 (m, 2H).

Examples 272 to 274

(Enantiomer 2)



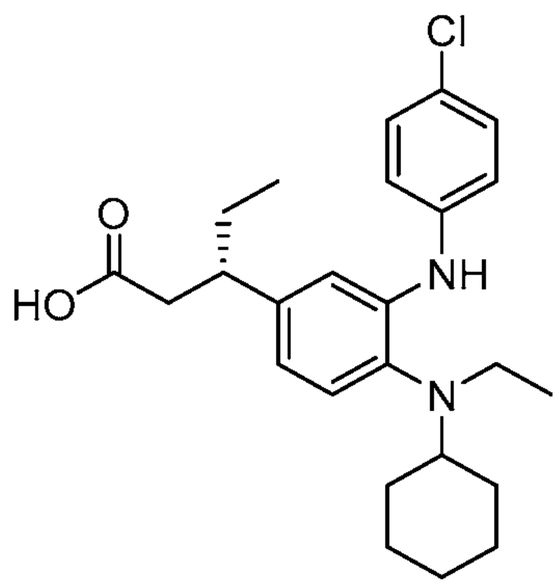
Examples 272 to 274 were prepared using 271B Enantiomer 2 and corresponding halides following the procedure described for the synthesis of Example 271.

Ex. No.	Name	R	T_r min	Method	(M+H)
272	(R)-3-(3-((4-cyanophenyl)amino)-4-((cyclopropylmethyl)(2-hydroxy-2-methylpropyl)amino) phenyl)pentanoic acid		1.823	O	436.2
273	(R)-3-(4-((cyclopropylmethyl)(2-hydroxy-2-methylpropyl)amino)-3-((4-fluorophenyl)amino) phenyl)pentanoic acid		2.066	O	429.3
274	(R)-3-(4-((cyclopropylmethyl)(2-hydroxy-2-methylpropyl)amino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl)pentanoic acid		1.700	O	457.3

Example 279

(Enantiomer 1)

(S)-3-(3-((4-Chlorophenyl)amino)-4-(cyclohexyl(ethyl)amino)phenyl)pentanoic acid



279A. N-Ethylcyclohexanamine, HCl

To a solution of ethanamine (2.53 g, 56.0 mmol) in MeOH (50 mL) was added cyclohexanone (5 g, 50.9 mmol) under nitrogen with 4 A° molecular sieves (2 g) at RT. Then the reaction mixture was stirred overnight. To the above mixture sodium

borohydride (5.78 g, 153 mmol) was added portionwise, at 0 °C. Then the reaction mixture was slowly allowed to RT and stirred for 2 h. The reaction mixture was quenched with satd. aq. Na_2CO_3 solution, extracted with diethyl ether (2 × 100 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure at lower temperature (35 °C). The resultant oil was dissolved in 10 mL of diethyl ether and slowly treated with 4M HCl in dioxane. The resultant precipitate was filtered and dried under vacuum to afford 279A (white solid, 3 g, 17.41 mmol, 34.2% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.92 - 2.89 (m, 3H), 2.02 - 1.99 (m, 2H), 1.76 - 1.73 (m, 2H), 1.62 - 1.58 (m, 2H), 1.35 - 1.27 (m, 4H), 1.22 (t, J = 8.40 Hz, 3H).

279B. 4-Bromo-N-cyclohexyl-N-ethyl-2-nitroaniline

To a solution of 4-bromo-1-fluoro-2-nitrobenzene (3 g, 13.64 mmol) in NMP (12 mL) at RT was added 279A (2.455 g, 15.00 mmol) followed by the addition of DIPEA (7.15 mL, 40.9 mmol). The reaction was sealed and heated at 120 °C for 16 h. The reaction mixture was cooled, poured into water and extracted with MTBE (2 × 150 mL). The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude sample was purified by flash chromatography using silica gel and 0-2% EtOAc in pet ether as eluent. The compound containing fractions were evaporated to afford 279B (red color oil, 2.5 g, 7.26 mmol, 53.2% yield). LC-MS Anal. Calc'd. for $C_{14}H_{19}BrN_2O_2$ 326.1, found [M+H] 329.2, T_r = 1.96 min (Method T).

279C. N-Cyclohexyl-N-ethyl-2-nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

To a stirred solution of 279B (2 g, 6.11 mmol), bis(pinacolato)diboron (2.328 g, 9.17 mmol) and potassium acetate (1.800 g, 18.34 mmol) in DMSO (20 mL) was purged with argon for 10 min. To this $PdCl_2$ (dppf)•CH_2Cl_2 Adduct (0.250 g, 0.306 mmol) was added and purged with argon for another 5 min. The reaction mixture was heated at 80 °C for 4 h. Reaction mixture was cooled to RT and poured into water (100 mL), extracted with EtOAc (2 × 100 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude sample was purified by flash chromatography using silica gel and 0-10% EtOAc in pet ether as eluent. The

compound containing fractions were evaporated to afford 279C (pale yellow oil, 2 g, 4.81 mmol, 79% yield). LC-MS Anal. Calc'd. for $C_{20}H_{31}BN_2O_4$ 374.2, found [M+H] 275.2, T_r = 1.48 min (Method AA).

279D. Methyl (S)-3-(4-(cyclohexyl(ethyl)amino)-3-nitrophenyl)pentanoate (E1)

To a stirring and bubbling with argon solution of 1,4-dioxane (20 mL), added the chlorobis(ethylene)rhodium(I) dimer (7.79 mg, 0.020 mmol), (R)-BINAP (0.018 g, 0.029 mmol) bubbled with argon for 10 minutes, 279C (0.5 g, 1.336 mmol), (E)-methyl pent-2-enoate (0.183 g, 1.603 mmol), sodium hydroxide (1.220 mL, 1.220 mmol) were added respectively and bubbled argon for another 5 minutes. The reaction mixture was heated at 50 °C for 3 h in sealed tube. Reaction mixture was cooled to room temperature and quenched with acetic acid (0.069 mL, 1.202 mmol) and it was stirred for 5 minutes before partitioned between ethyl acetate and water. Aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude sample was purified by flash chromatography using silica gel and 0-5% EtOAc in pet ether as eluent. The compound containing fractions were evaporated to afford 279D (pale yellow oil, 0.35 g, 0.966 mmol, 72.3% yield). LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_4$ 362.2, found [M+H] 363.6, T_r = 1.26 min (Method AA).

279E. Methyl (S)-3-(3-amino-4-(cyclohexyl(ethyl)amino)phenyl)pentanoate

To a sealable hydrogen stirring flask, charged with 279D (0.35 g, 0.966 mmol) and Pd/C (10%) (0.051 g, 0.048 mmol) was carefully added ethyl acetate (15 mL). The flask was sequentially evacuated then purged with nitrogen before being pressurized to 40 psi of hydrogen for 4 h. The reaction mixture was filtered through CELITE® bed, washed with methanol (2 × 15 ml). The combined filtrate was concentrated under reduced pressure to get 279E (gummy solid, 0.28 g, 0.800 mmol, 83% yield). LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_2$ 332.2, found [M+H] 333.6, T_r = 0.87 min (Method AA).

Chiral purity for 279E Enantiomer 1 found to be enantiomerically pure (95:5) which was taken further without purification. (279E Enantiomer 1, T_r =3.07; 279E Enantiomer 2, T_r = 4.02; Method BH).

279F. Methyl (S)-3-(3-((4-chlorophenyl)amino)-4(cyclohexyl(ethyl)amino)phenyl) pentanoate

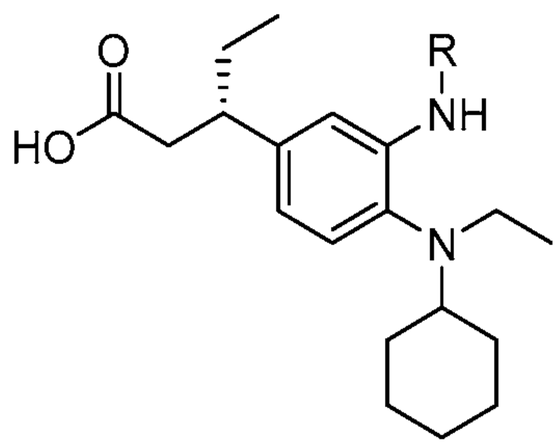
To a degasified solution of 279E Enantiomer 1 (0.035 g, 0.180 mmol) in 1,4-dioxane (2 mL) was added Cs_2CO_3 (0.147 g, 0.451 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.044 g, 0.075 mmol) followed by bis(dibenzylideneacetone)palladium (8.65 mg, 0.015 mmol). Then the reaction was heated to 110 °C for 16 h. The reaction mixture was cooled to RT and filtered through CELITE® bed; the filtrate was concentrated under reduced pressure. The crude sample was purified by flash chromatography using silica gel and 0-50% EtOAc in pet ether as eluent. The compound containing fractions were evaporated to afford 279F (pale yellow oil, 0.04 g, 0.072 mmol, 48.0% yield). LC-MS Analysis Calc'd. for $C_{26}H_{35}ClN_2O_2$ 442.2, found [M+H] 443.6, T_r = 1.02 min (Method BC).

Example 279 Enantiomer 1. (S)-3-(3-((4-Chlorophenyl)amino)-4-cyclohexyl(ethyl) amino)phenyl)pentanoic acid

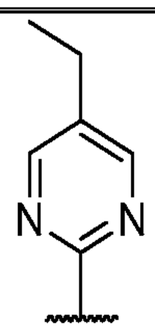
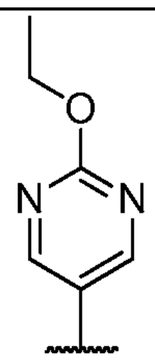
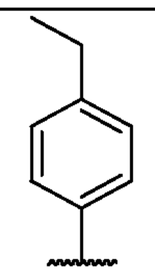
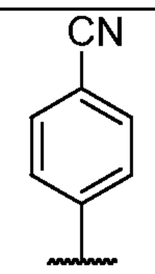
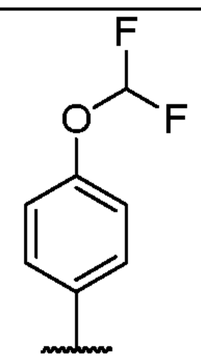
To a solution of 279F (0.04 g, 0.090 mmol) in mixture of THF (1 mL), MeOH (1 mL) and water (1 mL) was added NaOH (0.014 g, 0.361 mmol) at RT and stirred for 1 h. Removed the volatiles under reduced pressure, the crude was dissolved in 10 mL of water and acidified with 1.5N HCl solution, extracted with EtOAc (2 × 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The compound was purified by prep HPLC to afford Example 279 Enantiomer 1 (off-white solid, 0.27 g, 0.060 mmol, 66.9% yield). LC-MS Analysis Calc'd. for $C_{25}H_{33}ClN_2O_2$ 428.2, found [M+H] 429.2, T_r = 2.392 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 (s, 1H), 7.25 - 7.21 (m, 2H), 7.11 - 7.07 (m, 3H), 7.02 (d, *J* = 2.00 Hz, 1H), 6.73 - 6.71 (m, 1H), 2.99 - 2.92 (m, 2H), 2.86 - 2.75 (m, 1H), 2.60 - 2.54 (m, 2H), 2.49 - 2.43 (m, 1H), 1.62 - 1.61 (m, 2H), 1.65 -1.63 (m, 2H), 1.52-1.57 (m, 2H), 1.27 - 1.12 (m, 3H), 1.02 - 1.00 (m, 3H), 0.81 (t, *J* = 7.20 Hz, 3H), 0.73 (t, *J* = 6.80 Hz, 3H).

Examples 280 to 284

(Enantiomer 1)



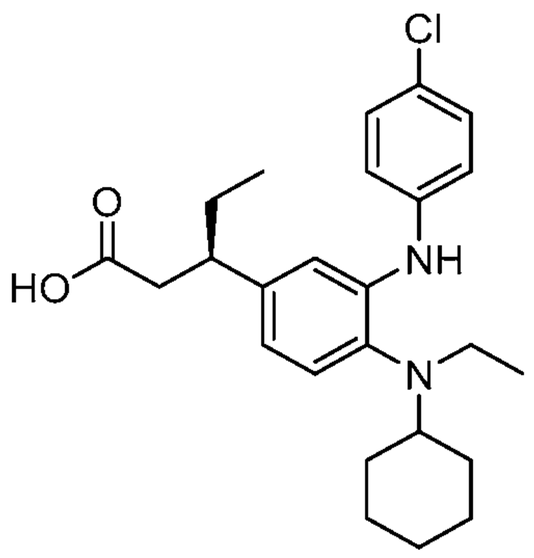
Examples 280 to 284 were prepared using 279E Enantiomer 1 and corresponding halides following the procedure described for the synthesis of Example 279.

Ex. No.	Name	R	T_r min	Method	(M+H)
280	(S)-3-(4-(cyclohexyl(ethyl) amino)-3-((5-ethylpyrimidin-2-yl)amino)phenyl)pentanoic acid		2.245	O	425.4
281	(S)-3-(4-(cyclohexyl(ethyl) amino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl)pentanoic acid		2.079	O	441.4
282	(S)-3-(4-(cyclohexyl(ethyl) amino)-3-((4-ethylphenyl)amino) phenyl)pentanoic acid		2.733	O	423.4
283	(S)-3-(3-((4-cyanophenyl) amino)-4-(cyclohexyl(ethyl) amino)phenyl)pentanoic acid		1.405	R	420.4
284	(S)-3-(4-(cyclohexyl(ethyl) amino)-3-((4-(difluoromethoxy) phenyl)amino)phenyl)pentanoic acid		2.450	O	461.4

Example 285

(Enantiomer 2)

3-(3-((4-Chlorophenyl)amino)-4-(cyclohexyl(ethyl)amino)phenyl)pentanoic acid



285A. Methyl (R)-3-(4-(cyclohexyl(ethyl)amino)-3-nitrophenyl)pentanoate

285A was prepared using S-BINAP and 279C following the procedure described for the synthesis of 279D. LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_4$ 362.2, found [M+H] 363.6, T_r = 1.26 min (Method AA).

285B. Methyl (R)-3-(3-amino-4-(cyclohexyl(ethyl)amino)phenyl)pentanoate

285B was prepared using 285A following the same procedure described for the synthesis of 279E Enantiomer 1 (gummy solid, 0.28 g, 0.800 mmol, 85% yield), LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_2$ 332.2, found [M+H] 333.6. T_r = 0.87 min (Method AA).

Chiral purity for 285B Enantiomer 2 found to be enantiomerically pure (5:95) which was taken further without purification. (285B Enantiomer 1: T_r =3.09; 285B Enantiomer 2: T_r = 3.92; Method BH).

285C. Methyl (R)-3-(3-((4-chlorophenyl)amino)-4(cyclohexyl(ethyl)amino)phenyl) pentanoate

285C was prepared using 285B Enantiomer 2 and 1-chloro-4-bromobenzene following the procedure described for the synthesis of 279F. LC-MS Analysis Calc'd. for $C_{26}H_{35}ClN_2O_2$ 442.2, found [M+H] 443.6, T_r = 1.02 min (Method BC).

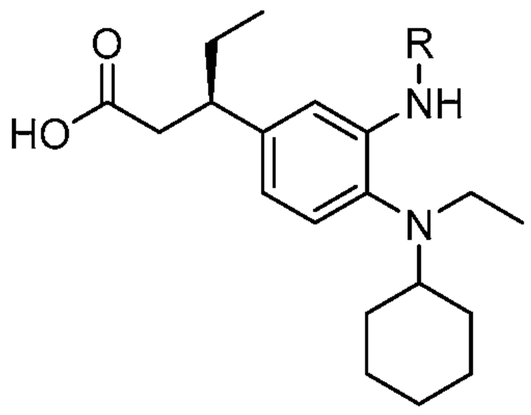
Example 285 Enantiomer 2. (R)-3-(3-((4-Chlorophenyl)amino)-4-(cyclohexyl(ethyl) amino)phenyl)pentanoic acid

Example 285 Enantiomer 2 was prepared using 285C following the procedure described for the synthesis of Example 279 Enantiomer 1. LC-MS Analysis Calc'd. for $C_{25}H_{33}ClN_2O_2$ 428.2, found [M+H] 429.2, T_r = 2.392 min (Method O). ^{1}H NMR (400

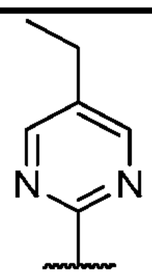
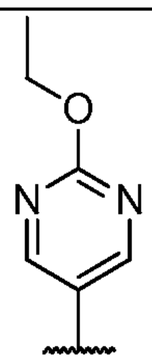
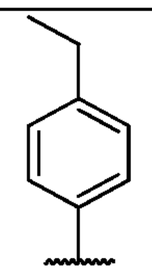
MHz, DMSO-d_6) δ 7.29 (s, 1H), 7.25 - 7.21 (m, 2H), 7.11 - 7.07 (m, 3H), 7.02 (d, *J* = 2.00 Hz, 1H), 6.73 - 6.71 (m, 1H), 2.99 - 2.92 (m, 2H), 2.86 - 2.75 (m, 1H), 2.60 - 2.54 (m, 2H), 2.49 - 2.43 (m, 1H), 1.62 - 1.61 (m, 2H), 1.65 -1.63 (m, 2H), 1.52-1.57 (m, 2H), 1.27 - 1.12 (m, 3H), 1.02 - 1.00 (m, 3H), 0.81 (t, *J* = 7.20 Hz, 3H), 0.73 (t, *J* = 6.80 Hz, 3H).

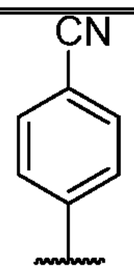
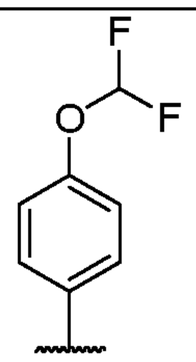
Examples 286 to 290

(Enantiomer 2)



Examples 286 to 290 Enantiomer 2 were prepared using 285B Enantiomer 2 and corresponding halides following the procedure described for the synthesis of Example 285.

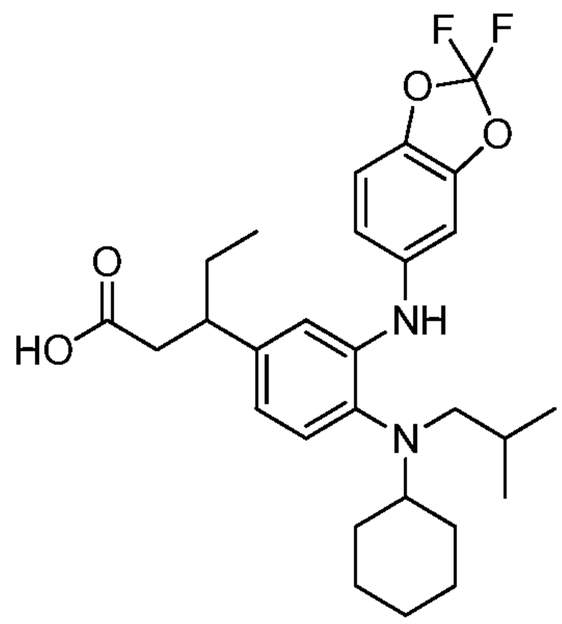
Ex. No.	Name	R	T_r min	Method	(M+H)
286	(R)-3-(4-(cyclohexyl(ethyl) amino)-3-((5-ethylpyrimidin-2-yl)amino)phenyl)pentanoic acid		2.218	O	425.4
287	(R)-3-(4-(cyclohexyl(ethyl) amino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl)pentanoic acid		2. 206	O	441.4
288	(R)-3-(4-(cyclohexyl(ethyl) amino)-3-((4-ethylphenyl)amino) phenyl)pentanoic acid		1.620	R	423.4

Ex. No.	Name	R	T_r min	Method	(M+H)
289	(R)-3-(3-((4-cyanophenyl)amino)-4-(cyclohexyl(ethyl)amino) phenyl)pentanoic acid		2.128	O	420.4
290	(R)-3-(4-(cyclohexyl(ethyl) amino)-3-((4-(difluoromethoxy) phenyl)amino)phenyl)pentanoic acid		1.488	R	461.4

Example 299

(Enantiomer 1)

3-(4-(Cyclohexyl(isobutyl)amino)-3-((2,2-difluorobenzo[d][1,3]dioxol-5-yl)amino) phenyl)pentanoic acid



299A. Methyl 3-(4-(cyclohexyl(isobutyl)amino)-3-((2,2-difluorobenzo[d][1,3]dioxol-5-yl)amino)phenyl)pentanoate

Racemic 3-(3-amino-4-(cyclohexyl(isobutyl)amino)phenyl)pentanoate 1073D was separated into individual antipodes by preparative chiral SFC on a CHIRALPAK® IC column with 10% acetonitrile/CO_2 (first peak, T_R = 3.51 min on a 250 mm × 4.6 mm CHIRALPAK® IC column with 3 g/min acetonitrile/CO_2, absolute stereochemistry unknown). To a degassing solution of resolved 3-(3-amino-4-(cyclohexyl(isobutyl) amino)phenyl)pentanoate (0.05 g, 0.139 mmol) in 1,4-dioxane (2 mL) was added 5-bromo-2,2-difluorobenzo[d][1,3]dioxole (0.039 g, 0.166 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.016 g, 0.028 mmol), cesium carbonate

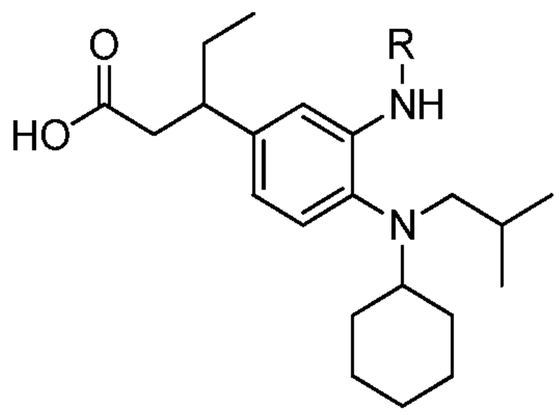
(0.136 g, 0.416 mmol) followed by the addition of bis(dibenzylideneacetone)palladium (7.97 mg, 0.014 mmol). Then the reaction temperature was raised to 110 °C and stirred for 16 h in a sealed tube. The reaction mixture was filtered through CELITE® bed, washed with EtOAc (25 ml). The organic layer was washed with water (2 × 10 ml) followed by brine solution (10 ml), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 299A (pale yellow oil, 0.05 g, 0.077 mmol, 55.8% yield). LC-MS Analysis Calc'd. for $C_{29}H_{38}F_2N_2O_4$ 516.2, found [M+H] 517.2, T_r = 1.27 min (Method BC).

Example 299 Enantiomer 1. 3-(4-(Cyclohexyl(isobutyl)amino)-3-((2,2-difluorobenzo[d][1,3]dioxol-5-yl)amino)phenyl)pentanoic acid

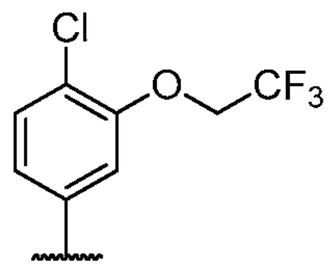
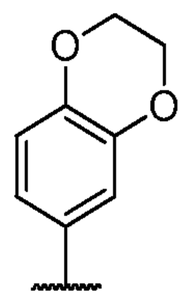
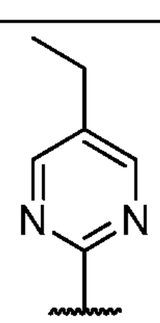
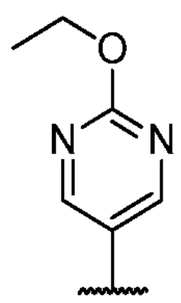
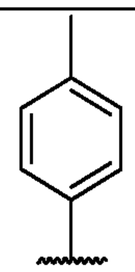
To a solution of 299A (0.05 g, 0.097 mmol) in mixture of THF (1 mL), MeOH (1 mL) and water (1 mL) was added NaOH (0.015 g, 0.387 mmol) at RT and stirred for 1 h. Removed the volatiles under reduced pressure, the salt was dissolved in 10 mL of water and acidified with 1.5 N HCl solution, extracted with EtOAc (2 × 20 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by prep HPLC to afford Example 299 Enantiomer 1 (absolute stereochemistry unknown, off-white solid, 0.047 g, 0.088 mmol, 91% yield). LC-MS Analysis Calc'd. for $C_{28}H_{36}F_2N_2O_4$ 502.2, found [M+H] 503.3, T_r = 3.080 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23 (d, *J* = 8.80 Hz, 1H), 7.11 - 7.10 (m, 4H), 6.83 - 6.80 (m, 1H), 6.73 (d, *J* = 8.00 Hz, 1H), 2.81 - 2.73 (m, 3H), 2.59 - 2.56 (m, 1H), 2.45 - 2.40 (m, 2H), 1.78 - 1.72 (m, 2H), 1.68 - 1.61 (m, 3H), 1.50 - 1.44 (m, 2H), 1.33 - 1.25 (m, 3H), 1.02 - 0.94 (m, 3H), 0.80 (d, *J* = 6.40 Hz, 6H), 0.72 (t, *J* = 6.40 Hz, 3H).

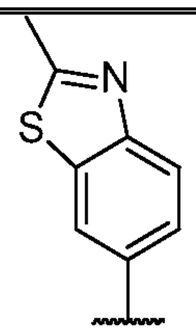
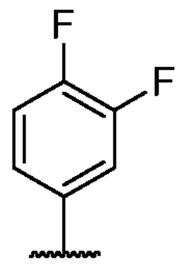
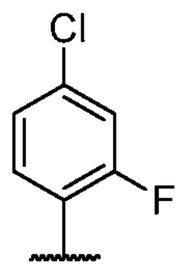
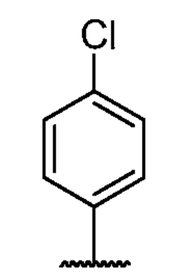
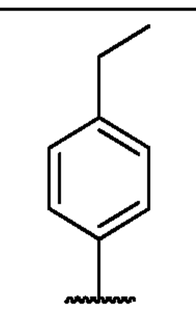
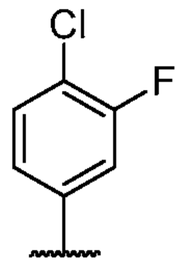
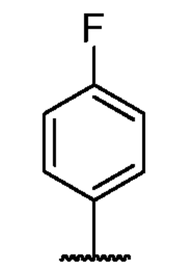
Examples 300 to 314

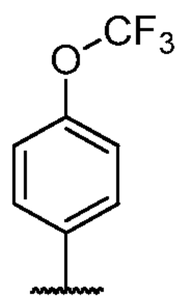
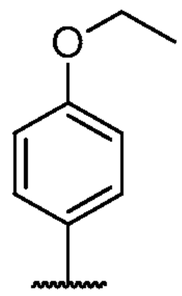
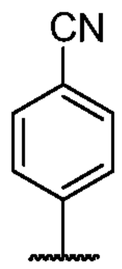
(Enantiomer 1)



Examples 300 to 314 were prepared using 299A and the corresponding halides following the procedure described for the synthesis of Example 299 (absolute stereochemistry not determined).

Ex. No.	Name	R	T_r min	Method	(M+H)
300	3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl) amino)-3-((4-fluorophenyl) amino)phenyl)-4-isopropoxybutanoic acid		3.208	O	555.3
301	3-(4-(cyclohexyl(isobutyl) amino)-3-((2,3-dihydrobenzo[b][1,4] dioxin-6-yl)amino)phenyl) pentanoic acid		2.162	R	481.3
302	3-(4-(cyclohexyl(isobutyl) amino)-3-((5-ethylpyrimidin-2-yl)amino) phenyl)pentanoic acid		2.848	O	453.3
303	3-(4-(cyclohexyl(isobutyl) amino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl)pentanoic acid		2.127	R	469.3
304	3-(4-(cyclohexyl(isobutyl) amino)-3-(*p*-tolylamino) phenyl)pentanoic acid		2.044	R	437.4

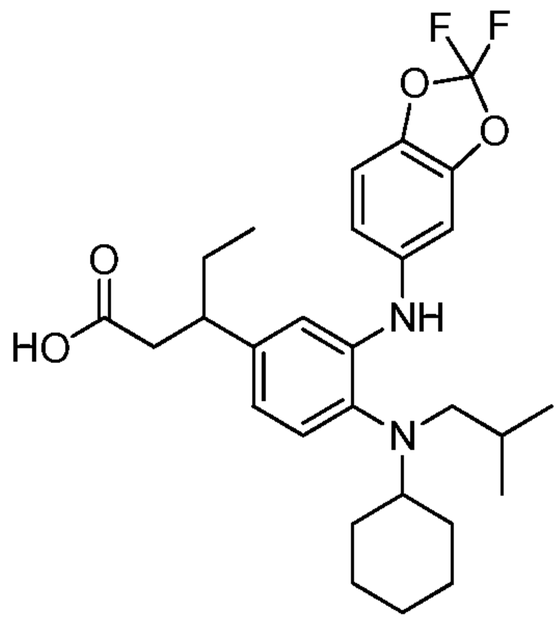
Ex. No.	Name	R	T_r min	Method	(M+H)
305	3-(4-(cyclohexyl(isobutyl) amino)-3-((2-methylbenzo [d]thiazol-6-yl)amino) phenyl)pentanoic acid		1.878	R	494.4
306	3-(4-(cyclohexyl(isobutyl) amino)-3-((3,4-difluorophenyl)amino) phenyl)pentanoic acid		2.080	R	459.4
307	3-(3-((4-chloro-2-fluorophenyl)amino)-4-(cyclohexyl(isobutyl) amino)phenyl)pentanoic acid		2.504	R	475.4
308	3-(3-((4-chlorophenyl) amino)-4-(cyclohexyl (isobutyl)amino)phenyl) pentanoic acid		2.975	O	457.4
309	3-(4-(cyclohexyl(isobutyl) amino)-3-((4-ethylphenyl) amino)phenyl)pentanoic acid		3.038	O	451.4
310	3-(3-((4-chloro-3-fluorophenyl)amino)-4-(cyclohexyl(isobutyl) amino)phenyl)pentanoic acid		2.484	O	475.3
311	3-(4-(cyclohexyl(isobutyl) amino)-3-((4-fluorophenyl) amino)phenyl)pentanoic acid		1.989	R	441.4

Ex. No.	Name	R	T_r min	Method	(M+H)
312	3-(4-(cyclohexyl(isobutyl) amino)-3-((4-(trifluoromethoxy)phenyl) amino)phenyl)pentanoic acid		2.985	O	507.4
313	3-(4-(cyclohexyl(isobutyl) amino)-3-((4-ethoxyphenyl)amino) phenyl)pentanoic acid		3.011	O	467.3
314	3-(3-((4-cyanophenyl) amino)-4-(cyclohexyl (isobutyl)amino)phenyl) pentanoic acid		2.239	O	448.3

Example 315

(Enantiomer 2)

3-(4-(Cyclohexyl(isobutyl)amino)-3-((2,2-difluorobenzo[d][1,3]dioxol-5-yl)amino) phenyl)pentanoic acid



315A. Methyl 3-(4-(cyclohexyl(isobutyl)amino)-3-((2,2-difluorobenzo[d][1,3]dioxol-5-yl)amino)phenyl)pentanoate

Racemic 3-(3-amino-4-(cyclohexyl(isobutyl)amino)phenyl)pentanoate 1073D was separated into individual antipodes by preparative chiral SFC on a CHIRALPAK® IC column with 10% acetonitrile/CO_2 (2nd peak, T_R = 4.61 min on a 250 mm × 4.6 mm

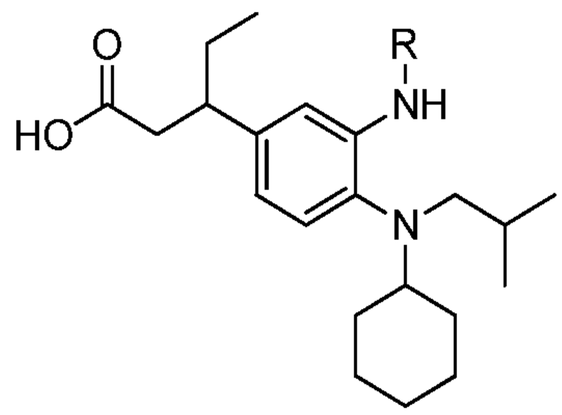
CHIRALPAK® IC column with 3 g/min acetonitrile/CO_2, absolute stereochemistry unknown). Compound 315A was prepared using optically pure 3-(3-amino-4-(cyclohexyl (isobutyl)amino)phenyl)pentanoate (peak 2 above) and 5-bromo-2,2-difluorobenzo[d] [1,3]dioxole following the procedure described for the synthesis of 299A. LC-MS Analysis Calc'd. for $C_{29}H_{38}F_2N_2O_4$ 516.2, found [M+H] 517.0, T_r = 1.26 min (Method BC).

Example 315 Enantiomer 2. 3-(4-(Cyclohexyl(isobutyl)amino)-3-((2,2-difluorobenzo[d] [1,3]dioxol-5-yl)amino)phenyl)pentanoic acid

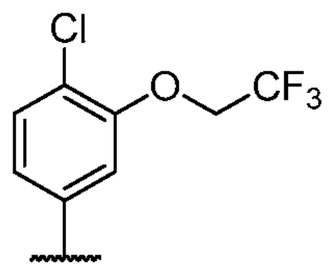
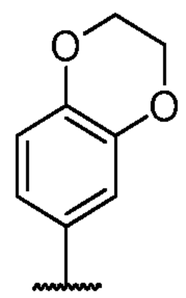
Example 315 Enantiomer 2 was prepared using 315A following the procedure described for the synthesis of Example 299 Enantiomer 1 (absolute stereochemistry unknown, off-white solid, 0.048 g, 0.096 mmol, 99% yield). LC-MS Analysis Calc'd. for $C_{28}H_{36}F_2N_2O_4$ 502.2, found [M+H] 503.3, T_r = 3.208 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23 (d, *J* = 8.80 Hz, 1H), 7.11 - 7.10 (m, 4H), 6.83 - 6.80 (m, 1H), 6.73 (d, *J* = 8.00 Hz, 1H), 2.81 - 2.73 (m, 3H), 2.59 - 2.56 (m, 1H), 2.45 - 2.40 (m, 2H), 1.78 - 1.72 (m, 2H), 1.68 - 1.61 (m, 3H), 1.50 - 1.44 (m, 2H), 1.33 - 1.25 (m, 3H), 1.02 - 0.94 (m, 3H), 0.80 (d, *J* = 6.40 Hz, 6H), 0.72 (t, *J* = 6.40 Hz, 3H).

Examples 316 and 317

(Enantiomer 2)



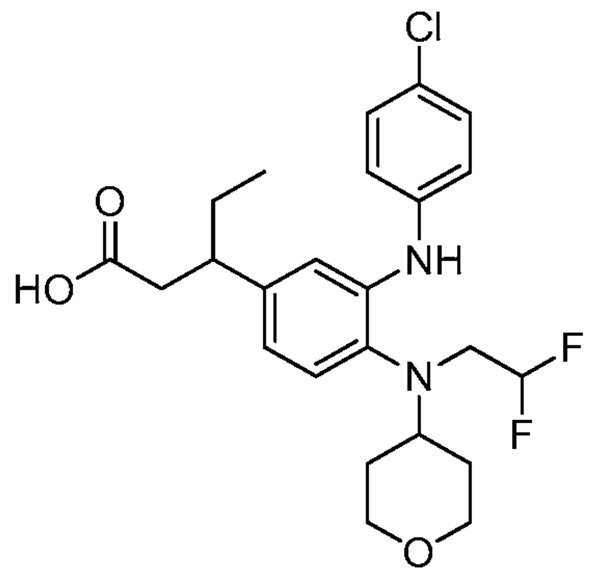
Examples 316 and 317 were prepared using optically pure 3-(3-amino-4-(cyclohexyl(isobutyl)amino)phenyl)pentanoate (peak 2 as described in 315A) and corresponding halides following the procedure described for the synthesis of Example 315 (absolute stereochemistry unknown).

Ex. No.	Name	R	T_r min	Method	(M+H)
316	3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl) amino)-3-((4-fluorophenyl) amino)phenyl)-4-isopropoxybutanoic acid		3.206	O	555.3
317	3-(4-(cyclohexyl(isobutyl) amino)-3-((2,3-dihydrobenzo[b][1,4] dioxin-6-yl)amino)phenyl) pentanoic acid		2.196	R	481.3

Example 318

(Enantiomer 1 and Enantiomer 2)

3-(3-((4-Chlorophenyl)amino)-4-((2,2-difluoroethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid



318A. 2-((Tetrahydro-2H-pyran-4-yl)amino)ethanol

A solution of dihydro-2H-pyran-4(3H)-one (5 g, 49.9 mmol) and 2-aminoethanol (3.66 g, 59.9 mmol) in ethanol (50 mL) was stirred for 2 h at RT. Then the reaction was cooled to ice bath and treated with sodium borohydride (2.83 g, 74.9 mmol) and stirred for 16 h at RT. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with DCM (2 × 100 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford

318A (colorless oil, 5.3 g, 32.9 mmol, 65.8% yield). ^{1}H NMR (300MHz, DMSO-d_6) δ 3.81 (dt, *J*=11.4, 3.5 Hz, 2H), 3.43 (q, *J*=5.7 Hz, 2H), 3.29 - 3.22 (m, 2H), 2.61 - 2.54 (m, 2H), 1.72 - 1.70 (m, 2H), 1.26 - 1.13, 1.08 (d, *J*=1.1 Hz, 1H), 1.07 - 1.00 (m, 2H).

318B. 2-((4-Bromo-2-nitrophenyl)(tetrahydro-2H-pyran-4-yl)amino)ethanol

To a solution of 4-bromo-1-fluoro-2-nitrobenzene (5 g, 22.73 mmol) in NMP (10 mL) was added 318A (3.30 g, 22.73 mmol) followed by DIPEA (9.92 mL, 56.8 mmol). Then the reaction mixture was heated to 120 °C for 16 h. The reaction mixture was poured into water and extracted with EtOAc (2 × 100 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude sample was purified by flash chromatography using silica gel and 0-40% EtOAc in pet ether as eluent. The compound containing fractions were evaporated to afford 318B (red color solid, 4 g, 11.01 mmol, 48.4% yield). LC-MS Anal. Calc'd. for $C_{13}H_{17}BrN_2O_4$ 344.1, found [M+H] 347.0, T_r = 1.09 min (Method BA).

318C. 2-((4-Bromo-2-nitrophenyl)(tetrahydro-2H-pyran-4-yl)amino)acetaldehyde

To a solution of 318B (3 g, 8.69 mmol) in DCM (60 mL) was added Dess-Martin periodinane (4.42 g, 10.43 mmol) at RT under nitrogen, stirred for 16 h. The crude was filtered through CELITE® bed, rinsed with DCM (60 ml). The filtrate was washed with $NaHCO_3$ solution (2 × 30 ml), brine (30 ml). The organic layers was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 318C (pale yellow oil, 3 g, 7.87 mmol, 91% yield). The crude was taken further without purification. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.44 (s, 1H), 8.10 - 8.05 (m, 1H), 7.82 - 7.76 (m, 1H), 7.48 (d, *J* = 11.60 Hz, 1H), 4.00 (s, 2H), 3.81- 3.85 (m, 2H), 3.27 - 3.10 (m, 2H), 2.93-2.89 (m, 1H), 1.33 - 1.21 (m, 4H).

318D. N-(4-Bromo-2-nitrophenyl)-N-(2,2-difluoroethyl)tetrahydro-2H-pyran-4-amine

To a stirred solution of 318C (4 g, 11.66 mmol) in DCM (100 mL) was added DAST (3.85 mL, 29.1 mmol) slowly at -20 °C. Then the reaction was allowed to RT for 16 h. The reaction mixture was cooled under ice bath and quenched with 10% $NaHCO_3$ solution (40 ml), aqueous was extracted with DCM (2 × 100 mL). The combined organic layers was washed with brine, dried over anhydrous sodium sulfate, filtered and

concentrated under reduced pressure. The crude sample was purified by flash chromatography using silica gel and 0-30% EtOAc in pet ether as eluent to afford the pure fractions were concentrated under reduced pressure to afford 318D (yellow oil, 3.7 g, 9.12 mmol, 78% yield). ^{1}H NMR (300MHz, DMSO-d_6) δ 8.10 - 8.05 (m, 1H), 7.82 - 7.76 (m, 1H), 7.63 (d, *J*=8.7 Hz, 1H), 6.05 - 5.62 (m, 1H), 3.84 (dd, *J*=11.1, 4.0 Hz, 2H), 3.51 (td, *J*=15.1, 4.2 Hz, 2H), 3.19 (td, *J*=11.6, 2.1 Hz, 2H), 3.11 - 3.02 (m, 1H), 1.65 - 1.44 (m, 2H), 1.17 (d, *J*= 7.2 Hz, 2H).

318E. N-(2,2-Difluoroethyl)-N-(4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2-nitrophenyl) tetrahydro-2H-pyran-4-amine

A mixture of 318D (2.5 g, 6.85 mmol), bis(neopentyl glycolato)diboron (2.010 g, 8.90 mmol) and potassium acetate (2.016 g, 20.54 mmol) in DMSO (50 mL), at room temperature in a sealable flask, was purged with argon for 20 minutes before $PdCl_2$ (dppf)•CH_2Cl_2 Adduct (0.168 g, 0.205 mmol) was added, the flask was sealed and the reaction heated at 80 °C for 6 hr. The reaction mixture was cooled to RT and poured into water (100 ml), extracted with EtOAc (2 × 150 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude sample was purified by flash chromatography using silica gel and 0-40% EtOAc in pet ether as eluent to afford the pure fractions were concentrated under reduced pressure to afford 318E (red color oil, 2.3 g, 5.20 mmol, 76% yield). LC-MS Anal. Calc'd. for $C_{18}H_{25}BF_2N_2O_5$ 398.2, found [M+H] 331 for parent boronic acid, T_r = 0.98 min (Method BA).

318F. Methyl 3-(4-((2,2-difluoroethyl)(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl) pentanoate

To a stirring and argon bubbling solution of 318E (0.5 g, 1.256 mmol) and (E)-methyl pent-2-enoate (0.430 g, 3.77 mmol) in 1,4-dioxane (10 mL) was added sodium hydroxide (1.146 mL, 1.146 mmol), bubbling continued, then chloro(1,5-cyclooctadiene) rhodium(I) dimer (0.012 g, 0.025 mmol) was added and bubbled argon for another 5 minutes. The reaction mixture was heated at 50 °C for 2 h in sealed tube. Reaction mixture was cooled to room temperature and quenched with acetic acid (0.065 mL, 1.130 mmol) and it was stirred for 5 minutes before partitioned between ethyl acetate (2 × 50

ml) and water (50 ml). Aqueous layer was extracted with ethyl acetate (50 ml). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude sample was purified via flash chromatography using silica gel and 0-40% EtOAc in pet ether as eluent to afford the pure fractions were concentrated under reduced pressure to afford 318F (yellow oil, 0.4 g, 0.749 mmol, 59.7% yield). LC-MS Anal. Calc'd. for $C_{19}H_{26}F_2N_2O_5$ 400.1, found [M+H] 401.2. T_r = 1.28 min (Method BA).

318G. Methyl 3-(3-amino-4-((2,2-difluoroethyl)(tetrahydro-2H-pyran-4-yl)amino) phenyl)-4-methoxybutanoate

To a stirred solution of 318F (0.49 g, 1.224 mmol) in ethyl acetate (15 mL) was carefully added Pd/C (0.065 g, 0.061 mmol). The flask was sequentially evacuated then purged with nitrogen before being pressurized to 40 psi of hydrogen for 3 h. The reaction mixture was filtered through CELITE® bed, washed with methanol (30 ml) and the filtrate was concentrated under reduced pressure to get 318G racemic (0.23 g, 0.538 mmol, 45% yield).

Chiral separation of 318G racemic gave 318G Enantiomer 1 and 318G Enantiomer 2 as single enantiomers. Enantiomer 1 T_r = 2.54 min and Enantiomer 2 T_r = 2.92 min (Method CR).

318G Enantiomer 1 (absolute stereochemistry unknown). (0.11 g, 0.282 mmol, 23% yield). LC-MS Anal. Calc'd. for $C_{19}H_{28}F_2N_2O_3$ 370.2, found [M+H] 371.3, T_r = 1.30 min (Method BA).

318G Enantiomer 2 (absolute stereochemistry unknown). (0.1 g, 0.256 mmol, 21% yield). LC-MS Anal. Calc'd. for $C_{19}H_{28}F_2N_2O_3$ 370.2, found [M+H] 371.3, T_r = 1.30 min (Method BA).

318H. Methyl 3-(3-((4-chlorophenyl)amino)-4-((2,2-difluoroethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

To a degassing solution 318G Enantiomer 1 (0.031 g, 0.162 mmol), 1-chloro-4-bromobenzene (0.031 g, 0.162 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (7.81 mg, 0.013 mmol), cesium carbonate (0.066 g, 0.202 mmol) by argon followed by the addition of bis(dibenzylideneacetone)palladium (3.88 mg, 6.75 µmol). The mixture

bubbled with argon for another 5 minutes. Then the reaction was heated at 110 °C and stirred for 16 h. The reaction mixture was poured into water (10 ml) and extracted with EtOAc (2 × 25 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford crude 318H (0.05 g, 0.078 mmol, 57.8% yield). The crude was taken further without purification. LC-MS Anal. Calc'd. for $C_{25}H_{31}ClF_2N_2O_3$ 480.1, found [M+H] 481.3, T_r = 1.54 min (Method AA).

