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(54) Title: SUBSTITUTED 3,4-DIHYDROQUINOLINONE INHIBITORS OF TSHR

(57) Abstract: Disclosed are compounds that are thyroid stimulating hormone receptor antagonists, and methods useful for preventing or treating a thyroid disease.

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SUBSTITUTED 3,4-DIHYDROQUINOLINONE INHIBITORS OF TSHR

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Application No. 63/393,411, filed July 29, 2022; the contents of which are hereby incorporated by reference in their entirety.

BACKGROUND

About 40% of hyperthyroidism patients suffer from Graves' disease (Morbus Basedow), an autoimmune disease in which autoantibodies activate the thyrotropin receptor, mimicking its natural hormone ligand, the thyroid-stimulating hormone (TSH). This pathological activation of TSH-Receptor (TSHR) leads to uncontrolled production of thyroid hormones (e.g., T3 and T4) causing hyperthyroidism. TSH and the TSHR are important proteins for controlling thyroid function. TSHR is primarily expressed in follicular epithelial cells of the thyroid gland, but also is expressed in a variety of additional cell types, such as retro-orbital fibroblasts, kidney cells, adipocytes and bone cells. TSH binds to its receptor and leads to the stimulation of second messenger pathways involving predominantly cAMP. Inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG) pathways are also activated at higher TSH concentrations.

The treatment of choice applied in the clinics for decades involves thyrostatic drugs that block the production of thyroid hormones. These medications play a role further downstream in the signal cascade of the thyroid upon activation of the TSHR. Since thyroid hormones T3 and T4 are secreted in the thyroid gland, thyrostatic drugs induce an inhibition of their synthesis. Thus, the current primary anti-thyroid treatment does not target the causative molecular activation of the TSHR by autoantibodies and patients are therefore burdened by a rate of at least 5% adverse effects. This demands frequent controls of the thyroid hormone levels and adjustments of thyrostatics dosage. In contrast to these drugs, which regulate the thyroid hormone level, another promising target is the TSHR itself. However, small allosteric antagonists acting directly at the TSHR are not available on the market yet.

Additionally, about 25% of Graves' disease patients also develop an orbitopathy referred to as “Graves' ophthalmopathy”, a related organ-specific autoimmune disease affecting the appearance and functioning of the eyes. There is considerable evidence that expression of the

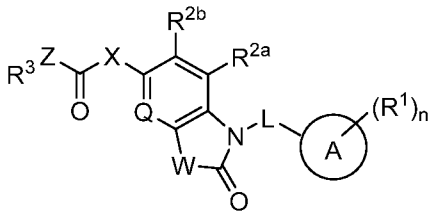
TSHR in the orbital fibroblasts and orbital adipocytes behind the eye may contribute to this difficult-to-treat orbitopathy, and thyroid stimulating antibodies titer tend to correlate with severity of Grave's ophthalmopathy. Orbital fibroblast has been recognized as primary target cells of autoimmune attack and TSHR acts as a primary autoantigen in Grave's ophthalmopathy. The pathological activation of TSHR leads to the production of the extracellular matrix by involvement of hyaluronanic acid, fibrosis and swelling of extraocular muscle as well as adipogenesis of orbital fibroblasts (orbital fat expansion). The increase in tissue volume in the orbit often causes diplopia and compression of the optic nerve and exophthalmos. Thus, the TSHR is also potential target for pharmacological intervention of Grave's ophthalmology and thyroid eye disease.

Accordingly, there is a need in the art to provide additional means for the treatment of hyperthyroidism, in particular compounds that act as TSHR antagonists.

SUMMARY

One aspect of the invention provides compounds, compositions, and methods useful for preventing or treating a thyroid disease, such as hyperthyroidism, Grave's disease, Grave's opthalmopathy, or thyroid eye disease.

Accordingly, provided herein in some embodiments is a compound having the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

A is (C_6-C_{10})aryl, 5- to 10-membered heteroaryl, (C_3-C_8)cycloalkyl, or 4- to 7-membered heterocycloalkyl;

n is 0, 1, 2, 3, 4, or 5;

R^1 is independently for each occurrence (C_1-C_6)alkyl, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy, (C_6-C_{10})aryl(C_1-C_6)alkyl, 4- to

7-membered heterocycloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo, cyano, amino, formyl, carboxy, or alkoxycarbonyl,

wherein (C_1-C_6)alkyl, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and 4- to 7-membered heterocycloalkyl are each optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, 4- to 7-membered heterocycloalkyl, 5- to 6-membered heteroaryl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)fluoroalkoxy, 5- to 6-membered heteroaryloxy, or

two vicinal occurrences of R^1 taken together with the atoms to which they are attached form a fused 5- to 7-membered cycloalkyl, 5- to 7-membered heterocycloalkyl ring, 5- to 6-membered heteroaryl ring or phenyl ring, any of which is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

Q is N or CR^{2c};

R^{2a}, R^{2b}, and R^{2c}, are each independently hydrogen, halo, cyano, (C_1-C_6)alkyl, or (C_3-C_8)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

R^3 is (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl), (C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkyl), or 4- to 7-membered heterocycloalkyl; each of which is optionally substituted with one or more substituents independently selected from halo, cyano, (C_1-C_6)haloalkyl, hydroxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and (C_1-C_6)alkoxy;

X and Z are independently NR^4, $C(R^5)_2$, or O;

R^4 and R^5 independently for each occurrence hydrogen or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy, or when Z is NR^4, R^3 and R^4 taken together with the nitrogen to which they are attached form a 4- to 7-member heterocycloalkyl optionally substituted with one or more (C_1-C_6)alkyl or halo;

L is (C_1-C_6)alkylene optionally substituted with one or more substituents independently selected from halo, hydroxy, C_1-C_6)alkoxy, and cyano;

W represents:

$–C(R^6)_2–C(R^7)_2–$,

$–C(R^7)_2–$,

$–O–C(R^8)_2–$,

$–C(R^8)_2–O–$,

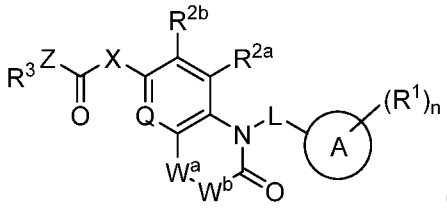
$–C(R^8)_2–NR^9–$,

$–N=C(R^{10})–$, or

–O–; and

R^6, R^7, R^8, R^9 and R^{10} are independently for each occurrence hydrogen, $(C_1\text{-}C_6)$alkyl,or NH_2, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one or more substituents independently selected from halo, cyano, hydroxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, and $(C_1\text{-}C_6)$alkoxy.

In some embodiments a compound has the structure of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof,

wherein

A is $(C_6\text{-}C_{10})$aryl, 5- to 10-membered heteroaryl, $(C_3\text{-}C_8)$cycloalkyl, or 4- to 7-membered heterocycloalkyl;

n is 0, 1, 2, 3, 4, or 5;

R^1 is independently for each occurrence $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkynyl, $(C_2\text{-}C_6)$alkenyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_3\text{-}C_8)$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, 4- to 7-membered heterocycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, halo, cyano, amino, formyl, carboxy, or alkoxycarbonyl,

wherein $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkynyl, $(C_2\text{-}C_6)$alkenyl, $(C_3\text{-}C_8)$cycloalkyl, $C_3\text{-}C_8)$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, and 4- to 7-membered heterocycloalkyl are each optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, 4- to 7-membered heterocycloalkyl, 5- to 6-membered heteroaryl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $(C_1\text{-}C_6)$fluoroalkoxy, 5- to 6-membered heteroaryloxy, or

two vicinal occurrences of R^1 taken together with the atoms to which they are attached form a fused 5- to 7-membered cycloalkyl, 5- to 7-membered heterocycloalkyl ring, 5- to 6-membered heteroaryl ring or phenyl ring, any of which is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

Q is N or CR^{2c};

R^{2a}, R^{2b}, and R^{2c}, are each independently hydrogen, halo, cyano, (C_1-C_6)alkyl, or (C_3-C_8)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

R^3 is (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl), (C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkyl), or 4- to 7-membered heterocycloalkyl; each of which is optionally substituted with one or more substituents independently selected from halo, cyano, (C_1-C_6)haloalkyl, hydroxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and (C_1-C_6)alkoxy;

X and Z are independently NR^4, $C(R^5)_2$, or O;

R^4 and R^5 independently for each occurrence hydrogen or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy, or when Z is NR^4, R^3 and R^4 taken together with the nitrogen to which they are attached form a 4- to 7-member heterocycloalkyl optionally substituted with one or more (C_1-C_6)alkyl or halo;