Example 318 Enantiomer 1. 3-(3-((4-Chlorophenyl)amino)-4-((2,2-difluoroethyl) (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid

To a solution of 318H (0.05 g, 0.104 mmol) in mixture of THF (1 mL), MeOH (1 mL) and water (1 mL) was added $LiOH•H_2O$ (9.96 mg, 0.416 mmol) at RT and stirred for 16 h. Removed the volatiles and the crude pH was adjusted to ~2 with saturated citric acid solution. The aqueous layer was extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude sample was purified by prep HPLC to afford Example 318 Enantiomer 1 (absolute stereochemistry unknown) (off-white solid 0.017 g, 0.035 mmol, 34.6% yield). LC-MS Anal. Calc'd. for $C_{24}H_{29}ClF_2N_2O_3$ 466.1, found [M+H] 467.2, T_r = 1.803 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 - 7.25 (m, 3H), 7.20 (d, *J* = 8.00 Hz, 1H), 7.11 - 7.08 (m, 2H), 7.02 (d, *J* = 2.00 Hz, 1H), 6.75 - 6.72 (m, 1H), 6.04 - 5.76 (m, 1H), 3.81 - 3.77 (m, 2H), 3.39 - 3.36 (m, 3H), 3.17 - 3.19 (m, 2H), 3.00 - 2.96 (m, 1H), 2.91 - 2.89 (m, 2H), 2.50 - 2.40 (m, 2H), 1.68 - 1.61 (m, 2H), 1.39 - 1.36 (m, 2H), 0.72 (t, *J* = 7.20 Hz, 3H).

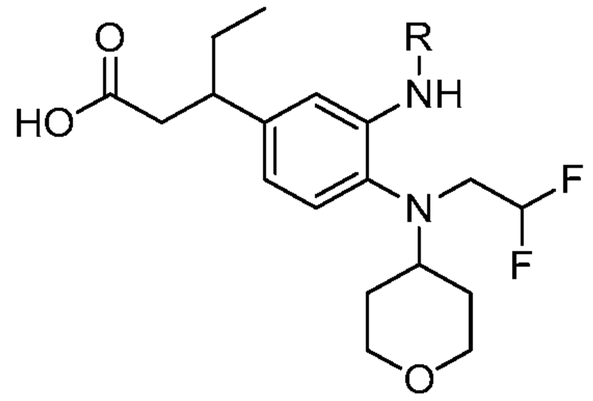
Example 318 Enantiomer 2. 3-(3-((4-Chlorophenyl)amino)-4-((2,2-difluoroethyl) (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid

Example 318 Enantiomer 2 was prepared using 318G Enantiomer 2 and 1-chloro-4-bromobenzene following the procedure described for the synthesis of Example 318 Enantiomer 1 (absolute stereochemistry unknown). LC-MS Anal. Calc'd. for $C_{24}H_{29}ClF_2N_2O_3$ 466.1, found [M+H] 467.1, T_r = 2.049 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 - 7.25 (m, 3H), 7.20 (d, *J* = 8.00 Hz, 1H), 7.11 - 7.08 (m, 2H), 7.02 (d, *J* = 2.00 Hz, 1H), 6.75 - 6.72 (m, 1H), 6.04 - 5.76 (m, 1H), 3.81 - 3.77 (m, 2H),

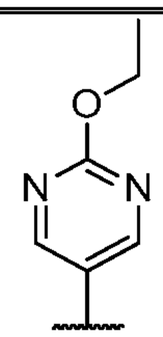
3.39 - 3.36 (m, 3H), 3.17 - 3.19 (m, 2H), 3.00 - 2.96 (m, 1H), 2.91 - 2.89 (m, 2H), 2.50 - 2.40 (m, 2H), 1.68 - 1.61 (m, 2H), 1.39 - 1.36 (m, 2H), 0.72 (t, J = 7.20 Hz, 3H).

Example 319

(Enantiomer 1)

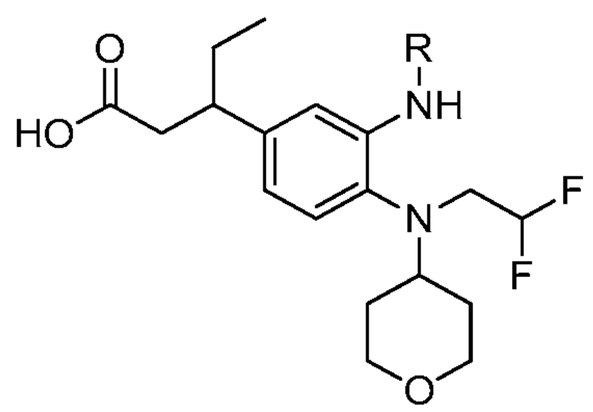


Example 319 was prepared using 318G Enantiomer 1 and corresponding halides following the procedure described for the synthesis Example 318 (absolute stereochemistry unknown).

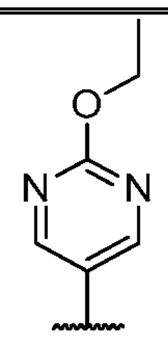
Ex. No.	Name	R	T_r min	Method	(M+H)
319	methyl 3-(3-((4-chlorophenyl) amino)-4-((2,2-difluoroethyl) (tetrahydro-2H-pyran-4-yl)amino) phenyl)-4-methoxybutanoate		1.391	O	479.3

Example 320

(Enantiomer 2)



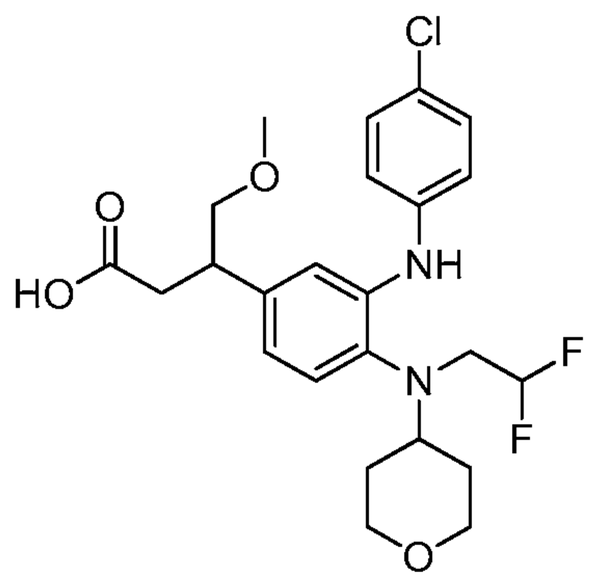
Example 320 (Enantiomer 2) was prepared using 318G Enantiomer 2 and corresponding halides following the procedure described for the synthesis of Example 318 (absolute stereochemistry unknown).

Ex. No.	Name	R	T_r min	Method	(M+H)
320	methyl 3-(3-((4-chlorophenyl) amino)-4-((2,2-difluoroethyl) (tetrahydro-2H-pyran-4-yl)amino) phenyl)-4-methoxybutanoate		1.389	O	479.3

Example 321

(Enantiomer 1 and Enantiomer 2)

3-(3-((4-Chlorophenyl)amino)-4-((2,2-difluoroethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid



321A. Methyl 3-(4-((2,2-difluoroethyl)(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)-4-methoxybutanoate

To a stirring and argon bubbling solution of 318E (0.8 g, 2.009 mmol) and (E)-methyl 4-methoxybut-2-enoate 168A (0.784 g, 6.03 mmol) in 1,4-dioxane (16 mL) was added sodium hydroxide (1.834 mL, 1.834 mmol), bubbling continued, then chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.020 g, 0.040 mmol) was added and bubbled argon for another 5 minutes. The reaction mixture was heated at 50 °C for 2 h in sealed tube. Reaction mixture was cooled to room temperature and quenched with acetic acid (0.104 mL, 1.808 mmol) and it was stirred for 5 minutes before partitioned between ethyl acetate (150 ml) and water (50 ml). Aqueous layer was extracted with ethyl acetate (2 × 50 ml). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude material. The crude sample was purified via flash chromatography to afford 321A (red color oil 0.5 g, 1.081 mmol, 53.8% yield). ^{1}H NMR (300MHz, DMSO-d_6) δ 7.68 (d, *J*=1.9 Hz, 1H), 7.56

- 7.51 (m, 2H), 6.03 - 5.59 (m, 1H), 3.85 - 3.79 (m, 4H), 3.51 (s, 3H), 3.39 (s, 3H), 3.38 - 3.29 (m, 3H), 3.25 - 3.15 (m, 2H), 2.70 - 2.61 (m, 2H), 1.62 -1.58 (m, 3H), 1.47 (d, *J*=9.4 Hz, 2H).

321B. Methyl 3-(3-amino-4-((2,2-difluoroethyl)(tetrahydro-2H-pyran-4-yl)amino) phenyl)-4-methoxybutanoate

To a stirred solution of 321A (0.56 g, 1.345 mmol) in ethyl acetate (15 mL) was carefully added Pd/C (0.072 g, 0.067 mmol). The flask was sequentially evacuated then purged with nitrogen before being pressurized to 40 psi of hydrogen for 3 h. The reaction mixture was filtered through CELITE® bed, washed with methanol (50 ml) and the filtrate was concentrated under reduced pressure to get 321B racemic compound (0.23 g, 0.536 mmol, 40% yield).

Chiral separation of 321B racemic gave 321B Enantiomer 1 and 321B Enantiomer 2 as single enantiomers. Enantiomer 1 T_r = 3.02 min and Enantiomer 2 T_r = 3.62 min (Method CR).

321B Enantiomer 1 (absolute stereochemistry unknown): (0.12 g, 0.295 mmol, 22% yield). LC-MS Anal. Calc'd. for $C_{19}H_{28}F_2N_2O_4$ 386.2, found [M+H] 387.4, T_r = 1.14 min (Method BA).

321B Enantiomer 2 (absolute stereochemistry unknown): (0.1 g, 0.241 mmol, 18% yield). LC-MS Anal. Calc'd. for $C_{19}H_{28}F_2N_2O_4$ 386.2, found [M+H] 387.4, T_r = 1.14 min (Method BA).

321C. Methyl 3-(3-((4-chlorophenyl)amino)-4-((2,2-difluoroethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoate

To a degassing solution of 321B Enantiomer 1 (0.05 g, 0.129 mmol) in 1,4-dioxane (2 mL) was added 1-bromo-4-chlorobenzene (0.030 g, 0.155 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (7.49 mg, 0.013 mmol), cesium carbonate (0.063 g, 0.194 mmol) followed by the addition of bis(dibenzylideneacetone)palladium (3.72 mg, 6.47 µmol). Then the reaction temperature was raised to 110 °C overnight in a sealed tube. The reaction mixture was poured into water (10 ml) and extracted with EtOAc (2 × 25 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford crude 321C (0.05 g,

0.075 mmol, 58.3% yield). The crude was taken further without purification. LC-MS Anal. Calc'd. for $C_{25}H_{31}ClF_2N_2O_4$ 496.1, found [M+H] 497.3, T_r = 1.53 min (Method BA).

Example 321 Enantiomer 1. 3-(3-((4-Chlorophenyl)amino)-4-((2,2-difluoroethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid

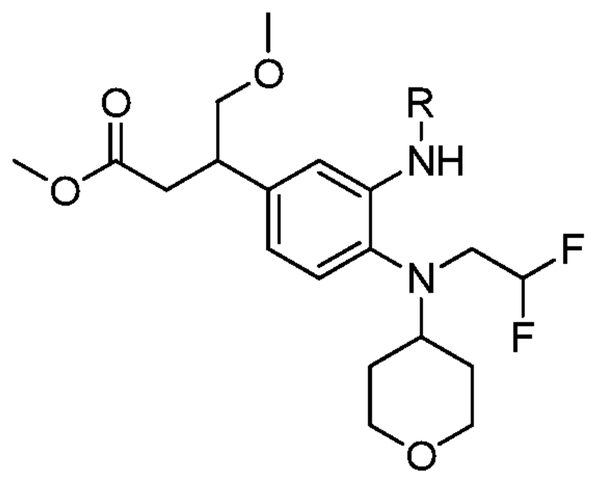
To a solution of 321C (0.05 g, 0.101 mmol) in a mixture of THF (1 mL), MeOH (1 mL) and water (1 mL) was added $LiOH•H_2O$ (9.64 mg, 0.402 mmol) at RT and stirred for 2 h. Removed the volatiles and the crude pH was adjusted to ~2 with saturated citric acid solution. The aqueous layer was extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude sample was purified by prep HPLC to afford Example 321 Enantiomer 1 (absolute stereochemistry unknown) (off-white solid, 0.017 g, 0.035 mmol, 34.6% yield). LC-MS Anal. Calc'd. for $C_{24}H_{29}ClF_2N_2O_4$ 482.1, found [M+H] 483.2, T_r = 1.165 min (Method BB). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (d, *J* = 2.40 Hz, 3H), 7.26 (d, *J* = 2.40 Hz, 1H), 7.11 - 7.09 (m, 3H), 6.79 - 6.76 (m, 1H), 6.03 - 5.59 (m, 1H), 3.81 - 3.77 (m, 2H), 4.08 - 3.40 (m, 4H), 3.22 (s, 3H), 3.19 - 3.10 (m, 3H), 2.99 - 2.95 (m, 1H), 2.62 - 2.60 (m, 1H), 2.33 - 2.32 (m, 1H), 1.68 - 1.65 (m, 2H), 1.43 - 1.38 (m, 2H).

Example 321 Enantiomer 2. 3-(3-((4-Chlorophenyl)amino)-4-((2,2-difluoroethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid

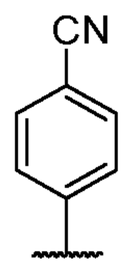
Example 321 Enantiomer 2 was prepared using 321B Enantiomer 2 and 1-bromo-4-chlorobenzene following the procedure described for the synthesis of Example 321 Enantiomer 1 (absolute stereochemistry unknown). LC-MS Anal. Calc'd. for $C_{24}H_{29}ClF_2N_2O_4$ 482.1, found [M+H] 483.2, T_r = 1.171 min (Method BB). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (d, *J* = 2.40 Hz, 3H), 7.26 (d, *J* = 2.40 Hz, 1H), 7.11 - 7.09 (m, 3H), 6.79 - 6.76 (m, 1H), 6.03 - 5.59 (m, 1H), 3.81 - 3.77 (m, 2H), 4.08 - 3.40 (m, 4H), 3.22 (s, 3H), 3.19 - 3.10 (m, 3H), 2.99 - 2.95 (m, 1H), 2.62 - 2.60 (m, 1H), 2.33 - 2.32 (m, 1H), 1.68 - 1.65 (m, 2H), 1.43 - 1.38 (m, 2H).

Example 322

(Enantiomer 1)

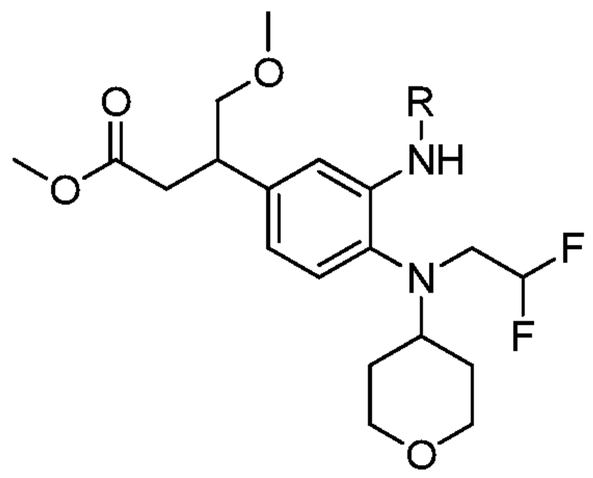


Example 322 was prepared using 321B Enantiomer 1 and corresponding halide following the procedure of described for the synthesis of Example 321 (absolute stereochemistry unknown).

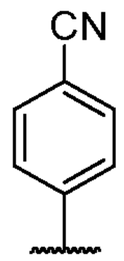
Ex. No.	Name	R	T_r min	Method	(M+H)
322	3-(3-((4-cyanophenyl)amino)-4-((2,2-difluoroethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.237	O	474.3

Example 323

(Enantiomer 2)



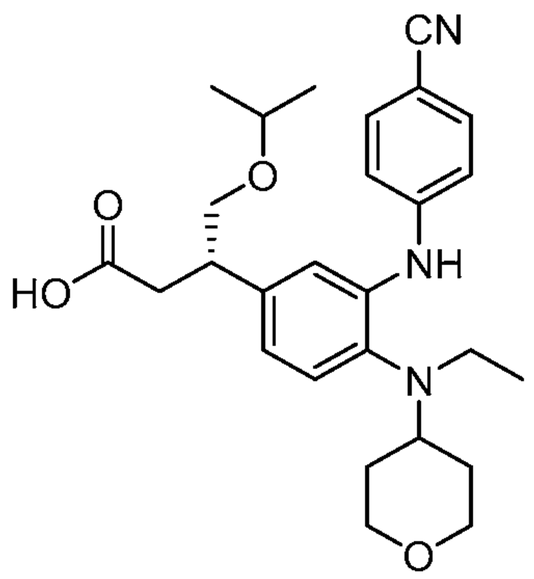
Example 323 was prepared using 321B Enantiomer 2 and corresponding halide following the procedure described for the synthesis of Example 321 (absolute stereochemistry unknown).

Ex. No.	Name	R	T_r min	Method	(M+H)
323	3-(3-((4-cyanophenyl)amino)-4-((2,2-difluoroethyl)(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.243	O	474.3

Example 324

(Enantiomer 1)

(S)-3-(3-((4-Cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-isopropoxybutanoic acid



324A. (E)-Methyl 4-isopropoxybut-2-enoate

To a stirred solution of (E)-methyl 4-bromobut-2-enoate (10 g, 55.9 mmol) in 2-propanol (50 mL) was added silver oxide (12.95 g, 55.9 mmol) at RT, and stirred for 16 h. Reaction mixture was filtered through the pad of CELITE®, washed with DCM (100 ml), filtrates were concentrated under reduced pressure. The crude was dissolved in diethylether (200 mL), washed with water, brine solution, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude sample was purified via flash chromatography to afford 324A (colorless oil, 8 g, 50.6 mmol, 91% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.95 - 6.89 (m, 1H), 6.03 - 5.98 (m, 1H), 4.12 (d, J = 2.00 Hz, 2H), 3.60 (s, 3H), 3.59 - 3.32 (m, 1H), 1.10 (d, J = 4.40 Hz, 6H).

324B. Methyl (S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)-4-isopropoxybutanoate

To a stirring and argon bubbling solution of N-(4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2-nitrophenyl)-N-ethyltetrahydro-2H-pyran-4-amine (455C) (2 g, 5.52 mmol) and 324A (3.49 g, 22.09 mmol) in 1,4-dioxane (40 mL) was added sodium hydroxide (1.0 molar) (5.04 mL, 5.04 mmol) and (R)-BINAP (0.172 g, 0.276 mmol), bubbling with argon continued for 5 minutes, then chlorobis(ethylene)rhodium(I)dimer (0.043 g, 0.110 mmol) was added and bubbled argon for another 5 minutes. The reaction mixture was heated at 50 °C for 2 h in sealed tube. Then cooled to room temperature and quenched with acetic acid (0.284 mL, 4.97 mmol) and it was stirred for 5 minutes before partitioned between ethyl acetate (200 ml) and water (100 ml). Aqueous layer was extracted with ethyl acetate (2 × 50 ml). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude sample was purified via flash chromatography to afford 324B (pale yellow oil, 0.85 g, 1.873 mmol, 33.9% yield). LC-MS Analysis Calc'd. for $C_{21}H_{32}N_2O_6$ 408.2, found [M+H] 409.6, T_r = 1.46 min (Method AY).

324C. Methyl (S)-3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-isopropoxybutanoate

To a stirred solution of 324B (0.85 g, 2.081 mmol) in ethyl acetate (15 mL) was carefully added Pd/C (10%) (0.111 g, 0.104 mmol). The flask was sequentially evacuated then purged with nitrogen before being pressurized to 40 psi of hydrogen for 3 h. The reaction mixture was filtered through CELITE® bed, washed with methanol, filtrate was concentrated under reduced pressure to afford enantiomeric mixture 324C.

Chiral separation of enantiomeric mixture (94:6) of 324C yielded 324C Enantiomer 1, T_r = 4.39 min, 324C Enantiomer 2, T_r = 5.26 min (Method BK).

324C Enantiomer 1; (pale yellow oil, 0.65 g, 1.631 mmol, 78.0% yield) as. Calc'd. for $C_{21}H_{34}N_2O_4$ 378.2, found [M+H] 379.5, T_r = 1.39 min (Method AY).

324D. Methyl (S)-3-(3-((4-cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-isopropoxybutanoate

To a degassing solution of 324C Enantiomer 1 (0.05 g, 0.132 mmol) in 2-propanol (2 mL) by argon was added 4-bromobenzonitrile (0.029 g, 0.159 mmol), 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (5.61 mg, 0.013 mmol) and potassium

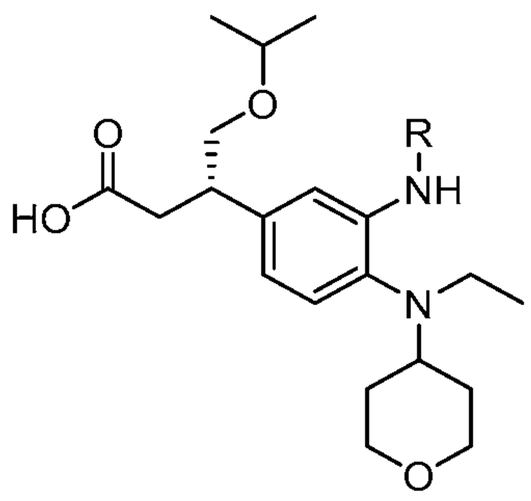
acetate (0.039 g, 0.396 mmol) followed by the addition of tris(dibenzylideneacetone) dipalladium(0) (6.05 mg, 6.60 μmol). Then the reaction temperature was raised to 100 °C for 16 h in a sealed vial. The reaction mixture was poured into water (10 ml) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford crude 324D. The crude material was taken further without any purification. LC-MS Analysis Calc'd. for $C_{28}H_{37}N_3O_4$ 479.2, found [M+H] 480.3, T_r = 1.04 min (Method AY).

Example 324 Enantiomer 1. (S)-3-(3-((4-Cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-isopropoxybutanoic acid

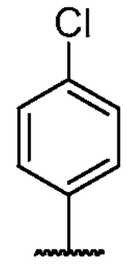
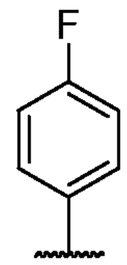
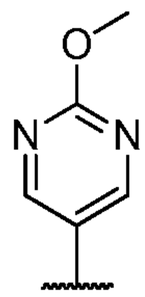
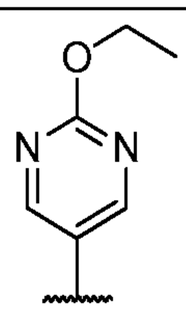
To a solution of 324D (0.03 g, 0.031 mmol) in mixture of THF (1 mL), MeOH (1 mL) and water (1 mL) was added $LiOH•H_2O$ (3.00 mg, 0.125 mmol) at RT and stirred for 16 h. Removed the volatiles under reduced pressure and the crude pH as adjusted to ~2 with 1.5N HCl solution. The aqueous was extracted with DCM (2 × 10 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude sample was purified by prep HPLC to afford Example 324 Enantiomer 1 (off-white solid, 0.011 g, 0.022 mmol). LC-MS Analysis Calc'd. for $C_{27}H_{35}N_3O_4$ 465.2, found [M+H] 466.4, T_r = 1.210 min (Method R). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 1H), 7.54 (d, *J* = 8.80 Hz, 2H), 7.18 - 7.10 (m, 4H), 6.94 - 6.92 (m, 1H), 3.78 - 3.75 (m, 2H), 3.51 - 3.48 (m, 3H), 3.19 - 3.10 (m, 3H), 2.97 - 2.95 (m, 3H), 2.69 - 2.66 (m, 1H), 2.48 - 2.45 (m, 1H), 1.57 - 1.54 (m, 2H), 1.44 - 1.41 (m, 2H), 1.03 (t, *J* = 6.40 Hz, 6H), 0.80 (t, *J* = 6.80 Hz, 3H).

Examples 325 to 328

(Enantiomer 1)



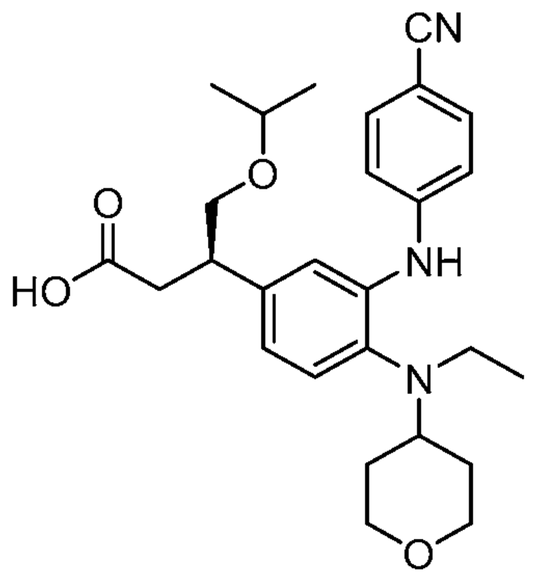
Examples 325 to 328 were prepared using 324C Enantiomer 1 and corresponding halides following the procedure described for the synthesis of Example 324.

Ex. No.	Name	R	T_r min	Method	(M+H)
325	(S)-3-(3-((4-chlorophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino) phenyl)-4-isopropoxybutanoic acid		2.204	O	475.1
326	(S)-3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((4-fluorophenyl)amino)phenyl)-4-isopropoxybutanoic acid		1.751	O	459.4
327	(S)-3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((2-methoxypyrimidin-5-yl)amino)phenyl)-4-isopropoxybutanoic acid		1.603	R	473.1
328	(S)-3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((2-ethoxypyrimidin-5-yl)amino) phenyl)-4-isopropoxybutanoic acid		1.716	O	487.1

Example 329

(Enantiomer 2)

3-(3-((4-Cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-isopropoxybutanoic acid



329A. Methyl (R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)-4-isopropoxybutanoate

329A was prepared using S-BINAP and 455C and following the procedure described for the synthesis of 324B. LC-MS Analysis Calc'd. for $C_{21}H_{32}N_2O_6$ 408.2 found [M+H] 409.6. T_r = 1.46 min (Method AY).

329B. Methyl (R)-3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-isopropoxybutanoate

329B was prepared using 329A following the procedure described for the synthesis of 324C.

Chiral separation of enantiomeric mixture 329B (6:94) yielded 329B Enantiomer 1 T_r = 4.46 min, 329B Enantiomer 2 T_r = 5.18 min (Method BK).

329B Enantiomer 2; (pale yellow oil, 0.67 g, 1.682 mmol, 68.7% yield). Calc'd. for $C_{21}H_{34}N_2O_4$ 378.2, found [M+H] 379.5, T_r = 1.39 min (Method AY).

329C. Methyl (R)-3-(3-((4-cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-isopropoxybutanoate

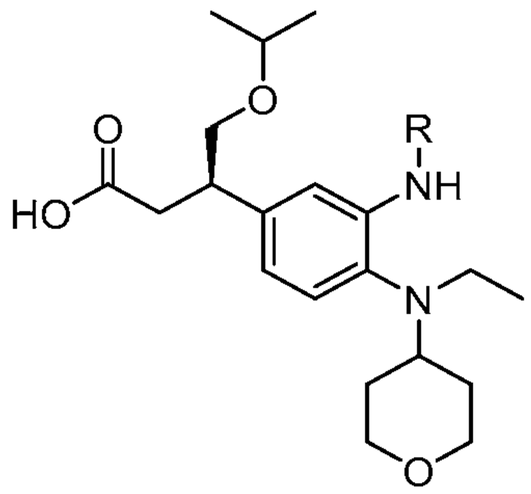
329C was prepared using 329B Enantiomer 2 and 4-bromo benzonitrile following the procedure described for the synthesis of 324D. LC-MS Analysis Calc'd. for $C_{28}H_{37}N_3O_4$ 479.2, found [M+H] 480.3, T_r = 1.04 min (Method AY).

Example 329 Enantiomer 2. (R)-3-(3-((4-Cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-isopropoxybutanoic acid

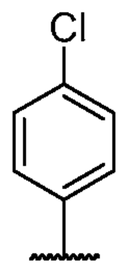
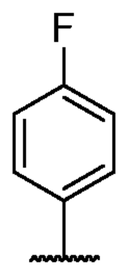
Example 329 Enantiomer 2 was prepared using 329C following the procedure described for the synthesis of Example 324 Enantiomer 1. LC-MS Analysis Calc'd. for $C_{27}H_{35}N_3O_4$ 465.2, found [M+H] 466.4, T_r = 1.218 min (Method R). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 1H), 7.54 (d, *J* = 8.80 Hz, 2H), 7.18 - 7.10 (m, 4H), 6.94 - 6.92 (m, 1H), 3.78 - 3.75 (m, 2H), 3.51 - 3.48 (m, 3H), 3.19 - 3.10 (m, 3H), 2.97 - 2.95 (m, 3H), 2.69 - 2.66 (m, 1H), 2.48 - 2.45 (m, 1H), 1.57 - 1.54 (m, 2H), 1.44 - 1.41 (m, 2H), 1.03 (t, *J* = 6.40 Hz, 6H), 0.80 (t, *J* = 6.80 Hz, 3H).

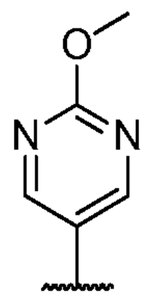
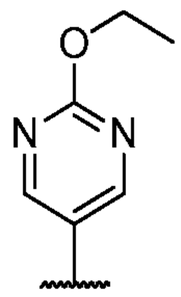
Examples 330 to 333

(Enantiomer 2)



Examples 330 to 333 were prepared using 329B Enantiomer 2 and corresponding aryl halides following the procedure described for the synthesis of Example 329.

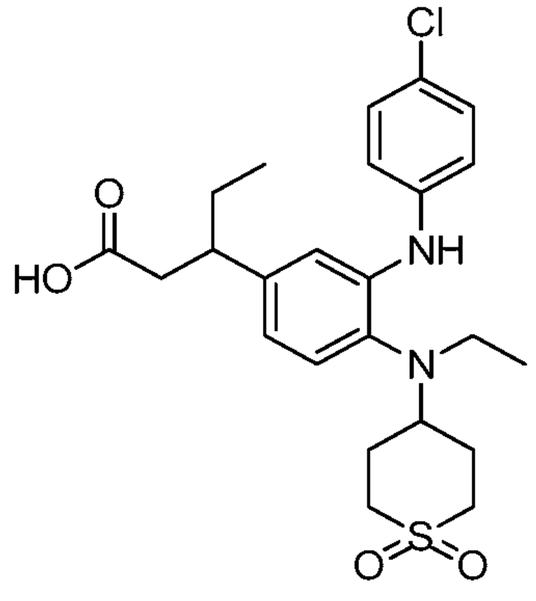
Ex. No.	Name	R	T_r min	Method	(M+H)
330	(R)-3-(3-((4-chlorophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino) phenyl)-4-isopropoxybutanoic acid		2.213	O	475.1
331	(R)-3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((4-fluorophenyl)amino)phenyl)-4-isopropoxybutanoic acid		1.758	O	459.4

Ex. No.	Name	R	T_r min	Method	(M+H)
332	(R)-3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((2-methoxypyrimidin-5-yl)amino)phenyl)-4-isopropoxybutanoic acid		1.600	O	473.1
333	(R)-3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((2-ethoxypyrimidin-5-yl)amino)phenyl)-4-isopropoxybutanoic acid		1.741	O	487.1

Example 334

(Enantiomer 1 and Enantiomer 2)

3-(3-((4-Chlorophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl)pentanoic acid



334A. N-Ethyltetrahydro-2H-thiopyran-4-amine

To a stirred solution of dihydro-2H-thiopyran-4(3H)-one (6.0 g, 51.6 mmol) and ethanamine (28.4 mL, 56.8 mmol) under nitrogen in dry THF (50 mL)-MeOH (50 mL) was added molecular sieves (5.0 g). The reaction was stirred at room temperature overnight. The reaction was cooled to 0 °C and treated with $NaBH_4$ (5.86 g, 155 mmol) portionwise over 10 minutes. The reaction was then stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure to afford a semi-solid. To this was added sat. $NaHCO_3$ (200 mL) and this mixture was stirred overnight. The

resulting mixture was partitioned between EtOAc (400 ml) and water (100 ml). The organic extract was washed with brine (100 ml), dried over Na_2SO_4 and concentrated to afford N-ethyltetrahydro-2H-thiopyran-4-amine (6.5 g, 44.7 mmol, 87% yield) as light yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63-2.72 (m, 6H), 2.41-2.50 (m, 1H), 2.13-2.20 (m, 2H), 1.45-1.52 (m, 2H), 1.09 (t, J = 7.2 Hz, 3H).

334B. Methyl 3-(4-(ethyl(tetrahydro-2H-thiopyran-4-yl)amino)-3-nitrophenyl)pentanoate

To a stirred solution of methyl 3-(4-fluoro-3-nitrophenyl)pentanoate (443B) (0.5 g, 1.959 mmol), 334A (0.427 g, 2.94 mmol), DIPEA (1.026 mL, 5.88 mmol) in NMP (5 mL) stirred for 10 minutes at room temperature. Reaction heated to 135 °C and maintained for 48 h. The reaction mixture was poured into water (50 ml) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude sample was purified by flash chromatography using silica gel and 0-10% EtOAc in pet ether as eluent. The compound containing fractions were evaporated to afford 334B (yellow oil, 0.5 g, 0.788 mmol, 40.2% yield). LC-MS Analysis Calc'd. for $C_{19}H_{28}N_2O_4S$ 380.1, found [M+H] 381.5, T_r = 1.63 min (Method AY).

334C. Methyl 3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-nitrophenyl)pentanoate

To a solution of 334B (0.4 g, 0.631 mmol) in acetonitrile (2 mL) and water (1.538 mL) was cooled to 0 °C and added OXONE® (1.163 g, 1.892 mmol) followed by sodium bicarbonate (0.530 g, 6.31 mmol). Then the reaction was slowly warmed to RT and stirred for 2 h. The reaction mixture was poured into water (50 ml) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude sample was purified by flash chromatography using silica gel and 0-50% EtOAc in pet ether as eluent. The compound containing fractions were evaporated to afford 334C (yellow oil, 0.25 g, 0.576 mmol, 91% yield). LC-MS Analysis Calc'd. for $C_{19}H_{28}N_2O_6S$ 412.1, found [M+H] 413.5, T_r = 0.87 min (Method BC).

334D. Methyl 3-(3-amino-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino) phenyl)pentanoate

To a stirred solution of 334C (0.35 g, 0.848 mmol) in ethyl acetate (10 mL) was carefully added Pd/C (10%) (0.045 g, 0.042 mmol). The flask was sequentially evacuated then purged with nitrogen before being pressurized to 40 psi of hydrogen for 3 h. The reaction mixture was filtered through CELITE® bed, washed with methanol (50 ml). The combined filtrate was concentrated under reduced pressure to get crude compound 334D (0.28 g, 0.695 mmol, 80% yield).

Chiral separation of 334D racemic gave 334D Enantiomer 1 and 334D Enantiomer 2 as single enantiomers. Enantiomer 1 T_r = 3.56 min and Enantiomer 2 T_r = 5.87 min (Method BT).

334D Enantiomer 1 (absolute stereochemistry unknown): (0.14 g, 0.348 mmol, 41% yield). LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_4S$ 382.1, found [M+H] 383.5, T_r = 0.55 min (Method BC).

334D Enantiomer 2 (absolute stereochemistry unknown): (0.135 g, 0.335 mmol, 40% yield). LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_4S$ 382.1, found [M+H] 383.5, T_r = 0.55 min (Method BC).

334E. Methyl 3-(3-((4-chlorophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl)pentanoate

To a degassing solution of 334D Enantiomer 1 (0.025 g, 0.065 mmol) in 1,4-dioxane (2 mL) by argon was added 1-bromo-4-chlorobenzene (0.015 g, 0.078 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (7.56 mg, 0.013 mmol), cesium carbonate (0.064 g, 0.196 mmol) followed by the addition of bis(dibenzylideneacetone) palladium (3.76 mg, 6.54 µmol). Then the reaction temperature was raised to 110 °C for 16 h in a sealed vessel. The reaction mixture was filtered through CELITE® plug, washed the plug with EtOAc (2 × 20 ml). The filtrate was concentrated under reduced pressure to afford crude 334E (0.03 g, 0.030 mmol, 46.5% yield). The crude was taken further without purification. LC-MS Analysis Calc'd. for $C_{25}H_{33}ClN_2O_4S$ 492.1, found [M+H] 493.5, T_r = 1.72 min (Method AY).

Example 334 Enantiomer 1. 3-(3-((4-Chlorophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl)pentanoic acid

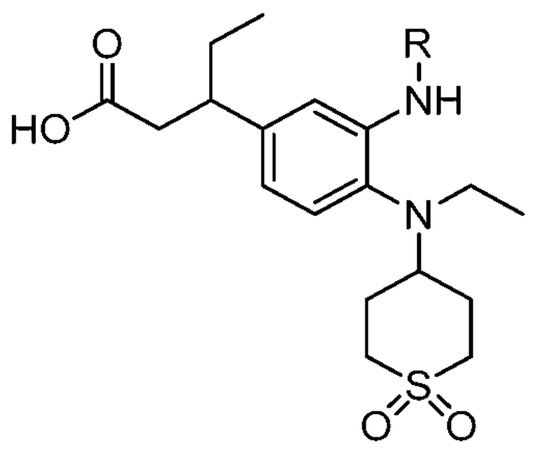
To a solution of 334E (0.04 g, 0.081 mmol) in mixture of THF (1 mL), MeOH (1 mL) and water (1 mL) was added $LiOH•H_2O$ (7.77 mg, 0.325 mmol) at RT and stirred for 16 h. Removed the volatiles and the crude pH as adjusted to ~2 with 1.5N HCl solution. The aqueous was extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude compound was purified by prep HPLC to afford Example 334 Enantiomer 1 (absolute stereochemistry unknown) (off-white solid, 0.011 g, 0.023 mmol, 32.8% yield) as. LC-MS Analysis Calc'd. for $C_{24}H_{31}ClN_2O_4S$ 478.1, found [M+H] 479.2, T_r = 1.813 min (Method R). ^1H NMR (400 MHz, MeOD) δ 7.27 - 7.24 (m, 2H), 7.19 -7.10 (m, 4H), 6.77 (dd, *J* = 1.60, 8.20 Hz, 1H), 3.28 - 3.26 (m, 1H), 3.14 - 3.07 (m, 4H), 3.01 - 2.98 (m, 3H), 2.63 - 2.62 (m, 1H), 2.54 - 2.50 (m, 1H), 2.22 - 2.17 (m, 4H), 1.72 - 1.69 (m, 1H), 1.72 - 1.56 (m, 1H), 0.95 (t, *J* = 7.60 Hz, 3H), 0.83 (t, *J* = 7.20 Hz, 3H).

Example 334 Enantiomer 2. 3-(3-((4-Chlorophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl)pentanoic acid

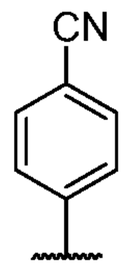
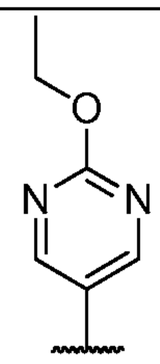
Example 334 Enantiomer 2 was prepared using compound 334D Enantiomer 2 and 1-bromo-4-chlorobenzene following the procedure described for the synthesis of Example 334 Enantiomer 1 (absolute stereochemistry unknown). LC-MS Analysis Calc'd. for $C_{24}H_{31}ClN_2O_4S$ 478.1, found [M+H] 479.2, T_r = 1.812 min (Method R). ^1H NMR (400 MHz, MeOD) δ 7.27 - 7.24 (m, 2H), 7.19 -7.10 (m, 4H), 6.77 (dd, *J* = 1.60, 8.20 Hz, 1H), 3.28 - 3.26 (m, 1H), 3.14 - 3.07 (m, 4H), 3.01 - 2.98 (m, 3H), 2.63 - 2.62 (m, 1H), 2.54 - 2.50 (m, 1H), 2.22 - 2.17 (m, 4H), 1.72 - 1.69 (m, 1H), 1.72 - 1.56 (m, 1H), 0.95 (t, *J* = 7.60 Hz, 3H), 0.83 (t, *J* = 7.20 Hz, 3H).

Examples 335 and 336

(Enantiomer 1)

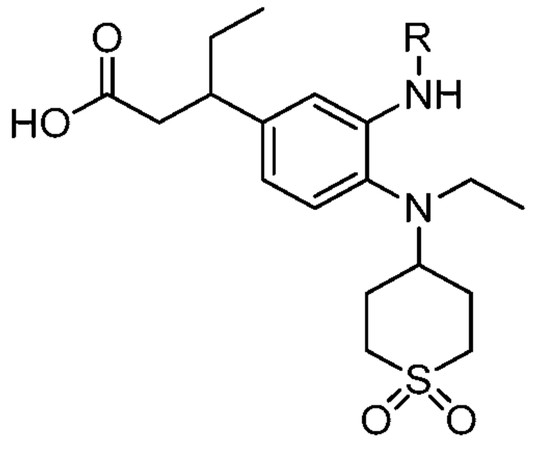


Examples 335 and 336 were prepared using 334D Enantiomer 1 and corresponding halides and following the procedure for Example 334 Enantiomer 1 (absolute stereochemistry unknown).

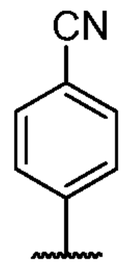
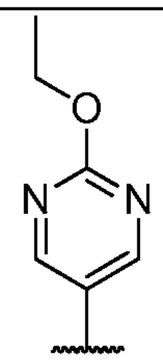
Ex. No.	Name	R	T_r min	Method	(M+H)
335	3-(3-((4-cyanophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl) pentanoic acid		1.518	O	470.2
336	3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((4-fluorophenyl)amino)phenyl)-4-isopropoxybutanoic acid		0.74	BC	491.5

Examples 337 and 338

(Enantiomer 2)



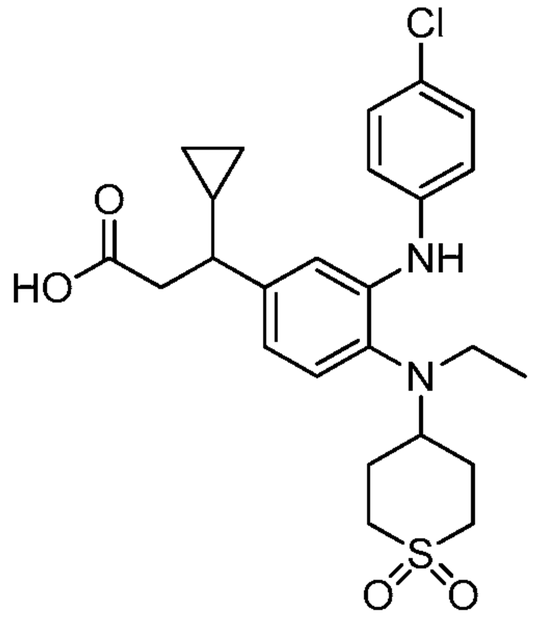
Examples 337 and 338 were prepared using 334D Enantiomer 2 and corresponding halides and following the procedure described for the synthesis of Example 334 Enantiomer 2 (absolute stereochemistry unknown).

Ex. No.	Name	R	T_r min	Method	(M+H)
337	3-(3-((4-cyanophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl) pentanoic acid		1.549	O	470.2
338	3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((4-fluorophenyl)amino)phenyl)-4-isopropoxybutanoic acid		0.74	BC	491.5

Example 339

(Enantiomer 1 and Enantiomer 2)

3-(4-((1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((4-fluorophenyl) amino)phenyl)-4-isopropoxybutanoic acid



339A. N-(4-Bromo-2-nitrophenyl)-N-ethyltetrahydro-2H-thiopyran-4-amine

To a solution of 4-bromo-1-fluoro-2-nitrobenzene (5 g, 22.73 mmol) in NMP (15 mL) at RT was added 334A (4.95 g, 34.1 mmol) followed by the addition of DIPEA (7.94 mL, 45.5 mmol). The reaction was sealed and heated at 130 °C for 16 h. The reaction mixture was poured into water (50 ml), extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude sample was purified via flash chromatography to afford 339A (red color oil, 5.2 g, 14.31 mmol, 63.0% yield). LC-MS

Analysis Calc'd. for $C_{13}H_{17}BrN_2O_2S$ 344.2, found [M+H] 347.1, T_r = 1.66 min (Method AY).

339B. N-(4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-2-nitrophenyl)-N-ethyltetrahydro-2H-thiopyran-4-amine

A mixture of 339A (5 g, 14.48 mmol), bis(neopentyl glycolato)diboron (4.25 g, 18.83 mmol) and potassium acetate (4.26 g, 43.4 mmol) in DMSO (50 mL), at room temperature in a sealable flask, was purged with argon for 20 minutes before $PdCl_2$ (dppf)•CH_2Cl_2 Adduct (0.355 g, 0.434 mmol) was added, the flask was sealed and the reaction heated at 80 °C for 6 h. The reaction mixture was cooled to RT and poured into water (500 ml), extracted with EtOAc (2 × 250 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude sample was purified via flash chromatography to afford 339B (red color oil, 4.5 g, 10.71 mmol, 73.9% yield). LC-MS Analysis Calc'd. for $C_{18}H_{27}BN_2O_4S$ 378.2, found [M+H] 311.2 for parent boronic acid, T_r = 1.22 min (Method AY).