L is (C_1-C_6)alkylene optionally substituted with one or more substituents independently selected from halo, hydroxy, C_1-C_6)alkoxy, and cyano;

W represents:

$–C(R^6)_2–C(R^7)_2–$,

$–C(R^7)_2–$,

$–O–C(R^8)_2–$,

$–C(R^8)_2–O–$,

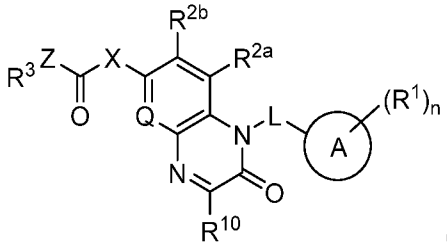
$–C(R^8)_2–NR^9–$,

$–N=C(R^{10})–$, or

–O–; and

R^6, R^7, R^8, R^9 and R^{10} are independently for each occurrence hydrogen, $(C_1\text{-}C_6)$alkyl,or NH_2, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one or more substituents independently selected from halo, cyano, hydroxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, and $(C_1\text{-}C_6)$alkoxy.

In some embodiments a compound has the structure of Formula (III):



(III),

or a pharmaceutically acceptable salt thereof,

wherein:

A is $(C_6\text{-}C_{10})$aryl, 5- to 10-membered heteroaryl, $(C_3\text{-}C_8)$cycloalkyl, or 4- to 7-membered heterocycloalkyl;

n is 0, 1, 2, 3, 4, or 5;

R^1 is independently for each occurrence $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkynyl, $(C_2\text{-}C_6)$alkenyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_3\text{-}C_8)$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, 4- to 7-membered heterocycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, halo, cyano, amino, formyl, carboxy, or alkoxycarbonyl,

wherein $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkynyl, $(C_2\text{-}C_6)$alkenyl, $(C_3\text{-}C_8)$cycloalkyl, $C_3\text{-}C_8)$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, and 4- to 7-membered heterocycloalkyl are each optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, 4- to 7-membered heterocycloalkyl, 5- to 6-membered heteroaryl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$haloalkoxy, $(C_1\text{-}C_6)$fluoroalkoxy, 5- to 6-membered heteroaryloxy, or

two vicinal occurrences of R^1 taken together with the atoms to which they are attached form a fused 5- to 7-membered cycloalkyl, 5- to 7-membered heterocycloalkyl ring, 5- to 6-membered heteroaryl ring or phenyl ring, any of which is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl $(C_3\text{-}C_8)$cycloalkyl, and $(C_1\text{-}C_6)$alkoxy;

Q is N or CR^{2c};

R^{2a}, R^{2b}, and R^{2c}, are each independently hydrogen, halo, cyano, $(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_8)$cycloalkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and $(C_1\text{-}C_6)$alkoxy;

R^3 is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_3\text{-}C_8)$cycloalkyl$(C_1\text{-}C_6)$alkyl), $(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl), or 4- to 7-membered heterocycloalkyl; each of which is optionally substituted with one or more substituents independently selected from halo, cyano, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, hydroxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, and $(C_1\text{-}C_6)$alkoxy;

X and Z are independently NR^4, $C(R^5)_2$, or O;

R^4 and R^5 independently for each occurrence hydrogen or $(C_1\text{-}C_6)$alkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and $(C_1\text{-}C_6)$alkoxy, or when Z is NR^4, R^3 and R^4 taken together with the nitrogen to which they are attached form a 4- to 7-member heterocycloalkyl optionally substituted with one or more $(C_1\text{-}C_6)$alkyl or halo, or when Z is $C(R^5)_2$, R^3 and one R^5 taken together with the carbon to which they are attached form a 4, $(C_3\text{-}C_8)$cycloalkyl optionally substituted with one or more $(C_1\text{-}C_6)$alkyl or halo;

L is $(C_1\text{-}C_6)$alkylene optionally substituted with one or more substituents independently selected from halo, hydroxy, $C_1\text{-}C_6)$alkoxy, and cyano;

R^{10} is hydrogen, $(C_1\text{-}C_6)$alkyl,or NH_2, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one or more substituents independently selected from halo, cyano, hydroxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, and $(C_1\text{-}C_6)$alkoxy.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features, objects, and advantages of the invention will be apparent from the detailed description, and from the claims.

DETAILED DESCRIPTION

Definitions

For convenience, before further description of the present invention, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

In order for the present invention to be more readily understood, certain terms and phrases are defined below and throughout the specification.

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

The phrase "and/or," as used herein in the specification and in the claims, should be understood to mean "either or both" of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with "and/or" should be construed in the same fashion, i.e., "one or more" of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the "and/or" clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to "A and/or B", when used in conjunction with open-ended language such as "comprising" can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

As used herein in the specification and in the claims, "or" should be understood to have the same meaning as "and/or" as defined above. For example, when separating items in a list, "or" or "and/or" shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as "only one of" or "exactly one of," or, when used in the claims, "consisting of," will refer to the inclusion of exactly one element of a number or list of elements. In general, the term "or" as used herein shall only be interpreted as indicating exclusive alternatives (i.e., "one or the other but not both") when preceded by terms of

exclusivity, such as "either," "one of," "only one of," or "exactly one of." "Consisting essentially of," when used in the claims, shall have its ordinary meaning as used in the field of patent law.

As used herein in the specification and in the claims, the phrase "at least one," in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase "at least one" refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, "at least one of A and B" (or, equivalently, "at least one of A or B," or, equivalently "at least one of A and/or B") can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

It should also be understood that, unless clearly indicated to the contrary, in any methods claimed herein that include more than one step or act, the order of the steps or acts of the method is not necessarily limited to the order in which the steps or acts of the method are recited.

In the claims, as well as in the specification above, all transitional phrases such as "comprising," "including," "carrying," "having," "containing," "involving," "holding," "composed of," and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases "consisting of" and "consisting essentially of" shall be closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, polymers of the present invention may also be optically active. The present invention contemplates all such compounds, including cis- and trans-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention.

Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

“Geometric isomer" means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon- carbon double bond may be in an E (substituents are on opposite sides of the carbon- carbon double bond) or Z (substituents are oriented on the same side) configuration. "R," "S," "S*," "R*," "E," "Z," "cis," and "trans," indicate configurations relative to the core molecule. Certain of the disclosed compounds may exist in “atropisomeric” forms or as “atropisomers.” Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. The compounds of the invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from a mixture of isomers. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods.

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

Percent purity by mole fraction is the ratio of the moles of the enantiomer (or diastereomer) or over the moles of the enantiomer (or diastereomer) plus the moles of its optical isomer. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or

depicted stereoisomer is at least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by mole fraction pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by mole fraction pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by mole fraction pure.

When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses either enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound or mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has two or more chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a number of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s) or mixtures of diastereomers in which one or more diastereomer is enriched relative to the other diastereomers. The invention embraces all of these forms.

Structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds produced by the replacement of a hydrogen with deuterium or tritium, or of a carbon with a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

The term “prodrug” as used herein encompasses compounds that, under physiological conditions, are converted into therapeutically active agents. A common method for making a prodrug is to include selected moieties that are hydrolyzed under physiological conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal.

The phrase “pharmaceutically acceptable excipient” or “pharmaceutically acceptable carrier” as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject chemical 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, not injurious to the patient, and substantially non-pyrogenic. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose, and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol, and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations. In certain embodiments, pharmaceutical compositions of the present invention are non-pyrogenic, i.e., do not induce significant temperature elevations when administered to a patient.

The term "pharmaceutically acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of the compound(s). These salts can be prepared in situ during the final isolation and purification of the compound(s), or by separately reacting a purified compound(s) in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts, and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19.)

In other cases, the compounds useful in the methods of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances refers to the relatively non-toxic inorganic and organic base addition salts of a compound(s). These salts can likewise be prepared in situ during the final isolation and purification of the compound(s), or by separately reacting the purified compound(s) in its free acid form with a suitable base, such as the hydroxide, carbonate, or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable

organic primary, secondary, or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts, and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like (see, for example, Berge et al., *supra*).

The term "pharmaceutically acceptable cocrystals" refers to solid coformers that do not form formal ionic interactions with the small molecule.

A "therapeutically effective amount" (or "effective amount") of a compound with respect to use in treatment, refers to an amount of the compound in a preparation which, when administered as part of a desired dosage regimen (to a mammal, preferably a human) alleviates a symptom, ameliorates a condition, or slows the onset of disease conditions according to clinically acceptable standards for the disorder or condition to be treated or the cosmetic purpose, e.g., at a reasonable benefit/risk ratio applicable to any medical treatment.