339C. Methyl 3-cyclopropyl-3-(4-(ethyl(tetrahydro-2H-thiopyran-4-yl)amino)-3-nitrophenyl)propanoate

To a stirring and argon bubbling solution of 339B (2 g, 5.29 mmol) and (E)-methyl 3-cyclopropylacrylate (33C) (2.001 g, 15.86 mmol) in 1,4-dioxane (40 mL) was added sodium hydroxide (1.0 molar) (4.83 mL, 4.83 mmol), bubbling with argon continued for 5 minutes, then chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.052 g, 0.106 mmol) was added and bubbled argon for another 5 minutes. The reaction mixture was heated at 50 °C for 2 h in sealed tube. Reaction mixture was cooled to room temperature and quenched with acetic acid (0.272 mL, 4.76 mmol) and it was stirred for 5 minutes before partitioned between ethyl acetate (100 ml) and water (50 ml). Aqueous layer was extracted with ethyl acetate (2 × 100 ml). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude sample was purified via flash chromatography to afford 339C (yellow oil, 1.43 g, 3.28 mmol, 62.0% yield). LC-MS Analysis Calc'd. for $C_{20}H_{28}N_2O_4S$ 392.1, found [M+H] 393.3, T_r = 1.56 min (Method AY).

339D. Methyl 3-cyclopropyl-3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl) amino)-3-nitrophenyl)propanoate

A solution of 339C (1.43 g, 3.64 mmol) in acetonitrile (15 mL) and water (11.54 mL) was cooled to 0 °C and treated with OXONE® (6.72 g, 10.93 mmol) followed by sodium bicarbonate (3.06 g, 36.4 mmol). Then the reaction was slowly warmed to RT and stirred for 2 h. The reaction mixture was poured into water (50 ml) and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude sample was purified via flash chromatography to afford 339D (yellow oil, 1 g, 2.238 mmol, 61.4% yield). LC-MS Analysis Calc'd. for $C_{20}H_{28}N_2O_6S$ 424.1, found [M+H] 425.2, T_r = 1.22 min (Method AY).

339E. Methyl 3-(3-amino-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino) phenyl)-3-cyclopropylpropanoate

To a stirred solution of 339D (0.9 g, 2.120 mmol) in ethyl acetate (20 mL) was carefully added Pd/C (10%) (0.113 g, 0.106 mmol). The flask was sequentially evacuated then purged with nitrogen before being pressurized to 40 psi of hydrogen for 3 h. The reaction mixture was filtered through CELITE® bed, washed with methanol (50 ml). The combined filtrate was concentrated under reduced pressure to get crude compound 339E (0.7 g, 1.686 mmol, 80% yield).

Chiral separation of 339E racemic gave 339E Enantiomer 1 and 339E Enantiomer 2 as single enantiomers (Method BS). Enantiomer 1 T_r = 3.92 min and Enantiomer 2 T_r = 5.53 min (Method BS).

339E Enantiomer 1 (absolute stereochemistry unknown): (0.35 g, 0.843 mmol, 40% yield). LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_4S$ 394.5, found [M+H] 395.4, T_r = 1.24 min (Method AY).

339E Enantiomer 2 (absolute stereochemistry unknown): (0.35 g, 0.843 mmol, 40% yield), LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_4S$ 394.5, found [M+H] 395.4, T_r = 1.24 min (Method AY).

339F. Methyl 3-(3-((4-chlorophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl)-3-cyclopropylpropanoate

To a degassing solution of 339E Enantiomer 1 (0.05 g, 0.127 mmol) in 1,4-dioxane (2 mL) by argon was added 1-bromo-4-chlorobenzene (0.029 g, 0.152 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (7.33 mg, 0.013 mmol), cesium carbonate (0.062 g, 0.190 mmol) followed by bis(dibenzylideneacetone)palladium (3.64 mg, 6.34 µmol). Then the reaction temperature was raised to 110 °C overnight in a sealed tube. The reaction mixture was poured into water (25 ml) and extracted with EtOAc (2 × 25 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 339F (pale yellow oil, 0.06 g, 0.095 mmol, 80% yield). LC-MS Analysis Calc'd. for $C_{26}H_{33}ClN_2O_4S$ 504.1, found [M+H] 505.3, T_r = 1.52 min (Method AY).

Example 339 Enantiomer 1. 3-(3-((4-Chlorophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl)-3-cyclopropylpropanoic acid

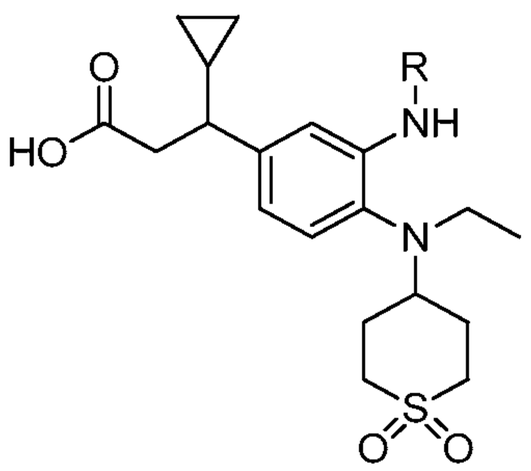
To a solution of 339F (0.05 g, 0.099 mmol) in mixture of THF (1 mL), MeOH (1 mL) and water (1 mL) was added $LiOH•H_2O$ (9.48 mg, 0.396 mmol) at RT and stirred for 16 h. Removed the volatiles under reduced pressure and the crude pH as adjusted to ~2 with 1.5N HCl solution. The aqueous layer was extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by prep HPLC to afford Example 339 Enantiomer 1 (absolute stereochemistry unknown): (off-white solid, 0.033 g, 0.066 mmol, 66.5% yield). LC-MS Analysis Calc'd. for $C_{25}H_{31}ClN_2O_4S$ 490.169, Found [M+H] 491.0, T_r = 1.855 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (s, 1H), 7.27 (d, *J* = 8.80 Hz, 2H), 7.16 - 7.10 (m, 4H), 6.81 - 6.79 (m, 1H), 3.29 - 3.21 (m, 2H), 3.18 - 3.13 (m, 2H), 3.09 - 2.94 (m, 4H), 2.28 - 2.26 (m, 1H), 2.23 - 2.21 (m, 1H), 2.15 - 2.06 (m, 2H), 1.96 - 1.94 (m, 2H), 1.02 - 0.96 (m, 1H), 0.85 (t, *J* = 7.20 Hz, 3H), 0.49 - 0.39 (m, 2H), 0.24 - 0.13 (m, 2H).

Example 339 Enantiomer 2. 3-(3-((4-Chlorophenyl)amino)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl)-3-cyclopropylpropanoic acid

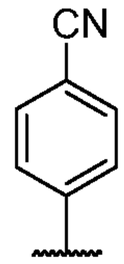
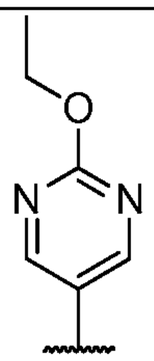
Example 339 Enantiomer 2 was prepared using 339E Enantiomer 2 and 1-bromo-4-chlorobenzene following the procedure described for the synthesis of Example 339 Enantiomer 1 (absolute stereochemistry unknown). LC-MS Analysis Calc'd. for $C_{25}H_{31}ClN_2O_4S$ 490.169, Found [M+H] 491.0, T_r = 1.835 min (Method O). ^1H NMR (400 MHz, DMSO-d_6) δ 7.42 (s, 1H), 7.27 (d, *J* = 8.80 Hz, 2H), 7.16 - 7.10 (m, 4H), 6.81 - 6.79 (m, 1H), 3.29 - 3.21 (m, 2H), 3.18 - 3.13 (m, 2H), 3.09 - 2.94 (m, 4H), 2.28 - 2.26 (m, 1H), 2.23 - 2.21 (m, 1H), 2.15 - 2.06 (m, 2H), 1.96 - 1.94 (m, 2H), 1.02 - 0.96 (m, 1H), 0.85 (t, *J* = 7.20 Hz, 3H), 0.49 - 0.39 (m, 2H), 0.24 - 0.13 (m, 2H).

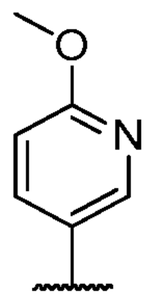
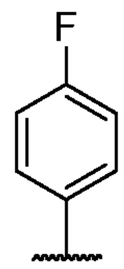
Examples 340 to 343

(Enantiomer 1)



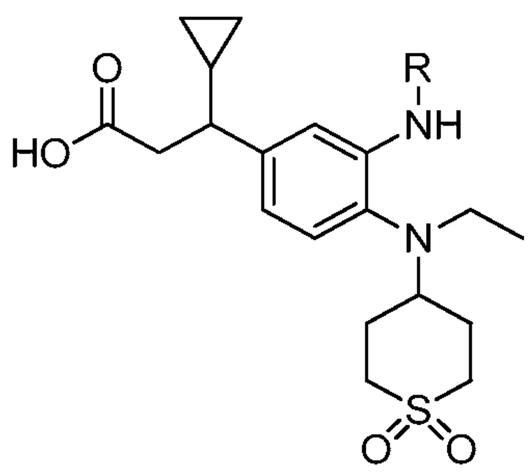
Examples 340 to 343 were prepared using 339E Enantiomer 1 and corresponding halides and following the procedure described for the synthesis of Example 339 (absolute stereochemistry unknown).

Ex. No.	Name	R	T_r min	Method	(M+H)
340	3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((4-fluorophenyl)amino)phenyl)-4-isopropoxybutanoic acid		1.567	O	482.1
341	3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((4-fluorophenyl)amino)phenyl)-4-isopropoxybutanoic acid		1.468	O	503.0

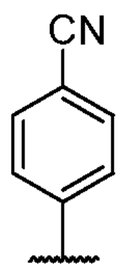
Ex. No.	Name	R	T_r min	Method	(M+H)
342	3-cyclopropyl-3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((6-methoxypyridin-3-yl)amino) phenyl)propanoic acid		1.312	O	488.3
343	3-cyclopropyl-3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((4-fluorophenyl)amino)phenyl) propanoic acid		1.494	O	475.2

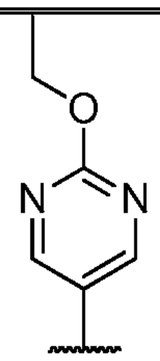
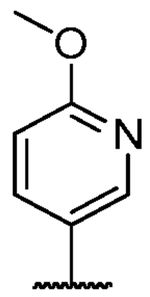
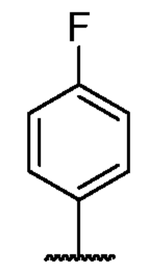
Examples 344 to 347

(Enantiomer 2)



Examples 344 to 347 were prepared using 339E Enantiomer 2 and corresponding halides, following the procedure described for the synthesis of Example 339 (absolute stereochemistry unknown).

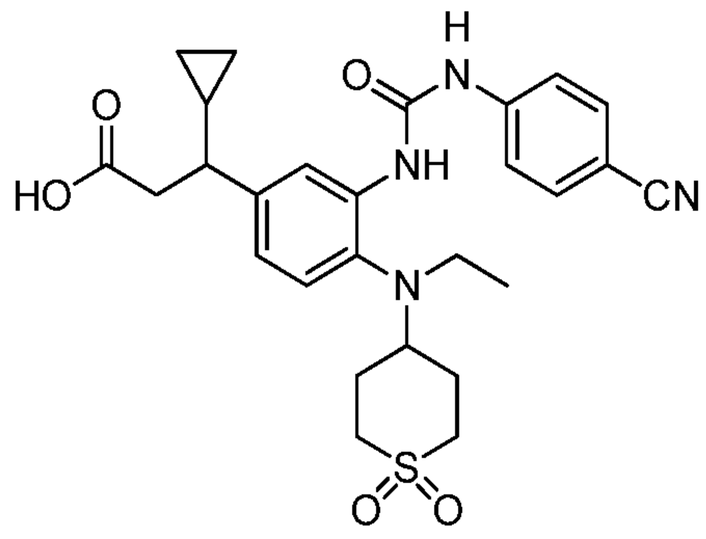
Ex. No.	Name	R	T_r min	Method	(M+H)
344	3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((4-fluorophenyl)amino)phenyl)-4-isopropoxybutanoic acid		1.571	O	482.1

Ex. No.	Name	R	T_r min	Method	(M+H)
345	3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((4-fluorophenyl)amino)phenyl)-4-isopropoxybutanoic acid		1.462	O	503.1
346	3-cyclopropyl-3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((6-methoxypyridin-3-yl)amino) phenyl)propanoic acid		1.407	O	488.1
347	3-cyclopropyl-3-(4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)-3-((4-fluorophenyl)amino)phenyl) propanoic acid		1.499	O	475.2

Example 348

(Enantiomer 1 and Enantiomer 2)

3-(3-(3-(4-Cyanophenyl)ureido)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl) amino)phenyl)-3-cyclopropylpropanoic acid



348A. Methyl 3-(3-(3-(4-cyanophenyl)ureido)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl)-3-cyclopropylpropanoate

To a solution of 339E Enantiomer 1 (0.025 g, 0.063 mmol) in THF (1 mL) was added 4-isocyanatobenzonitrile (10.96 mg, 0.076 mmol) under nitrogen. Then the

reaction was stirred for 16 h at RT. Removed volatiles under reduced pressure to afford crude 348A (0.03 g, 0.050 mmol, 79% yield). LC-MS Analysis Calc'd. for $C_{28}H_{34}N_4O_5S$ 538.2, Found [M+H] 539.3, T_r = 1.26 min (Method AY).

Example 348 Enantiomer 1. 3-(3-(3-(4-Cyanophenyl)ureido)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl)-3-cyclopropylpropanoic acid

To a solution of 348A (0.025 g, 0.046 mmol) in mixture of THF (1 mL), MeOH (1 mL) and water (1 mL) was added $LiOH•H_2O$ (4.45 mg, 0.186 mmol) at RT and stirred for 16 h. Removed the volatiles under reduced pressure and the crude pH was adjusted to ~2 with 1.5N HCl solution. The aqueous layer was extracted with DCM (2 × 10 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by prep HPLC to afford Example 348 Enantiomer 1 (absolute stereochemistry unknown) (off-white solid, 0.005 g, 9.53 µmol, 20.3% yield). LC-MS Analysis Calc'd. for $C_{27}H_{32}N_4O_5S$ 524.2, Found [M+H] 525.1, T_r = 1.454 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.61 (s, 1H), 8.16 (d, *J* = 1.60 Hz, 1H), 7.74 - 7.67 (m, 4H), 7.19 (d, *J* = 8.00 Hz, 1H), 6.93 - 6.91 (m, 1H), 3.23 - 3.14 (m, 3H), 3.07 - 3.01 (m, 4H), 2.64 - 2.57 (m, 2H), 2.30 - 2.24 (m, 3H), 1.91 - 1.86 (m, 2H), 1.01 - 0.99 (m, 1H), 0.83 (t, *J* = 7.20 Hz, 3H), 0.55 - 0.35 (m, 2H), 0.25 - 0.14 (m, 2H).

348B. Methyl 3-(3-(3-(4-cyanophenyl)ureido)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl)-3-cyclopropylpropanoate

348B prepared using 339E Enantiomer 2 following the procedure described for the synthesis of 348A. LC-MS Analysis Calc'd. for $C_{28}H_{34}N_4O_5S$ 538.2 Found [M+H] 539.3. T_r = 1.26 min (Method AY).

Example 348 Enantiomer 2. 3-(3-(3-(4-Cyanophenyl)ureido)-4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)(ethyl)amino)phenyl)-3-cyclopropylpropanoic acid

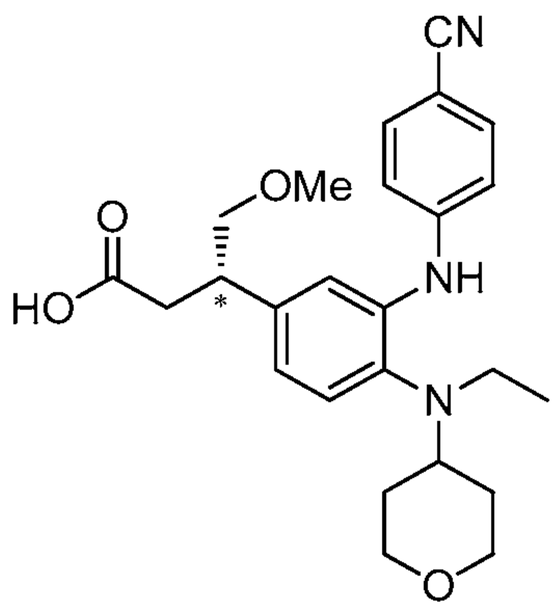
Example 348 Enantiomer 2 was prepared using 384B following the procedure described for the synthesis of Example 348 Enantiomer 1 (absolute stereochemistry unknown). LC-MS Analysis Calc'd. for $C_{27}H_{32}N_4O_5S$ 524.2 Found [M+H] 525.1, T_r = 1.454 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6 ppm) δ 10.06 (s, 1H), 8.61 (s,

1H), 8.16 (d, *J* = 1.60 Hz, 1H), 7.74 - 7.67 (m, 4H), 7.19 (d, *J* = 8.00 Hz, 1H), 6.93 - 6.91 (m, 1H), 3.23 - 3.14 (m, 3H), 3.07 - 3.01 (m, 4H), 2.64 - 2.57 (m, 2H), 2.30 - 2.24 (m, 3H), 1.91 - 1.86 (m, 2H), 1.01 - 0.99 (m, 1H), 0.83 (t, *J* = 7.20 Hz, 3H), 0.55 - 0.35 (m, 2H), 0.25 - 0.14 (m, 2H).

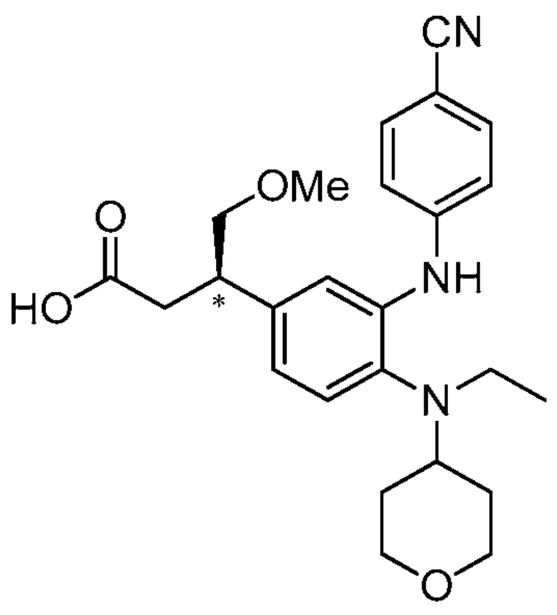
Example 349

(Enantiomer 1 and Enantiomer 2)

3-(3-((4-Cyanophenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid



Enantiomer 1



Enantiomer 2

349A. Methyl 3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)-4-methoxybutanoate

In a pressure tube equipped with Teflon cap, 455C (5.5 g, 15.18 mmol) and 1,4-dioxane (60 ml) were added followed by sodium hydroxide (13.67 ml, 13.67 mmol). To it argon gas was passed through for 15 minutes and then (E)-methyl 4-methoxybut-2-enoate (5.3 g, 40.7 mmol) and chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.374 g, 0.759 mmol) were added. Argon gas was further passed through it for 5 minutes. Reaction was screw-capped and heated at 50 °C for 3 h. To the reaction mixture 0.869 mL of acetic acid was added a followed by water (100 mL) and it was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over sodium sulfate and concentrated to afford the crude which was purified via flash silica gel column chromatography using ethyl acetate in pet ether (0-20%) as an eluant to afford 349A (orange oil, 5.25 g, 12.75 mmol, 84% yield). LC-MS Anal. Calc'd. for $C_{19}H_{28}N_2O_6$ 380.195, found [M+H] 381.2, T_r =3.009 min (Method U).

349B. Methyl 3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoate

The solution of 349A (4.2 g, 11.04 mmol) in ethyl acetate (40 mL) was evacuated and purged with nitrogen for 3 times. Then carefully added Pd/C (0.47 g, 0.442 mmol) under nitrogen atmosphere and the suspension was hydrogenated (60 psi, autoclave) at RT for 4 h. The suspension was filtered through a pad of CELITE® and the filter cake was rinsed with ethyl acetate (200 mL). The combined filtrate was concentrated under reduced pressure to afford the racemic 349B (brown oil, 3.5 g, 9.97 mmol, 90%). LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_4$ 350.221, found [M+H)] 351.2, T_r =2.4 min (Method U).

Chiral SFC separation of racemic 349B gave 349B Enantiomer 1 T_r = 2.92 min (Method BZ) and 349B Enantiomer 2 T_r = 3.76 min (Method BZ) as single enantiomers.

349B Enantiomer 1 (brown oil, 1.5 g, 4.24 mmol, 38.4% yield). LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_4$ 350.221, found [M+H] 351.2, T_r = 2.414 min (Method U).

349B Enantiomer 2 (brown oil, 1.5 g, 4.24 mmol, 38.4% yield). LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_4$ 350.221, found [M+H] 351.2, T_r = 2.304 min (Method U).

349C. Methyl (S)-3-(3-((4-cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)-4-methoxybutanoate

To a solution of 349B Enantiomer 1 (1.5 g, 4.28 mmol) in 1,4-dioxane (15 mL) were added 4-bromobenzonitrile (0.935 g, 5.14 mmol), Xantphos (0.248 g, 0.428 mmol), Cs_2CO_3 (4.18 g, 12.84 mmol) in a sealed tube. Then argon was purged for 10 min, followed by the addition of bis(dibenzylideneacetone)palladium (0.123 g, 0.214 mmol). Argon was again purged for another 5 min. The reaction mixture was heated to 108 °C for 6 h. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure to afford brown colored residue. The residue was purified via flash silica gel column chromatography using ethyl acetate in pet ether (0-30%) as an eluant to afford 349C Enantiomer 1 (light yellow semi-solid, 1.6 g, 3.40 mmol, 79% yield). LC-MS Anal. Calc'd. for $C_{26}H_{33}N_3O_4$ 451.247, found [M+H] 452.5, T_r = 1.46 min (Method AY).

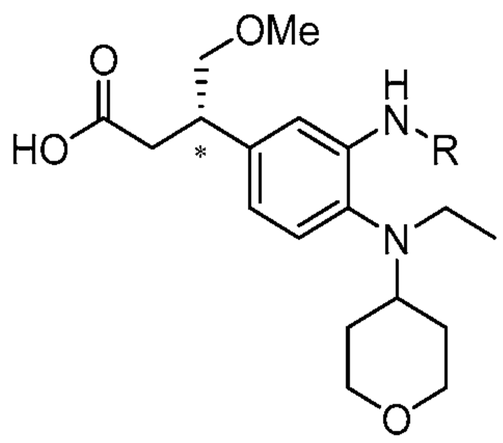
Example 349 Enantiomer 1. (S)-3-(3-((4-Cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid

To a stirred solution of 349C (130 mg, 0.288 mmol) in methanol (2 mL), water (2 mL) and THF (2 mL), LiOH (27.6 mg, 1.152 mmol) was added and stirred at RT for 4 h. The reaction mixture was concentrated and the aqueous solution was acidified with saturated citric acid solution (pH~4-5). The aqueous solution was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to afford brown colored residue. The residue was purified by prep HPLC to afford Example 349 Enantiomer 1 (absolute stereochemistry confirmed as "S" by single crystal x-ray crystallography) (off-white solid, 74 mg, 0.169 mmol, 58.6% yield). LC-MS Anal. Calc'd. for $C_{25}H_{31}N_3O_4$ 437.231, found [M+H] 438.2, T_r = 1.4648 min (Method U). ^{1}H NMR (400 MHz, CD_3OD) δ 7.52-7.54 (m, 2H), 7.30 (d, *J* = 2.00 Hz, 1H), 7.17-7.21 (m, 3H), 6.93-6.96 (m, 1H), 3.84-3.88 (m, 2H), 3.53-3.57 (m, 2H), 3.22-3.34 (m, 5H), 3.00-3.09 (m, 3H), 2.77-2.78 (m, 1H), 2.57-2.59 (m, 1H), 1.69-1.72 (m, 2H), 1.51-1.54 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H).

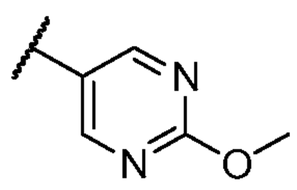
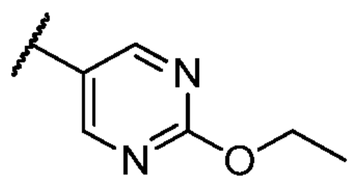
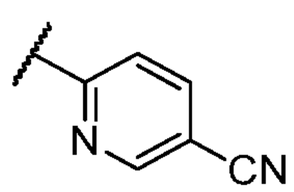
Example 349 Enantiomer 2. (R)-3-(3-((4-Cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid

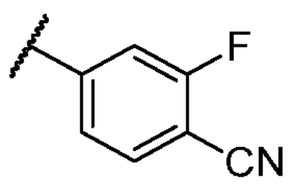
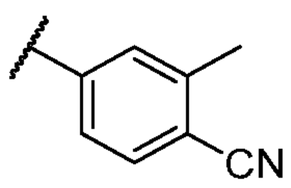
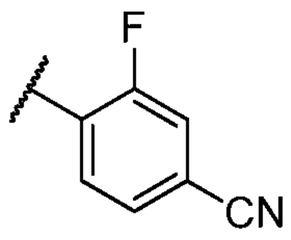
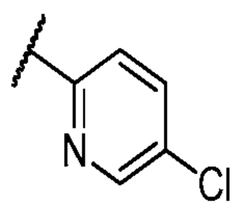
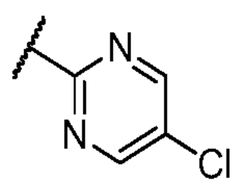
Example 349 Enantiomer 2 was prepared utilizing 349B Enantiomer 2 and 4-bromobenzonitrile following the procedure described for the synthesis of Example 349 Enantiomer 2 (absolute stereochemistry inferred from Example 349 Enantiomer 1). LC-MS Anal. Calc'd. for $C_{25}H_{31}N_3O_4$ 437.231, found [M+H] 438.2, T_r = 1.464 min (Method U). ^{1}H NMR (400 MHz, CD_3OD) δ 7.51-7.55 (m, 2H), 7.30 (d, *J* = 2.00 Hz, 1H), 7.17-7.21 (m, 3H), 6.94-6.96 (m, 1H), 3.84-3.88 (m, 2H), 3.53-3.57 (m, 2H), 3.22-3.34 (m, 5H), 2.99-3.07 (m, 3H), 2.75-2.76 (m, 1H), 2.56-2.57 (m, 1H), 1.69-1.72 (m, 2H), 1.50-1.53 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H).

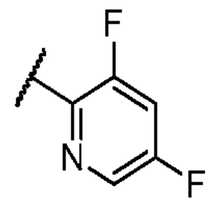
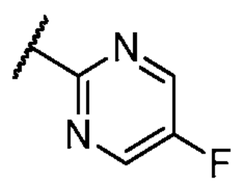
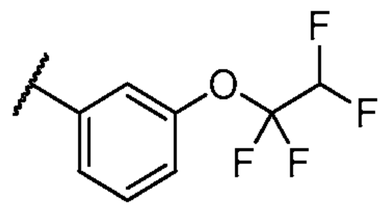
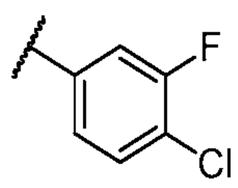
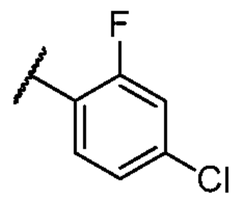
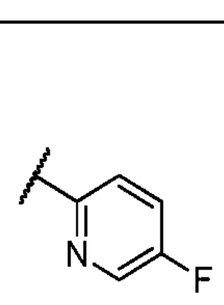
Examples 350 to 386
(Enantiomer 1)

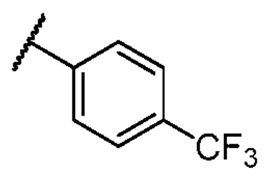
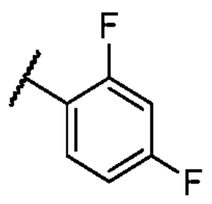
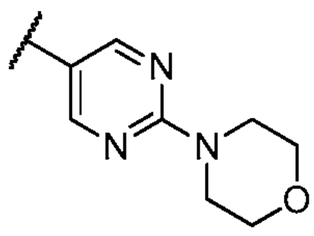
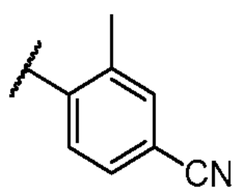
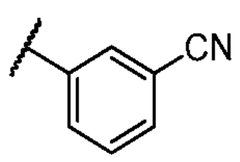


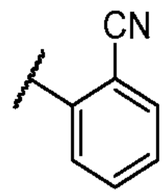
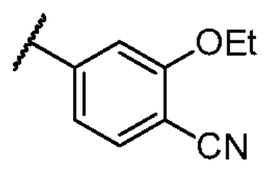
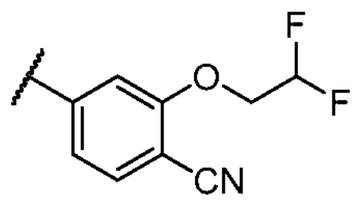
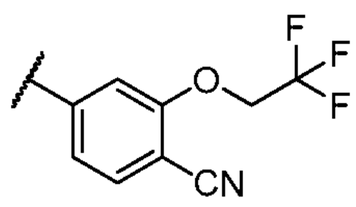
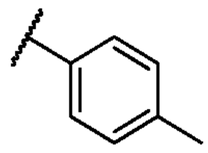
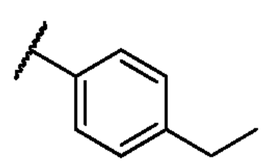
Examples 350 to 386 were prepared using the 349B Enantiomer 1 and corresponding aryl bromides following the procedure described for the synthesis of Example 349.

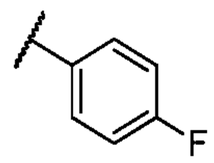
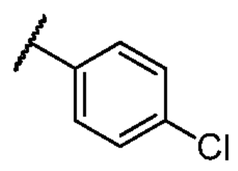
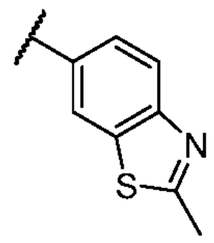
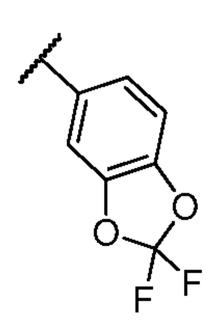
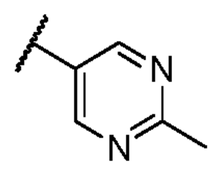
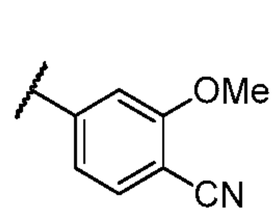
Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
350	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methoxypyrimidin-5-yl)amino)phenyl)-4-methoxybutanoic acid		1.297	445.2
351	(S)-3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.418	459.2
352	(S)-3-(3-((5-cyanopyridin-2-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.168	439.3

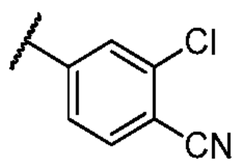
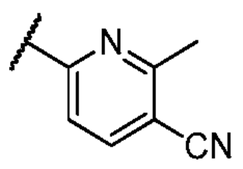
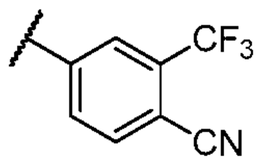
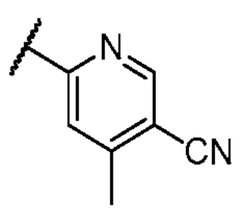
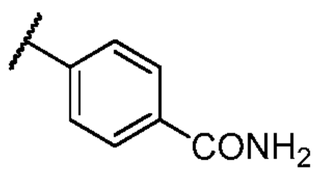
Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
353	(S)-3-(3-((4-cyano-3-fluorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.349	456.3
354	(S)-3-(3-((4-cyano-3-methylphenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.39	452.3
355	(S)-3-(3-((4-cyano-2-fluorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.406	456.3
356	(S)-3-(3-((5-chloropyridin-2-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.657	448.1
357	(S)-3-(3-((5-chloropyrimidin-2-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.581	449.0

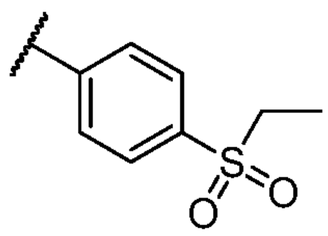
Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
358	(S)-3-(3-((3,5-difluoropyridin-2-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.443	450.3
359	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((5-fluoropyrimidin-2-yl)amino)phenyl)-4-methoxybutanoic acid		1.164	433.3
360	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((3-(1,1,2,2-tetrafluoroethoxy)phenyl)amino)phenyl)-4-methoxybutanoic acid		1.712	529.4
361	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((3-(1,1,2,2-tetrafluoroethoxy)phenyl)amino)phenyl)-4-methoxybutanoic acid		1.643	465.3
362	(S)-3-(3-((4-chloro-2-fluorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.697	465.3
363	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((5-fluoropyridin-2-yl)amino)phenyl)-4-methoxybutanoic acid		1.226	432.3

Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
364	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((4-(trifluoromethyl)phenyl) amino)phenyl)-4-methoxybutanoic acid		1.698	481.3
365	(S)-3-(3-((2,4-difluorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.545	449.3
366	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-(tetrahydro-2H-pyran-4-yl)pyrimidin-5-yl)amino) phenyl)-4-methoxybutanoic acid		1.21	500.4
367	(S)-3-(3-((4-cyano-2-methylphenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.436	452.3
368	(S)-3-(3-((3-cyanophenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)-4-methoxybutanoic acid		1.348	438.3

Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
369	(S)-3-(3-((2-cyanophenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)-4-methoxybutanoic acid		1.335	438.3
370	(S)-3-(3-((4-cyano-3-ethoxyphenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.439	482.4
371	(S)-3-(3-((4-cyano-3-(2,2-difluoroethoxy)phenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)-4-methoxybutanoic acid		1.431	518.4
372	(S)-3-(3-((4-cyano-3-(2,2,2-trifluoroethoxy)phenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)-4-methoxybutanoic acid		1.536	536.3
373	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(*p*-tolylamino)phenyl)-4-methoxybutanoic acid		1.804	427.3
374	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((4-ethylphenyl)amino)phenyl)-4-methoxybutanoic acid		1.96	441.3

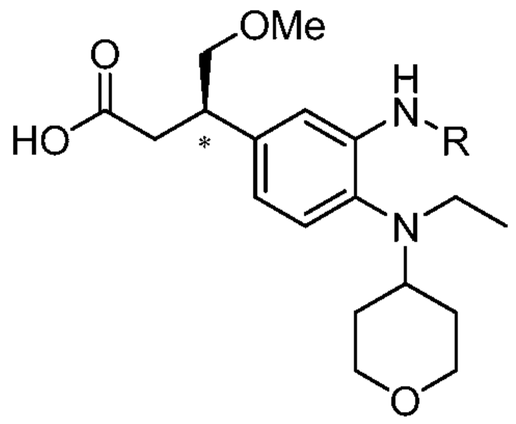
Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
375	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((4-fluorophenyl)amino)phenyl)-4-methoxybutanoic acid		1.689	431.2
376	(S)-3-(3-((4-chlorophenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)-4-methoxybutanoic acid		1.831	447.2
377	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methylbenzo[d]thiazol-6-yl)amino)phenyl)-4-methoxybutanoic acid		1.603	484.2
378	(S)-3-(3-((2,2-difluorobenzo [d][1,3]dioxol-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.940	493.2
379	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methylpyrimidin-5-yl)amino)phenyl)-4-methoxybutanoic acid		1.188	429.2
380	(S)-3-(3-((4-cyano-3-ethoxyphenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.528	468.1

Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
381	(S)-3-(3-((3-chloro-4-cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.627	472.0
382	(S)-3-(3-((5-cyano-6-methylpyridin-2-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.459	453.0
383	(S)-3-(3-((4-cyano-3-(trifluoromethyl)phenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)-4-methoxybutanoic acid		1.701	506.1
384	(S)-3-(3-((5-cyano-4-methylpyridin-2-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.451	453.1
385	(S)-3-(3-((4-carbamoylphenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.029	456.8

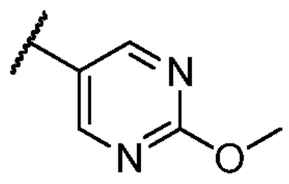
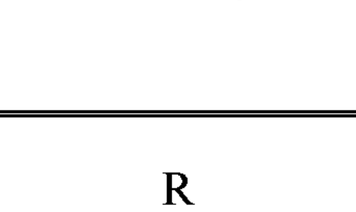
Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
386	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((4-(ethylsulfonyl)phenyl) amino)phenyl)-4-methoxybutanoic acid		1.390	505.1

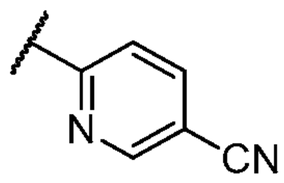
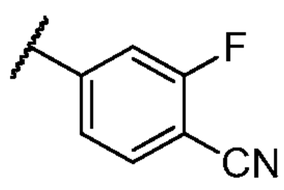
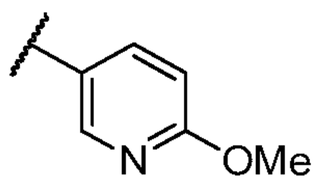
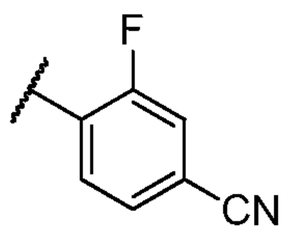
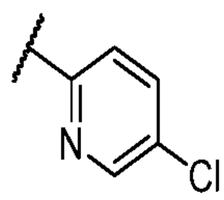
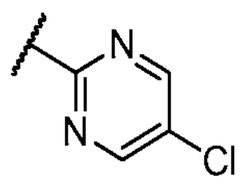
Examples 387 to 421

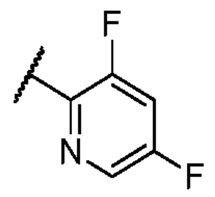
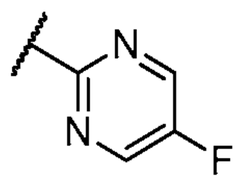
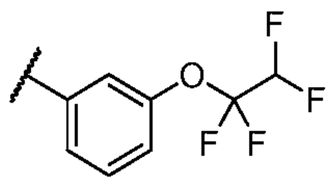
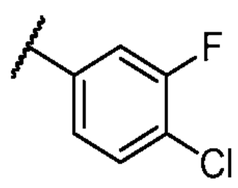
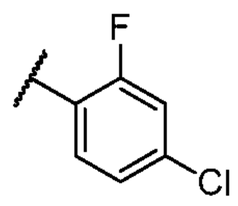
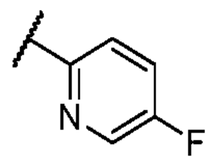
(Enantiomer 2)

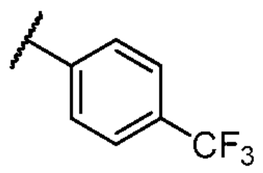
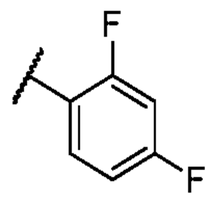
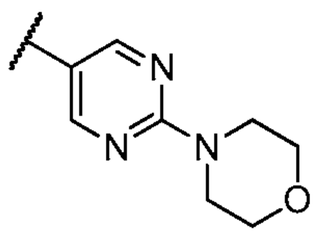
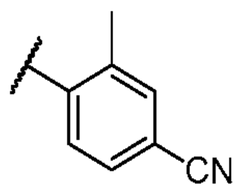
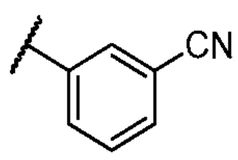
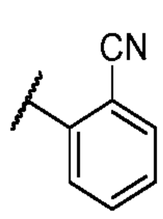


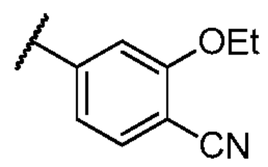
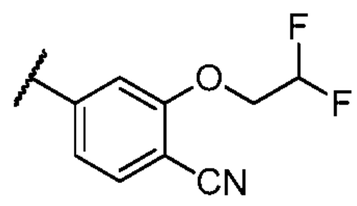
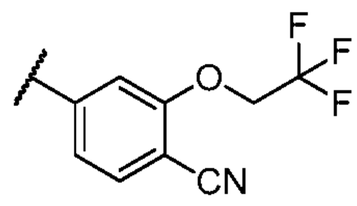
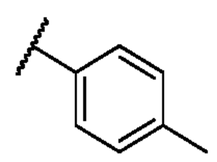
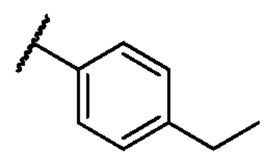
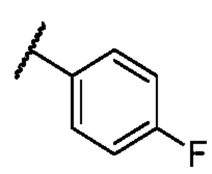
Examples 387 to 421 were prepared using 349B Enantiomer 2 and corresponding aryl bromides following the procedure described for the synthesis of Example 349.

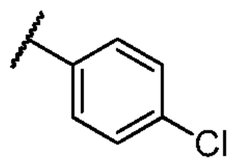
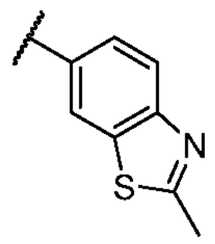
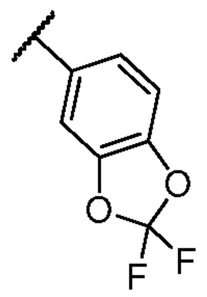
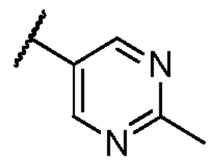
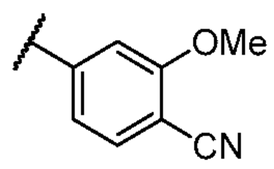
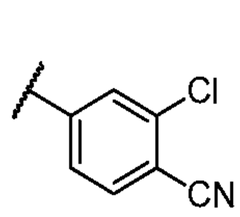
Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
387	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methoxypyrimidin-5-yl)amino)phenyl)-4-methoxybutanoic acid		1.300	445.2
388	(R)-3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.420	459.2

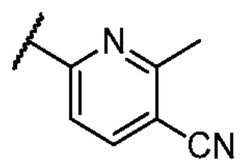
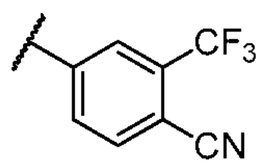
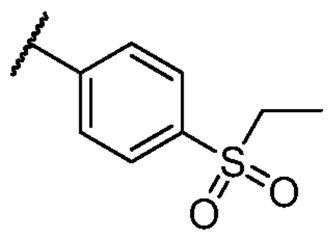
Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
389	(R)-3-(3-((5-cyanopyridin-2-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.422	439.2
390	(R)-3-(3-((4-cyano-3-fluorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.551	456.1
391	(R)-3-(3-((4-cyano-3-methylphenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.266	444.3
392	(R)-3-(3-((4-cyano-2-fluorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.622	456.1
393	(R)-3-(3-((5-chloropyridin-2-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.672	448.1
394	(R)-3-(3-((5-chloropyrimidin-2-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.567	449.1

Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
395	(R)-3-(3-((3,5-difluoropyridin-2-yl)amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.704	450.1
396	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((5-fluoropyrimidin-2-yl)amino) phenyl)-4-methoxybutanoic acid		1.212	433.3
397	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((3-(1,1,2,2-tetrafluoroethoxy) phenyl)amino)phenyl)-4-methoxybutanoic acid		1.994	529.1
398	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((3-(1,1,2,2-tetrafluoroethoxy) phenyl)amino)phenyl)-4-methoxybutanoic acid		1.913	465.0
399	(R)-3-(3-((4-chloro-2-fluorophenyl)amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.969	465.0
400	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((5-fluoropyridin-2-yl)amino) phenyl)-4-methoxybutanoic acid		1.470	432.1

Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
401	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((4-trifluoromethyl)phenyl)amino) phenyl)-4-methoxybutanoic acid		1.964	481.1
402	(R)-3-(3-((2,4-difluorophenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.580	449.3
403	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-(tetrahydro-2H-pyran-4-yl)pyrimidin-5-yl)amino) phenyl)-4-methoxybutanoic acid		1.248	500.4
404	(R)-3-(3-((4-cyano-2-methylphenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.682	452.1
405	(R)-3-(3-((3-cyanophenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.382	438.3
406	(R)-3-(3-((2-cyanophenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.362	438.3

Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
407	(R)-3-(3-((4-cyano-3-ethoxyphenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.454	482.4
408	(R)-3-(3-((4-cyano-3-(2,2-difluoroethoxy)phenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.445	518.4
409	(R)-3-(3-((4-cyano-3-(2,2,2-trifluoroethoxy)phenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.536	536.3
410	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(*p*-tolylamino)phenyl)-4-methoxybutanoic acid		1.602	427.3
411	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((4-ethylphenyl)amino)phenyl)-4-methoxybutanoic acid		1.739	441.4
412	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((4-fluorophenyl)amino)phenyl)-4-methoxybutanoic acid		1.478	431.3

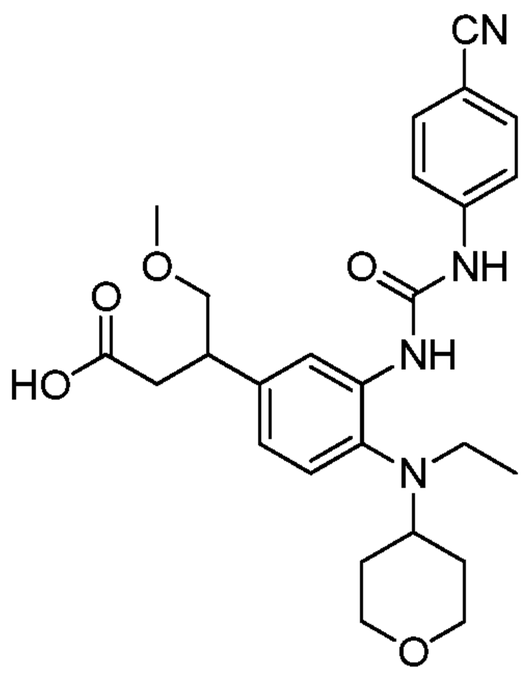
Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
413	(R)-3-(3-((4-chlorophenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.627	447.3
414	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methylbenzo[d]thiazol-6-yl)amino)phenyl)-4-methoxybutanoic acid		1.392	484.3
415	(R)-3-(3-((2,2-difluorobenzo [d][1,3]dioxol-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.724	493.3
416	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methylpyrimidin-5-yl)amino) phenyl)-4-methoxybutanoic acid		1.509	429.3
417	(R)-3-(3-((4-cyano-3-methoxyphenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.509	468.1
418	(R)-3-(3-((3-chloro-4-cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.627	472.0

Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
419	(R)-3-(3-((5-cyano-6-methylpyridin-2-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.466	453.0
420	(R)-3-(3-((4-cyano-3-(trifluoromethyl)phenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.710	506.1
421	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((4-(ethylsulfonyl)phenyl)amino) phenyl)-4-methoxybutanoic acid		1.404	505.1

Example 422

(Enantiomer 1 and Enantiomer 2)

3-(3-(3-(4-Cyanophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid



422A. Methyl (S)-3-(3-(3-(4-cyanophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)-4-methoxybutanoate

To a stirred solution of 349B Enantiomer 1 (100 mg, 0.285 mmol) in DCM (5 mL), was added 4-isocyanatobenzonitrile (49.4 mg, 0.342 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4 h. The solvent was removed under vacuum. The crude material was recrystallized from methanol to afford 422A (off-white solid, 104 mg, 0.210 mmol, 73.7% yield). LC-MS Anal. Calc'd. for $C_{27}H_{34}N_4O_5$ 494.253, found [M+H] 495.5, T_r = 1.33 min (Method AY).