The term "prophylactic or therapeutic" treatment is art-recognized and includes administration to the host of one or more of the subject compositions. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic, (i.e., it protects the host against developing the unwanted condition), whereas if it is administered after manifestation of the unwanted condition, the treatment is therapeutic, (i.e., it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

The term "patient" or "subject" refers to a mammal in need of a particular treatment. In certain embodiments, a patient is a primate, canine, feline, or equine. In certain embodiments, a patient is a human.

An aliphatic chain comprises the classes of alkyl, alkenyl and alkynyl defined below. A straight aliphatic chain is limited to unbranched carbon chain moieties. As used herein, the term "aliphatic group" refers to a straight chain, branched-chain, or cyclic aliphatic hydrocarbon group and includes saturated and unsaturated aliphatic groups, such as an alkyl group, an alkenyl group, or an alkynyl group.

"Alkyl" refers to a fully saturated cyclic or acyclic, branched or unbranched carbon chain moiety having the number of carbon atoms specified, or up to 30 carbon atoms if no specification is made. For example, alkyl of 1 to 8 carbon atoms refers to moieties such as

methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, and octyl, and those moieties which are positional isomers of these moieties. Alkyl of 10 to 30 carbon atoms includes decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, eicosyl, heneicosyl, docosyl, tricosyl and tetracosyl. In certain embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C_1-C_{30} for straight chains, C_3-C_{30} for branched chains), and more preferably 20 or fewer. Alkyl goups may be substituted or unsubstituted.

As used herein, the term "heteroalkyl" refers to an alkyl moiety as hereinbefore defined which contain one or more oxygen, sulfur, nitrogen, phosphorus, or silicon atoms in place of carbon atoms.

As used herein, the term "haloalkyl" refers to an alkyl group as hereinbefore defined substituted with at least one halogen.

As used herein, the term "hydroxyalkyl" refers to an alkyl group as hereinbefore defined substituted with at least one hydroxyl.

As used herein, the term "alkylene" refers to an alkyl group having the specified number of carbons, for example from 2 to 12 carbon atoms, that contains two points of attachment to the rest of the compound on its longest carbon chain. Non-limiting examples of alkylene groups include methylene -(CH_2)-, ethylene -(CH_2CH_2)-, n-propylene -($CH_2CH_2CH_2$)-, isopropylene -($CH_2CH(CH_3)$)-, and the like. Alkylene groups can be cyclic or acyclic, branched or unbranched carbon chain moiety, and may be optionally substituted with one or more substituents.

"Cycloalkyl" means mono- or bicyclic or bridged or spirocyclic, or polycyclic saturated carbocyclic rings, each having from 3 to 12 carbon atoms. Preferred cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably have 3-6 carbons in the ring structure. Cycloalkyl groups may be substituted or unsubstituted.

As used herein, the term "halocycloalkyl" refers to an cycloalkyl group as hereinbefore defined substituted with at least one halogen.

"Cycloheteroalkyl" refers to an cycloalkyl moiety as hereinbefore defined which contain one or more oxygen, sulfur, nitrogen, phosphorus, or silicon atoms in place of carbon atoms. Preferred cycloheteroalkyls have from 4-8 carbon atoms and heteroatoms in their ring structure, and more preferably have 4-6 carbons and heteroatoms in the ring structure. Cycloheteroalkyl groups may be substituted or unsubstituted.

Unless the number of carbons is otherwise specified, "lower alkyl," as used herein, means an alkyl group, as defined above, but having from one to ten carbons, more preferably from one to six carbon atoms in its backbone structure such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and tert-butyl. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths. Throughout the application, preferred alkyl groups are lower alkyls. In certain embodiments, a substituent designated herein as alkyl is a lower alkyl.

"Alkenyl" refers to any cyclic or acyclic, branched or unbranched unsaturated carbon chain moiety having the number of carbon atoms specified, or up to 26 carbon atoms if no limitation on the number of carbon atoms is specified; and having one or more double bonds in the moiety. Alkenyl of 6 to 26 carbon atoms is exemplified by hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodenyl, tridecenyl, tetradecenyl, pentadecenyl, hexadecenyl, heptadecenyl, octadecenyl, nonadecenyl, eicosenyl, heneicosoenyl, docosenyl, tricosenyl, and tetracosenyl, in their various isomeric forms, where the unsaturated bond(s) can be located anywhere in the moiety and can have either the (Z) or the (E) configuration about the double bond(s).