Example 422 Enantiomer 1. (S)-3-(3-(3-(4-Cyanophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid

To a stirred solution of 422A (100 mg, 0.202 mmol) in MeOH (5 mL), water (5 mL) and THF (5 mL) was added LiOH (19.37 mg, 0.809 mmol). The resulting mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated and the aqueous solution was acidified with saturated citric acid solution (pH~4-5). The aqueous solution was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to afford a brown colored residue. The residue was purified via preparative LC-MS to afford Example 422 Enantiomer 1 (off-white solid, 73.7 mg, 0.149 mmol, 73.6% yield). LC-MS Anal. Calc'd. for $C_{26}H_{32}N_4O_5$ 480.237, found [M+H] 481.3, T_r = 1.253 min (Method O). ^{1}H NMR (400MHz, methanol-d_4) δ 8.16 (d, *J* = 1.60 Hz, 1H), 7.64-7.72 (m, 4H), 7.22 (d, *J* = 8.40 Hz, 1H), 6.97-7.00 (m, 1H), 3.91-3.94 (m, 2H), 3.58-3.61 (m, 2H), 3.33-3.43 (m, 6H), 3.05-3.10 (m, 3H), 2.75-2.76 (m, 1H), 2.59-2.60 (m, 1H), 1.79-1.82 (m, 2H), 1.51-1.54 (m, 2H), 0.90 (t, *J* = 7.20 Hz, 3H).

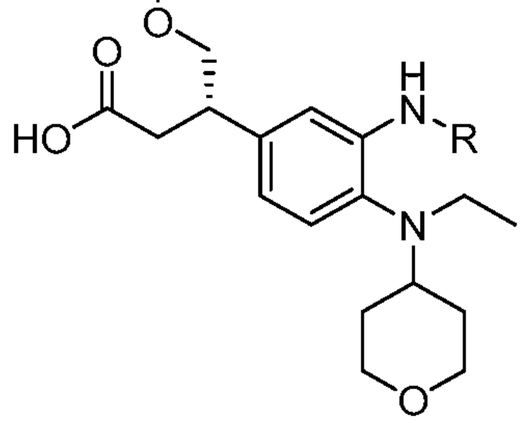
Example 422 Enantiomer 2. (R)-3-(3-(3-(4-Cyanophenyl) ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid

Example 422 Enantiomer 2 was prepared utilizing 349B Enantiomer 2 and 4-isocyanatobenzonitrile following the procedure described for the synthesis of Example 422 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{26}H_{32}N_4O_5$ 480.237, found [M+H] 481.3, T_r = 1.57 min (Method O). ^{1}H NMR (400MHz, CD_3OD) δ 8.16 (d, *J* = 1.60 Hz, 1H), 7.64-7.72 (m, 4H), 7.21 (d, *J* = 8.40 Hz, 1H), 6.95-7.00 (m, 1H), 3.91-3.93 (m, 2H), 3.59-3.62

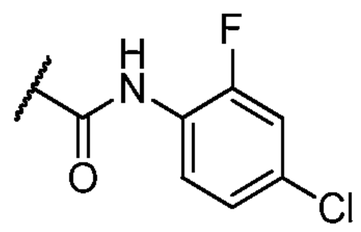
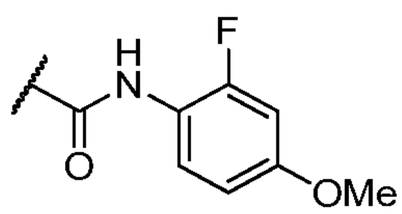
(m, 2H), 3.33-3.44 m, 6H), 3.05-3.10 (m, 3H), 2.71-2.76 (m, 1H), 2.53-2.59 (m, 1H), 1.79-1.82 (m, 2H), 1.51-1.54 (m, 2H), 0.90 (t, J = 7.20 Hz, 3H).

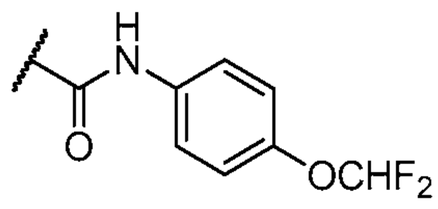
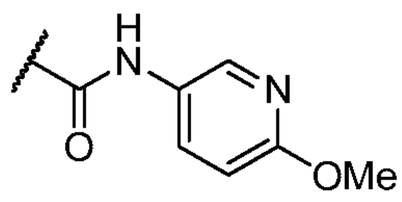
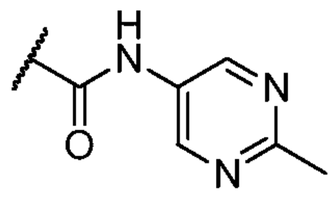
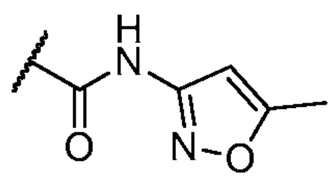
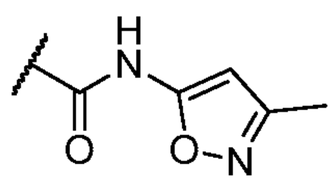
Examples 423 to 433

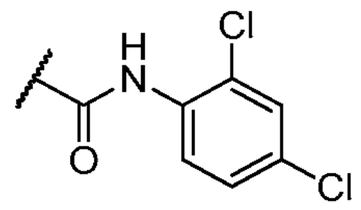
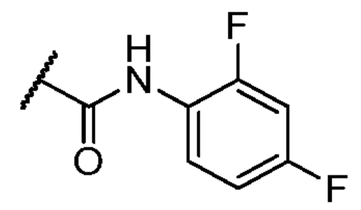
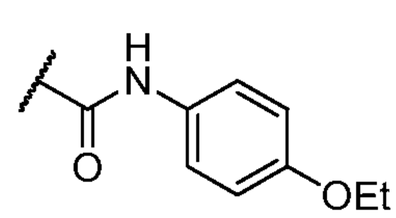
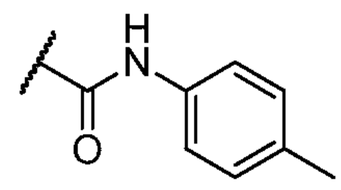
(Enantiomer 1)



Examples 423 to 433 were prepared from 349B Enantiomer 1 and the corresponding isocyanates following the procedure described for the synthesis of Example 422.

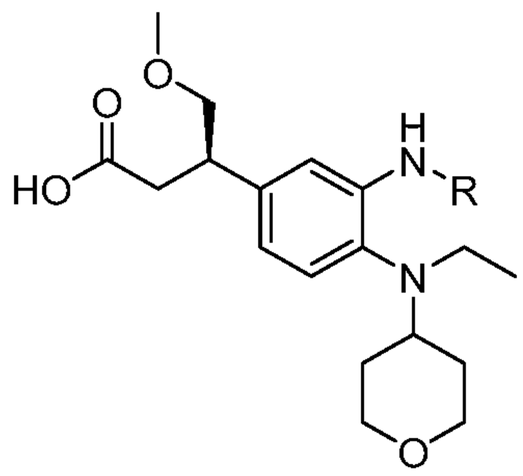
Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
423	(S)-3-(3-(3-(4-chloro-2-fluorophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)-4-methoxybutanoic acid		1.699	508.2
424	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(2-fluoro-4-methoxyphenyl)ureido) phenyl)-4-methoxybutanoic acid		1.457	504.3

Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
425	(S)-3-(3-(3-(4-(difluoromethoxy)phenyl) ureido)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.577	522.2
426	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(6-methoxypyridin-3-yl)ureido)phenyl)-4-methoxybutanoic acid		1.268	487.2
427	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(2-methylpyrimidin-5-yl)ureido)phenyl)-4-methoxybutanoic acid		1.1	472.3
428	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(5-methylisoxazol-3-yl)ureido)phenyl)-4-methoxybutanoic acid		1.104	461.3
429	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(3-methylisoxazol-5-yl)ureido)phenyl)-4-methoxybutanoic acid		1.281	461.3

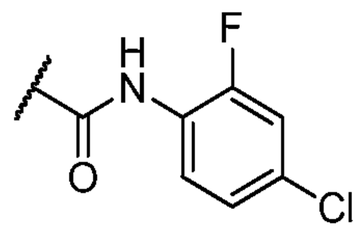
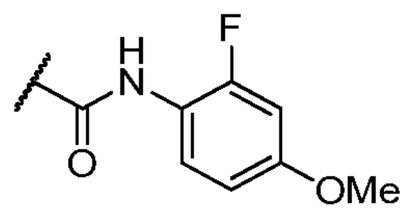
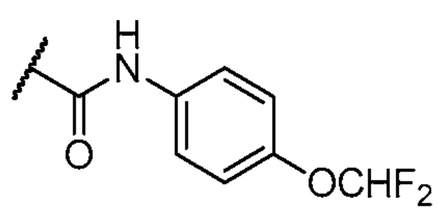
Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
430	(S)-3-(3-(3-(2,4-dichlorophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)-4-methoxybutanoic acid		1.721	524.1
431	(S)-3-(3-(3-(2,4-difluorophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)-4-methoxybutanoic acid		1.495	492.2
432	(S)-3-(3-(3-(4-ethoxyphenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)-4-methoxybutanoic acid		1.357	500.3
433	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido) phenyl)-4-methoxybutanoic acid		1.514	470.43

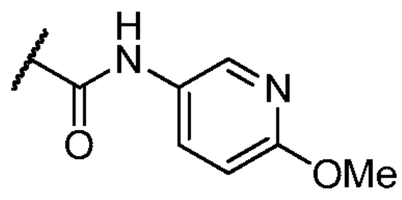
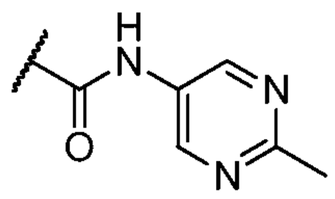
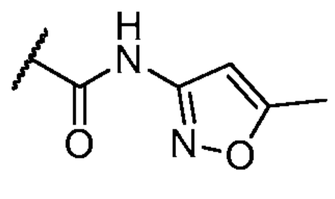
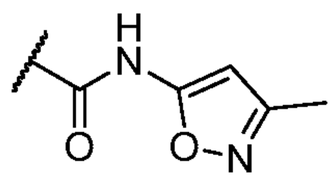
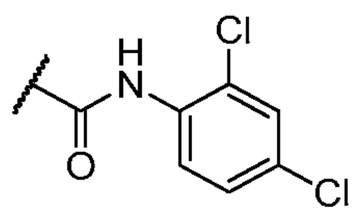
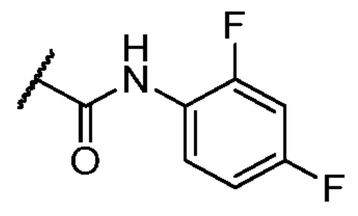
Examples 434 to 442

(Enantiomer 2)



Examples 434 to 442 were prepared using 349B Enantiomer 2 and the corresponding isocyanates following the procedure described for the synthesis of Example 422 (absolute stereochemistry not determined).

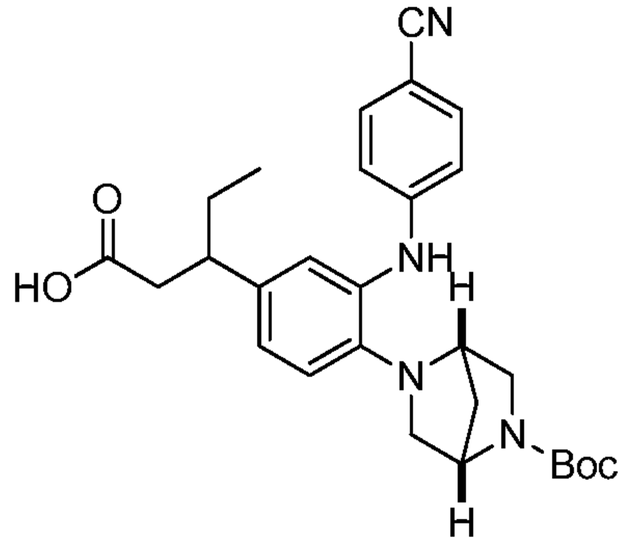
Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
434	(R)-3-(3-(3-(4-chloro-2-fluorophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.700	508.1
435	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(2-fluoro-4-methoxyphenyl)ureido) phenyl)-4-methoxybutanoic acid		1.224	504.4
436	(R)-3-(3-(3-(4-(difluoromethoxy) phenyl)ureido)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.343	522.3

Ex. No.	Name	R	T_r (min) (Method O)	$[M+H]^+$
437	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(6-methoxypyridin-3-yl)ureido)phenyl)-4-methoxybutanoic acid		1.067	487.3
438	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(2-methylpyrimidin-5-yl)ureido)phenyl)-4-methoxybutanoic acid		0.906	472.4
439	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(5-methylisoxazol-3-yl)ureido)phenyl)-4-methoxybutanoic acid		1.123	461.3
440	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(3-methylisoxazol-5-yl)ureido)phenyl)-4-methoxybutanoic acid		1.297	461.2
441	(R)-3-(3-(3-(2,4-dichlorophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.721	524.2
442	(R)-3-(3-(3-(2,4-difluorophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.493	492.2

Example 443

(Diastereomer 1 and Diastereomer 2)

3-(4-((1S,4S)-5-(*tert*-Butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-3-((4-cyanophenyl)amino)phenyl)pentanoic acid



443A. 2-(4-Fluoro-3-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

A stirred solution of 4-bromo-1-fluoro-2-nitrobenzene (10 g, 45.5 mmol), 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi(1,3,2-dioxaborolane) (16.16 g, 63.6 mmol), and potassium acetate (13.38 g, 136 mmol) in dioxane (100 mL), was purged with argon for 5 min. Then $PdCl_2$ (dppf)•CH_2Cl_2 Adduct (3.71 g, 4.55 mmol) was added to the reaction mixture under argon and the mixture was heated to 108 °C for 12 h. The reaction mixture was allowed to cool to room temperature and then filtered through CELITE® pad and subsequently washed with ethyl acetate (100 mL). The organic layers were washed with water (50 mL) and the aqueous layer was separated and extracted with ethyl acetate (2 × 100 mL). The combined the organic layers were washed with brine, dried over sodium sulfate, filtered and evaporated under reduced pressure to give the crude product as a brown colored residue. The residue was purified via flash silica gel column chromatography using 30% ethyl acetate in pet ether to afford 443A (light yellow solid, 10.4 g, 38.9 mmol, 86% yield). LC-MS Anal. Calc'd. for $C_{12}H_{15}BFNO_4$ 267.108, found $[M+NH_4]$ 285.2, T_r = 1.07 (Method AY).

443B. Methyl 3-(4-fluoro-3-nitrophenyl)pentanoate

To a stirred solution of 443A (5 g, 18.72 mmol) in dioxane (80 mL) and (E)-methyl pent-2-enoate (5.34 g, 46.8 mmol) was added NaOH (16.85 mL, 16.85 mmol). The reaction mixture was then purged with argon gas for 15 min followed by addition of

chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.462 g, 0.936 mmol) and then purged again with argon for 5 minutes. The reaction suspension was stirred at 50 °C for 6 h followed by cooling to room temperature. The reaction was then quenched with AcOH (0.965 mL, 16.85 mmol) and it was stirred for 5 minutes before it was partitioned between ethyl acetate (100 mL) and water (80 mL). The aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography using ethyl acetate in pet ether as an eluant to afford Racemate 443B (brown oil, 4.0 g, 15.74 mmol, 84% yield). LC-MS Anal. Calc'd. for $C_{12}H_{13}FNO_4$ 255.091, found [M+NH_4] 273.0, T_r = 2.751 (Method U).

Chiral separation of 443B racemic gave 443B Enantiomer 1 T_r = 8.991 min (Method CB) and 443B Enantiomer 2 T_r = 12.02 min (Method CB) as single enantiomers.

443B Enantiomer 1 (absolute stereochemistry not determined) (1.65 g, 6.23 mmol, 33.3% yield). LC-MS Anal. Calc'd. for $C_{12}H_{14}FNO_4$ 255.091, found [M+ NH_4] 273.2, T_r = 1.953 min (Method BB).

443B Enantiomer 2 (absolute stereochemistry not determined) (1.62 g, 5.99 mmol, 32.0% yield). LC-MS Anal. Calc'd. for $C_{12}H_{14}FNO_4$ 255.091 found [M+ NH_4] 273.2, T_r = 1.953 min (Method BB).

443C. (1S,4S)-*tert*-Butyl 5-(4-(1-methoxy-1-oxopentan-3-yl)-2-nitrophenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

A stirred solution of 443B Enantiomer 1 (1 g, 3.92 mmol), (1S,4S)-*tert*-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (0.932 g, 4.70 mmol) and DIPEA (2.053 mL, 11.75 mmol) in NMP (10 mL) was heated at 120 °C for 6 h. The mixture was allowed to cool to room temperature and was partitioned between MTBE (50 mL) and water (50 mL). The layers were separated and the organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude residue. The crude product was purified by silica gel column chromatography using ethyl acetate in pet ether as an eluant to afford 443C Diastereomer 1 (absolute and relative stereochemistry not confirmed, brown oil, 0.85 g, 1.961 mmol, 50.0% yield). LC-

MS Anal. Calc'd. for $C_{22}H_{31}N_3O_6$ 433.221, found [M+H] 434.5, T_r = 1.54 min (Method AY).

443D. (1S,4S)-*tert*-Butyl 5-(2-amino-4-(1-methoxy-1-oxopentan-3-yl)phenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

To a stirred solution of 443C Diastereomer 1 (0.8 g, 1.845 mmol) in ethanol (10 mL) was added water (0.5 mL) followed by ammonium chloride (494 mg, 9.23 mmol). The mixture was stirred for 5 min, and then treated with zinc powder (121 mg, 1.845 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h. The reaction mixture was then concentrated under reduced pressure to afford the crude product. The crude material was diluted with ethyl acetate (30 mL), washed with water (30 mL), brine (30 mL), dried over sodium sulfate, filtered and concentrated to afford the crude residue. The residue was purified by silica gel column chromatography using ethyl acetate in pet ether as an eluant to afford 443D Diastereomer 1 (absolute and relative stereochemistry not determined, brown oil, 600 mg, 1.487 mmol, 81% yield). LC-MS Anal. Calc'd. for $C_{22}H_{33}N_3O_4$ 403.515, found [M+H] 406.4, T_r = 3.019 min (Method U).

443E. (1S,4S)-*tert*-Butyl 5-(2-((4-cyanophenyl)amino)-4-(1-methoxy-1-oxopentan-3-yl)phenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

A mixture of 443D Diastereomer 1 (160 mg, 0.397 mmol), 4-bromobenzonitrile (144 mg, 0.793 mmol), Xantphos (92 mg, 0.159 mmol), Cs_2CO_3 (646 mg, 1.983 mmol) in 1,4-dioxane (5 mL) was purged with argon gas for 5 minutes. Then the bis(dibenzylideneacetone)palladium (22.80 mg, 0.040 mmol) was added and the argon gas was bubbled through the mixture for 5 additional minutes. The reaction mixture was sealed and heated in microwave at 120 °C for 2 h. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure to afford the residue. The residue was reconstituted in a mixture of ethyl acetate (20 mL) and water (20 mL). The organic layers were separated and the aqueous layers were extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography using ethyl acetate in pet ether as an eluant to afford 443E Diastereomer

1 (absolute and relative stereochemistry not determined, brown solid, 120 mg, 0.238 mmol, 60.0% yield). LC-MS Anal. Calc'd. for $C_{29}H_{36}N_4O_4$ 504.274, found [M+H] 505.3, T_r = 1.40 (Method AA).

Example 443 Diastereomer 1. 3-(4-((1S,4S)-5-(*tert*-Butoxycarbonyl)-2,5-diazabicyclo [2.2.1]heptan-2-yl)-3-((4-cyanophenyl)amino)phenyl)pentanoic acid

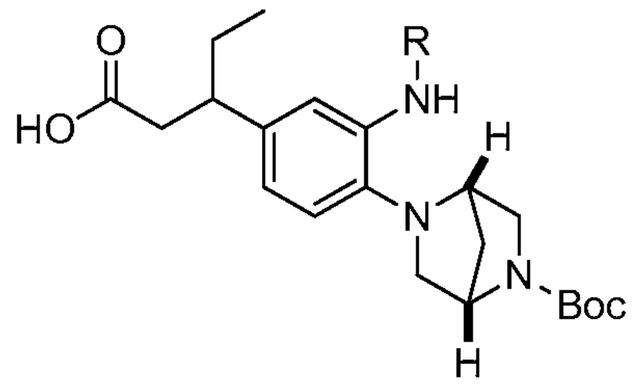
To a stirred solution of 443E Diastereomer 1 (50 mg, 0.099 mmol) in a mixture of MeOH (2 mL), THF (2 mL) and water (2 mL), was added LiOH (9.49 mg, 0.396 mmol). The resulting mixture was stirred at room temperature for 4 h. The reaction mixture was then concentrated and the aqueous solution was acidified with saturated citric acid solution (pH ~ 4-5). The aqueous layer was diluted with water (5 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the residue. The residue was purified by preparative LCMS to afford Example 443 Diastereomer 1 (absolute and relative stereochemistry not confirmed, off-white solid, 14.2 mg, 0.029, 29.2% yield). LC-MS Anal. Calc'd. for $C_{28}H_{34}N_4O_4$ 490.258, found [M+H] 491.1, T_r = 1.794 (Method O). ^{1}H NMR (400 MHz, CD_3OD) δ 7.42-7.44 (m, 2H), 6.99-7.02 (m, 2H), 6.86-6.88 (m, 1H), 6.66-6.68 (m, 2H), 4.32-4.34 (m, 2H), 3.28-3.52 (m, 3H), 2.88-3.02 (m, 2H), 2.48-2.63 (m, 2H), 1.80-1.83 (m, 2H), 1.57-1.60 (m, 2H), 1.41 (s, 9H), 0.89 (t, *J* = 7.2 Hz, 3H).

Example 443 Diastereomer 2. 3-(4-((1S,4S)-5-(*tert*-Butoxycarbonyl)-2,5-diazabicyclo [2.2.1]heptan-2-yl)-3-((4-cyanophenyl)amino)phenyl)pentanoic acid

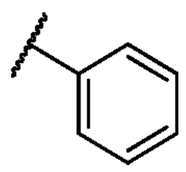
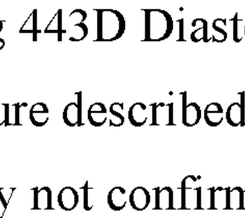
Example 443 Diastereomer 2 was prepared utilizing 443D Enantiomer 2 and 4-bromobenzonitrile following the procedure described for the synthesis of Example 443 Diastereomer 1 (absolute and relative stereochemistry not confirmed). LC-MS Anal. Calc'd. for $C_{28}H_{34}N_4O_4$ 490.258, found [M+H] 491.4, T_r = 1.594 (Method O). ^{1}H NMR (400 MHz, CD_3OD) δ 7.42-7.44 (m, 2H), 6.99-7.02 (m, 2H), 6.86-6.88 (m, 1H), 6.66-6.68 (m, 2H), 4.33-4.34 (m, 2H), 3.29-3.53 (m, 3H), 2.87-2.98 (m, 2H), 2.51-2.61 (m, 2H), 1.70-1.84 (m, 3H), 1.54-1.68 (m, 1H), 1.40-1.42 (m, 9H), 0.83 (t, *J*=7.20 Hz, 3H).

Examples 444 and 445

(Diastereomer 1)

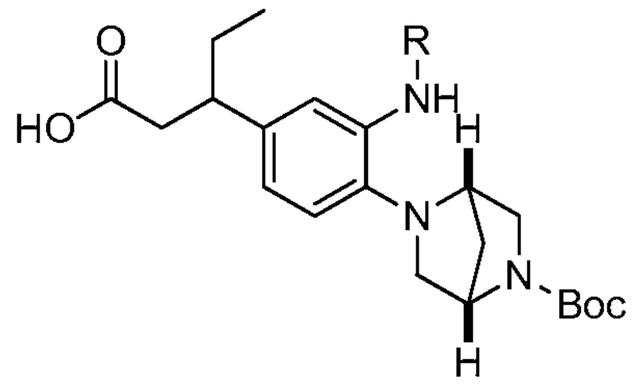


Examples 444 and 445 were prepared using 443D Diastereomer 1 and the corresponding aryl bromides following the procedure described for the synthesis of Example 443 (absolute and relative stereochemistry not confirmed).

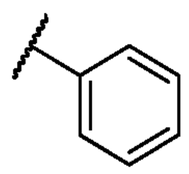
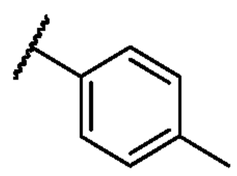
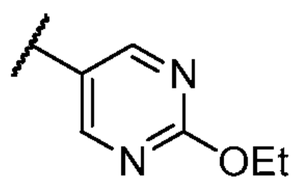
Ex. No.	Name	R	T_r (min)	$[M+H]^+$
444	3-(4-((1S,4S)-5-(*tert*-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-3-(phenylamino)phenyl)pentanoic acid		2.055 (Method O)	466.2
445	3-(4-((1S,4S)-5-(*tert*-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-3-(*p*-tolylamino)phenyl)pentanoic acid		2.202 (Method O)	480.2

Examples 446 to 448

(Diastereomer 2)



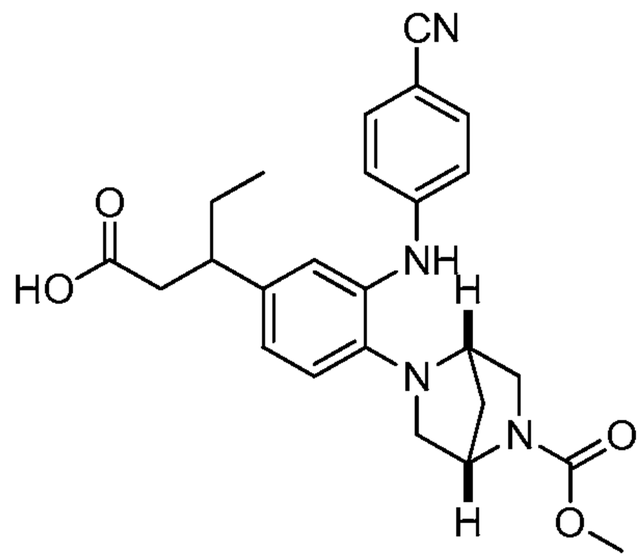
Examples 446 to 448 were prepared using the 443D Diastereomer 2 and corresponding aryl bromides following the procedure described for the synthesis of Example 443 (absolute and relative stereochemistry not confirmed).

Ex. No.	Name	R	T_r (min)	$[M+H]^+$
446	3-(4-((1S,4S)-5-(*tert*-butoxycarbonyl)-2,5-diazabicyclo [2.2.1]heptan-2-yl)-3-(phenylamino)phenyl)pentanoic acid		2.059 (Method O)	466.3
447	3-(4-((1S,4S)-5-(*tert*-butoxycarbonyl)-2,5-diazabicyclo [2.2.1]heptan-2-yl)-3-(*p*-tolylamino)phenyl)pentanoic acid		2.201 (Method O)	480.3
448	3-(4-((1S,4S)-5-(*tert*-butoxycarbonyl)-2,5-diazabicyclo [2.2.1]heptan-2-yl)-3-((2-ethoxypyrimidin-5-yl)amino) phenyl) pentanoic acid		1.866 (Method R)	512.4

Example 449

(Diastereomer 2)

3-(3-((4-Cyanophenyl)amino)-4-((1S,4S)-5-(methoxycarbonyl)-2,5-diazabicyclo [2.2.1]heptan-2-yl)phenyl)pentanoic acid



449A. Methyl 3-(4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-3-((4-cyanophenyl) amino)phenyl)pentanoate

A stirred solution of 443E Diastereomer 2 (150 mg, 0.297 mmol) in DCM (5 mL) was cooled at 0 °C. To this was added TFA (0.115 mL, 1.486 mmol) dropwise and stirred

at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure to get brown colored semi-solid. The solid compound was partitioned between saturated aqueous sodium bicarbonate solution (20 mL) and ethyl acetate (20 mL). The organic layers were separated out and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 449A Diastereomer 2 (brown solid, 90 mg, 0.222 mmol, 74.9%). LC-MS Anal. Calc'd. for $C_{24}H_{28}N_4O_2$ 404.221, found [M+H] 405.3, T_r = 1.00 (Method AA).

449B. (1S,4S)-Methyl 5-(2-((4-cyanophenyl)amino)-4-(1-methoxy-1-oxopentan-3-yl)phenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

A solution of 449A Diastereomer 2 (40 mg, 0.099 mmol), methyl carbonochloridate (14.02 mg, 0.148 mmol), DIPEA (0.052 mL, 0.297 mmol) in DCM (5 mL) was added DMAP (1.208 mg, 9.89 μmol). The resulting mixture was stirred at room temperature under nitrogen for 6 h. After evaporation of volatiles, the residue was diluted with DCM (10 mL), and washed with saturated $NaHCO_3$ (10 mL). The organic layers were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford the crude material. The crude residue was purified via silica gel flash chromatography using ethyl acetate in pet ether as an eluant to afford 449B Diastereomer 2 (absolute and relative stereochemistry not confirmed, brown solid, 38 mg, 0.082 mmol, 83% yield). LC-MS Anal. Calc'd. for $C_{26}H_{30}N_4O_4$ 462.227, found [M+H] 463.2, T_r = 3.038 (Method AD).

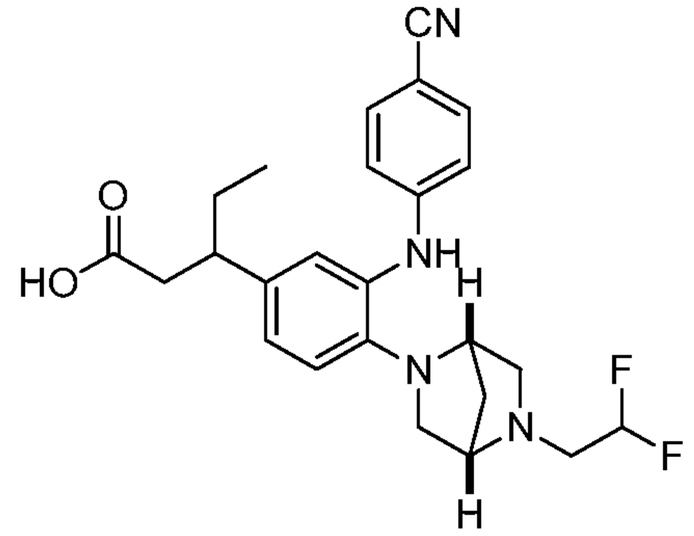
449 Diastereomer 2. 3-(3-((4-Cyanophenyl)amino)-4-((1S,4S)-5-(methoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)pentanoic acid

Example 449 Diastereomer 2 was prepared by using the 449B following the procedure described for the synthesis of Example 443 (absolute and relative stereochemistry not confirmed). LC-MS Anal. Calc'd. for $C_{25}H_{28}N_4O_4$ 448.211, found [M+H] 449.1, T_r = 1.517 (Method O). ^{1}H NMR (400 MHz, CD_3OD) δ 7.42-7.45 (m, 2H), 6.99-7.02 (m, 2H), 6.86-6.88 (m, 1H), 6.67-6.69 (m, 2H), 4.35-4.40 (m, 2H), 3.56-3.65 (m, 4H), 3.32-3.41 (m, 2H), 2.87-3.02 (m, 2H), 2.51-2.61 (m, 2H), 1.83-1.85 (m, 2H), 1.60-1.71 (m, 2H), 0.83 (t, *J* = 7.20 Hz, 3H).

Example 450

(Diastereomer 2)

3-(3-((4-Cyanophenyl)amino)-4-((1S,4S)-5-(2,2-difluoroethyl)-2,5-diazabicyclo [2.2.1]heptan-2-yl)phenyl)pentanoic acid



450A. Methyl 3-(3-((4-cyanophenyl)amino)-4-((1S,4S)-5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)pentanoate

A stirred solution of 449A Diastereomer 2 (40 mg, 0.099 mmol) in ACN (5 mL) was cooled at 0 °C and DIPEA (0.052 mL, 0.297 mmol) was added followed by 2,2-difluoroethyl trifluoromethane sulfonate (31.8 mg, 0.148 mmol). The reaction suspension was stirred at room temperature for 4 h. After evaporation of volatiles, the residue was diluted with ethyl acetate (20 mL), and washed with brine (10 ml), dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford the crude residue. The crude residue was purified via silica gel flash chromatography to afford 450A Diastereomer 2 (absolute and relative stereochemistry not confirmed, brown solid, 37 mg, 0.079 mmol, 80% yield). LC-MS Anal. Calc'd. for $C_{26}H_{30}F_2N_4O_2$ 468.234, found [M+H] 469.4, T_r = 3.77 (Method U).

Example 450 Diastereomer 2. 3-(3-((4-Cyanophenyl)amino)-4-((1S,4S)-5-(2,2-difluoroethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)pentanoic acid

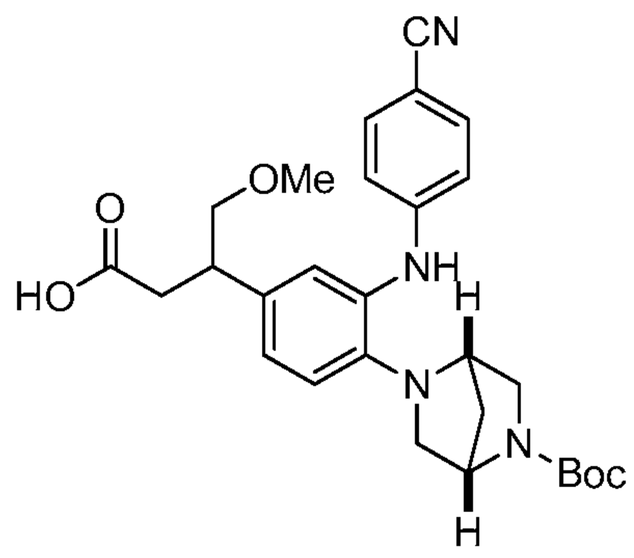
Example 450 Diastereomer 2 were prepared using 450A Diastereomer 2 following the procedure described for the synthesis of Example 449 (absolute and relative stereochemistry not confirmed). LC-MS Anal. Calc'd. for $C_{25}H_{28}F_2N_4O_2$ 454.218, found [M+H] 455.0, T_r = 1.632 (Method O). ^{1}H NMR (400 MHz, CD_3OD) δ 7.46-7.49 (m, 2H), 7.05-7.07 (m, 2H), 6.92-6.95 (m, 1H), 6.73-6.75 (m, 2H), 6.13-6.42 (m, 1H), 4.50 (s, 1H),

4.36 (s, 1H), 3.67-3.81 (m, 2H), 3.32-3.51 (m, 4H), 2.89-2.92 (m, 1H), 2.47-2.66 (m, 2H), 2.06-2.21 (m, 2H), 1.69-1.74 (m, 1H), 1.58-1.63 (m, 1H), 0.82 (t, J = 7.2 Hz, 3H).

Example 451

(Diastereomer 1 and Diastereomer 2)

3-(4-((1S,4S)-5-(*tert*-Butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-3-((4-cyanophenyl)amino)phenyl)-4-methoxybutanoic acid



451A. Methyl 3-(4-fluoro-3-nitrophenyl)-4-methoxybutanoate

451A was prepared using the 443A and (E)-methyl 4-methoxybut-2-enoate following the procedure described for the synthesis of 443B. LC-MS Anal. Calc'd. for $C_{12}H_{14}FNO_5$ 271.086, found [M+H] 272.0, T_r = 2.339 (Method U).

451B. (1S,4S)-*tert*-Butyl 5-(4-(1,4-dimethoxy-4-oxobutan-2-yl)-2-nitrophenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

451B was prepared using the 451A following the procedure described for the synthesis of 443C. LC-MS Anal. Calc'd. for $C_{22}H_{31}N_3O_7$ 449.216, found [M+H] 450.5, T_r = 1.34 (Method AY).

451C. (1S,4S)-*tert*-Butyl 5-(2-amino-4-(1,4-dimethoxy-4-oxobutan-2-yl)phenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

451C was prepared using the 451B following the procedure described for the synthesis of 443D. LC-MS Anal. Calc'd. for $C_{22}H_{33}N_3O_5$ 419.242, found [M+H] 420.4, T_r = 2.514 (Method U).

Separation of 451C diastereomeric mixture gave the 451C Diastereomer 1, T_r = 4.0 min (Method CC) and 451C Diastereomer 2, T_r = 5.0 min (Method CC) as single diastereomers.

451C Diastereomer 1 (absolute and relative stereochemistry not determined, brown solid, 0.25 g, 0.596 mmol, 32.7% yield). LC-MS Anal. Calc'd. for $C_{22}H_{33}N_3O_5$ 419.242, found [M+H] 420.5, T_r = 1.27 (Method AY).

451C Diastereomer 2 (absolute and relative stereochemistry not determined, brown solid, 0.26 g, 0.620 mmol, 34.0% yield). LC-MS Anal. Calc'd. for $C_{22}H_{33}N_3O_5$ 419.242, found [M+H] 420.5, T_r = 1.27 (Method AY).

451D. (1S,4S)-*tert*-Butyl 5-(2-((4-cyanophenyl)amino)-4-(1, 4-dimethoxy-4-oxobutan-2-yl)phenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

451D Diastereomer 1 was prepared using the 451C Diastereomer 1 and 4-bromobenzonitrile following the procedure described for the synthesis of 443E Diastereomer 1. LC-MS Anal. Calc'd. for $C_{29}H_{36}N_4O_5$ 520.269, found [M+H] 521.4, T_r = 1.44 (Method AY).

Example 451 Diastereomer 1. 3-(4-((1S,4S)-5-(*tert*-Butoxycarbonyl)-2,5-diazabicyclo [2.2.1]heptan-2-yl)-3-((4-cyanophenyl)amino)phenyl)-4-methoxybutanoic acid

Example 451 Diastereomer 1 were prepared using the 451D Diastereomer 1 following the procedure described for the synthesis of Example 443 Diastereomer 1 (absolute and relative stereochemistry not confirmed). LC-MS Anal. Calc'd. for $C_{28}H_{34}N_4O_5$ 506.253, found [M+H] 507.4, T_r = 1.392 (Method O). ^{1}H NMR (400 MHz, CD_3OD) δ 7.40-7.44 (m, 2H), 7.03-7.05 (m, 2H), 6.84-6.86 (m, 1H), 6.65-6.66 (m, 2H), 4.318 (s, 2H), 3.42-3.52 (m, 4H), 3.27-3.36 (m, 5H), 2.93-3.00 (m, 1H), 2.73-2.78 (m, 1H), 2.48-2.54 (m, 1H), 1.78-1.83 (m, 2H), 1.39 (s, 9H).

Example 451 Diastereomer 2. 3-(4-((1S,4S)-5-(*tert*-Butoxycarbonyl)-2,5-diazabicyclo [2.2.1]heptan-2-yl)-3-((4-cyanophenyl)amino)phenyl)-4-methoxybutanoic acid

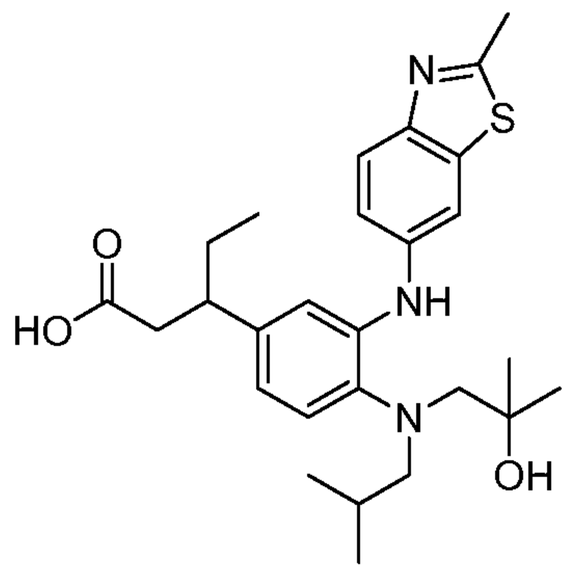
Example 451 Diastereomer 2 was prepared by using the 451C Diastereomer 2 and 4-bromobenzonitrile following the procedure described for the synthesis of Example 443 Diastereomer 1 (absolute and relative stereochemistry not confirmed). LC-MS Anal.

Calc'd. for $C_{28}H_{34}N_4O_5$ 506.253, found [M+H] 507.4, T_r = 1.379 (Method O). ^1H NMR (400 MHz, CD_3OD) δ 7.40-7.42 (m, 2H), 7.03-7.05 (m, 2H), 6.84-6.86 (m, 1H), 6.64-6.66 (m, 2H), 4.32 (s, 2H), 3.47-3.51 (m, 4H), 3.27-3.37 (m, 5H), 2.91-2.96 (m, 1H), 2.71-2.76 (m, 1H), 2.45-2.53 (m, 1H), 1.78-1.81 (m, 2H), 1.39 (s, 9H).

Example 452

(Racemate)

3-(4-((2-Hydroxy-2-methylpropyl)(isobutyl)amino)-3-((2-methylbenzo[d]thiazol-6-yl)amino)phenyl)pentanoic acid



452A. 1-(Isobutylamino)-2-methylpropan-2-ol

To a solution of 1-amino-2-methylpropan-2-ol (10 g, 112 mmol) in THF (50 mL) and MeOH (50 mL) was added isobutyraldehyde (8.90 g, 123 mmol), followed by 4Aº molecular sieves (3 g). The reaction was stirred at room temperature for 6 h. The reaction mixture was cooled to 0 ºC and $NaBH_4$ (12.73 g, 337 mmol) was added portionwise followed by stirring at RT for 2 h. The solvent was evaporated and the resultant residue was quenched with 10% $NaHCO_3$ solution (50 ml) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 452A (colorless oil, 11 g, 76 mmol, 67.5% yield). LC-MS Anal. Calc'd. for $C_8H_{19}NO$ 145.147, found [M+H] 146.4, T_r = 0.44 (Method AY).

452B. 1-((4-Bromo-2-nitrophenyl)(isobutyl)amino)-2-methylpropan-2-ol

To sealable reaction flask containing 4-bromo-1-fluoro-2-nitrobenzene (5 g, 22.73 mmol), was added 452A (3.96 g, 27.3 mmol), DIPEA (11.91 mL, 68.2 mmol) followed

by NMP (20 mL). The flask was sealed and the reaction was heated at 120 °C for 6 h. The reaction mixture was allowed to cool to room temperature and was partitioned between MTBE (50 mL) and water (50 mL). The layers were separated and the organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford a residue. The residue was purified by silica gel flash column chromatography using ethyl acetate in pet ether as an eluant to afford 452B (orange oil, 5.6 g, 16.22 mmol, 71.4% yield). LC-MS Anal. Calc'd. for $C_{14}H_{21}BrN_2O_3$ 344.074, found [M+H] 345.0, T_r =3.261 (Method U).

452C. (E)-Methyl 3-(4-((2-hydroxy-2-methylpropyl)(isobutyl)amino)-3-nitrophenyl)pent-2-enoate

A pressure tube equipped with Teflon cap, was charged with 452B (2 g, 5.79 mmol), (E)-methyl pent-2-enoate (1.984 g, 17.38 mmol), tetrabutylammonium bromide (0.934 g, 2.90 mmol) and dioxane (20 mL). Argon gas was bubbled through this mixture for 10 min and then dichloro-bis-(tri-o-tolylphosphine)palladium(II) (0.455 g, 0.579 mmol) was added at room temperature. Argon gas was bubbled through the mixture for another 5 min. The tube was crew-capped and heated at 110 °C for 14 h. The reaction mixture was allowed to cool to room temperature, filtered through pad of CELITE®. The CELITE® pad was washed with ethyl acetate (50 mL). The organic layers were washed with water (50 mL) and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford the crude residue. The residue was purified via silica gel flash column chromatography using ethyl acetate in pet ether to afford 452C (orange oil, 0.6 g, 1.585 mmol, 27.4% yield). LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_5$ 378.215, found [M+H] 379.6, T_r =1.19 (Method AA).

452D. Methyl 3-(3-amino-4-((2-hydroxy-2-ethylpropyl)(isobutyl)amino)phenyl) pentanoate

The solution of 452C (1 g, 2.64 mmol) in methanol (10 mL) was charged to a sealable hydrogen flask. The solution was sequentially evacuated and purged with nitrogen gas for 3 times. To this carefully added 10% palladium on carbon (0.562g, 0.528 mmol) under nitrogen atmosphere. The reaction mixture was stirred under hydrogen

atmosphere at room temperature for 12 h. The reaction mixture was filtered through a CELITE® pad and the residue on the pad was thoroughly rinsed with MeOH (3 × 20 mL). The combined filtrates were concentrated under reduced pressure to afford 452D (brown oil, 0.6 g, 7.712 mmol, 64.8% yield). LC-MS Anal. Calc'd. for $C_{20}H_{34}N_2O_3$ 350.257, found [M+H] 351.8, T_r = 1.15 min (Method AY).

452E. Methyl 3-(4-((2-hydroxy-2-methylpropyl)(isobutyl)amino)-3-((2-methylbenzo[d]thiazol-6-yl)amino)phenyl)pentanoate

A microwave tube equipped with Teflon cap was charged with 452D (100 mg, 0.285 mmol), 6-bromo-2-methylbenzo[d]thiazole (65.1 mg, 0.285 mmol), Xantphos (41.3 mg, 0.071 mmol), Cs_2CO_3 (93 mg, 0.285 mmol) and dioxane (5 mL). The resulting mixture was stirred at room temperature while argon gas was bubbled through the mixture for 5 min. Then bis(dibenzylideneacetone)palladium (16.41 mg, 0.029 mmol) was added and the argon gas was bubbled through the mixture for an additional 5 min. The reaction mixture was sealed and heated in microwave at 110 °C for 2 h. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure to afford the residue. The residue was reconstituted in a mixture of ethyl acetate (20 mL) and water (20 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography using ethyl acetate in pet ether as an eluant to afford 452E (brown solid, 80 mg, 0.161 mmol, 56.3% yield). LC-MS Anal. Calc'd. for $C_{28}H_{39}N_3O_3S$ 497.271, found [M+H] 498.2, T_r = 1.05 (Method AA).

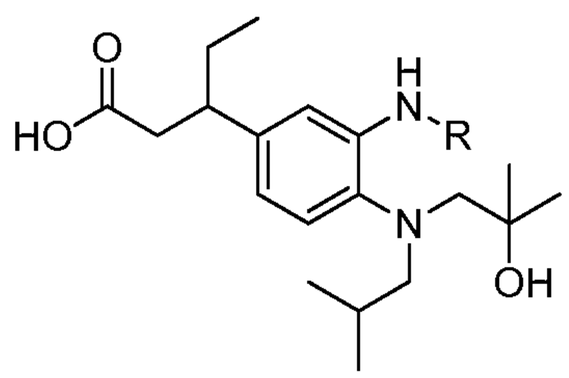
Example 452. 3-(4-((2-Hydroxy-2-methylpropyl)(isobutyl)amino)-3-((2-methylbenzo[d]thiazol-6-yl)amino)phenyl)pentanoic acid

To a stirred solution of 452E (80 mg, 0.161 mmol) in a mixture of MeOH (2 mL), THF (2 mL) and water (2 mL) was added LiOH (15.40 mg, 0.643 mmol). The resulting mixture was stirred at RT for 4 h. The reaction mixture was concentrated and the aqueous solution was acidified with saturated citric acid solution (pH ~ 4-5). The aqueous layer was diluted with water (5 mL) and extracted with ethyl acetate (2 × 10 mL). The

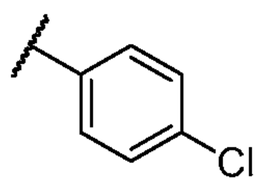
combined organic layers were washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the residue. The residue was purified by preparative LCMS to afford racemic Example 452 (off-white solid, 14.2 mg, 0.029 mmol, 18.26% yield). LC-MS Anal. Calc'd. for $C_{27}H_{37}N_3O_3S$ 483.256, found [M+H] 484.3, T_r = 2.168 (Method O). ^1H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 1H), 7.72-7.74 (m, 1H), 7.57-7.58 (m, 1H), 7.10-7.21 (m, 4H), 6.68-6.71 (m, 1H), 4.78 (s, 1H), 3.16-3.17 (m, 2H), 2.79-2.83 (m, 3H), 2.71 (s, 3H), 2.39-2.45 (m, 2H), 1.59-1.61 (m, 1H), 1.40-1.47 (m, 2H), 1.07-1.07 (m, 6H), 0.70-0.76 (m, 9H).

Example 453

(Racemate)



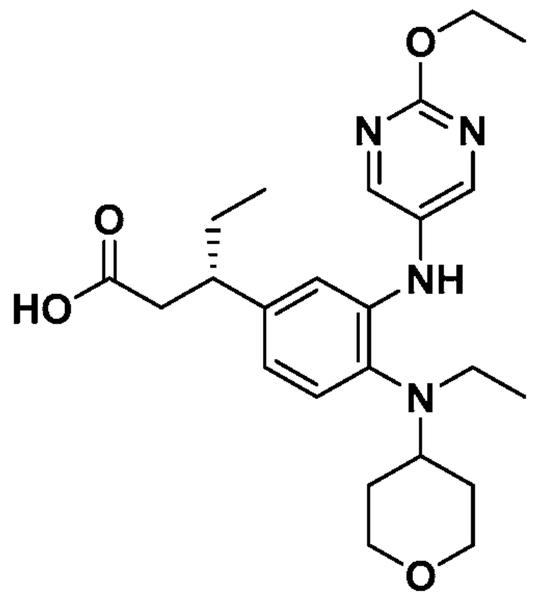
Example 453 was prepared using 452D and 1-bromo-4-chloro benzene following the procedure described for the synthesis of Example 452.

Ex. No.	Name	R	T_r (min)	$[M+H]^+$
453	3-(3-((4-chlorophenyl)amino)-4-((2-hydroxy-2-methylpropyl)(isobutyl)amino)phenyl)pentanoic acid		2.336 (Method O)	447.2

Example 455

(Enantiomer 1)

(S)-3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid



455A. N-Ethyltetrahydro-2H-pyran-4-amine

To a stirred solution MeOH (100 mL) and THF (50 mL) containing 10 g of powdered and activated 4 Å molecular sieves was added sequentially dihydro-2H-pyran-4(3H)-one (9.22 mL, 100 mmol), 2M ethanamine in THF (49.9 mL, 100 mmol) and the reaction mixture was stirred for 6 h at room temperature. The reaction mixture was then cooled to 0 °C, and $NaBH_4$ (11.34 g, 300 mmol) was added portionwise followed by stirring at room temperature for 6 h. The reaction mixture was then quenched with ice cold water (250 mL) and concentrated under reduced pressure to remove the volatiles. Then the aqueous solution was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under vacuum pressure to afford 455A (colorless liquid, 8 g, 61.9 mmol, 62.0% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.79-3.84 (m, 2H), 3.25-3.30 (m, 2H), 2.51-2.60 (m, 3H), 1.71-1.77 (m, 3H), 1.19-1.25 (m, 2H), 0.98-1.11 (m, 3H).

455B. N-(4-Bromo-2-nitrophenyl)-N-ethyltetrahydro-2H-pyran-4-amine

To a stirred solution of 4-bromo-1-fluoro-2-nitrobenzene (12 g, 54.5 mmol) in a sure seal bottle was added 455A (8.46 g, 65.5 mmol) followed by NMP (25 mL). The reaction mixture was sealed and heated at 120 °C for 16 h. The reaction mixture was then cooled to room temperature, diluted with water (200 mL) and extracted with ethyl acetate (2 × 200 mL). The combined organic layers were combined and washed with brine solution (1 × 75 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give the crude product. The crude material was purified via silica gel flash chromatography gave 455B (pale orange solid, 10 g, 30.4 mmol, 55.7% yield). LCMS Anal. Calc'd. $C_{13}H_{17}BrN_2O_3$ 329.2, found [M+2H] 331.2, T_r = 2.9 min (Method N).

455C. N-(4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-2-nitrophenyl)-N-ethyltetrahydro-2H-pyran-4-amine

A mixture of 455B (9 g, 27.3 mmol), bis(neopentyl glycolato)diboron (8.03 g, 35.5 mmol) and potassium acetate (8.05 g, 82 mmol) in DMSO (90 mL), at room temperature in a sealable flask, was purged with argon for 20 minutes. Then $PdCl_2$ (dppf)•CH_2Cl_2 Adduct (0.670 g, 0.820 mmol) was added and the flask was sealed and the reaction heated at 80 °C for 6 h. Then the reaction mixture was cooled to room temperature and poured into water (250 mL), extracted with EtOAc (2 × 150 mL). The combined organic layers were washed with brine (1 × 150 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified via silica gel flash chromatography gave 455C (pale orange liquid, 9 g, 24.85 mmol, 91% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.78-7.81 (m, 1H), 7.41 (d, J = 8.00 Hz, 1H), 3.83-3.86 (m, 2H), 3.76 (s, 4H), 3.19-3.27 (m, 3H), 3.11-3.17 (m, 2H), 1.58-1.63 (m, 4H), 0.96 (s, 6H), 0.88-0.85 (m, 3H).

455D. Methyl (S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)pentanoate (Enantiomer 1)

1,4-Dioxane (50 mL) was purged with argon for 10 minutes, then chlorobis (ethylene)rhodium(I)dimer (0.064 g, 0.166 mmol) and R-BINAP (0.151 g, 0.243 mmol) were added followed by purging with argon for 5 minutes. To the above reaction mixture was added 455C (4 g, 11.04 mmol), E-methyl pent-2-enoate (4.11 mL, 33.1 mmol), sodium hydroxide (9.94 mL, 9.94 mmol) and the mixture purged with argon for another 5 minutes. The reaction mixture was heated at 50 °C with stirring for 3 h. The reaction mixture was then cooled to room temperature and quenched with acetic acid (0.569 mL, 9.94 mmol) followed by partitioning between ethyl acetate (125 mL) and water (125 mL). The aqueous layer was extracted with ethyl acetate (100 mL) and the combined organic layers were washed with brine (75 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give the crude product. Purification via silica gel flash chromatography gave 455D (pale orange solid, 2.35 g, 6.33 mmol, 57.3%). LC-MS Anal. Calc'd. for $C_{19}H_{28}N_2O_5$ 364.4, found [M+H] 365.2, T_r = 3.2 min (Method N).

455E. Methyl (S)-3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoate

A solution of 455D (10.2 g, 28.0 mmol) in ethyl acetate (150 mL) was charged to a sealable hydrogen flask. The flask was sequentially evacuated and purged with nitrogen gas. 10% palladium on carbon (1.02 g, 0.958 mmol) was then added under nitrogen atmosphere. The reaction mixture was stirred under a 40 psi hydrogen atmosphere at room temperature for 4 h. The reaction mixture was then filtered through a CELITE® pad and the residue on the pad was thoroughly rinsed with MeOH (3 × 15 mL). The combined filtrate was concentrated under reduced pressure. The enantiomeric mixture (90:10) were resolved via preparative SFC (Method AF) to yield 455E Enantiomer 1 (RT=3.39) as a the major product. The fractions were collected and concentrated under reduced pressure to afford 455E (pale red liquid, 6.75 g, 20.2 mmol, 72%). LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_3$ 334.4, found [M+H] 335.4, T_r = 2.9 min (Method N).

455F. Methyl (S)-3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

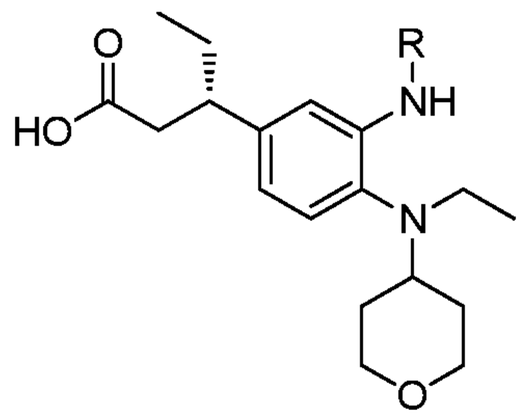
To a stirred solution of 455E (60 mg, 0.179 mmol) in 1,4-dioxane (4 mL) was added 5-bromo-2-ethoxypyrimidine (364 mg, 1.794 mmol) and cesium carbonate (731 mg, 2.242 mmol) and the mixture purged with argon for 10 min. To the above reaction mixture was added 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (87 mg, 0.149 mmol), bis(dibenzylideneacetone)palladium (43.0 mg, 0.075 mmol) followed by purging with argon for another 10 min. Then the reaction temperature was raised to 110 °C and the mixture stirred for 3 h. The reaction mixture was then cooled to room temperature, concentrated to dryness and diluted with ethyl acetate (15 mL). The organic layer was washed with water (1 × 10 mL), brine (1 × 10 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure to afford the crude residue. The crude material was purified by flash silica column chromatography using 0-40% EtOAc in pet ether as an eluent to afford 455F (pale yellow liquid, 40 mg, 0.081 mmol, 45.4% yield). LC-MS Anal. Calc'd. for $C_{25}H_{36}N_4O_4$ 456.5, found [M+H] 457.3, T_r = 3.9 min (Method N).

Example 455 Enantiomer 1. (S)-3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid

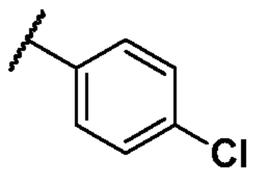
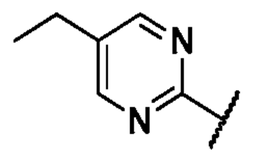
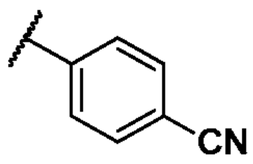
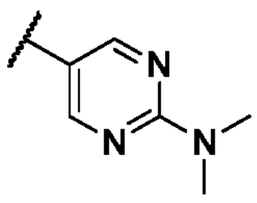
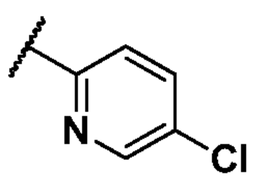
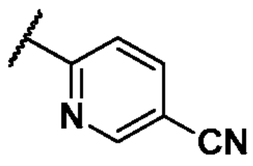
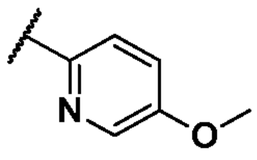
To a stirred solution of 455F (40 mg, 0.088 mmol) in a mixture of THF (1 mL), MeOH (1 mL) and H_2O (0.5 mL) was added LiOH (16.78 mg, 0.701 mmol). The resulting mixture was stirred at room temperature for 12 h. The reaction mixture was then concentrated and the resulting residue was diluted with water (15 mL), acidified with saturated citric acid solution and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified via preparative LC/MS to give Example 455 Enantiomer 1 (pale yellow solid, 25 mg, 0.056 mmol 63.8%). Absolute stereochemistry was assigned based on the expected enantiomer produced in the conjugate addition using (R)-BINAP to prepare 455D. LC-MS Anal. Calc'd. for $C_{24}H_{34}N_4O_4$ 442.5, found [M+H] 443.6, T_r = 2.11 min. (Method N). ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (s, 2H), 7.17 (d, *J* = 8.00 Hz, 1H), 6.84 (d, *J* = 1.20 Hz, 1H), 6.74 (d, *J* = 8.00 Hz, 1H), 4.38-4.43 (m, 2H), 3.90 (dd, *J* = 10.80, 3.00 Hz, 2H), 3.36-3.38 (m, 2H), 3.04-3.09 (m, 3H), 2.86 (s, 1H), 2.57-2.62 (m, 1H), 2.47-2.51 (m, 1H), 1.77-1.80 (m, 2H), 1.67-1.69 (m, 1H), 1.54-1.55 (m, 3H), 1.39-1.43 (m, 3H), 0.91 (t, *J* = 7.20 Hz, 3H), 0.80 (t, *J* = 7.20 Hz, 3H).

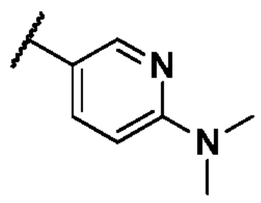
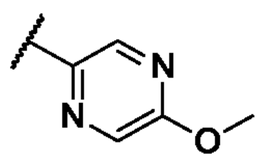
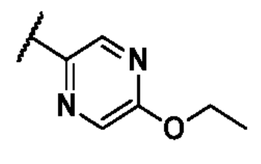
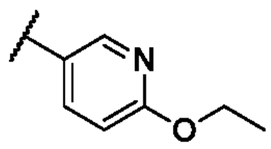
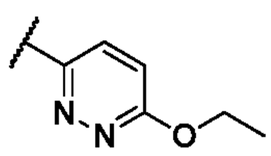
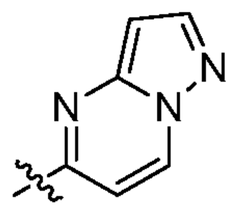
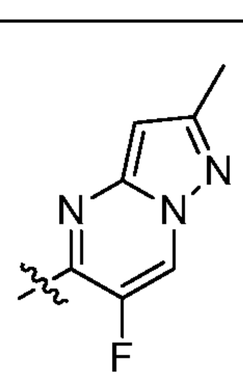
Examples 456 to 486

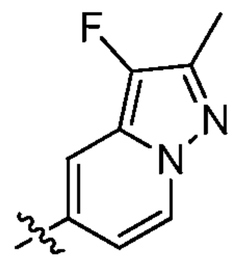
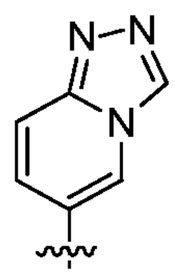
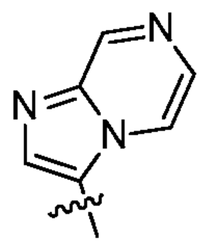
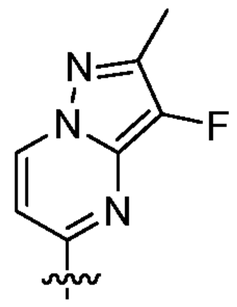
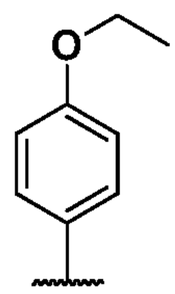
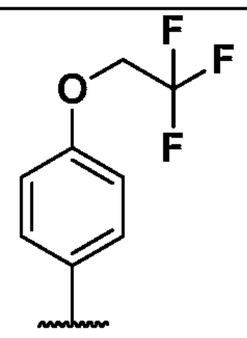
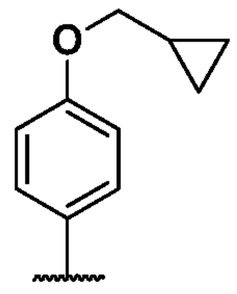
(Enantiomer 1)

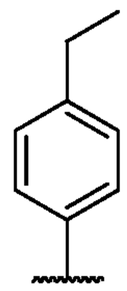
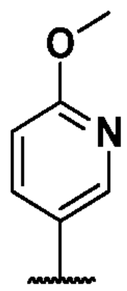
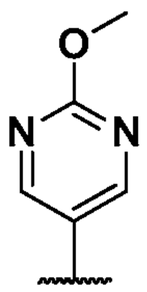
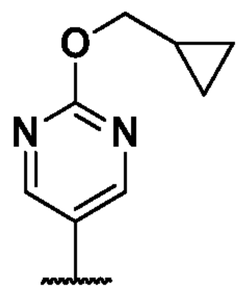
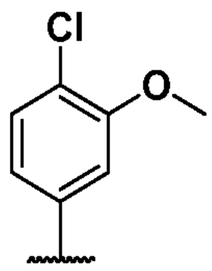
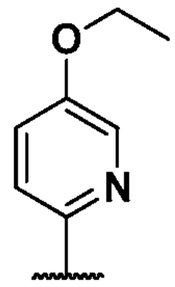
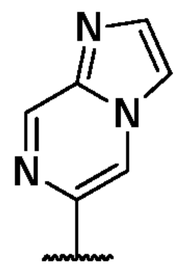


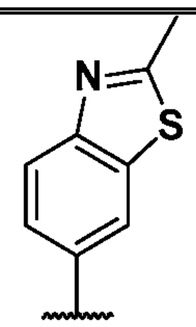
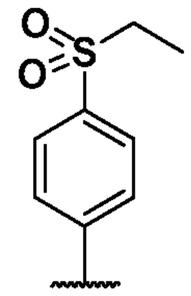
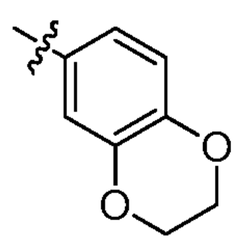
Examples 456 to 486 were prepared using 455E and corresponding aryl halides following the procedure described for the synthesis of Example 455 Enantiomer 1. Absolute stereochemistry was assigned based on the expected enantiomer produced in the conjugate addition using (R)-BINAP to prepare 455D.

Ex. No.	Name	R	T_r min	Method	(M+H)
456	(S)-3-(3-((4-chlorophenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.77	O	431.2
457	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((5-ethylpyrimidin-2-yl)amino) phenyl)pentanoic acid		1.30	R	427.3
458	(S)-3-(3-((4-cyanophenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.81	O	422.1
459	(S)-3-(3-((2-(dimethylamino) pyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.78	O	442.1
460	(S)-3-(3-((5-chloropyridin-2-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.98	O	432.1
461	(S)-3-(3-((5-cyanopyridin-2-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.69	O	423.1
462	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((5-methoxypyridin-2-yl)amino) phenyl)pentanoic acid		1.72	O	428.1

Ex. No.	Name	R	T_r min	Method	(M+H)
463	(S)-3-(3-((6-(dimethylamino) pyridine-3-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.84	O	441.1
464	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((5-methoxypyrazin-2-yl)amino) phenyl)pentanoic acid		1.72	O	429.1
465	(S)-3-(3-((5-ethoxypyrazin-2-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.88	O	443.1
466	(S)-3-(3-((6-ethoxypyridin-3-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.93	O	442.1
467	(S)-3-(3-((6-ethoxypyridazin-3-yl)amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl) amino)phenyl)pentanoic acid		1.68	O	443.1
468	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(pyrazolo [1,5-a]pyrimidin-5-ylamino) phenyl)pentanoic acid		1.59	O	438
469	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((6-fluoro-2-methylpyrazolo[1,5-a] pyrimidin-5-yl)amino)phenyl) pentanoic acid		1.74	O	470

Ex. No.	Name	R	T_r min	Method	(M+H)
470	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((3-fluoro-2-methylpyrazolo[1,5-a]pyridine-5-yl)amino)phenyl) pentanoic acid		1.84	O	469
471	(S)-3-(3-([1,2,4]triazolo[4,3-a]pyridine-6-ylamino)-4-(ethyl (tetrahydro-2H-pyran-4-yl) amino)phenyl)pentanoic acid		1.36	O	438
472	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(imidazo [1,2-a]pyrazin-3-ylamino) phenyl)pentanoic acid		1.37	O	438
473	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((3-fluoro-2-methylpyrazolo[1,5-a]pyrimidin-5-yl)amino)phenyl) pentanoic acid		1.52	O	470
474	(S)-3-(3-((4-ethoxyphenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.355	R	441.4
475	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((4-(2,2,2-trifluoroethoxy)phenyl) amino)phenyl)pentanoic acid		1.979	O	495.4
476	(S)-3-(3-((4-(cyclopropylmethoxy)phenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.501	R	467.4

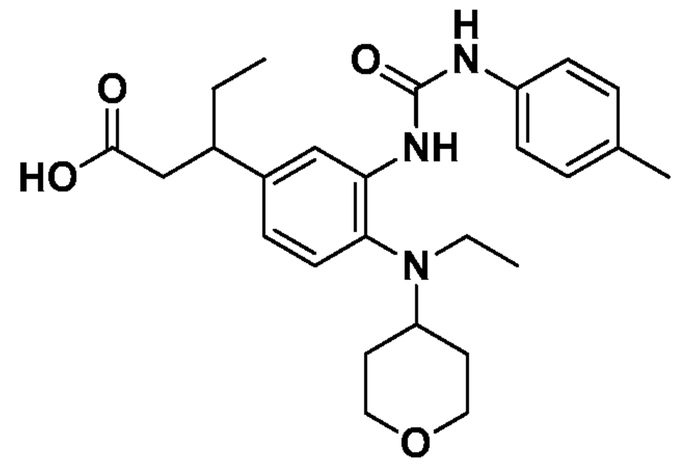
Ex. No.	Name	R	T_r min	Method	(M+H)
477	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((4-ethylphenyl)amino)phenyl) pentanoic acid		1.488	R	425.4
478	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((6-methoxypyridin-3-yl)amino) phenyl)pentanoic acid		1.776	O	428.2
479	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methoxypyrimidin-5-yl)amino) phenyl)pentanoic acid		1.326	R	429.3
480	(S)-3-(3-((2-(cyclopropylmethoxy) pyrimidin-5-yl)amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl) amino)phenyl)pentanoic acid		1.661	R	469.3
481	(S)-3-(3-((4-chloro-3-methoxyphenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.706	R	461.3
482	(S)-3-(3-((5-ethoxypyridin-2-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.894	O	442.2
483	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(imidazo [1,2-a]pyrazin-6-ylamino) phenyl)pentanoic acid		1.098	O	438.3

Ex. No.	Name	R	T_r min	Method	(M+H)
484	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methylbenzo[d]thiazol-6-yl) amino)phenyl)pentanoic acid		1.650	O	468.3
485	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((4-(ethylsulfonyl)phenyl)amino) phenyl)pentanoic acid		1.637	O	489.1
486	(S)-3-(3-((2,3-dihydrobenzo[b] [1,4]dioxin-6-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.75	O	455

Example 487

(Enantiomer 1 and Enantiomer 2)

3-(4-(Ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoic acid



487A. Methyl 3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)pentanoate (Racemate)

1,4-Dioxane (10 mL) was purged with argon for 10 minutes, then chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.116 g, 0.235 mmol) was added and purging continued with argon for 5 minutes. 455C (1.7 g, 4.69 mmol), E-methyl pent-2-enoate (1.53 mL, 14.08 mmol) and sodium hydroxide (4.28 mL, 4.28 mmol) were added and the mixture purged argon for another 5 minutes. The reaction mixture was then heated at 50

°C and stirred for 3 h followed by cooling to room temperature. The reaction was then quenched with acetic acid (0.242 mL, 4.22 mmol) before it was partitioned between ethyl acetate (50 mL) and water (50 mL). Aqueous layer was extracted with ethyl acetate (100 mL) and the combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification via flash chromatography gave 487A (pale orange liquid, 1 g, 2.74 mmol, 58.5%). LC-MS Anal. Calc'd. for $C_{19}H_{28}N_2O_5$ 364.4, found [M+H] 365.2, T_r = 3.05 min (Method N).

487B. Methyl 3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

Compound 487B was prepared using compound 487A following the procedure described for the synthesis of 455E. LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_3$ 334.4, found [M+H] 335.2, T_r = 2.90 min. (Method N).

487C. Methyl 3-(3-(3-(4-chloro-2-fluorophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

To a stirred solution of 487B (60 mg, 0.179 mmol) in THF (1.5 mL) was added 1-isocyanato-4-methylbenzene (28.7 mg, 0.215 mmol) under nitrogen. The reaction was stirred at room temperature for 3 h followed by concentration under reduced pressure to give 487C (pale yellow liquid, 63.8 mg, 0.136 mmol, 76%). LC-MS Anal. Calc'd. for $C_{27}H_{37}N_3O_4$ 467.6, found [M+H] 468.2, T_r = 3.4 min. (Method U).

Example 487 Enantiomer 1 and Enantiomer 2. 3-(4-(Ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoic acid

Example 487 was prepared using compound 487C (racemate) following the hydrolysis procedure described for the synthesis of Example 455. LC-MS Anal. Calc'd. for $C_{26}H_{35}N_3O_4$ 453.2, found [M+H] 454.3, T_r = 2.06 min. (Method N).

Chiral separation of racemate Example 487 gave 487 Enantiomer 1 and 487 Enantiomer 2 (Method BM). Enantiomer 1 T_r = 2.41 min, Enantiomer 2 T_r = 3.66 min (Method BM).

Example 487 Enantiomer 1 (absolute stereochemistry not determined). LC-MS Anal. Calc'd. for $C_{26}H_{35}N_3O_4$ 453.2, found [M+H] 454.3, T_r = 1.54 min. (Method N). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.08 (d, *J* = 2.00 Hz, 1H), 7.37 (d, *J* = 8.4

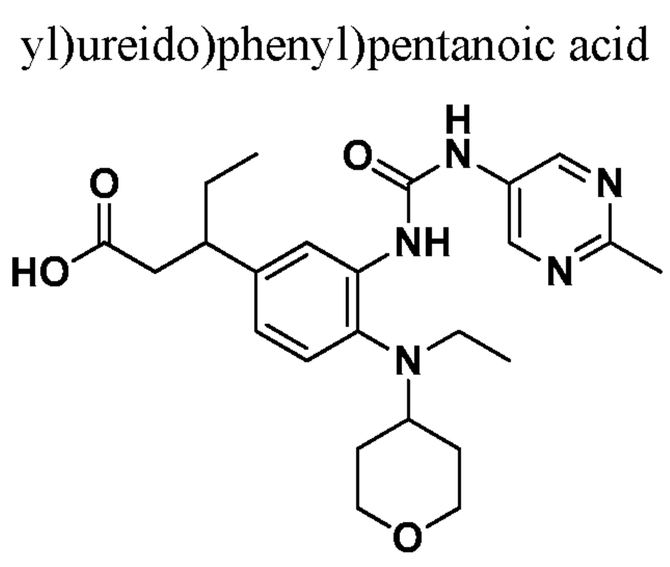
Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.78 (dd, *J* = 8.0, 2.00 Hz, 1H), 3.81 (d, *J* = 2.80 Hz, 2H), 3.28-3.43 (m, 3H), 3.20-3.26 (m, 3H), 2.97 (d, *J* = 7.20 Hz, 3H), 2.67-2.71 (m, 1H), 2.39-2.41 (m, 1H), 2.24 (s, 3H), 1.64-1.71 (m, 2H), 1.36-1.40 (m, 2H), 0.78 (t, *J* = 7.2 Hz, 3H), 0.69-0.71 (t, *J* = 7.2 Hz, 3H).

Example 487 Enantiomer 2 (absolute stereochemistry not determined). LC-MS Anal. Calc'd. for $C_{26}H_{35}N_3O_4$ 453.2, found [M+H] 454.3, T_r = 1.54 min. (Method N). ^1H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.08 (d, *J* = 2.00 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.78 (dd, *J* = 8.0, 2.00 Hz, 1H), 3.81 (d, *J* = 2.80 Hz, 2H), 3.28-3.43 (m, 3H), 3.20-3.26 (m, 3H), 2.97 (d, *J* = 7.20 Hz, 3H), 2.67-2.71 (m, 1H), 2.39-2.41 (m, 1H), 2.24 (s, 3H), 1.64-1.71 (m, 2H), 1.36-1.40 (m, 2H), 0.78 (t, *J* = 7.2 Hz, 3H), 0.69-0.71 (t, *J* = 7.2 Hz, 3H).

Example 488

(Enantiomer 1 and Enantiomer 2)

3-(4-(Ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(2-methylpyrimidin-5-yl)ureido)phenyl)pentanoic acid



488A. Methyl 3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(((4-nitrophenoxy)carbonyl)amino)phenyl)pentanoate

To a stirred solution of 487B (120 mg, 0.359 mmol) in THF (6 mL) was added 4-nitrophenyl carbonochloridate (72.3 mg, 0.359 mmol). The reaction was stirred at room temperature for 2 h. The reaction mixture was then concentrated and the residue was partitioned between ethyl acetate (2 × 50 mL) and water (50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure gave 488A. LC-MS Anal. Calc'd. for $C_{26}H_{33}N_3O_7$ 499.5 found [M+H] 500.6, T_r = 1.08 min. (Method AA).

488B. Methyl 3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(2-methylpyrimidin-5-yl)ureido)phenyl)pentanoate

To a solution of 488A (140 mg, 0.280 mmol) in THF (6 mL) was added pyridine (0.057 mL, 0.701 mmol) and a catalytic amount of DMAP (3.42 mg, 0.028 mmol). To the above reaction mixture 2-methylpyrimidin-5-amine (36.7 mg, 0.336 mmol) was added and stirred at 60 °C for 4 h. The reaction mixture was concentrated and the residue was portioned between ethyl acetate (2 × 50 mL) and water (50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash silica column chromatography using 0-40% EtOAc in pet ether as an eluent to afford 488B (pale yellow liquid, 100 mg, 0.213 mmol, 76% yield). LC-MS Anal. Calc'd. for $C_{25}H_{35}N_5O_4$ 469.5, found [M+H] 470.2, T_r = 2.59 min (Method N).

Example 488 Enantiomer 1 and Enantiomer 2. 3-(4-(Ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(2-methylpyrimidin-5-yl)ureido)phenyl)pentanoic acid

Example 488 was prepared using compound 488B (racemate) following the hydrolysis procedure described for the synthesis of Example 455. LC-MS Anal. Calc'd. for $C_{24}H_{33}N_5O_4$ 455.5, found [M+H] 456.3, T_r = 1.16 min. (Method O).

Chiral separation of Example 488 racemate gave Example 488 Enantiomer 1 and Example 488 Enantiomer 2 (Method CN). Enantiomer 1 T_r = 7.4 min, Enantiomer 2 T_r = 9.1 min (Method CN).

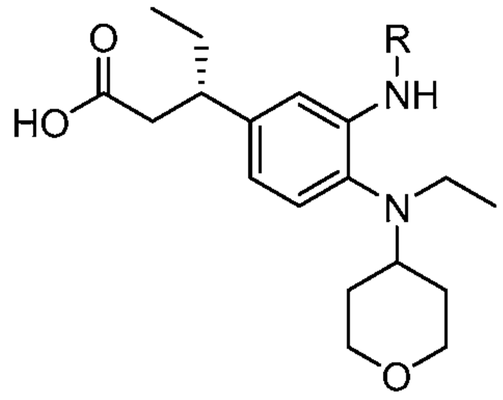
Example 488 Enantiomer 1 (absolute stereochemistry not determined). LC-MS Anal. Calc'd. for $C_{24}H_{33}N_5O_4$ 455.5, found [M+H] 456.3, T_r = 1.18 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 8.82 (s, 2H), 8.17 (s, 1H), 8.09 (d, *J* = 2.00 Hz, 1H), 7.18 (d, *J* = 8.00 Hz, 1H), 6.84 (dd, *J* = 8.00, 2.00 Hz, 1H), 3.83 (t, *J* = 2.80 Hz, 2H), 3.22-3.28 (m, 3H), 2.99-3.01 (m, 3H), 2.96-2.97 (m, 1H), 2.56 (s, 3H), 2.42-2.44 (m, 1H), 1.70-1.73 (m, 2H), 1.41-1.42 (m, 2H), 0.95 (d, *J* = 6.40 Hz, 2H), 0.80 (t, *J* = 7.20 Hz, 3H), 0.72 (t, *J* = 7.20 Hz, 3H).

Example 488 Enantiomer 2 (absolute stereochemistry not determined). LC-MS Anal. Calc'd. for $C_{24}H_{33}N_5O_4$ 455.5, found [M+H] 456.3, T_r = 1.18 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 8.82 (s, 2H), 8.17 (s, 1H), 8.09 (d, *J* = 2.00 Hz, 1H), 7.18 (d, *J* = 8.00 Hz, 1H), 6.84 (dd, *J* = 8.00, 2.00 Hz, 1H), 3.83 (t, *J* = 2.80 Hz,

2H), 3.22-3.28 (m, 3H), 2.99-3.01 (m, 3H), 2.96-2.97 (m, 1H), 2.56 (s, 3H), 2.42-2.44 (m, 1H), 1.70-1.73 (m, 2H), 1.41-1.42 (m, 2H), 0.95 (d, J = 6.40 Hz, 2H), 0.80 (t, J = 7.20 Hz, 3H), 0.72 (t, J = 7.20 Hz, 3H).

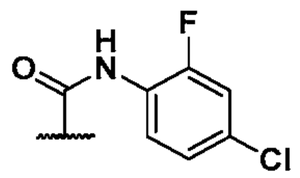
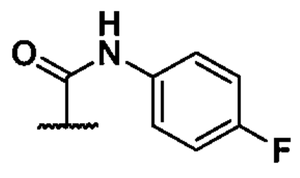
Examples 489 to 497

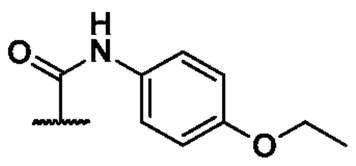
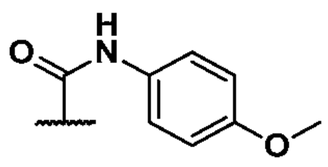
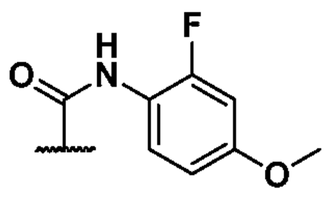
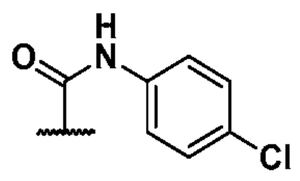
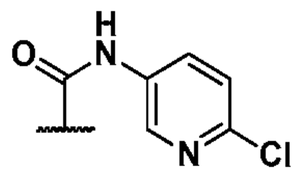
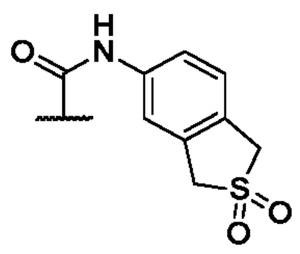
(Enantiomer 1)

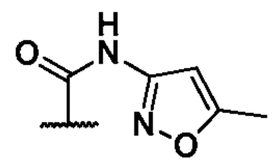


Examples 489 to 495 were prepared using 455E instead of 487B and the corresponding isocyanates following the procedure described for the synthesis of Example 487.

Examples 496 and 497 were prepared by using 455E instead of 487B and the corresponding amines (as in step 488B) following the procedure described for the synthesis of Example 488.

Ex. No.	Name	R	T_r min	Method	(M+H)
489	(S)-3-(3-(3-(4-chloro-2-fluorophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.653	O	492.3
490	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(4-fluorophenyl)ureido) phenyl)pentanoic acid		1.332	R	458.3

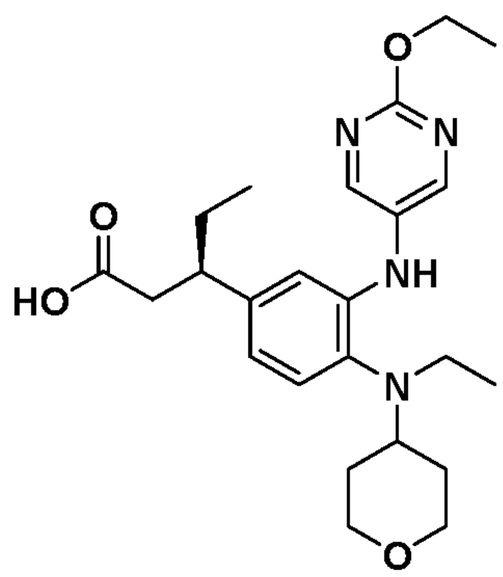
Ex. No.	Name	R	T_r min	Method	(M+H)
491	(S)-3-(3-(3-(4-ethoxyphenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.418	R	484.4
492	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(4-methoxyphenyl) ureido)phenyl)pentanoic acid		1.288	R	470.4
493	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(2-fluoro-4-methoxyphenyl)ureido) phenyl)pentanoic acid		1.411	O	488.4
494	(S)-3-(3-(3-(3-(4-chlorophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.787	R	474.2
495	(S)-3-(3-(3-(3-(6-chloropyridin-3-yl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.649	O	475.2
496	(S)-3-(3-(3-(3-(2,2-dioxido-1,3-dihydrobenzo[c] thiophen-5-yl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.417	R	530.2

Ex. No.	Name	R	T_r min	Method	(M+H)
497	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(5-methylisoxazol-3-yl)ureido)phenyl)pentanoic acid		1.260	R	445.3

Example 498

(Enantiomer 2)

(R)-3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid



498A. Methyl (R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)pentanoate

Compound 498A was prepared utilizing S-BINAP and 455C following the procedure described for the synthesis of 455D. LC-MS Anal. Calc'd. for $C_{19}H_{28}N_2O_5$ 364.4, found [M+H] 365.2, T_r = 3.16 min. (Method N).

498B. Methyl (R)-3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoate

Compound 498B was prepared using compound 498A following the procedure described for the synthesis of 455E. SFC chiral purity shows 94.7% ee (T_r = 4.86 min. (Method AF). LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_3$ 334.4, found [M+H] 335.2, T_r = 2.90 min. (Method N).

498C. Methyl (R)-3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

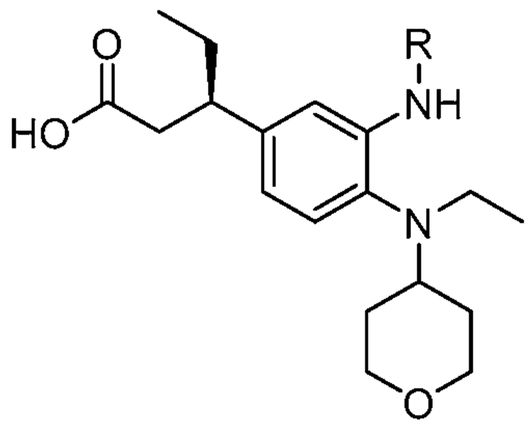
Compound 498C was prepared using compound 498B and 5-bromo-2-ethoxy-pyrimidine following the procedure described for the synthesis of 455F. LC-MS Anal. Calc'd. for $C_{25}H_{36}N_4O_4$ 456.5, found [M+H] 457.3, T_r = 3.9 min (Method N).

Example 498. (R)-3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid

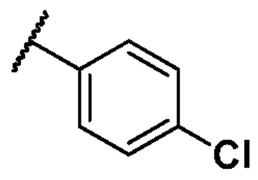
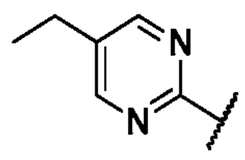
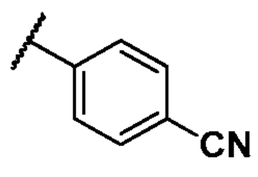
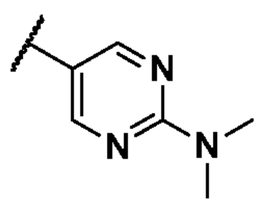
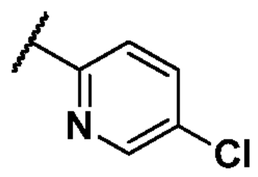
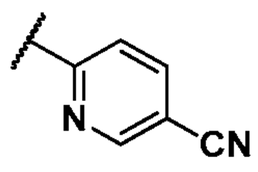
Example 498 was prepared using compound 498C following the procedure described for the synthesis of Example 455 Enantiomer 1. Absolute stereochemistry of Example 498 was assigned based on the expected enantiomer produced in the conjugate addition using (S)-BINAP to prepare 498A.LC-MS Anal. Calc'd. for $C_{24}H_{34}N_4O_4$ 442.5, found [M+H] 443.6, T_r = 2.13 min. (Method N). ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (s, 2H), 7.17 (d, *J* = 8.00 Hz, 1H), 6.84 (d, *J* = 1.20 Hz, 1H), 6.74 (d, *J* = 8.00 Hz, 1H), 4.38-4.43 (m, 2H), 3.90 (dd, *J* = 10.80, 3.00 Hz, 2H), 3.36-3.38 (m, 2H), 3.04-3.09 (m, 3H), 2.86 (s, 1H), 2.57-2.62 (m, 1H), 2.47-2.51 (m, 1H), 1.77-1.80 (m, 2H), 1.67-1.69 (m, 1H), 1.54-1.55 (m, 3H), 1.39-1.43 (m, 3H), 0.91 (t, *J* = 7.20 Hz, 3H), 0.80 (t, *J* = 7.20 Hz, 3H).