"Alkynyl" refers to hydrocarbyl moieties of the scope of alkenyl, but having one or more triple bonds in the moiety.

The term "aryl" as used herein includes 3- to 12-membered substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon (i.e., carbocyclic aryl) or where one or more atoms are heteroatoms (i.e., heteroaryl). Preferably, aryl groups include 5- to 12-membered rings, more preferably 6- to 10-membered rings The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Carboycyclic aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like. Heteroaryl groups include substituted or unsubstituted aromatic 3- to 12-membered ring structures, more preferably 5- to 12-membered rings, more preferably 5- to 10-membered rings, whose ring structures include one to four heteroatoms. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Aryl and heteroaryl can be monocyclic, bicyclic, or polycyclic.

The term "halo", "halide", or "halogen" as used herein means halogen and includes, for example, and without being limited thereto, fluoro, chloro, bromo, iodo and the like, in both radioactive and non-radioactive forms. In a preferred embodiment, halo is selected from the group consisting of fluoro, chloro and bromo.

The terms "heterocyclyl" or "heterocyclic group" or "heterocycloalkyl" refer to 3- to 12-membered ring structures, more preferably 5- to 12-membered rings, more preferably 5- to 10-membered rings, whose ring structures include one to four heteroatoms. Heterocycles can be monocyclic, bicyclic, spirocyclic, or polycyclic. Heterocyclyl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, chromane, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring can be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphate, phosphonate, phosphinate, carbonyl, carboxyl, silyl, sulfamoyl, sulfinyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, and the like.

The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any

permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. In preferred embodiments, the substituents on substituted alkyls are selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, carbonyl, cyano, or hydroxyl. In more preferred embodiments, the substituents on substituted alkyls are selected from fluoro, carbonyl, cyano, or hydroxyl. It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. Unless specifically stated as "unsubstituted," references to chemical moieties herein are understood to include substituted variants. For example, reference to an "aryl" group or moiety implicitly includes both substituted and unsubstituted variants.

As used herein, the definition of each expression, e.g., alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

As used herein, "small molecules" refers to small organic or inorganic molecules of molecular weight below about 3,000 Daltons. In general, small molecules useful for the invention have a molecular weight of less than 3,000 Daltons (Da). The small molecules can be, e.g., from at least about 100 Da to about 3,000 Da (e.g., between about 100 to about 3,000 Da, about 100 to about 2500 Da, about 100 to about 2,000 Da, about 100 to about 1,750 Da, about 100 to about 1,500 Da, about 100 to about 1,250 Da, about 100 to about 1,000 Da, about 100 to about 750 Da, about 100 to about 500 Da, about 200 to about 1500, about 500 to about 1000, about 300 to about 1000 Da, or about 100 to about 250 Da).

In some embodiments, a "small molecule" refers to an organic, inorganic, or organometallic compound typically having a molecular weight of less than about 1000. In some embodiments, a small molecule is an organic compound, with a size on the order of 1 nm. In some embodiments, small molecule drugs of the invention encompass oligopeptides and other biomolecules having a molecular weight of less than about 1000.

An “effective amount” is an amount sufficient to effect beneficial or desired results. For example, a therapeutic amount is one that achieves the desired therapeutic effect. This amount can be the same or different from a prophylactically effective amount, which is an amount necessary to prevent onset of disease or disease symptoms. An effective amount can be administered in one or more administrations, applications or dosages. A therapeutically effective amount of a composition depends on the composition selected. The compositions can be administered from one or more times per day to one or more times per week; including once every other day. The skilled artisan will appreciate that certain factors may influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of the compositions described herein can include a single treatment or a series of treatments.

The terms “decrease,” “reduce,” “reduced”, “reduction”, “decrease,” and “inhibit” are all used herein generally to mean a decrease by a statistically significant amount relative to a reference. However, for avoidance of doubt, “reduce,” “reduction” or “decrease” or “inhibit” typically means a decrease by at least 10% as compared to a reference level and can include, for example, a decrease by at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, up to and including, for example, the complete absence of the given entity or parameter ascompared to the reference level, or any decrease between 10-99% as compared to the absence of a given treatment.

The terms “increased”, “increase” or “enhance” or “activate” are all used herein to generally mean an increase by a statically significant amount; for the avoidance of any doubt, the terms “increased”, “increase” or “enhance” or “activate” means an increase of at least 10% as compared to a reference level, for example an increase of at least about 20%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, or at least about 90% or up to and including a 100% increase or any increase between 10-100% as compared to a reference level, or at least about a 2-fold, or at least about a 3-fold, or at least about a 4-fold, or at least about a 5-fold or at least about a 10-

fold increase, or any increase between 2-fold and 10-fold or greater as compared to a reference level.