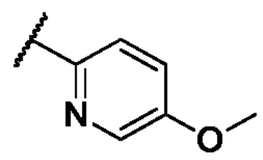
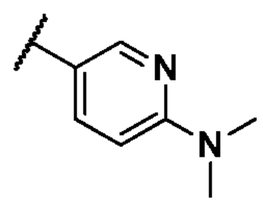
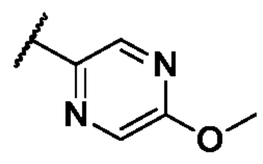
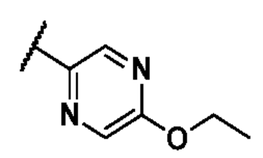
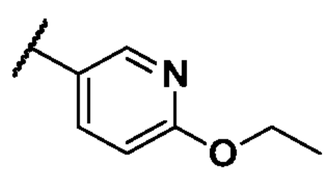
Examples 499 to 525

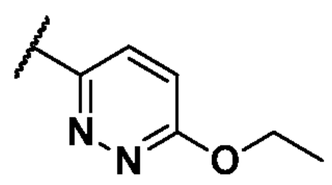
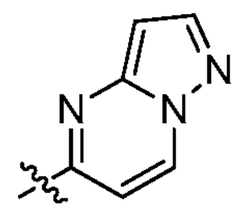
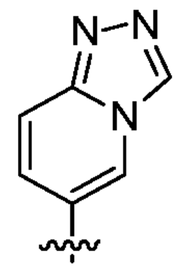
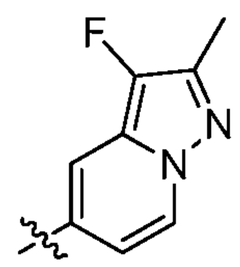
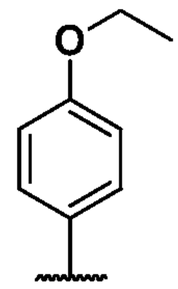
(Enantiomer 2)

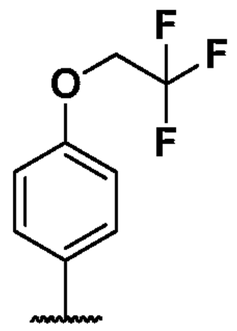
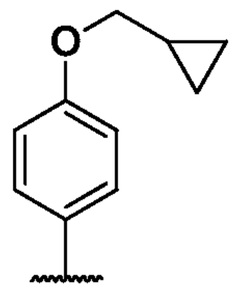
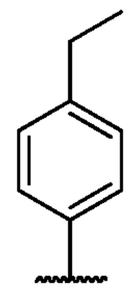
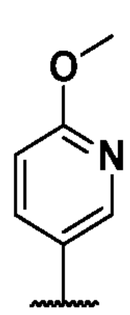
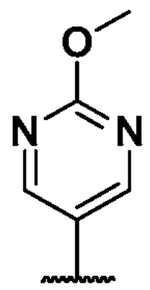
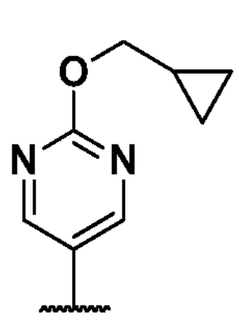


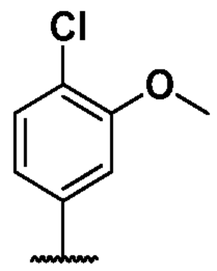
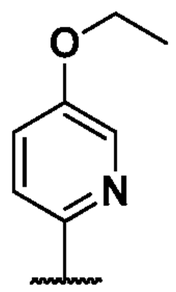
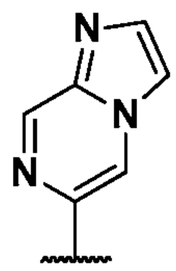
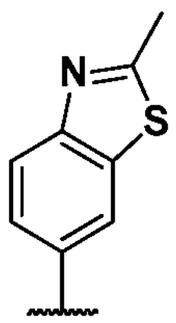
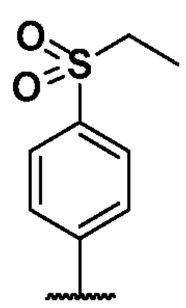
Examples 499 to 525 were prepared using 498B and corresponding aryl halides (as in step 498C) following the procedure described for the synthesis of Example 498 Enantiomer 2.

Ex. No.	Name	R	T_r min	Method	(M+H)
499	(R)-3-(3-((4-chlorophenyl) amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		2.1	O	431.2
500	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((5-ethylpyrimidin-2-yl) amino)phenyl)pentanoic acid		1.84	O	427.3
501	(R)-3-(3-((4-cyanophenyl) amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.81	O	422.1
502	(R)-3-(3-((2-(dimethylamino)pyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.79	O	442.1
503	(R)-3-(3-((5-chloropyridin-2-yl)amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.98	O	432.1
504	(R)-3-(3-((5-cyanopyridin-2-yl)amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.70	O	423.1

Ex. No.	Name	R	T_r min	Method	(M+H)
505	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((5-methoxypyridin-2-yl)amino)phenyl)pentanoic acid		1.70	O	428.1
506	(R)-3-(3-((6-(dimethylamino)pyridin-3-yl)amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.81	O	441.2
507	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((5-methoxypyrazin-2-yl)amino)phenyl)pentanoic acid		1.72	O	429.1
508	(R)-3-(3-((5-ethoxypyrazin-2-yl)amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.87	O	443.1
509	(R)-3-(3-((6-ethoxypyridin-3-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.92	O	442.1

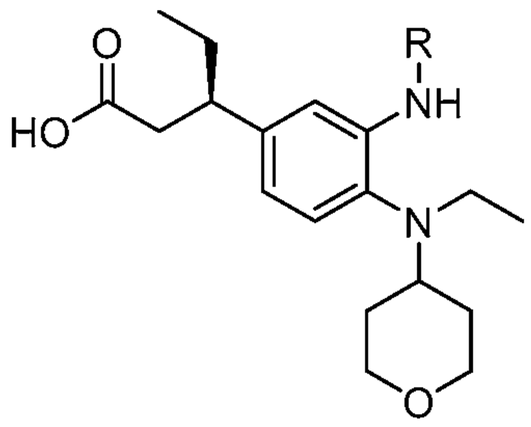
Ex. No.	Name	R	T_r min	Method	(M+H)
510	(R)-3-(3-((6-ethoxypyridazin-3-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.69	O	443.1
511	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(pyrazolo[1,5-a]pyrimidin-5-ylamino)phenyl) pentanoic acid		1.48	O	438
512	(R)-3-(3-([1,2,4]triazolo[4,3-a]pyridin-6-ylamino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.15	O	438
513	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((3-fluoro-2-methylpyrazolo[1,5-a] pyridin-5-yl)amino)phenyl) pentanoic acid		1.85	O	469
514	(R)-3-(3-((4-ethoxyphenyl) amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.35	R	441.4

Ex. No.	Name	R	T_r min	Method	(M+H)
515	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((4-(2,2,2-trifluoroethoxy)phenyl)amino)phenyl)pentanoic acid		1.480	R	495.4
516	(R)-3-(3-((4-(cyclopropylmethoxy)phenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.483	R	467.4
517	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((4-ethylphenyl)amino)phenyl)pentanoic acid		2.068	O	425.4
518	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((6-methoxypyridin-3-yl)amino)phenyl)pentanoic acid		1.331	R	428.2
519	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methoxypyrimidin-5-yl)amino)phenyl)pentanoic acid		1.294	O	429.3
520	(R)-3-(3-((2-(cyclopropylmethoxy)pyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.867	O	469.3

Ex. No.	Name	R	T_r min	Method	(M+H)
521	(R)-3-(3-((4-chloro-3-methoxyphenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.668	O	461.3
522	(R)-3-(3-((5-ethoxypyridin-2-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.822	O	442.2
523	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(imidazo[1,2-a]pyrazin-6-ylamino)phenyl)pentanoic acid		1.098	O	438.3
524	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methylbenzo[d]thiazol-6-yl)amino)phenyl) pentanoic acid		1.177	R	468.3
525	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((4-(ethylsulfonyl)phenyl) amino)phenyl)pentanoic acid		1.637	O	489.1

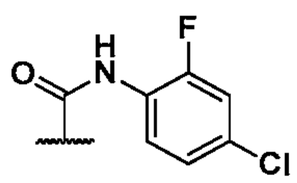
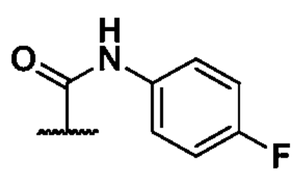
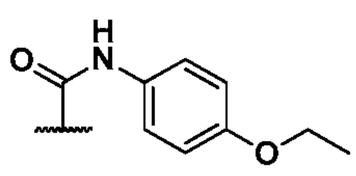
Examples 526 to 534

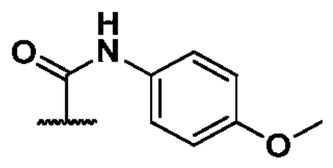
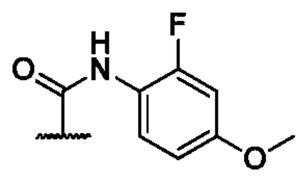
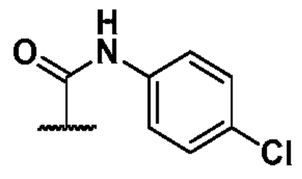
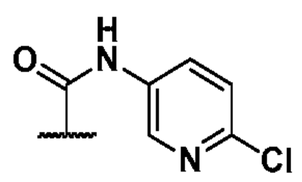
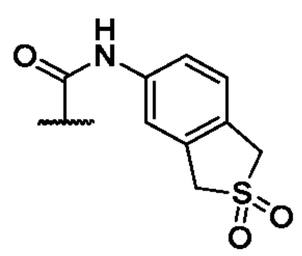
(Enantiomer 2)

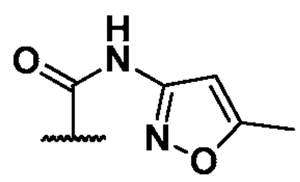


Examples 526 to 532 were prepared using 498B (instead of 487B) and corresponding isocyanates following the procedure described for the synthesis of Example 487.

Examples 533 and 534 were prepared using 498B (instead of 487B) and corresponding amines (as in step 488B) following the procedure described for the synthesis of Example 488.

Ex. No.	Name	R	T_r min	Method	(M+H)
526	(R)-3-(3-(3-(4-chloro-2-fluorophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.527	R	492.3
527	(R)-3-(4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-3-(3-(4-fluorophenyl)ureido) phenyl)pentanoic acid		1.473	O	458.3
528	(R)-3-(3-(3-(4-ethoxyphenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.414	R	484.4

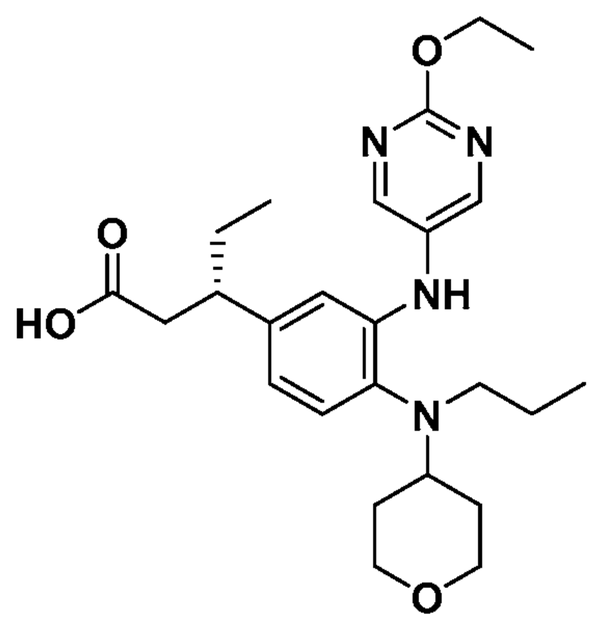
Ex. No.	Name	R	T_r min	Method	(M+H)
529	(R)-3-(4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-3-(3-(4-methoxyphenyl)ureido) phenyl)pentanoic acid		1.278	R	470.4
530	(R)-3-(4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-3-(3-(2-fluoro-4-methoxyphenyl)ureido) phenyl)pentanoic acid		1.396	O	488.4
531	(R)-3-(3-(3-(4-chlorophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.814	O	474.2
532	(R)-3-(3-(3-(6-chloropyridin-3-yl)ureido)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.569	O	475.2
533	(R)-3-(3-(3-(2,2-dioxido-1,3-dihydrobenzo[c] thiophen-5-yl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.441	R	530.2

Ex. No.	Name	R	T_r min	Method	(M+H)
534	(R)-3-(4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-3-(3-(5-methylisoxazol-3-yl)ureido)phenyl) pentanoic acid		1.287	R	445.3

Example 535

(Enantiomer 1)

(S)-3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid



535A. N-Propyltetrahydro-2H-pyran-4-amine

To a solution of MeOH (100 mL) and THF (100 mL) containing 10 g of powdered and activated 4 Å molecular sieves, was added sequentially propan-1-amine (9.07 mL, 110 mmol), and dihydro-2H-pyran-4(3H)-one (9.22 mL, 100 mmol). Then the reaction mixture was stirred for 6 h at room temperature. The reaction mixture was then cooled to 0 °C, $NaBH_4$ (11.34 g, 300 mmol) was then added portionwise and the resulting mixture was stirred at RT for 6 h. The reaction mixture was then quenched with ice cold water (250 mL) and concentrated under reduced pressure. Then the aqueous solution was then extracted with ethyl acetate (2 × 250 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 535A (pale yellow liquid, (10 g, 69.8 mmol, 69.9% yield). LC-MS Anal. Calc'd. for $C_8H_{17}NO$ 143.2, found [M+H] 144.4, T_r =0.46 min. (Method N).

535B. N-(4-Bromo-2-nitrophenyl)-N-propyltetrahydro-2H-pyran-4-amine

535B was prepared utilizing 535A and 5-bromo-2-fluoro-1-nitro benzene following the procedure described for the synthesis of 455B. LC-MS Anal. Calc'd. for $C_{14}H_{19}BrN_2O_3$ 343.2, found [M-H] 344.4, T_r = 3.34 min. (Method N).

535C. N-(4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-2-nitrophenyl)-N-propyltetrahydro-2H-pyran-4-amine.

Compound 535C was prepared utilizing compound 535B following the procedure described for the synthesis of 455C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, J = 2.00 Hz, 1H), 7.76 (dd, J = 10.80, 1.80 Hz, 1H), 7.38 (d, J = 11.20 Hz, 1H), 3.99-4.04 (m, 2H), 3.47 (s, 4H), 3.13-3.26 (m, 3H), 3.05-3.09 (m, 2H), 1.56-1.68 (m, 4H), 1.22-1.30 (m, 2H), 0.95 (s, 6H), 0.75-0.80 (m, 3H).

535D. Methyl (S)-3-(3-nitro-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoate

535D was prepared utilizing compound 535C and R-BINAP following the procedure described for the synthesis of 455D. LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_5$ 378.4, found [M+H] 379.6, T_r = 3.92 min. (Method N).

535E. Methyl (S)-3-(3-amino-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoate

535E was prepared utilizing compound 535D following the procedure described for the synthesis of 455E Enantiomer 1. SFC chiral purity shows 100% ee (T_r = 2.55 min) (Method AF) of 535E Enantiomer 1. LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_3$ 348.4, found [M+H] 349.6, T_r = 3.92 min. (Method N).

535F. Methyl (S)-3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

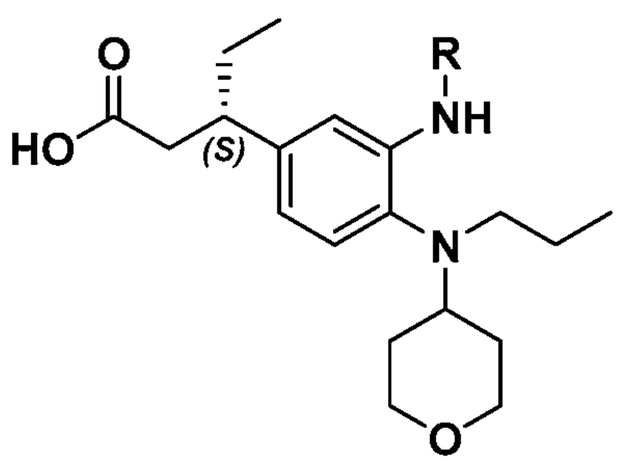
535F was prepared utilizing compound 535E and 5-bromo-2-ethoxy-pyrimidine following the procedure described for the synthesis of 455F. LC-MS Anal. Calc'd. for $C_{26}H_{38}N_4O_4$ 470.6, found [M+H] 471.2, T_r = 3.72 min. (Method N).

Example 535 Enantiomer 1. (S)-3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(propyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid

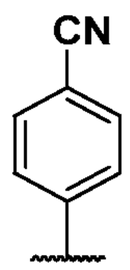
Example 535 was prepared utilizing compound 535F following the procedure described for the synthesis of Example 455. LC-MS Anal. Calc'd. for $C_{25}H_{36}N_4O_4$ 456.5, found [M+H] 457.3, T_r = 1.79 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 2H), 7.24 (s, 1H), 7.12 (d, *J* = 8.00 Hz, 1H), 6.81 (s, 1H), 6.67 (d, *J* = 7.60 Hz, 1H), 4.29 (dd, *J* = 14.00, 7.00 Hz, 2H), 3.81 (d, *J* = 8.00 Hz, 2H), 3.16-3.20 (m, 2H), 2.87-2.91 (m, 3H), 2.76-2.77 (m, 1H), 2.41-2.43 (m, 1H), 1.67 (d, *J* = 12.40 Hz, 2H), 1.58-1.61 (m, 1H), 1.45-1.47 (m, 3H), 1.32 (t, *J* = 7.20 Hz, 3H), 1.21-1.23 (m, 2H), 0.77 (t, *J* = 7.20 Hz, 3H), 0.70 (t, *J* = 7.60 Hz, 3H) (Note: one multiplet of CH is buried under the solvent peak).

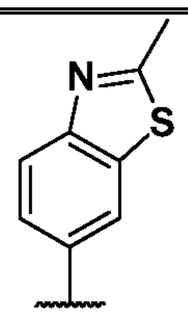
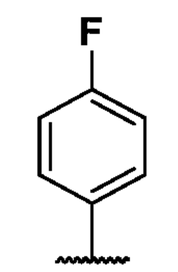
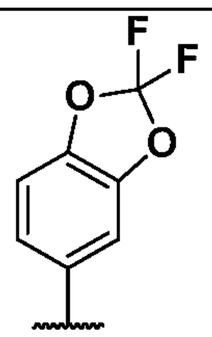
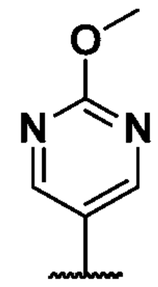
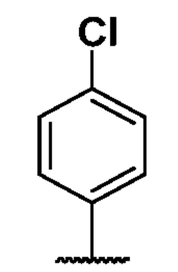
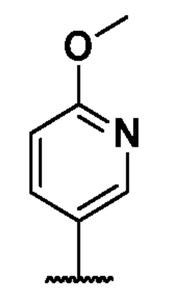
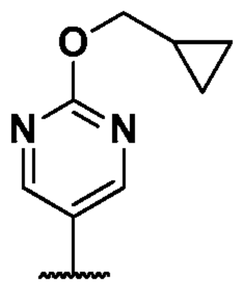
Examples 536 to 543

(Enantiomer 1)



Examples 536 to 543 were prepared using 535E and corresponding aryl halides (as in Step 535F) following the procedure described for the synthesis of Example 535.

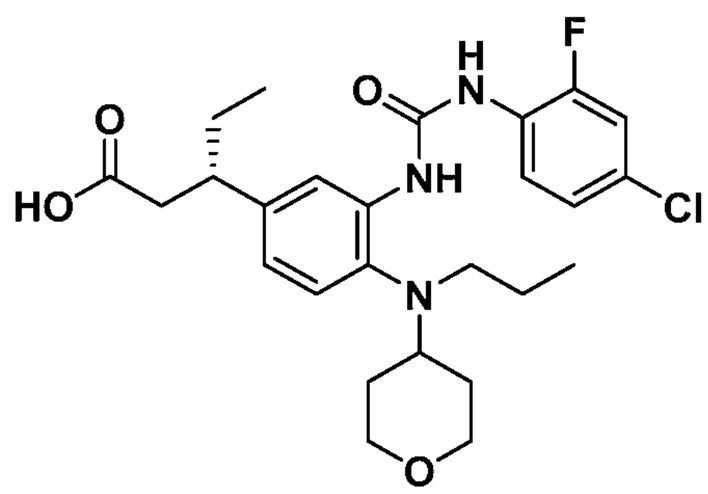
Ex. No.	Name	R	T_r min	Method	(M+H)
536	(S)-3-(3-((4-cyanophenyl) amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.91	O	436.3

Ex. No.	Name	R	T_r min	Method	(M+H)
537	(S)-3-(3-((2-methylbenzo[d] thiazol-6-yl)amino)-4-(propyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.98	O	482.3
538	(S)-3-(3-((4-fluorophenyl) amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		2.16	O	429.2
539	(S)-3-(3-((2,2-difluorobenzo[d] [1,3]dioxol-5-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		2.37	O	491.2
540	(S)-3-(3-((2-methoxypyrimidin-5-yl)amino)-4-(propyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.7	O	443.3
541	(S)-3-(3-((4-chlorophenyl) amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		2.39	O	445.2
542	(S)-3-(3-((6-methoxypyridin-3-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.94	O	442.3
543	(S)-3-(3-((2-(cyclopropylmethoxy)pyrimidin-5-yl)amino)-4-(propyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.52	O	499.4

Example 544

(Enantiomer 1)

(S)-3-(3-(3-(4-Chloro-2-fluorophenyl)ureido)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid



544A. Methyl 3-(3-(3-(4-chloro-2-fluorophenyl)ureido)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

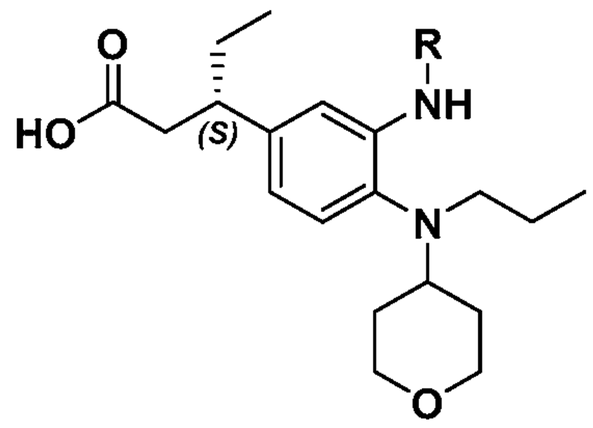
544A was prepared using compound 535E Enantiomer 1 and 4-chloro-2-fluoro-1-isocyanatobenzene following the procedure described for the synthesis of 487C. LC-MS Anal. Calc'd. for $C_{27}H_{35}ClFN_3O_4$ 520.03, found [M+2H] 522.4, T_r = 1.7 min. (Method AY).

Example 544 Enantiomer 1. 3-(3-(3-(4-Chloro-2-fluorophenyl)ureido)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid

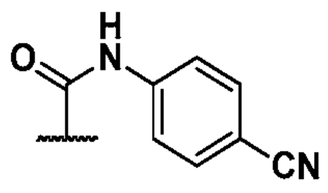
Example 544 Enantiomer 1 was prepared utilizing compound 544A following the procedure described for the synthesis of Example 455 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{26}H_{33}ClFN_3O_4$ 505, found [M+H] 506.2, T_r = 1.88 min. ^{1}H NMR (400 MHz, MeOD) δ 7.99-8.03 (m, 2H), 7.15-7.25 (m, 3H), 6.89 (dd, *J* = 8.40, 1.80 Hz, 1H), 3.91 (dd, *J* = 11.20, 3.00 Hz, 2H), 3.30-3.38 (m, 2H), 2.92-2.95 (m, 4H), 2.56-2.62 (m, 2H), 1.49-1.78 (m, 6H), 1.25-1.29 (m, 2H), 0.81 (t, *J* = 7.60 Hz, 6H).

Example 545

(Enantiomer 1)



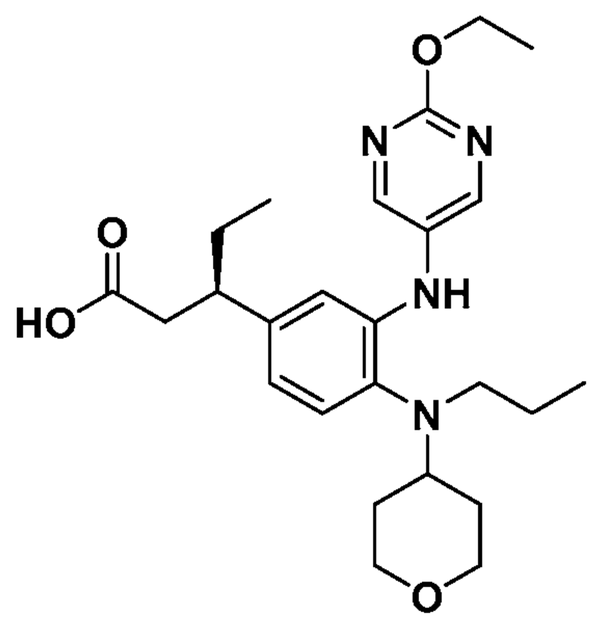
Example 545 was using 535E Enantiomer 1 and corresponding isocyanates following the procedure described for the synthesis of Example 487.

Ex. No.	Name	R	T_r min	Method	(M+H)
545	(S)-3-(3-(3-(4-cyanophenyl) ureido)-4-(propyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.82	O	479.3

Example 546

(Enantiomer 2)

(R)-3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid



546A. Methyl 3-(3-nitro-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

546A was prepared utilizing 535C and S-BINAP following the procedure described for the synthesis of 455D. LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_5$ 378.4, found [M+H] 379.2, T_r = 3.37 min. (Method N).

546B. Methyl 3-(3-amino-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

546B was prepared utilizing compound 546A following the procedure described for the synthesis of 455E Enantiomer 1. SFC chiral purity of 546B Enantiomer 2 shows 93.5% ee (T_r = 3.59 min. (Method AF). LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_3$ 348.4, found [M+H] 349.2, T_r = 3.92 min. (Method N).

546C. Methyl 3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

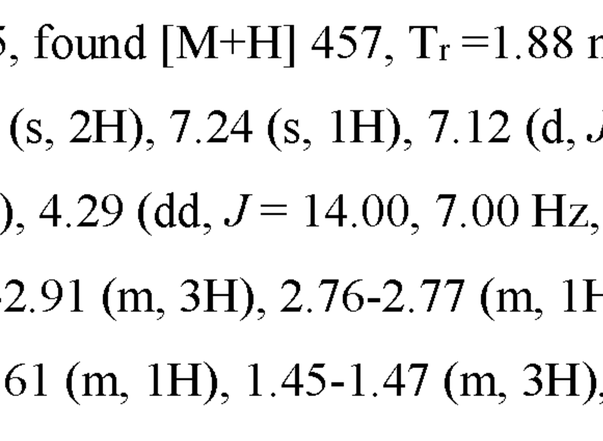
546C was prepared utilizing compound 546B Enantiomer 2 following the procedure described for the synthesis of 455F. LC-MS Anal. Calc'd. for $C_{26}H_{38}N_4O_4$ 470.6, found [M+H] 471.2, T_r = 3.72 min. (Method N).

Example 546 Enantiomer 2. 3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid

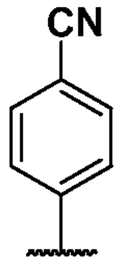
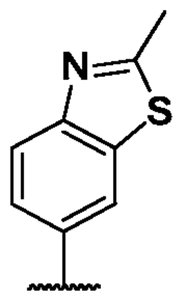
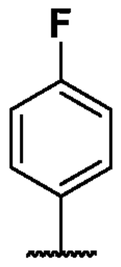
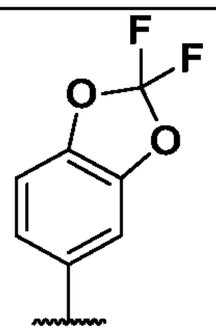
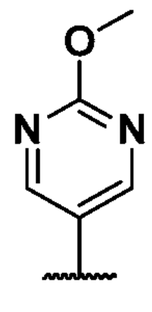
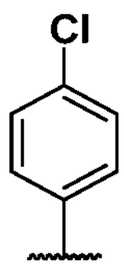
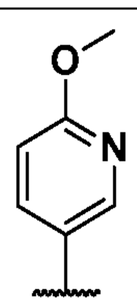
Example 546 Enantiomer 2 was prepared utilizing compound 546C following the procedure described for the synthesis of Example 455 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{25}H_{36}N_4O_4$, 456.5, found [M+H] 457, T_r =1.88 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 2H), 7.24 (s, 1H), 7.12 (d, *J* = 8.00 Hz, 1H), 6.81 (s, 1H), 6.67 (d, *J* = 7.60 Hz, 1H), 4.29 (dd, *J* = 14.00, 7.00 Hz, 2H), 3.81 (d, *J* = 8.00 Hz, 2H), 3.16-3.20 (m, 2H), 2.87-2.91 (m, 3H), 2.76-2.77 (m, 1H), 2.41-2.43 (m, 1H), 1.67 (d, *J* = 12.40 Hz, 2H), 1.58-1.61 (m, 1H), 1.45-1.47 (m, 3H), 1.32 (t, *J* = 7.20 Hz, 3H), 1.21-1.23 (m, 2H), 0.77 (t, *J* = 7.20 Hz, 3H), 0.70 (t, *J* = 7.60 Hz, 3H) (Note: one multiplet of CH is buried under the solvent peak).

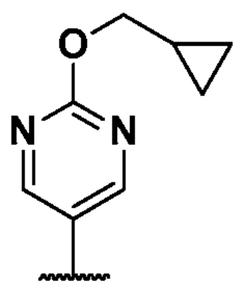
Examples 547 to 554

(Enantiomer 2)



Examples 547 to 554 were prepared using 546B and corresponding aryl halides following the procedure described for the synthesis of Example 546.

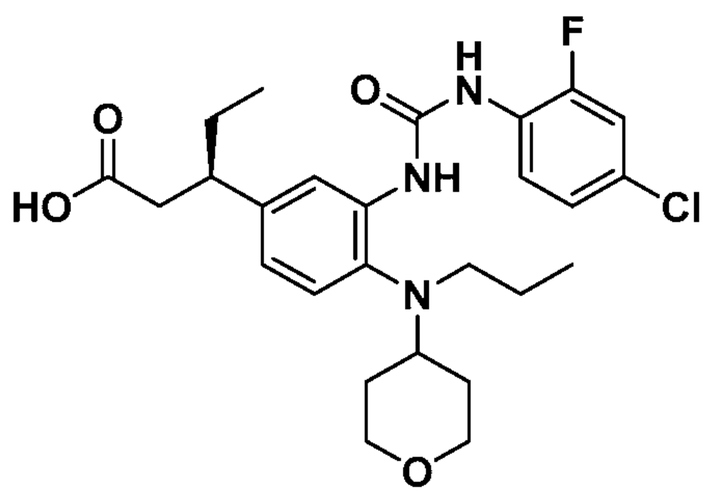
Ex. No.	Name	R	T_r min	Method	(M+H)
547	(R)-3-(3-((4-cyanophenyl) amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		1.91	O	436.3
548	(R)-3-(3-((2-methylbenzo[d] thiazol-6-yl)amino)-4-(propyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.98	O	482.3
549	(R)-3-(3-((4-fluorophenyl) amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		2.16	O	429.2
550	(R)-3-(3-((2,2-difluorobenzo[d] [1,3]dioxol-5-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		2.37	O	491.2
551	(R)-3-(3-((2-methoxypyrimidin-5-yl)amino)-4-(propyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.7	O	443.3
552	(R)-3-(3-((4-chlorophenyl) amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		2.39	O	445.2
553	(R)-3-(3-((6-methoxypyridin-3-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) pentanoic acid		442.3	O	442.3

Ex. No.	Name	R	T_r min	Method	(M+H)
554	(R)- 3-(3-((2-(cyclopropylmethoxy)pyrimidin-5-yl)amino)-4-(propyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		2.12	O	483.3

Example 555

(Enantiomer 2)

(R)-3-(3-(3-(4-Chloro-2-fluorophenyl)ureido)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid



555A. Methyl (R)-3-(3-(3-(4-chloro-2-fluorophenyl)ureido)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

555A was prepared using 546B Enantiomer 2 and 4-chloro-2-fluoro-1-isocyanatobenzene following the procedure described for the synthesis of 487C. LC-MS Anal. Calc'd. for $C_{27}H_{35}ClFN_3O_4$ 519.2, found [M+H] 520.4, T_r = 1.7 min. (Method AY).

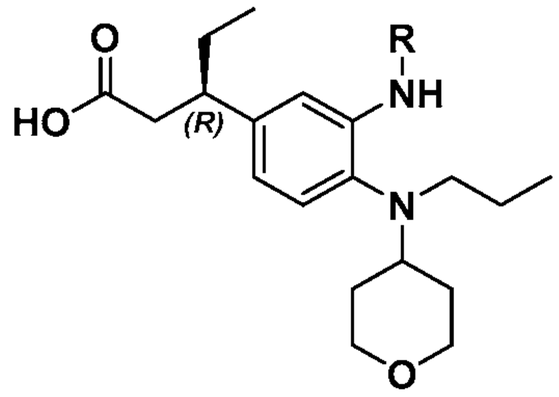
Example 555 Enantiomer 2. (R)-3-(3-(3-(4-Chloro-2-fluorophenyl)ureido)-4-(propyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid

Example 555 Enantiomer 2 was prepared utilizing compound 555A following the procedure described for the synthesis of Example 555 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{26}H_{33}ClFN_3O_4$ 505.0, found [M+H] 506.2, T_r = 2.0 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.53 (s, 1H), 8.80 (s, 1H), 8.12 (t, *J* = 8.80 Hz, 1H), 8.02 (d, *J* = 1.60 Hz, 1H), 7.44 (dd, *J* = 11.20, 2.00 Hz, 1H), 7.15-7.22 (m, 2H), 6.82 (dd, *J* = 8.00, 1.40 Hz, 1H), 3.81-3.83 (m, 2H), 3.17-3.25 (m, 3H), 2.82-2.95 (m, 3H), 2.54-2.56

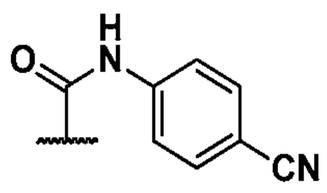
(m, 1H), 2.43-2.45 (m, 1H), 1.63-1.71 (m, 3H), 1.37-1.41 (m, 3H), 1.16-1.22 (m, 2H), 0.69-0.79 (m, 6H).

Example 556

(Enantiomer 2)



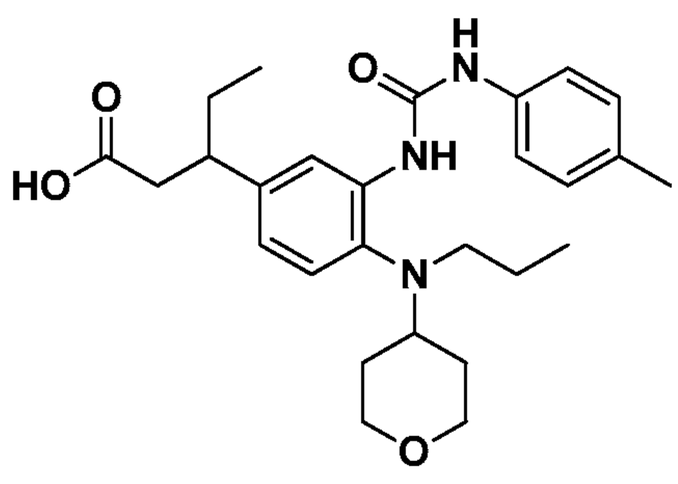
Example 556 was prepared using 546B and corresponding isocyanate following the procedure described for the synthesis of Example 544.

Ex. No.	Name	R	T_r min	Method	(M+H)
556	(R)-3-(3-(3-(4-cyanophenyl) ureido)-4-(propyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.82	O	479.3

Example 557

(Enantiomer 1 and Enantiomer 2)

3-(4-(Propyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido) phenyl)pentanoic acid



557A. Methyl 3-(3-nitro-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate (Racemate)

557A was prepared using compound 535C following the procedure described for the synthesis of 487A. LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_5$ 378.4, found [M+H] 379.2, T_r = 3.29 min. (Method N).

557B. Methyl 3-(3-amino-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

557B was prepared using compound 557A following the procedure described for the synthesis of 455E. LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_3$ 348.4, found [M+H] 349.2, T_r = 3.18 min. (Method N).

557C. Methyl 3-(4-(propyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido) phenyl)pentanoate

557C was prepared using compound 557B following the procedure described for the synthesis of 487C. LC-MS Anal. Calc'd. for $C_{28}H_{39}N_3O_4$ 481.6, found [M+H] 482.2, T_r = 3.59 min. (Method N).

Example 557 Enantiomer 1 and Enantiomer 2. 3-(4-(Propyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)pentanoic acid

Example 557 was prepared using 557C (racemate) following the procedure described for the synthesis of Example 455. LC-MS Anal. Calc'd. for $C_{27}H_{37}N_3O_4$ 467.6, found [M+H] 468.2, T_r = 1.65 min. (Method O).

Chiral separation of Example 557 racemate gave Example 557 Enantiomer 1 and Example 557 Enantiomer 2 (Method BM). Enantiomer 1 T_r = 2.22 min, Enantiomer 2 T_r = 2.97 min (Method BM).

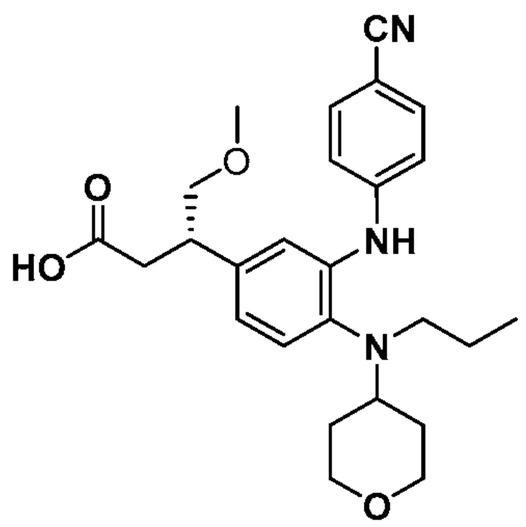
Example 557 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{27}H_{37}N_3O_4$ 467.6, found [M+H] 468.3, T_r = 1.62 min. (Method R). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.06 (d, *J* = 2.00 Hz, 1H), 7.37 (d, *J* = 8.40 Hz, 2H), 7.07-7.14 (m, 3H), 6.77 (dd, *J* = 8.00, 2.00 Hz, 1H), 3.80-3.84 (m, 2H), 3.17-3.25 (m, 5H), 2.85-2.93 (m, 3H), 2.39-2.41 (m, 1H), 2.24 (s, 3H), 1.68-1.71 (m, 3H), 1.37-1.41 (m, 3H), 1.18-1.20 (m, 2H), 0.71 (t, *J* = 7.60 Hz, 3H), 0.77 (t, *J* = 7.60 Hz, 3H).

Example 557 Enantiomer 2 LC-MS Anal. Calc'd. for $C_{27}H_{37}N_3O_4$ 467.6, found [M+H] 468.3, T_r = 1.65 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.06 (d, *J* = 2.00 Hz, 1H), 7.37 (d, *J* = 8.40 Hz, 2H), 7.07-7.14 (m, 3H), 6.77 (dd, *J* = 8.00, 2.00 Hz, 1H), 3.80-3.84 (m, 2H), 3.17-3.25 (m, 5H), 2.85-2.93 (m, 3H), 2.39-2.41 (m, 1H), 2.24 (s, 3H), 1.68-1.71 (m, 3H), 1.37-1.41 (m, 3H), 1.18-1.20 (m, 2H), 0.71 (t, *J* = 7.60 Hz, 3H), 0.77 (t, *J* = 7.60 Hz, 3H).

Example 558

(Enantiomer 1)

(S)-3-(3-((4-Cyanophenyl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid



558A. Methyl 4-methoxy-(S)-3-(3-nitro-4-(propyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)butanoate

1,4-Dioxane (35 mL) was purged with argon for 10 minutes before chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.059 g, 0.120 mmol) and (R)-BINAP (0.109 g, 0.175 mmol) were added. The reaction was then purged with argon for 5 minutes. To the above reaction mixture 535C (3 g, 7.97 mmol), (E)-methyl 4-methoxybut-2-enoate (1.245 g, 9.57 mmol), sodium hydroxide (7.28 ml, 7.28 mmol) were added respectively and purged argon for another 5 minutes. The reaction mixture was heated at 50 °C and stirred for 3 h before being cooled to room temperature and quenched with acetic acid (0.411 mL, 7.18 mmol) and it was stirred for 5 minutes before it was partitioned between ethyl acetate (125 mL) and water (125 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were washed with brine (75 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification via silica gel flash chromatography gave 558A (pale orange

solid, 2.3 g, 5.83 mmol, 73.1% yield). LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_6$ 394.4, found [M+H] 395.2, T_r = 2.9 min (Method N).

558B. Methyl (S)-3-(3-amino-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoate

558B was prepared utilizing compound 558A following the procedure described for the synthesis of 455E. SFC chiral purity shows 100% ee (T_r = 6.39 min). (Method AF). LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_4$ 364.4, found [M+H] 365.2, T_r = 2.76 min. (Method N).

558C. Methyl (S)-3-(3-((4-cyanophenyl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoate

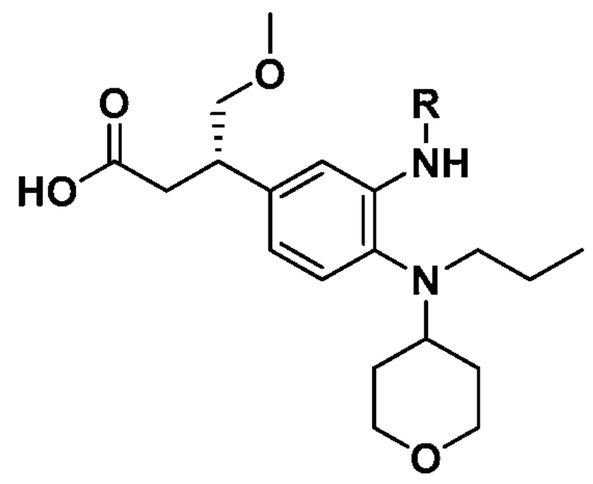
558C was prepared utilizing compound 558B and 4-bromobenzonitrile following the procedure described for the synthesis of 455F. LC-MS Anal. Calc'd. for $C_{27}H_{35}N_3O_4$ 465.5, found [M+H] 466.2, T_r = 3.26 min. (Method N).

Example 558 Enantiomer 1. (S)-3-(3-((4-Cyanophenyl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid

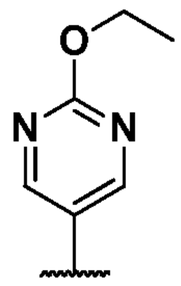
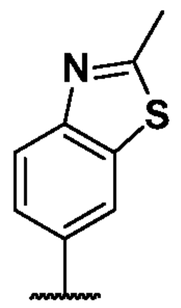
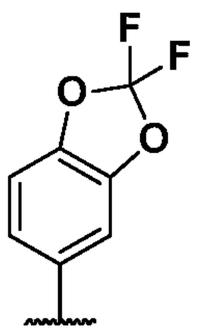
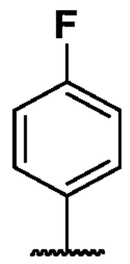
Example 558 Enantiomer 1 was prepared utilizing 558C following the procedure described for the synthesis of Example 455 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{26}H_{33}N_3O_4$ 451.5, found [M+H] 452.2, T_r = 1.72 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.57 (d, *J* = 8.80 Hz, 2H), 7.17-7.18 (m, 2H), 7.09-7.11 (m, 2H), 6.94 (dd, *J* = 8.40, 1.80 Hz, 1H), 3.76-3.80 (m, 2H), 3.42-3.47 (m, 2H), 3.24-3.34 (m, 4H), 3.05-3.10 (m, 2H), 2.88-2.91 (m, 3H), 2.64-2.68 (m, 1H), 2.48-2.51 (m, 1H), 1.55-1.58 (m, 2H), 1.47-1.47 (m, 2H), 1.21-1.25 (m, 2H), 0.76 (t, *J* = 7.20 Hz, 3H).

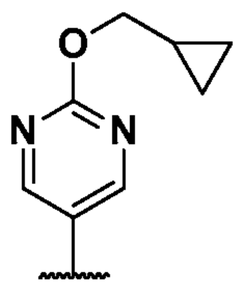
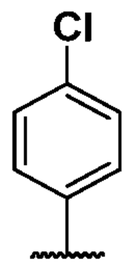
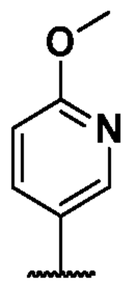
Examples 559 to 565

(Enantiomer 1)



Examples 559 to 565 were prepared using 558 B and the corresponding aryl halides following the procedure described for the synthesis of Example 558.

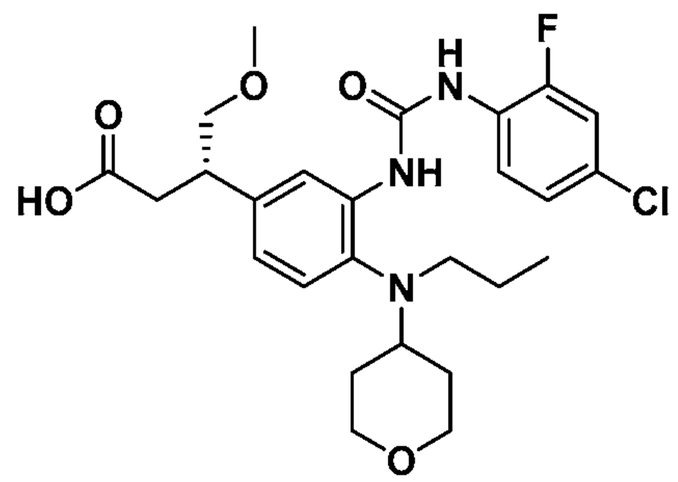
Ex. No.	Name	R	T_r min	Method	(M+H)
559	(S)-3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.66	O	473.3
560	4-methoxy-(S)-3-(3-((2-methylbenzo[d]thiazol-6-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) butanoic acid		1.75	O	498.2
561	(S)-3-(3-((2,2-difluorobenzo[d][1,3]dioxol-5-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		2.15	O	507.2
562	(S)-3-(3-((4-fluorophenyl) amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.93	O	445.2

Ex. No.	Name	R	T_r min	Method	(M+H)
563	(S)-3-(3-((2-(cyclopropylmethoxy)pyrimidin-5-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.52	O	499.4
564	(S)-3-(3-((4-chlorophenyl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.78	O	461.3
565	4-methoxy-(S)-3-(3-((6-methoxypyridin-3-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)butanoic acid		1.65	O	458.2

Example 566

(Enantiomer 1)

(S)-3-(3-(3-(4-Chloro-2-fluorophenyl)ureido)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid



566A. Methyl (S)-3-(3-(3-(4-chloro-2-fluorophenyl)ureido)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoate

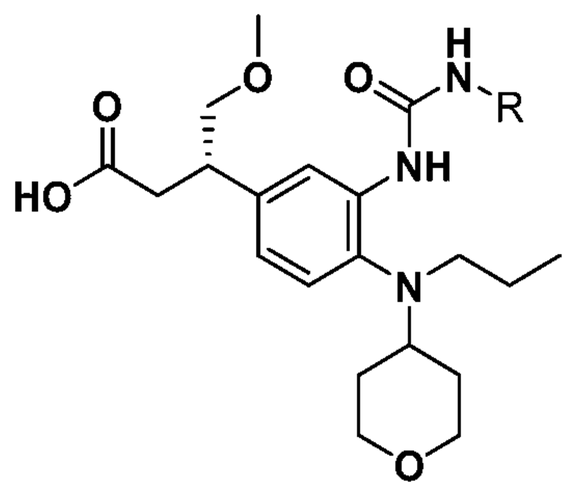
566A was prepared using compound 558B and 4-chloro-2-fluoro-1-isocyanato benzene following the procedure described for the synthesis of 487C. LC-MS Anal. Calc'd. for $C_{27}H_{35}ClFN_3O_5$ 535.2, found [M+H] 536.4, T_r = 1.61 min. (Method BA).

Example 566 Enantiomer 1. (S)-3-(3-(3-(4-Chloro-2-fluorophenyl)ureido)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid

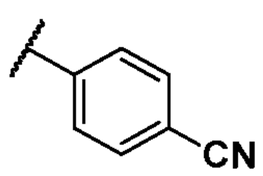
Example 566 Enantiomer 1 was prepared utilizing compound 566A following the procedure described for the synthesis of Example 486 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{26}H_{33}ClFN_3O_5$ 521.2, found [M+H] 522.2. T_r = 1.76 min ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (s, 1H), 8.78 (s, 1H), 8.12 (t, J = 8.80 Hz, 1H), 8.05 (s, 1H), 7.45 (dd, J = 11.20, 2.40 Hz, 1H), 7.21-7.23 (m, 1H), 7.16 (d, J = 8.00 Hz, 1H), 6.86 (d, J = 7.60 Hz, 1H), 3.80-3.83 (m, 2H), 3.17-3.40 (m, 6H), 2.85-2.89 (m, 3H), 2.61-2.67 (m, 1H), 2.43-2.45 (m, 1H), 1.68-1.71 (m, 2H), 1.38-1.41 (m, 2H), 1.18-1.20 (m, 2H), 0.77 (t, J = 7.60 Hz, 3H) (2H is buried under the Solvent residual peak).

Example 567

(Enantiomer 1)



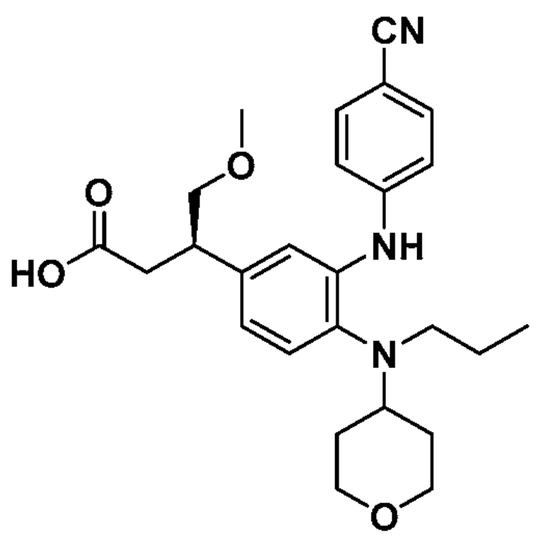
Example 567 was prepared using 558B and corresponding isocyanates following the procedure described for the synthesis of Example 566.

Ex. No.	Name	R	T_r min	Method	(M+H)
567	(S)-3-(3-(3-(4-cyanophenyl) ureido)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.54	O	495.3

Example 568

(Enantiomer 2)

(R)-3-(3-((4-Cyanophenyl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid



568A. Methyl 4-methoxy-(R)-3-(3-nitro-4-(propyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)butanoate

568A was prepared utilizing S-BINAP and 535C following the procedure described for the synthesis of 558A. LC-MS Anal. Calc'd. for $C_{20}H_{30}N_2O_6$ 394.4, found [M+H] 395.4, T_r = 2.81 min. (Method N).

568B. Methyl (R)-3-(3-amino-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoate

568B was prepared using 568A following the procedure described for the synthesis of 558B. Enantiomer 1. SFC chiral purity of 568B Enantiomer 2 shows 100% ee (T_r = 5.23 min. (Method AF). LC-MS Anal. Calc'd. for $C_{20}H_{32}N_2O_4$ 364.4, found [M+H] 365.2, T_r = 2.69 min. (Method N).

568C. Methyl (R)-3-(3-((4-cyanophenyl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoate

568C was prepared using 568B Enantiomer 2 and 4-bromobenzonitrile following the procedure described for the synthesis of 558C. LC-MS Anal. Calc'd. for $C_{27}H_{35}N_3O_4$ 465.5, found [M+H] 466.2, T_r = 3.6 min. (Method N).

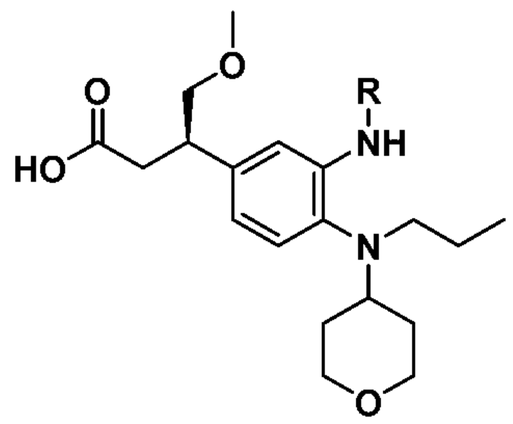
Example 568 Enantiomer 2. (R)-3-(3-((4-Cyanophenyl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid

Example 568 Enantiomer 2 was prepared utilizing compound 568C following the procedure described for the synthesis of Example 455 Enantiomer 1. LC-MS Anal.

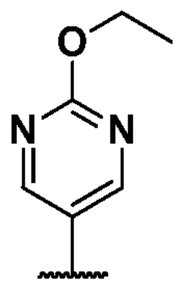
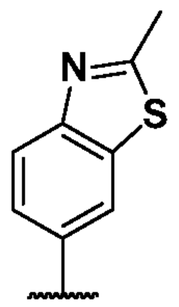
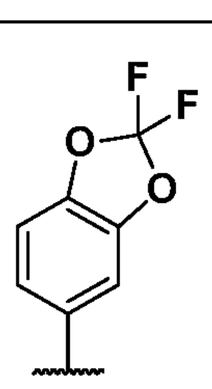
Calc'd. for $C_{26}H_{33}N_3O_4$ 451.2, found [M+H] 452.2, T_r = 1.72 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.57 (d, *J* = 8.80 Hz, 2H), 7.17-7.18 (m, 2H), 7.07-7.09 (m, 2H), 6.94 (dd, *J* = 8.40, 1.80 Hz, 1H), 3.76-3.80 (m, 2H), 3.42-3.47 (m, 2H), 3.24-3.34 (m, 4H), 3.05-3.10 (m, 2H), 2.88-2.91 (m, 3H), 2.64-2.68 (m, 1H), 1.55-1.58 (m, 2H), 1.43-1.48 (m, 2H), 1.21-1.25 (m, 2H), 0.76 (t, *J* = 7.20 Hz, 3H). (1H is buried under solvent peak).

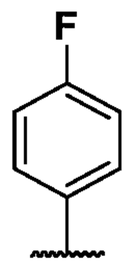
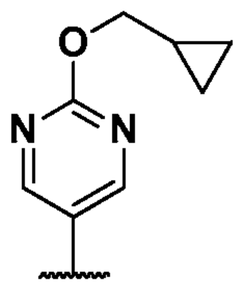
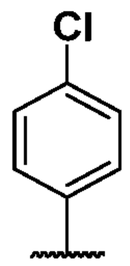
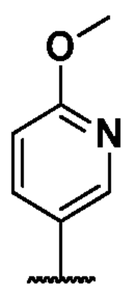
Examples 569 to 575

(Enantiomer 2)



Examples 569 to 575 were prepared using 568B and corresponding aryl halides following the procedure described for the synthesis of Example 568.

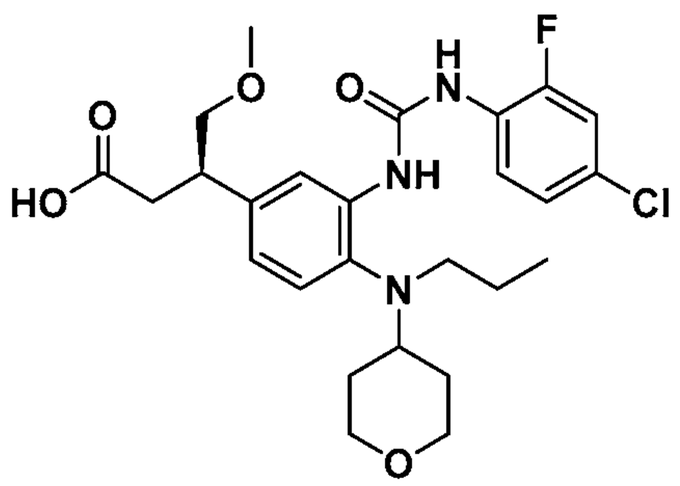
Ex. No.	Name	R	T_r min	Method	(M+H)
569	(R)-3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.56	O	473.3
570	4-methoxy-(R)-3-(3-((2-methylbenzo[d]thiazol-6-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) butanoic acid		1.75	O	498.2
571	3-(3-((2,2-difluorobenzo[d][1,3] dioxol-5-yl)amino)-4-(propyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		2.04	O	507.2

Ex. No.	Name	R	T_r min	Method	(M+H)
572	(R)-3-(3-((4-fluorophenyl) amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.82	O	445.2
573	(R)-3-(3-((2-(cyclopropylmethoxy)pyrimidin-5-yl)amino)-4-(propyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.51	O	499.4
574	(R)-3-(3-((4-chlorophenyl) amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.78	O	461.3
575	4-methoxy-(R)-3-(3-((6-methoxypyridin-3-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)butanoic acid		1.65	O	458.2

Example 576

(Enantiomer 2)

(R)-3-(3-(3-(4-Chloro-2-fluorophenyl)ureido)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid



576A. Methyl (R)-3-(3-(3-(4-chloro-2-fluorophenyl)ureido)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoate

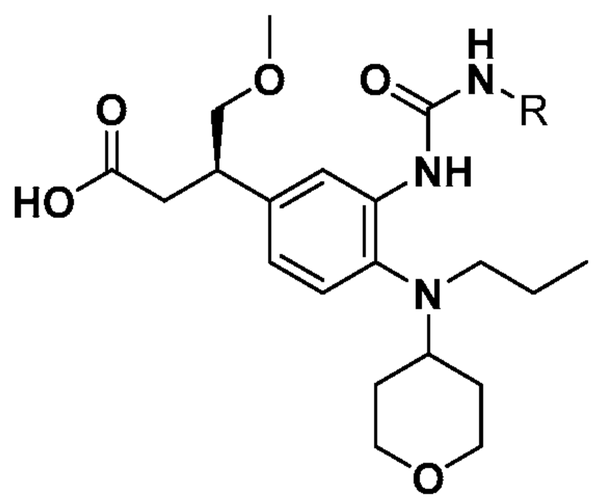
576A was prepared using compound 568B and 4-chloro-2-fluoro-1-isocyanatobenzene following the procedure described for the synthesis of 487C. LC-MS Anal. Calc'd. for $C_{27}H_{35}ClFN_3O_5$ 535.2, found [M+H] 536.4, T_r = 1.59 min. (Method BA).

Example 576 Enantiomer 2. (R)-3-(3-(3-(4-Chloro-2-fluorophenyl)ureido)-4-(propyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid

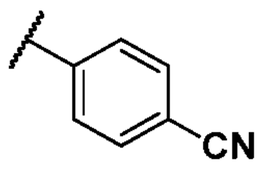
Example 576 Enantiomer 2 was prepared utilizing compound 576A following the procedure described for the synthesis of Example 455 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{26}H_{33}ClFN_3O_5$ 521.2, found [M+H] 522.2. T_r = 1.76 min ^{1}H NMR 400 MHz, DMSO-d_6: δ 9.54 (s, 1H), 8.78 (s, 1H), 8.12 (t, J = 8.80 Hz, 1H), 8.05 (s, 1H), 7.45 (dd, J = 11.20, 2.40 Hz, 1H), 7.21-7.23 (m, 1H), 7.16 (d, J = 8.00 Hz, 1H), 6.86 (d, J = 7.60 Hz, 1H), 3.80-3.83 (m, 2H), 3.17-3.40 (m, 6H), 2.85-2.89 (m, 3H), 2.61-2.67 (m, 1H), 2.43-2.45 (m, 1H), 1.68-1.71 (m, 2H), 1.38-1.41 (m, 2H), 1.18-1.20 (m, 2H), 0.77 (t, J = 7.60 Hz, 3H) (2H is buried under the Solvent residual peak).

Example 577

(Enantiomer 2)



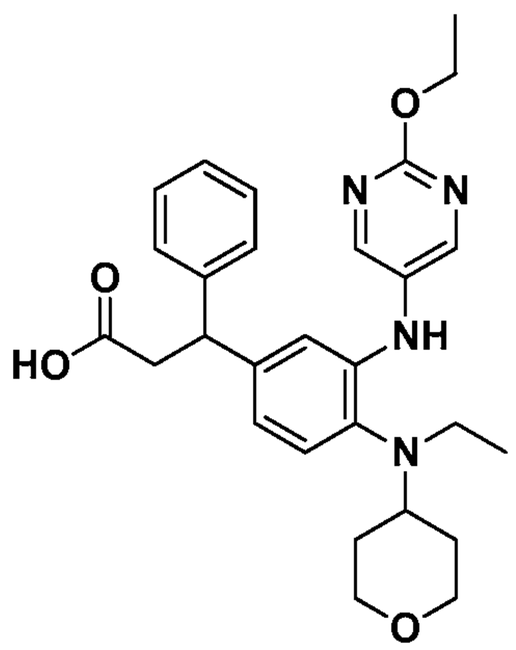
Example 577 was prepared using 568B and corresponding isocyanates following the procedure described for the synthesis of Example 576.

Ex. No.	Name	R	T_r min	Method	(M+H)
577	(R)-3-(3-(3-(4-cyanophenyl) ureido)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4-methoxybutanoic acid		1.54	O	495.2

Example 578

(Enantiomer 1)

3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-phenylpropanoic acid



578A. Methyl 3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)-3-phenylpropanoate

1,4-Dioxane (20 mL) was purged with argon for 10 minutes, then chlorobis (ethylene)rhodium(I) dimer (0.032 g, 0.083 mmol), (R)-BINAP (0.076 g, 0.121 mmol) was added and purged with argon for 5 minutes. To the above reaction mixture 455C (2 g, 5.52 mmol), methyl cinnamate (1.075 g, 6.63 mmol), sodium hydroxide (5.04 mL, 5.04 mmol) were added respectively and purged argon for another 5 minutes. The reaction mixture was heated at 50 °C and stirred for 3 h. Reaction mixture was cooled to room temperature and quenched with acetic acid (0.284 mL, 4.97 mmol) and it was stirred for 5 minutes before it was partitioned between ethyl acetate (100 mL) and water (100 mL). Aqueous layer was extracted with ethyl acetate (2 × 75 mL). The combined organic layers were washed with brine (75 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification via silica gel flash chromatography

gave 578A (pale orange solid, 0.6 g, 1.396 mmol, 25.3% yield). LC-MS Anal. Calc'd. for $C_{23}H_{28}N_2O_5$ 412.4, found [M+H] 413.2, T_r = 1.175 min (Method N).

578B. Methyl 3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-phenylpropanoate

578B was prepared utilizing compound 578A following the procedure described for the synthesis of 455E. SFC chiral purity of 578B Enantiomer 1 shows 100% ee (T_r = 4.3 min). (Method Z). LC-MS Anal. Calc'd. for $C_{23}H_{30}N_2O_3$ 382.4, found [M+H] 383.1, T_r = 3.6 min. (Method N).

578C. Methyl 3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-phenylpropanoate

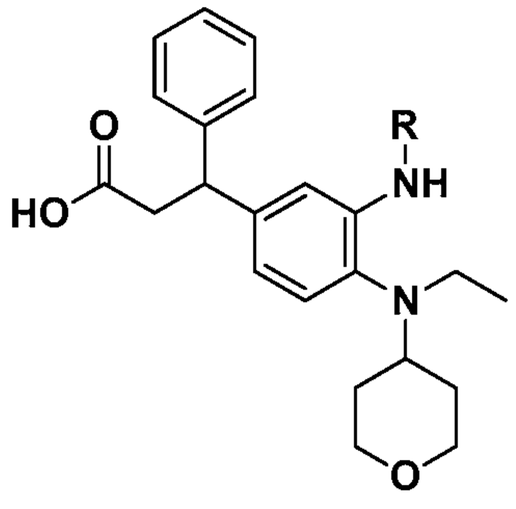
578C was prepared utilizing compound 578B and 5-bromo-2-ethoxypyrimidine following the procedure described for the synthesis of 455F. LC-MS Anal. Calc'd. for $C_{29}H_{36}N_4O_4$ 504.2, found [M+H] 505, T_r = 3.01 min. (Method N).

Example 578 Enantiomer 1. 3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-phenylpropanoic acid

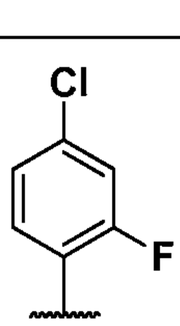
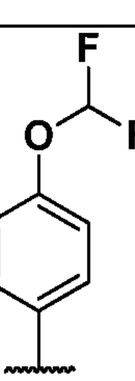
Example 578 Enantiomer 1 was prepared utilizing compound 578C following the procedure described for the synthesis of Example 455 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{28}H_{34}N_4O_4$ 490.2, found [M+H] 491.4, T_r = 1.84 min (Method R). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (s, 2H), 7.27-7.31 (m, 5H), 7.15-7.17 (m, 3H), 6.73-6.79 (m, 1H), 4.30-4.32 (m, 3H), 3.78-3.80 (m, 2H), 3.19-3.22 (m, 2H), 2.93-2.95 (m, 5H), 1.64-1.67 (m, 2H), 1.41-1.43 (m, 2H), 1.34 (t, *J* = 7.20 Hz, 3H), 0.81 (t, *J* = 10.40 Hz, 3H).

Examples 579 to 583

(Enantiomer 1)



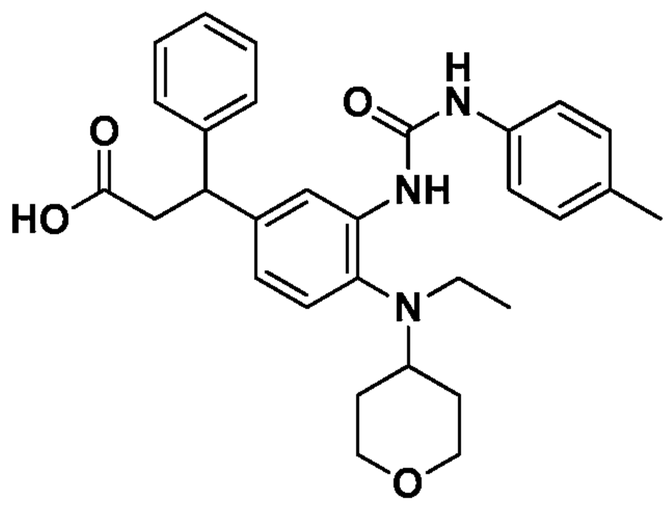
Examples 579 to 583 were prepared using 578B and corresponding aryl halides following the procedure described for the synthesis of Example 578 Enantiomer 1.

Ex. No.	Name	R	T_r min	Method	(M+H)
579	3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methylbenzo[d]thiazol-6-yl)amino)phenyl)-3-phenylpropanoic acid		1.544	R	516.2
580	3-(3-((4-chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-phenylpropanoic acid		2.184	R	479.2
581	3-(3-((4-cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-phenylpropanoic acid		1.54	R	470.2
582	3-(3-((4-chloro-2-fluorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-phenylpropanoic acid		2.052	R	497.2
583	3-(3-((4-(difluoromethoxy)phenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-phenylpropanoic acid		2.11	R	511.2

Example 584

(Enantiomer 1)

3-(4-(Ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)-3-phenylpropanoic acid



584A. Methyl 3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)-3-phenylpropanoate

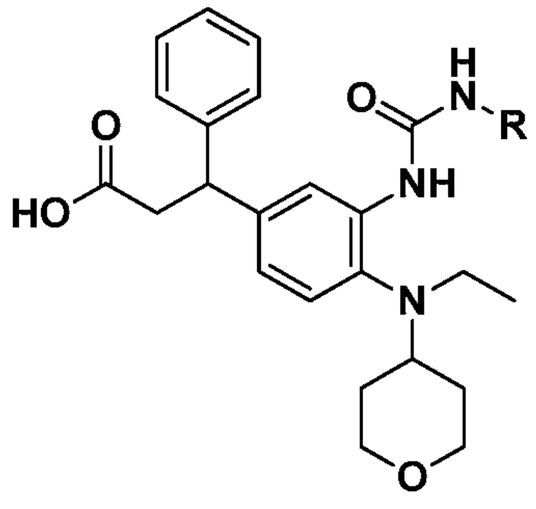
584A was prepared using compound 578B and 4-methyl-1-isocyanato benzene following the procedure described for the synthesis of 487C. LC-MS Anal. Calc'd. $C_{31}H_{37}N_3O_4$ for 515.28 found [M+H] 516.3 T_r = 1.81 min. (Method R).

Example 584 Enantiomer 1. 3-(4-(Ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)-3-phenylpropanoic acid

Example 584 Enantiomer 1 was prepared utilizing compound 584A following the procedure described for the synthesis of Example 487 Enantiomer 1. LC-MS Anal. Calc'd. $C_{30}H_{35}N_3O_4$ for 501.2, found [M+H] 502.3, T_r = 2.15 min. (Method R). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (s, 1H), 8.85 (s, 1H), 8.19 (s, 1H), 7.35-7.37 (m, 2H), 7.28-7.29 (m, 5H), 7.14-7.17 (m, 4H), 4.34 (s, 1H), 3.79-3.82 (m, 2H), 3.21-3.24 (m, 2H), 2.93-2.95 (m, 5H), 2.25 (s, 3H), 1.67-1.70 (m, 2H), 1.24-1.25 (m, 2H), 0.78 (t, *J* = 6.80 Hz, 3H).

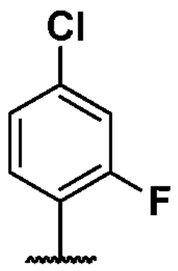
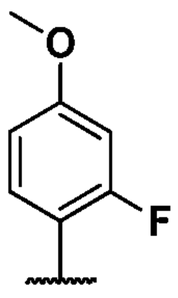
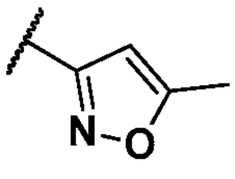
Examples 585 to 587

(Enantiomer 1)



Examples 585 and 586 were prepared by using 578B and corresponding isocyanates following the procedure described for the synthesis of Example 584.

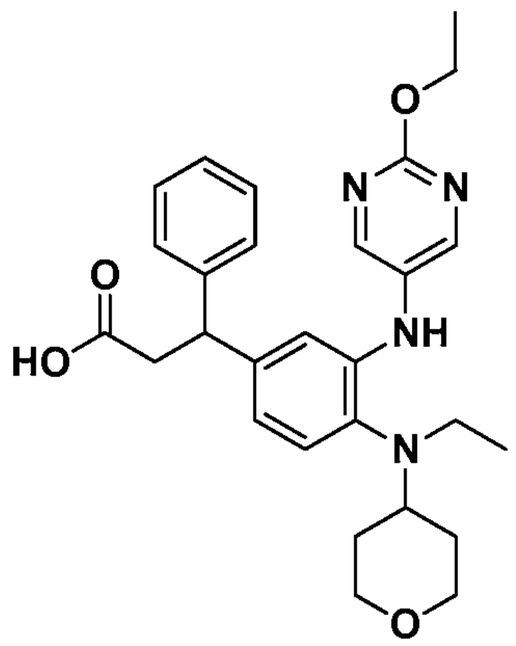
Example 587 were prepared using 578B and corresponding amines following the procedure described for the synthesis of Example 488.

Ex. No.	Name	R	T_r min	Method	(M+H)
585	3-(3-(3-(4-chloro-2-fluorophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-phenylpropanoic acid		2.29	O	540.2
586	3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(2-fluoro-4-methoxyphenyl)ureido)phenyl)-3-phenylpropanoic acid		2.065	O	536.4
587	3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(5-methylisoxazol-3-yl)ureido) phenyl)-3-phenylpropanoic acid		2.027	O	493.4

Example 588

(Enantiomer 2)

3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-phenylpropanoic acid



588A. Methyl 3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)-3-phenylpropanoate

588A was prepared utilizing S-BINAP and 455C following the procedure described for the synthesis of 578A. LC-MS Anal. Calc'd. for $C_{23}H_{28}N_2O_5$ 412.4, found [M+H] 413.2, T_r = 1.174 min (Method N).

588B. Methyl 3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-phenylpropanoate

588B was prepared utilizing compound 588A following the procedure described for the synthesis of 455E. SFC chiral purity of 588B Enantiomer 2 shows 97.6% ee (T_r = 4.9 min). (Method Z). LC-MS Anal. Calc'd. for $C_{23}H_{30}N_2O_3$ 382.4, found [M+H] 383.1, T_r = 3.01 min. (Method N).

588C. Methyl 3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-phenylpropanoate

588C was prepared utilizing compound 588B and 5-bromo-2-ethoxypyrimidine following the procedure described for the synthesis of 455F. LC-MS Anal. Calc'd. for $C_{29}H_{36}N_4O_4$ 504.2, found [M+H] 505, T_r = 3.01 min. (Method N).

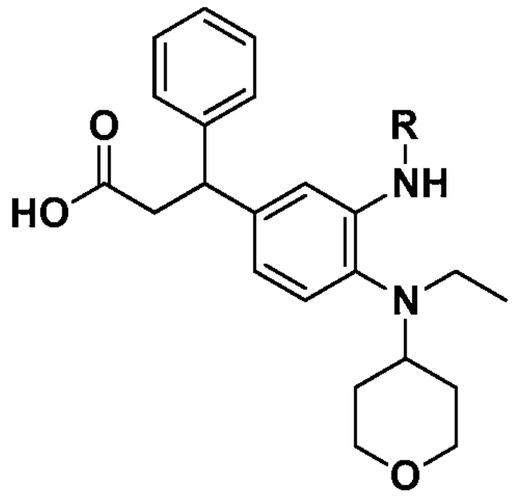
Example 588 Enantiomer 2. 3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-phenylpropanoic acid

Example 588 Enantiomer 2 was prepared utilizing compound 588C following the procedure described for the synthesis of Example 455 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{28}H_{34}N_4O_4$ 490.2, found [M+H] 491.4, T_r = 1.87 min. (Method R). ^{1}H NMR

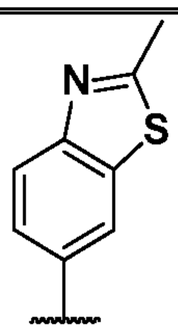
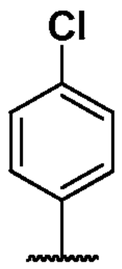
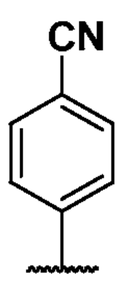
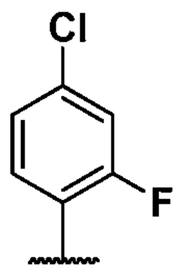
(400 MHz, DMSO-d_6) δ 8.40 (s, 2H), 7.27-7.31 (m, 5H), 7.15-7.17 (m, 3H), 6.73-6.79 (m, 1H), 4.30-4.32 (m, 3H), 3.78-3.80 (m, 2H), 3.19-3.22 (m, 2H), 2.93-2.95 (m, 5H), 1.64-1.67 (m, 2H), 1.41-1.43 (m, 2H), 1.31 - 1.39 (m, 3H), 0.81 (t, J = 10.40 Hz, 3H).

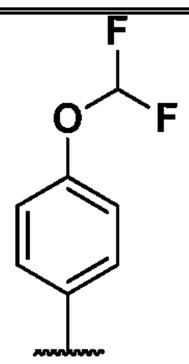
Examples 589 to 593

(Enantiomer 2)



Examples 589 to 593 were prepared using 588B and corresponding aryl halides following the procedure described for the synthesis of Example 588.

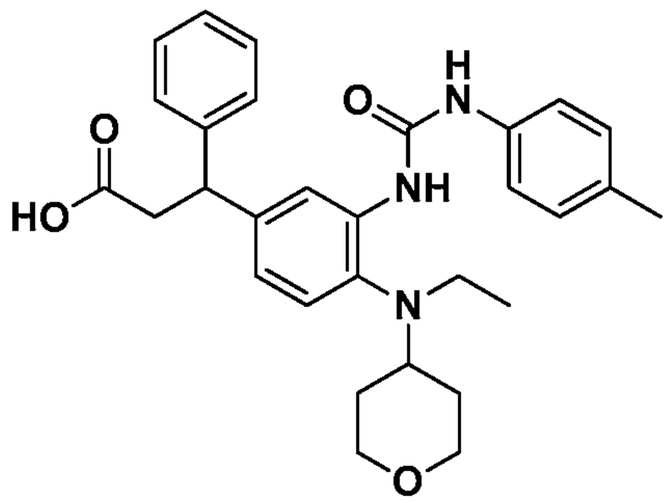
Ex. No.	Name	R	T_r min	Method	(M+H)
589	3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methylbenzo[d]thiazol-6-yl)amino)phenyl)-3-phenylpropanoic acid		1.895	R	516.3
590	3-(3-((4-chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-phenylpropanoic acid		2.16	R	479.3
591	3-(3-((4-cyanophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-phenylpropanoic acid		1.9	R	470.3
592	3-(3-((4-chloro-2-fluorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-phenylpropanoic acid		2.41	R	497.3

Ex. No.	Name	R	T_r min	Method	(M+H)
593	3-(3-((4-(difluoromethoxy)phenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-phenylpropanoic acid		2.11	R	511.2

Example 594

(Enantiomer 2)

3-(4-(Ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)-3-phenylpropanoic acid



594A. Methyl 3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl)ureido)phenyl)-3-phenylpropanoate

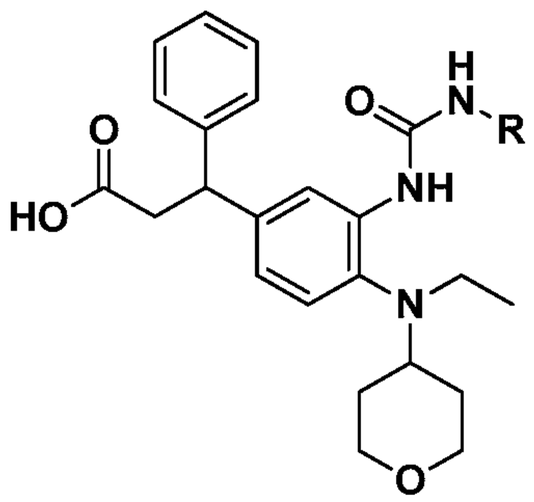
594A was prepared using 588B and 4-methyl-1-isocyanatobenzene following the procedure described for the synthesis of 584A. LC-MS Anal. Calc'd. $C_{31}H_{37}N_3O_4$ for 515.28, found [M+H] 516.3, T_r = 1.81 min. (Method R).

Example 594 Enantiomer 2. 3-(4-(Ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(*p*-tolyl) ureido)phenyl)-3-phenylpropanoic acid

Example 594 Enantiomer 2 was prepared utilizing compound 594A following the procedure described for the synthesis of Example 455 Enantiomer 1. LC-MS Anal. Calc'd. $C_{30}H_{35}N_3O_4$ for 501.2, found [M+H] 502.3, T_r = 2.15 min. (Method R). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (s, 1H), 8.85 (s, 1H), 8.19 (s, 1H), 7.35-7.37 (m, 2H), 7.28-7.29 (m, 5H), 7.14-7.17 (m, 4H), 4.34 (s, 1H), 3.79-3.82 (m, 2H), 3.21-3.24 (m, 2H), 2.93-2.95 (m, 5H), 2.25 (s, 3H), 1.67-1.70 (m, 2H), 1.24-1.25 (m, 2H), 0.78 (t, *J* = 6.80 Hz, 3H).

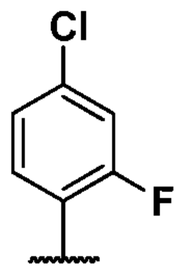
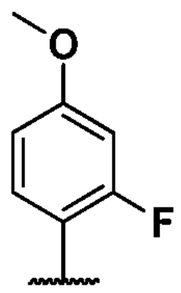
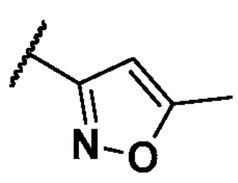
Examples 595 to 597

(Enantiomer 2)



Examples 595 and 596 were prepared using 588B and corresponding isocyanates following the procedure described for the synthesis of Example 487.

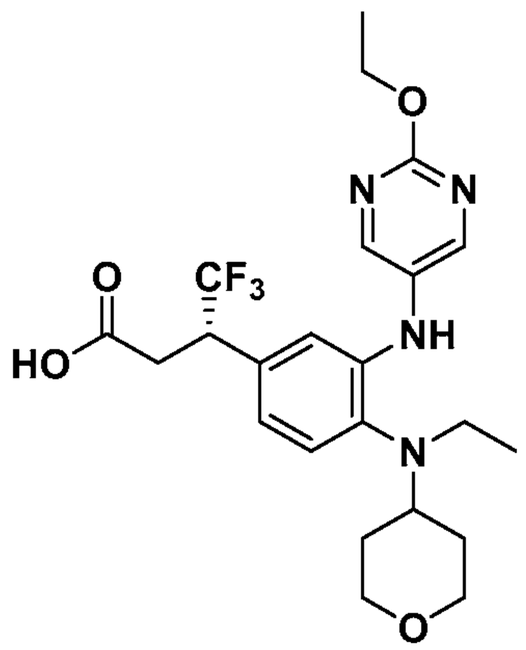
Example 597 was prepared using 588B and corresponding amines following the procedure described for the synthesis of Example 488.

Ex. No.	Name	R	T_r min	Method	(M+H)
595	3-(3-(3-(4-chloro-2-fluorophenyl)ureido)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-3-phenylpropanoic acid		1.198	O	540.2
596	3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(2-fluoro-4-methoxyphenyl)ureido)phenyl)-3-phenylpropanoic acid		1.702	O	536.3
597	3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(5-methylisoxazol-3-yl)ureido) phenyl)-3-phenylpropanoic acid		1.661	O	493.2

Example 598

(Enantiomer 1)

(S)-3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4,4,4-trifluorobutanoic acid



598A. Methyl (S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)-4,4,4-trifluorobutanoate

1,4-Dioxane (6 mL) was purged with argon for 10 minutes, then chlorobis (ethylene)rhodium(I) dimer (8.05 mg, 0.021 mmol) and (R)-BINAP (18.91 mg, 0.030 mmol) was added and the mixture purged with argon for another 10 minutes. To the above reaction mixture was added N-(4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2-nitrophenyl)-N-ethyltetrahydro-2H-pyran-4-amine (500 mg, 1.380 mmol), (E)-methyl 4,4,4-trifluorobut-2-enoate (277 mg, 1.794 mmol) and sodium hydroxide (1.242 mL, 1.242 mmol). The resulting mixture was then purged with argon for 10 minutes. The reaction mixture was heated at 50 °C for 3 h in a sealed tube and then cooled to room temperature followed by quenching with acetic acid (0.071 mL, 1.242 mmol). Stirring was continued for 5 minutes before it was partitioned between ethyl acetate (25 ml) and water (25 mL). The aqueous layer was extracted with ethyl acetate (2 × 15 mL) and the combined organic layers were washed with brine (25 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification via silica gel flash chromatography gave 598A (pale orange liquid, (230 mg, 0.596 mmol, 41.2%). LC-MS Anal. Calc'd. for $C_{18}H_{23}F_3N_2O_5$ 404.38, found [M+H] 405.2, T_r = 3.12 min. (Method N).

598B. Methyl (S)-3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4,4,4-trifluorobutanoate

598B was prepared utilizing compound 598A following the procedure described for the synthesis of 455E. SFC chiral purity of 598B Enantiomer 1 shows 100% ee (T_r = 1.82 min). (Method AF). LC-MS Anal. Calc'd. for $C_{18}H_{25}F_3N_2O_3$ 374.3 found [M+H] 375.2 T_r = 3.99 min. (Method N).

598C. Methyl (S)-3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4,4,4-trifluorobutanoate

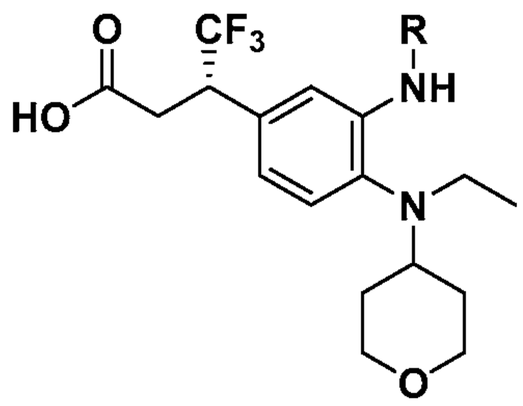
598C was prepared utilizing 598B and 5-bromo-2-ethoxypyrimidine following the procedure described for the synthesis of 455F. LC-MS Anal. Calc'd. for $C_{24}H_{31}F_3N_4O_4$ 496.5, found [M+H] 497.2, T_r = 1.53 min. (Method T).

Example 598 Enantiomer 1. (S)-3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)-4,4,4-trifluorobutanoic acid

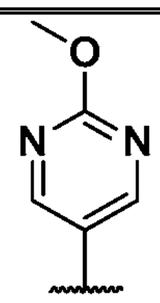
Example 598 Enantiomer 1 was prepared utilizing 598C following the procedure described for the synthesis of Example 455 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{23}H_{29}F_3N_4O_4$ 482.4, found [M+H] 483.1, T_r = 1.485 min. (Method O). ^{1}H NMR (400 MHz, MeOD) δ 8.42 (s, 2H), 7.23 (d, *J* = 8.40 Hz, 1H), 6.95 (s, 1H), 6.88 (d, *J* = 8.00 Hz, 1H), 4.39-4.44 (m, 2H), 3.89-3.90 (m, 2H), 3.85-3.86 (m, 1H), 3.33-3.36 (m, 2H), 3.08-3.11 (m, 3H), 2.91-2.92 (m, 1H), 2.81-2.83 (m, 1H), 1.77-1.80 (m, 2H), 1.54-1.60 (m, 2H), 1.41 (t, *J* = 7.20 Hz, 3H), 0.92 (t, *J* = 7.20 Hz, 3H).

Example 599

(Enantiomer 1)



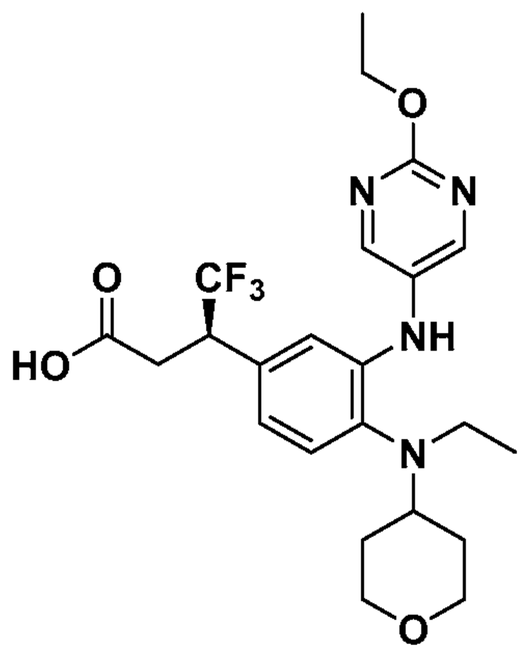
Example 599 was prepared using 598B and corresponding aryl halides (as in step 598C) following the procedure described for the synthesis of Example 598.

Ex. No.	Name	R	T_r min	Method	(M+H)
599	(S)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methoxypyrimidin-5-yl)amino) phenyl)-4,4,4-trifluorobutanoic acid		1.42	O	468.4

Example 600

(Enantiomer 2)

(R)-3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4,4,4-trifluorobutanoic acid



600A. Methyl (R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)-4,4,4-trifluorobutanoate

600A was prepared utilizing S-BINAP and 455C following the procedure described for the synthesis of 598A. LC-MS Anal. Calc'd. for $C_{18}H_{23}F_3N_2O_5$ 404.38, found [M+H] 405.2, T_r = 3.5 min. (Method N).

600B. Methyl (R)-3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4,4,4-trifluorobutanoate

600B was prepared utilizing compound 600A following the procedure described for the synthesis of 455E. SFC chiral purity of 600B shows 100% ee (T_r = 2.27 min). (Method AF). LC-MS Anal. Calc'd. for $C_{18}H_{25}F_3N_2O_3$ 374.3, found [M+H] 375.2, T_r = 2.9 min. (Method N).

600C. Methyl (R)-3-(3-((2-ethoxypyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-4,4,4-trifluorobutanoate

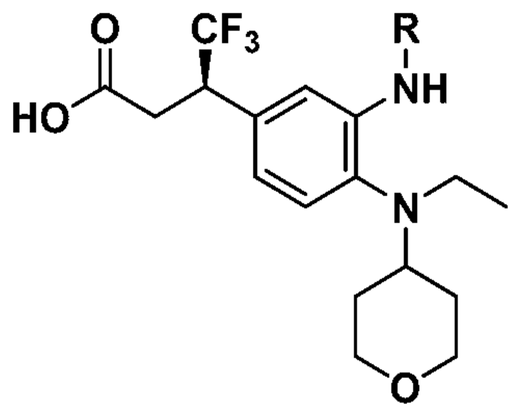
600C was prepared utilizing compound 600B and 5-bromo-2-ethoxypyrimidine following the procedure described for the synthesis of 455F. LC-MS Anal. Calc'd. for $C_{24}H_{31}F_3N_4O_4$ 496.5, found [M+H] 497.2, T_r = 1.53 min. (Method T).

Example 600 Enantiomer 2. (R)-3-(3-((2-Ethoxypyrimidin-5-yl)amino)-4-(ethyl (tetrahydro-2H-pyran-4-yl)amino)phenyl)-4,4,4-trifluorobutanoic acid

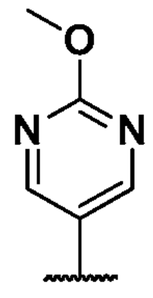
Example 600 Enantiomer 2 was prepared utilizing compound 600C following the procedure described for the synthesis of Example 455 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{23}H_{29}F_3N_4O_4$ 482.4, found [M+H] 483.1, T_r = 1.532 min (Method O). ^{1}H NMR (400 MHz, MeOD) δ 8.42 (s, 2H), 7.23 (d, *J* = 8.40 Hz, 1H), 6.95 (s, 1H), 6.88 (d, *J* = 8.00 Hz, 1H), 4.39-4.44 (m, 2H), 3.89-3.90 (m, 2H), 3.85-3.86 (m, 1H), 3.33-3.36 (m, 2H), 3.08-3.11 (m, 3H), 2.91-2.92 (m, 1H), 2.81-2.83 (m, 1H), 1.77-1.80 (m, 2H), 1.54-1.60 (m, 2H), 1.41 (t, *J* = 7.20 Hz, 3H), 0.92 (t, *J* = 7.20 Hz, 3H).

Example 601

(Enantiomer 2)



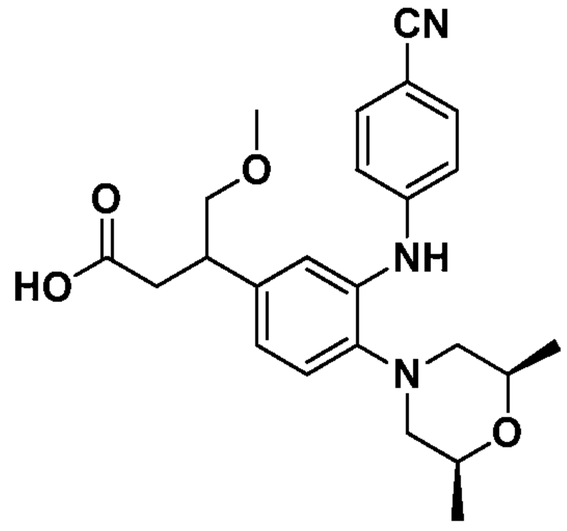
Example 601 was prepared using 600 B and corresponding aryl halides following the procedure described for the synthesis of Example 600.

Ex. No.	Name	R	T_r min	Method	(M+H)
601	(R)-3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-((2-methoxypyrimidin-5-yl)amino) phenyl)-4,4,4-trifluorobutanoic acid		1.43	O	469.1

Example 602

(Diastereomer 1 and Diastereomer 2)

3-(3-((4-Cyanophenyl)amino)-4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxybutanoic acid



602A. (2S,6R)-4-(4-Bromo-2-nitrophenyl)-2,6-dimethylmorpholine

To a stirred solution of 4-bromo-1-fluoro-2-nitrobenzene (5 g, 22.73 mmol) and (2S,6R)-2,6-dimethylmorpholine (2.62 g, 22.73 mmol) in NMP (10 mL) was added DIPEA (11.91 mL, 68.2 mmol). Then the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate (100 mL). The organic layers were then washed sequentially with 10% aq. AcOH solution, 10% $NaHCO_3$ solution, brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude material. Purification via silica gel flash chromatography gave 602A (pale orange solid, 6.2 g, 19.48 mmol, 86% yield). LCMS Anal. Calc'd. $C_{12}H_{15}BrN_2O_3$ 315.1, found [M+2H] 317.0, T_r = 3.8 min (Method N).

602B.(2S,6R)-4-(4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-2-nitrophenyl)-2,6-dimethylmorpholine

To a stirred solution of 602A (6.2 g, 19.67 mmol) in DMSO (70 mL) was added bis(neopentyl glycolato)diboron (5.78 g, 25.6 mmol) and potassium acetate (5.79 g, 59.0 mmol). The above reaction mixture was purged with argon for 10 minutes. Then $PdCl_2$ (dppf)•CH_2Cl_2 Adduct (0.482 g, 0.590 mmol) was added and the reaction mixture was purged for another 10 min. The flask was sealed and the reaction mixture heated at 80 °C and stirred for 12 hours. The reaction mixture was cooled to room temperature and then poured into water (100 mL) and extracted with EtOAc (2 × 75 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and

concentrated under reduced pressure to give the crude material. Purification via silica gel flash chromatography gave 602B (pale orange liquid, 3 g, 8.62 mmol, 43.8% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 2.00 Hz, 1H), 7.84 (dd, J = 10.80, 2.00 Hz, 1H), 7.02 (d, J = 11.20 Hz, 1H), 3.82-3.88 (m, 2H), 3.75 (s, 4H), 3.08-3.12 (m, 2H), 2.57-2.64 (m, 2H), 1.20 (d, J = 8.40 Hz, 6H), 1.01 (s, 6H).

602C. Methyl 3-(4-((2S,6R)-2,6-dimethylmorpholino)-3-nitrophenyl)-4-methoxybutanoate

602C was prepared utilizing compound 602B following the procedure described for the synthesis of 558A. LC-MS Anal. Calc'd. for $C_{18}H_{26}N_2O_6$ 366.4, found [M+H] 367.2, T_r = 2.49 min. (Method BE).

602D. Methyl 3-(3-amino-4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxybutanoate

602D was prepared utilizing compound 602C following the procedure described for the synthesis of 455E.

Chiral separation of 602D (Method CC) gave Diastereomer 1 and Diastereomer 2.

602D Diastereomer 1 (absolute and relative stereochemistry not determined): SFC chiral purity shows 100% ee (T_r = 4.87 min). (Method CC). LC-MS Anal. Calc'd. for $C_{18}H_{28}N_2O_4$ 336.4, found [M+H] 337.3, T_r = 2.8 min. (Method N).

602D Diastereomer 2 (absolute and relative stereochemistry not determined): SFC chiral purity shows 100% ee (T_r = 6.6 min). (Method CC). LC-MS Anal. Calc'd. for $C_{18}H_{28}N_2O_4$ 336.4, found [M+H] 337.3, T_r = 2.3 min. (Method N).

602E. Methyl 3-(3-((4-cyanophenyl)amino)-4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxybutanoate

602E was prepared utilizing 602D Diastereomer and 4-bromobenzonitrile following the procedure described for the synthesis of 455F. LC-MS Anal. Calc'd. for $C_{25}H_{31}N_3O_4$ 437.5, found [M+H] 438.2, T_r = 1.42 min. (Method BA).

Example 602 Diastereomer 1. 3-(3-((4-Cyanophenyl)amino)-4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxybutanoic acid (absolute and relative stereochemistry not determined)

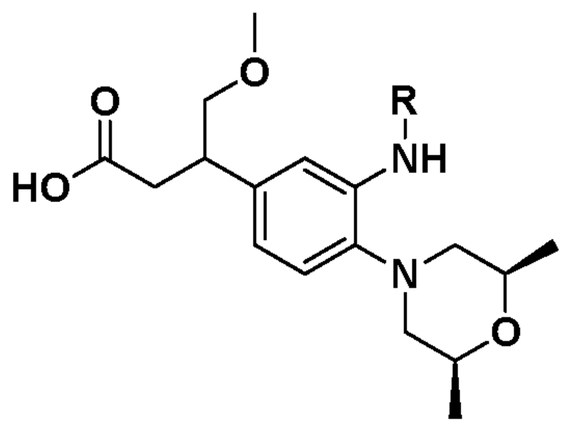
Example 602 Diastereomer 1 was prepared utilizing 602E following the procedure described for the synthesis of Example 455 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{24}H_{29}N_3O_4$ 423.5, found [M+H] 424.3, T_r = 1.28 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.51 (d, *J* = 8.80 Hz, 2H), 7.08 (s, 1H), 6.97 (s, 2H), 6.90 (d, *J* = 8.80 Hz, 2H), 3.16-3.21 (m, 6H), 2.97 (d, *J* = 10.80 Hz, 2H), 2.61-2.65 (m, 1H), 2.41-2.45 (m, 1H), 2.20-2.27 (m, 2H), 0.98-1.00 (m, 6H). (One multiplet of CH_2 is buried under the Solvent residual peak).

Example 602 Diastereomer 2. 3-(3-((4-Cyanophenyl)amino)-4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxybutanoic acid (absolute and relative stereochemistry not determined)

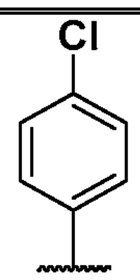
Example 602 Diastereomer 2 was prepared utilizing 602D Diastereomer 2 and 4-bromobenzonitrile following the procedure described for the synthesis of Example 455 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{24}H_{29}N_3O_4$ 423.5, found [M+H] 424.3, T_r = 1.28 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.51 (d, *J* = 8.80 Hz, 2H), 7.08 (s, 1H), 6.97 (s, 2H), 6.90 (d, *J* = 8.80 Hz, 2H), 3.16-3.21 (m, 6H), 2.97 (d, *J* = 10.80 Hz, 2H), 2.61-2.65 (m, 1H), 2.41-2.45 (m, 1H), 2.20-2.27 (m, 2H), 0.98-1.00 (m, 6H). (One multiplet of CH_2 is buried under the Solvent residual peak).

Example 603

(Diastereomer 1)

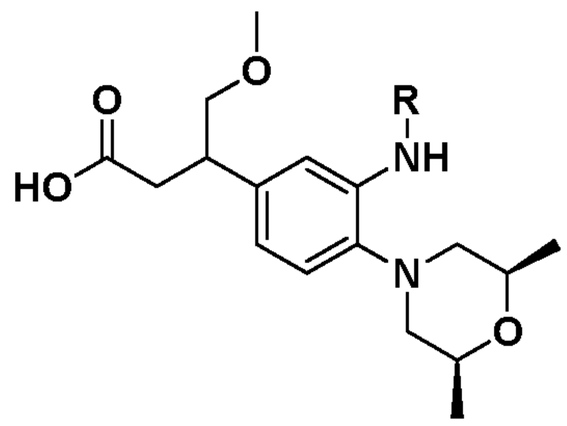


Example 603 was prepared using 602D Diastereomer 1 and corresponding aryl halides following the procedure described for the synthesis of Example 602 Diastereomer 1.

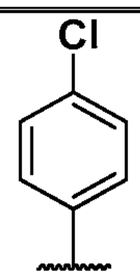
Ex. No.	Name	R	T_r min	Method	(M+H)
603	3-(3-((4-chlorophenyl)amino)-4-((2S,6R)-2,6-dimethylmorpholino) phenyl)-4-methoxybutanoic acid		1.86	O	433.1

Example 604

(Diastereomer 2)



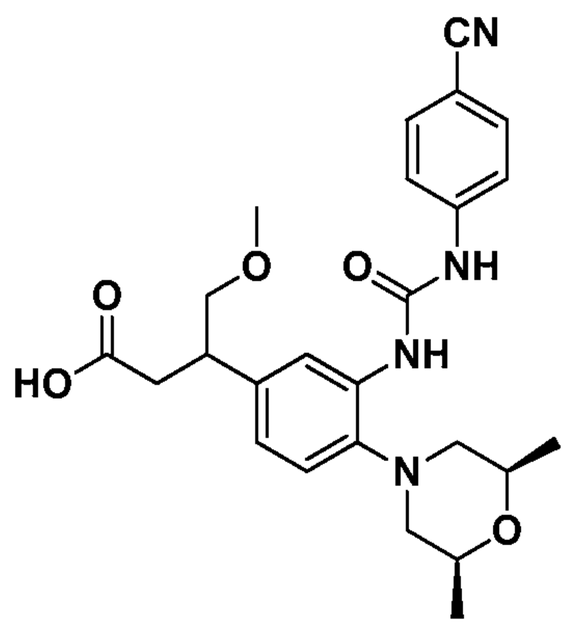
Example 604 were prepared using 602D Diastereomer 2 and corresponding aryl halides following the procedure described for the synthesis of Example 602 Diastereomer 2 (absolute and relative stereochemistry not determined).

Ex. No.	Name	R	T_r min	Method	(M+H)
604	3-(3-((4-chlorophenyl)amino)-4-((2S,6R)-2,6-dimethylmorpholino) phenyl)-4-methoxybutanoic acid		1.84	O	433.1

Example 605

(Diastereomer 1 and Diastereomer 2)

3-(3-(3-(4-Cyanophenyl)ureido)-4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxybutanoic acid



605A. Ethyl 3-(4-((2S,6R)-2,6-dimethylmorpholino)-3-nitrophenyl)-4-methoxybutanoate

605A was prepared using (E)-ethyl 4-methoxybut-2-enoate following the procedure described for the synthesis of 558A. LC-MS Anal. Calc'd. for $C_{19}H_{28}N_2O_6$ 380.4, found [M+H] 381.3, T_r = 4.089 min. (Method N).

605B. Ethyl 3-(3-amino-4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxybutanoate

605B was prepared utilizing 605A following the procedure described for the synthesis of 455E. Chiral separation of 605 B (Method CC) gave 605B Diastereomer 1 and 605B Diastereomer 2.

605B Diastereomer 1 (absolute and relative stereochemistry not determined): SFC chiral purity shows 100% ee (T_r = 4.89 min). (Method CC). LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_4$ 350.4, found [M+H] 351.2, T_r = 2.66 min. (Method N).

605B Diastereomer 2 (absolute and relative stereochemistry not determined): SFC chiral purity shows 100% ee (T_r = 6.97 min). (Method CC). LC-MS Anal. Calc'd. for $C_{19}H_{30}N_2O_4$ 350.4, found [M+H] 351.2, T_r = 2.66 min. (Method N).

605C. Ethyl 3-(3-(3-(4-cyanophenyl)ureido)-4-((2S,6R)-2,6-dimethylmorpholino) phenyl)-4-methoxybutanoate

605C was prepared using 605B Diastereomer 1 and 4-Cyano-1-isocyanatobenzene following the procedure described for the synthesis of 487C. LC-MS Anal. Calc'd. for $C_{27}H_{34}N_4O_5$ 494.2, found [M+2H] 495.3, T_r = 1.35 min. (Method BA).

Example 605 Diastereomer 1. 3-(3-(3-(4-Cyanophenyl)ureido)-4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxybutanoic acid (absolute and relative stereochemistry not determined)

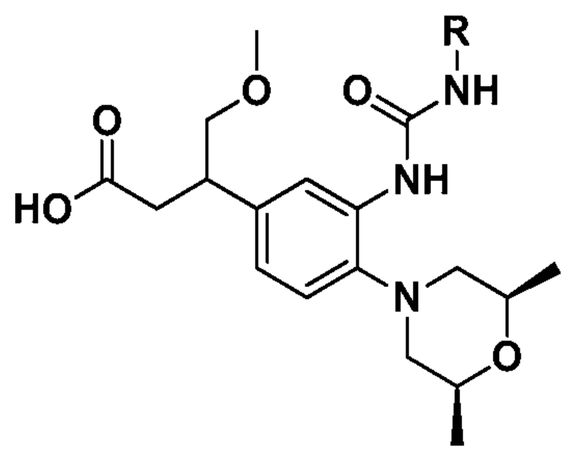
Example 605 Diastereomer 1 was prepared utilizing compound 605C following the procedure described for the synthesis of Example 455 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{25}H_{30}N_4O_5$ 466.5, found [M+H] 467.3, T_r = 1.314 min (Method O). ^{1}H NMR (400 MHz, MeOD) δ 8.05 (d, *J* = 2.00 Hz, 1H), 7.65-7.71 (m, 4H), 7.16 (d, *J* = 8.00 Hz, 1H), 6.97-6.99 (m, 1H), 3.95-3.99 (m, 2H), 3.53-3.57 (m, 2H), 3.33-3.38 (m, 4H), 2.77-2.86 (m, 3H), 2.55-2.61 (m, 1H), 2.42-2.48 (m, 2H), 1.19-1.21 (m, 6H).

Example 605 Diastereomer 2. 3-(3-(3-(4-Cyanophenyl)ureido)-4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxybutanoic acid (absolute and relative stereochemistry not determined)

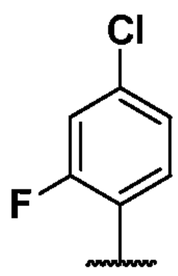
Example 605 Diastereomer 2 was prepared utilizing compound 605B Diastereomer 2 and 4-cyano-1-isocyanatobenzene following the procedure described for the synthesis of Example 605 Diastereomer 1 by. LC-MS Anal. Calc'd. for $C_{25}H_{30}N_4O_5$ 466.5, found [M+H] 467.3, T_r = 1.314 min. (Method O). ^{1}H NMR (400 MHz, MeOD) δ 8.05 (d, *J* = 2.00 Hz, 1H), 7.65-7.71 (m, 4H), 7.16 (d, *J* = 8.00 Hz, 1H), 6.97-6.99 (m, 1H), 3.95-3.99 (m, 2H), 3.53-3.57 (m, 2H), 3.33-3.38 (m, 4H), 2.77-2.86 (m, 3H), 2.55-2.61 (m, 1H), 2.42-2.48 (m, 2H), 1.19-1.21 (m, 6H).

Example 606

(Diastereomer 1)

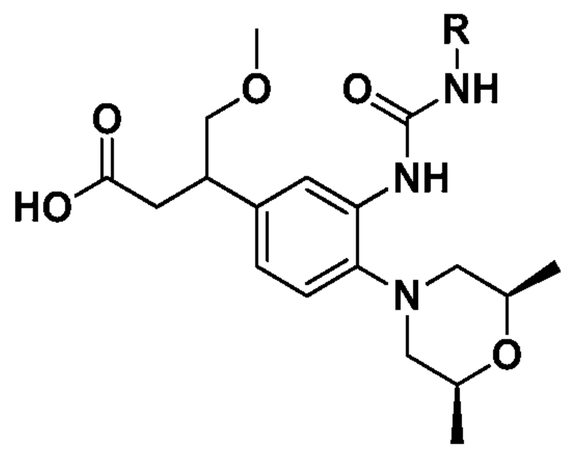


Example 606 was prepared using 605B Diastereomer 1 and corresponding isocyanate following the procedure described for the synthesis of Example 605 Diastereomer 1 (absolute and relative stereochemistry not determined).

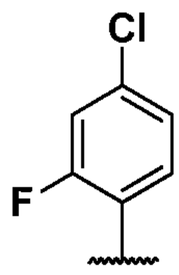
Ex. No.	Name	R	T_r min	Method	(M+H)
606	3-(3-(3-(4-chloro-2-fluorophenyl) ureido)-4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxybutanoic acid		1.55	O	494.1

Example 607

(Diastereomer 2)



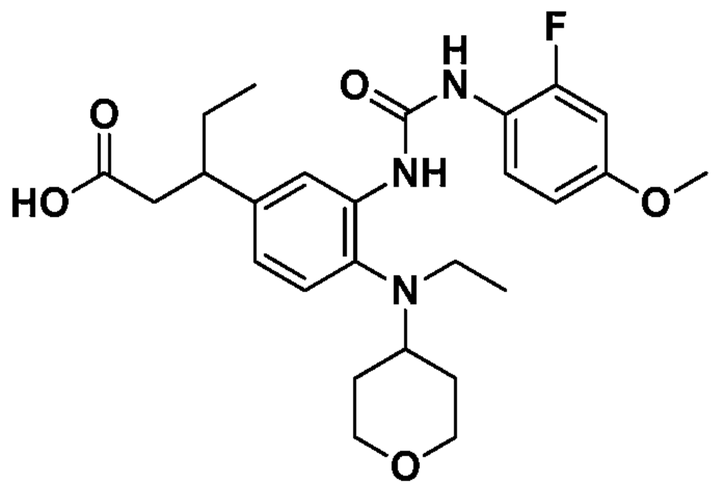
Example 607 was prepared using 605B Diastereomer 2 and corresponding isocyanates following the procedure described for the synthesis of Example 605 Diastereomer 1 (absolute and relative stereochemistry not determined).

Ex. No.	Name	R	T_r min	Method	(M+H)
607	3-(3-(3-(4-chloro-2-fluorophenyl) ureido)-4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-4-methoxybutanoic acid		1.55	O	494.1

Example 608

(Racemate)

3-(4-(Ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(2-fluoro-4-methoxyphenyl)ureido)phenyl)pentanoic acid



608A. Methyl 3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(2-fluoro-4-methoxyphenyl)ureido)phenyl)pentanoate

608A was prepared using compound 488A and 2-fluoro-4-methoxyphenyl amine following the procedure described for the synthesis of 488B. LC-MS Anal. Calc'd. for $C_{27}H_{36}FN_3O_5$ 501.5, found [M+H] 502.4, T_r = 3.56 min (Method N).

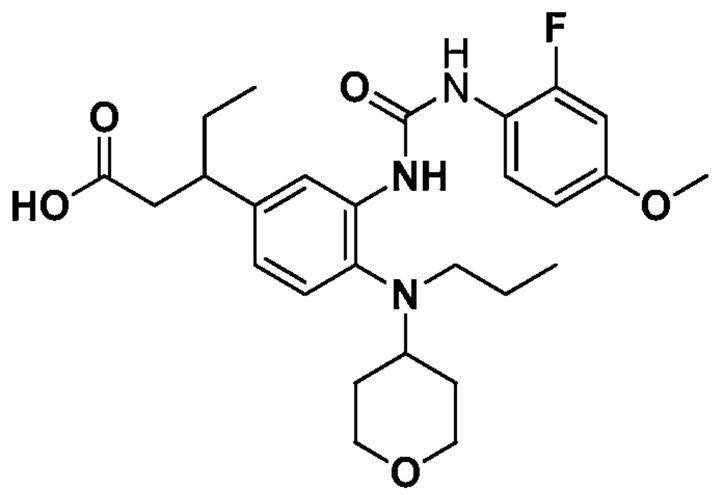
Example 608. 3-(4-(Ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-(3-(2-fluoro-4-methoxyphenyl)ureido)phenyl)pentanoic acid

Example 608 was prepared as a racemate using 608A following the procedure described for the synthesis of Example 455. LC-MS Anal. Calc'd. for $C_{26}H_{34}FN_3O_5$ 487.5, found [M+H] 488.2, T_r = 1.66 min. (Method O).^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.67 (s, 1H), 8.03 (d, *J* = 2.00 Hz, 1H), 7.71-7.74 (m, 1H), 7.14 (d, *J* = 8.00 Hz, 1H), 6.90 (dd, *J* = 12.80, 2.80 Hz, 1H), 6.74-6.80 (m, 2H), 3.82 (t, *J* = 2.80 Hz, 2H), 3.76 (s, 3H), 3.19-3.22 (m, 3H), 2.93-2.96 (m, 3H), 2.89-2.91 (m, 1H), 2.42-2.44 (m, 1H), 1.64-1.69 (m, 3H), 1.35-1.38 (m, 3H), 0.77 (t, *J* = 7.20 Hz, 3H), 0.71 (t, *J* = 7.20 Hz, 3H), 9.11 (s, 1H).

Example 609

(Racemate)

3-(3-(3-(2-Fluoro-4-methoxyphenyl)ureido)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid



609A. Methyl 3-(3-(((4-nitrophenoxy)carbonyl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

609A was prepared using compound 557B following the procedure described for the synthesis of 488A. LC-MS Anal. Calc'd. for $C_{27}H_{35}N_3O_7$ 513.5, found [M+H] 514.6, T_r = 1.54 min (Method DM).

609B. Methyl 3-(3-(3-(2-fluoro-4-methoxyphenyl)ureido)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

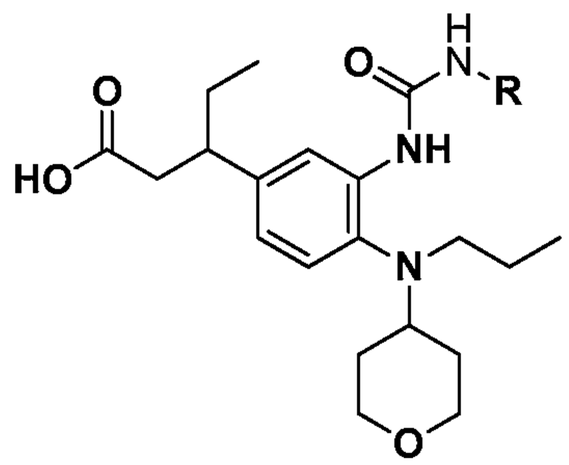
609B was prepared using compound 609A following the procedure described for the synthesis of 488B. LC-MS Anal. Calc'd. for $C_{28}H_{38}FN_3O_5$ 515.6, found [M+H] 516.7, T_r = 1.37 min (Method DM).

Example 609. 3-(3-(3-(2-Fluoro-4-methoxyphenyl)ureido)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid

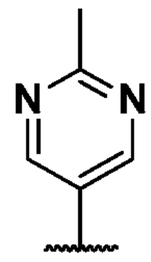
Example 609 was prepared using compound 609B as racemate following the procedure described for the synthesis of Example 455. LC-MS Anal. Calc'd. for $C_{27}H_{36}FN_3O_5$ 501.5, found [M+H] 502.2, T_r = 1.77 min (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.67 (s, 1H), 8.03 (d, *J* = 2.00 Hz, 1H), 7.71-7.74 (m, 1H), 7.14 (d, *J* = 8.00 Hz, 1H), 6.90 (dd, *J* = 12.80, 2.80 Hz, 1H), 6.74-6.80 (m, 2H), 3.82 (t, *J* = 2.80 Hz, 2H), 3.76 (s, 3H), 3.19-3.22 (m, 4H), 2.84-2.88 (m, 4H), 2.44-2.50 (m, 1H), 1.65-1.71 (m, 2H), 1.42-1.49 (m, 3H), 1.17-1.19 (m, 2H), 0.77 (t, *J* = 7.20 Hz, 3H), 0.71 (t, *J* = 7.20 Hz, 3H).

Example 610

(Racemate)



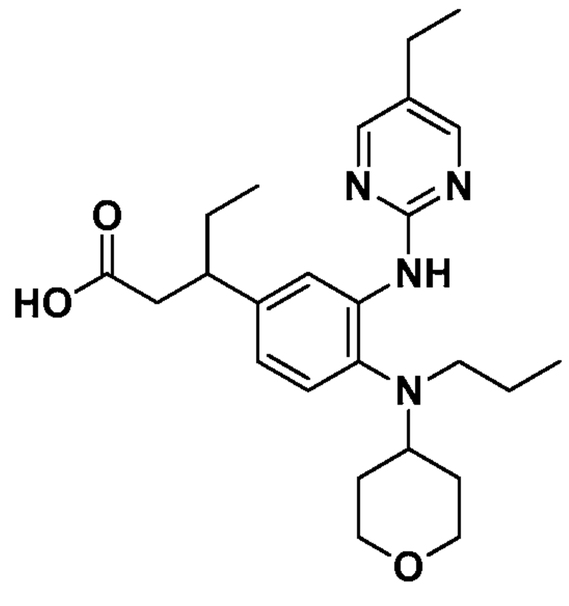
Example 610 was prepared using 609A and corresponding amine following the procedure described for the synthesis of Example 609.

Ex. No.	Name	R	T_r min	Method	(M+H)
610	3-(3-(3-(2-methylpyrimidin-5-yl)ureido)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid		1.25	O	470.2

Example 611

(Racemate)

3-(3-((5-Ethylpyrimidin-2-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid



611A. Methyl 3-(3-((5-ethylpyrimidin-2-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoate

611A was prepared utilizing compound 557B and 2-bromo-5-ethylpyrimidine following the procedure described for the synthesis of 455F. LC-MS Anal. Calc'd. for $C_{26}H_{38}N_4O_3$ 454.6, found [M+H] 455.6, T_r = 1.34 min (Method AV).

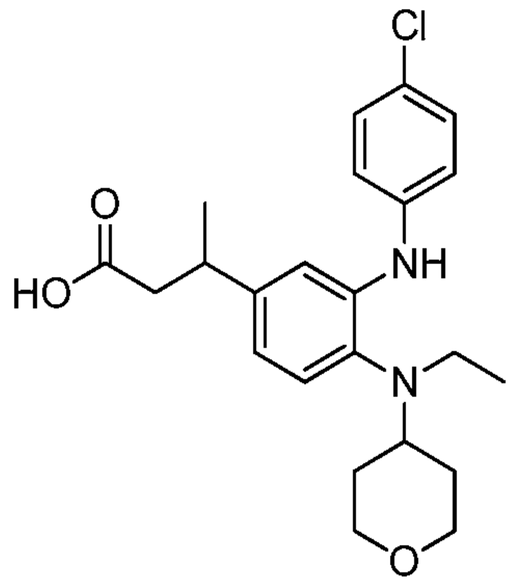
Example 611. 3-(3-((5-Ethylpyrimidin-2-yl)amino)-4-(propyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)pentanoic acid

Example 611 was prepared using 611A as racemate following the procedure described for the synthesis of Example 455. LC-MS Anal. Calc'd. for $C_{25}H_{36}N_4O_3$ 440.5, found [M+H] 441.3, T_r = 1.69 min. (Method O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.40 (t, *J* = 2.00 Hz, 3H), 7.18 (d, *J* = 0.00 Hz, 1H), 6.78 (dd, *J* = 2.00, 8.00 Hz, 1H), 3.79-3.82 (m, 2H), 3.17-3.35 (m, 5H), 2.93-2.97 (m, 5H), 2.41-2.46 (m, 3H), 1.68-1.71 (m, 3H), 1.15-1.19 (m, 5H), 0.80 (t, *J* = 7.60 Hz, 3H), 0.72 (t, J = 7.20 Hz, 3H).

Example 612

(Enantiomer 1 and Enantiomer 2)

3-(3-((4-Chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)butanoic acid



612A. Methyl 3-(4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-3-nitrophenyl)butanoate

In a pressure tube equipped with Teflon cap 455C (5 g, 13.80 mmol), 1,4-dioxane (50 ml) were added followed by sodium hydroxide (12.42 ml, 12.42 mmol). To it argon gas was passed through for 15 mins and then methyl crotonate (4.39 ml, 41.4 mmol) and chloro(1,5-cyclooctadiene)rhodium(I) dimer(0.340 g, 0.690 mmol) were added at room temperature. Argon gas was further passed through it for 5 mins. It was then screw-capped and heated at 50 ºC for 2 h. The reaction mixture was cooled to room temperature, quenched with acetic acid (0.790 mL, 13.80 mmol) and was stirred for 5 mins before it was diluted with water (100 mL). The aqueous layers were extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water (50 mL), brine (50

mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude material. The crude material was purified by flash silica gel column chromatography to afford 612A (orange oil, 3.5 g, 8.99 mmol, 65.1% yield). LC-MS Anal. Calc'd. for $C_{18}H_{26}N_2O_5$ 350.184, found [M+H] 351.2, T_r = 2.874 min (Method U).

612B. Methyl 3-(3-amino-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)butanoate

The solution of 612A (3 g, 8.56 mmol) in ethyl acetate (30 mL) was charged to a sealable hydrogen flask. The solution was sequentially evacuated and purged with nitrogen gas. To this 10% Pd-C (0.15 g, 0.141 mmol) was added under nitrogen atmosphere. The reaction mixture was stirred under pressurized 40 psi of hydrogen atmosphere at room temperature for 2 h. The reaction mixture was filtered through a CELITE® pad and the residue on the pad was thoroughly rinsed with ethyl acetate (75 mL). The combined filtrate was concentrated under reduced pressure to afford racemate (brown oil, 2.2g, 6.85 mmol, 80.29%). LC-MS Anal. Calc'd. for $C_{18}H_{28}N_2O_3$ 320.210, found [M+H] 321.2, T_r = 2.750 min (Method U).

Chiral separation of 612B racemate gave 612B Enantiomer 1 and 612B Enantiomer 2 (Method BM).

612B Enantiomer 1 (brown oil, 881 mg, 2.69 mmol, 31.5%) T_r= 3.75 min. (Method BM). LC-MS Anal. Calc'd. for $C_{18}H_{28}N_2O_3$ 320.210, found [M+H] 321.4, T_r = 2.576 min (Method U).

612B Enantiomer 2 (brown oil, 890 mg, 2.75 mmol, 31.5%) T_r= 7.15 min. (Method BM). LC-MS Anal. Calc'd. for $C_{18}H_{28}N_2O_3$ 320.210, found [M+H] 321.4, T_r = 2.750 min (Method U).

612C. Methyl 3-(3-((4-chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino) phenyl)butanoate

The mixture of 612B Enantiomer 1 (40 mg, 0.125 mmol), 1-bromo-4-chlorobenzene (23.90 mg, 0.125 mmol), Xantphos (14.45 mg, 0.025 mmol) and Cs_2CO_3 (102 mg, 0.312 mmol) in 1,4-dioxane (2 mL) was stirred for 5 minutes. Argon gas was bubbled through the mixture for 5 mins. Bis(dibenzylideneacetone)palladium (3.59 mg, 6.24 µmol) was added and argon gas was bubbled through the mixture for 5 mins. The

reaction mixture was sealed and placed in preheated oil bath at 110 °C for 16 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford a residue. The residue was reconstituted in a mixture of ethyl acetate (25 mL) and water (15 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 × 25 mL). The combined organic layers were washed with water (15 mL), brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford a residue. The residue was purified via flash silica gel column chromatography to afford 612C (yellow oil, 50 mg, 0.075 mmol, 60.4% yield). LC-MS Anal. Calc'd. for $C_{24}H_{31}ClN_2O_3$, 430.202, found [M+H] 431.4, T_r = 3.934 min (Method U).

Example 612 Enantiomer 1. 3-(3-((4-Chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-l)amino)phenyl)butanoic acid

To a stirred solution of 612C (50 mg, 0.116 mmol) in a mixture of THF (0.5 ml), methanol (1 ml) and water (0.25 mL) was added $LiOH•H_2O$ (13.89 mg, 0.580 mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure. The aqueous residue was acidified with saturated citric acid solution to pH ~3-4. The aqueous layer was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a residue. The residue was purified via preparative LCMS to afford Example 612 Enantiomer 1 (absolute stereochemistry not determined) (pale yellow solid, 5.9 mg, 0.014 mmol, 11.71% yield). LC-MS Anal. Calc'd. for $C_{23}H_{29}ClN_2O_3$, 416.187, found [M+H] 417.2, T_r = 2.019 min (Method O). ^{1}H NMR (400 MHz, CD_3OD) δ 7.23-7.26 (m, 2H), 7.11-7.18 (m, 4H), 6.79-6.82 (m, 1H), 3.88-3.91 (m, 2H), 3.29-3.37 (m, 2H), 3.17-3.19 (m, 1H), 3.02-3.08 (m, 3H), 2.55-2.57 (m, 2H), 1.76-1.79 (m, 2H), 1.42-1.52 (m, 2H), 1.30 (d, *J* = 7.20 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H).

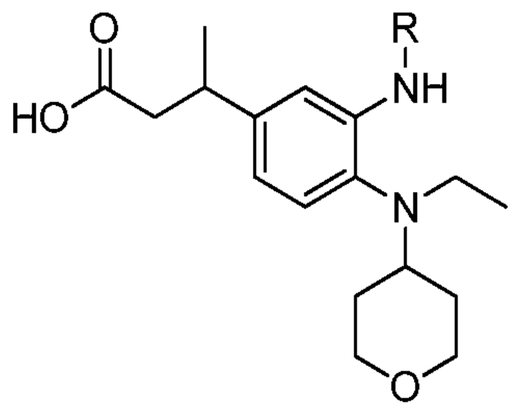
Example 612 Enantiomer 2. 3-(3-((4-Chlorophenyl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-l)amino)phenyl)butanoic acid

Example 612 Enantiomer 2 (absolute stereochemistry not determined) was prepared utilizing 612B Enantiomer 2 and 1-bromo-4-chlorobenzene following the

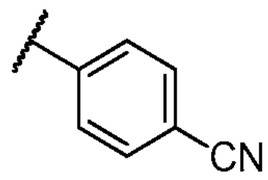
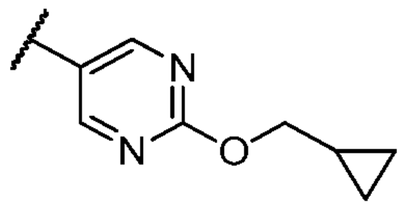
procedure described for the synthesis of Example 612 Enantiomer 1. LC-MS Anal. Calc'd. for $C_{23}H_{29}ClN_2O_3$, 416.187, found [M+H] 417.2, T_r = 2.019 min (Method O). ^{1}H NMR (400 MHz, CD_3OD) δ 7.23-7.26 (m, 2H), 7.11-7.18 (m, 4H), 6.79-6.82 (m, 1H), 3.88-3.91 (m, 2H), 3.29-3.37 (m, 2H), 3.17-3.19 (m, 1H), 3.02-3.08 (m, 3H), 2.55-2.57 (m, 2H), 1.76-1.79 (m, 2H), 1.53-1.54 (m, 2H), 1.30 (d, *J* = 6.80 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H).

Examples 613 to 623

(Enantiomer 1)



Examples 613 to 623 were prepared using 612B Enantiomer 1 and corresponding halides following the procedure described for the synthesis of Example 612 (absolute stereochemistry not determined).

Ex. No.	Name	R	T_R (min) Method O	$[M+H]^+$
613	3-(3-((4-cyanophenyl) amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl) butanoic acid		1.637	408.2
614	3-(3-((2-(cyclopropylmethoxy) pyrimidin-5-yl)amino)-4-(ethyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)butanoic acid		1.703	455.3

DEMANDE OU BREVET VOLUMINEUX

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

CECI EST LE TOME	1	DE	3
CONTENANT LES PAGES	1	À	433

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

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CONTAINING PAGES	1	TO	433

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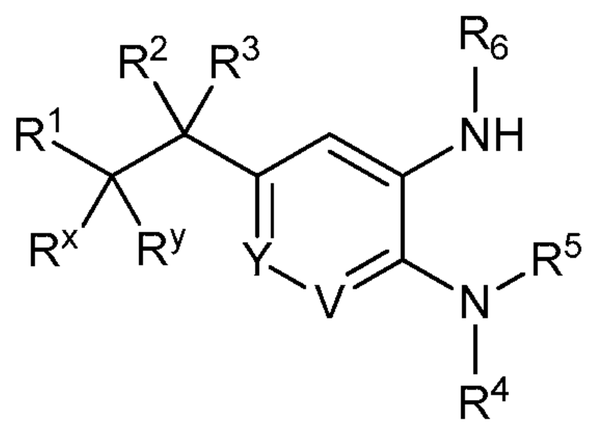
NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

WHAT IS CLAIMED IS:

1. A compound of Formula I:



(I)

wherein:

Y is CF and V is CH; or Y is CH and V is CF; or Y is CF and V is CF;

R^1 is -COOH, -COOC_1-C_6 alkyl, -$CONH_2$, -CN, optionally substituted heterocyclyl, optionally substituted heteroaryl, -$NHCONHR^{13}$, -$CONHSO_2R^{14}$, -$CONHCOR^{13}$, -SO_2NHCOR^{13}, -$CONHSO_2NR^{13}R^{14}$, -SO_2NHR^{13}, -$NHCONHSO_2R^{13}$, -$CHCF_3OH$, -$COCF_3$, -CR^2R^3OH, or -$NHSO_2R^{13}$;

R^{13} is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_2-C_{10} alkenyl or optionally substituted C_2-C_{10} alkynyl;

R^{14} is H or optionally substituted C_1-C_{10} alkyl;

R^2 is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted heterocyclyl, or optionally substituted aryl;

R^3 is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted heterocyclyl, or optionally substituted aryl; or

R^2 and R^3 are taken together with the carbon to which they are attached to form an optionally substituted 3- to 6-membered carbocyclic or a 3- to 6-membered heterocyclic ring;

R^x is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10} alkoxy, or optionally substituted C_3-C_8 cycloalkyl;

R^y is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10} alkoxy, or optionally substituted C_3-C_8 cycloalkyl; or

R^x and R^y are taken together with the carbon to which they are attached to form a 3- to 7-membered heterocyclic ring containing 1-3 heteroatoms selected from -N-, -S-, and -O-;

R^4 is optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, optionally substituted C_1-C_{10} alkoxy, optionally substituted aryl, optionally substituted aryl-C_1-C_{10}-alkyl, optionally substituted 5- to 8-membered heteroaryl, optionally substituted C_3-C_8 cycloalkyl or optionally substituted heterocyclyl;

R^5 is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, optionally substituted C_1-C_{10} alkoxy, optionally substituted aryl, optionally substituted aryl-C_1-C_{10}-alkyl, optionally substituted 5- to 8-membered heteroaryl, optionally substituted C_3-C_8 cycloalkyl or optionally substituted heterocyclyl; or

R^4 and R^5 are taken together with the nitrogen to which they are attached to form a 4- to 8-membered optionally substituted heterocyclic ring containing 0-3 additional heteroatoms selected from -N-, -S- and -O-; or

R^4 and R^5 are taken together with the nitrogen to which they are attached to form a 6- to 10-membered optionally substituted heterobicyclic ring containing 0-3 additional heteroatoms selected from -N-, -S-, and -O-;

R^6 is $-C(O)NHR^8$; and

R^8 is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C_3-C_8 cycloalkyl, or optionally substituted heterocyclyl;

or a stereoisomer thereof or a tautomer thereof;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein Y is CF and V is CH or Y is CH and V is CF.

3. The compound of claim 1 or claim 2, wherein R^1 is -COOH.

4. The compound of any one of the preceding claims, wherein one of R^2 and R^3 is H and the other is optionally substituted C_1-C_{10} alkyl, optionally substituted $C_{3\text{-}6}$cycloalkyl, optionally substituted heterocyclyl, or optionally substituted aryl.

5. The compound of any one of claims 1 to 3, wherein R^2 and R^3 are each independently optionally substituted C_1-C_{10} alkyl.

6. The compound of any one of the preceding claims, wherein R^x and R^y are each H.

7. The compound of any one of the preceding claims, wherein:

R^4 is optionally substituted C_1-C_{10} alkyl or optionally substituted C_3-C_8 cycloalkyl; and

R^5 is optionally substituted C_1-C_{10} alkyl or optionally substituted C_3-C_8 cycloalkyl.

8. The compound of any one of claims 1 to 6, wherein R^4 and R^5 are taken together with the nitrogen to which they are attached to form a 4- to 8-membered optionally substituted heterocyclic ring containing 0-3 additional heteroatoms selected from -N-, -S- and -O-.

9. The compound of any one of the preceding claims, wherein R^8 is optionally substituted aryl.

10. The compound of any one of claims 1 to 8, wherein R^8 is optionally substituted heteroaryl.

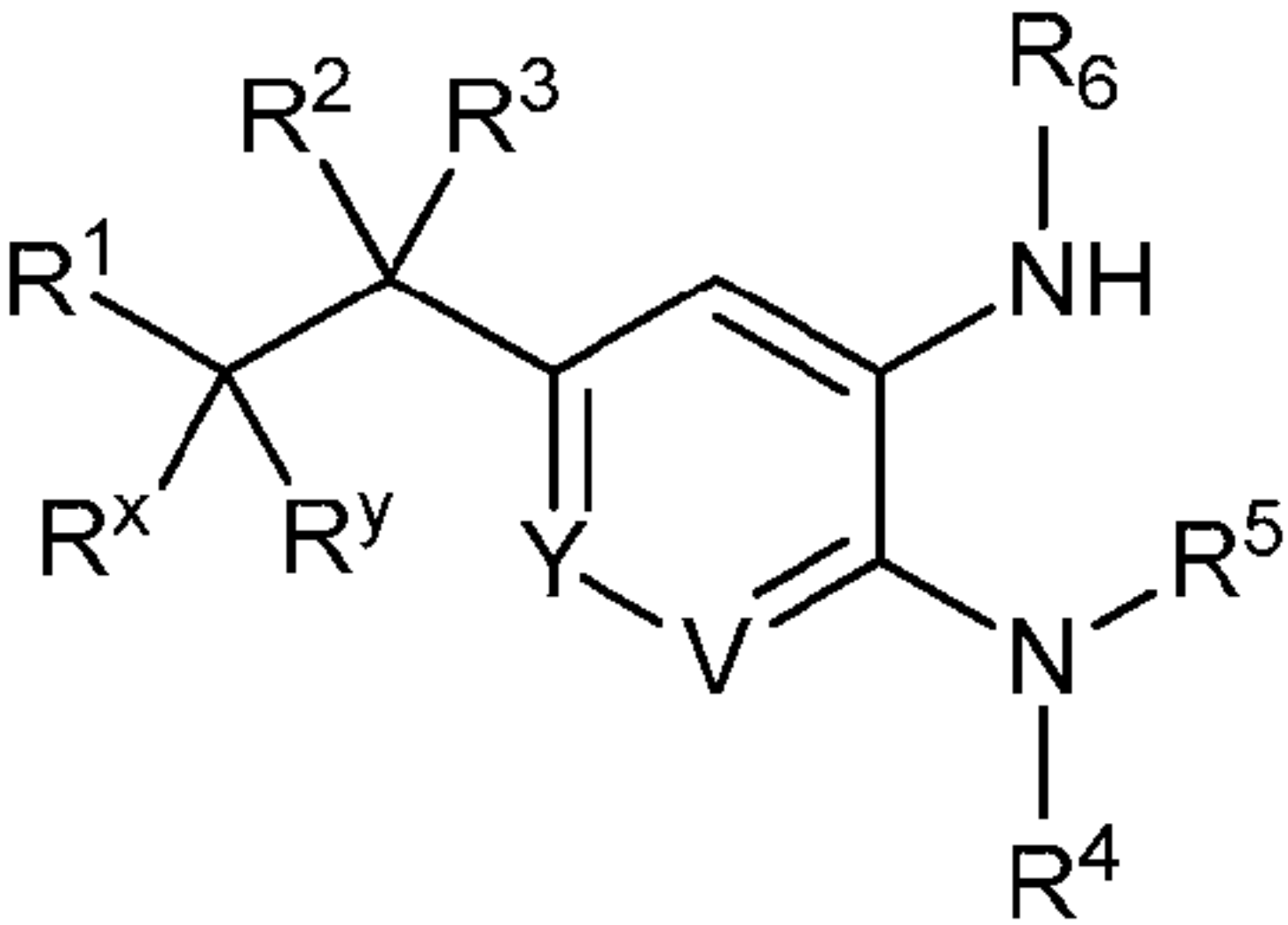
11. The compound of any one of claims 1 to 8, wherein R^8 is optionally substituted heterocyclyl.

12. A pharmaceutical composition comprising a compound of any one of the preceding claims and a pharmaceutically acceptable excipient.

13. A compound of any one of claims 1 to 11 for use in therapy.

14. A method of treating cancer is a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of a compound according to any one of claims 1 to 11.

15. The method of claim 14, wherein the cancer is a cancer of the colon, rectum, pancreas, cervix, stomach, endometrium, brain, liver, bladder, ovary, testis, head, neck, skin (including melanoma and basal carcinoma), mesothelial lining, white blood cell (including lymphoma and leukemia), esophagus, breast, muscle, connective tissue, lung (including small-cell lung carcinoma and non-small-cell carcinoma), adrenal gland, thyroid, kidney, or bone; or is glioblastoma, mesothelioma, renal cell carcinoma, gastric carcinoma, sarcoma (including Kaposi's sarcoma), choriocarcinoma, cutaneous basocellular carcinoma, or testicular seminoma



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