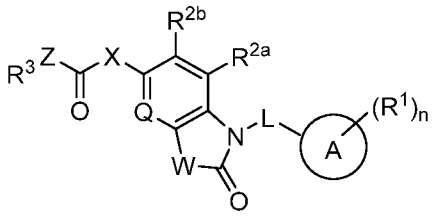
As used herein, the term "modulate" includes up-regulation and down-regulation, e.g., enhancing or inhibiting a response.

A "radiopharmaceutical agent," as defined herein, refers to a pharmaceutical agent which contains at least one radiation-emitting radioisotope. Radiopharmaceutical agents are routinely used in nuclear medicine for the diagnosis and/or therapy of various diseases. The radiolabelled pharmaceutical agent, for example, a radiolabelled antibody, contains a radioisotope (RI) which serves as the radiation source. As contemplated herein, the term "radioisotope" includes metallic and non-metallic radioisotopes. The radioisotope is chosen based on the medical application of the radiolabeled pharmaceutical agents. When the radioisotope is a metallic radioisotope, a chelator is typically employed to bind the metallic radioisotope to the rest of the molecule. When the radioisotope is a non-metallic radioisotope, the non-metallic radioisotope is typically linked directly, or via a linker, to the rest of the molecule.

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

Compounds of the Invention

One aspect of the invention relates to a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

A is (C_6-C_{10})aryl, 5- to 10-membered heteroaryl, (C_3-C_8)cycloalkyl, or 4- to 7-membered heterocycloalkyl;

n is 0, 1, 2, 3, 4, or 5;

R^1 is independently for each occurrence (C_1-C_6)alkyl, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy, (C_6-C_{10})aryl(C_1-C_6)alkyl, 4- to 7-membered heterocycloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo, cyano, amino, formyl, carboxy, or alkoxycarbonyl,

wherein (C_1-C_6)alkyl, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and 4- to 7-membered heterocycloalkyl are each optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, 4- to 7-membered heterocycloalkyl, 5- to 6-membered heteroaryl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)fluoroalkoxy, 5- to 6-membered heteroaryloxy, or

two vicinal occurrences of R^1 taken together with the atoms to which they are attached form a fused 5- to 7-membered cycloalkyl, 5- to 7-membered heterocycloalkyl ring, 5- to 6-membered heteroaryl ring or phenyl ring, any of which is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

Q is N or CR^{2c};

R^{2a}, R^{2b}, and R^{2c}, are each independently hydrogen, halo, cyano, (C_1-C_6)alkyl, or (C_3-C_8)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

R^3 is (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl), (C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkyl), or 4- to 7-membered heterocycloalkyl; each of which is optionally substituted with one or more substituents independently selected from halo, cyano, (C_1-C_6)haloalkyl, hydroxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and (C_1-C_6)alkoxy;

X and Z are independently NR^4, $C(R^5)_2$, or O;

R^4 and R^5 independently for each occurrence hydrogen or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy, or when Z is NR^4, R^3 and R^4 taken together with the nitrogen to which they are attached form a 4- to 7-member heterocycloalkyl optionally substituted with one or more (C_1-C_6)alkyl or halo;

L is (C_1-C_6)alkylene optionally substituted with one or more substituents independently selected from halo, hydroxy, C_1-C_6)alkoxy, and cyano;

W represents:

$–C(R^6)_2–C(R^7)_2–$,

$–C(R^7)_2–$,

$–O–C(R^8)_2–$,

$–C(R^8)_2–O–$,

$–C(R^8)_2–NR^9–$,

$–N=C(R^{10})$ –, or

–O–; and

R^6, R^7, R^8, R^9 and R^{10} are independently for each occurrence hydrogen, (C_1-C_6)alkyl,or NH_2, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, cyano, hydroxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and (C_1-C_6)alkoxy.

In some embodiments of the compound of Formula (I),

A is (C_6-C_{10})aryl or 5- to 10-membered heteroaryl;

n is 0, 1, 2, 3, 4, or 5;

R^1 is independently for each occurrence (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, 4- to 7-membered heterocycloalkyl, (C_1-C_6)alkoxy, halo, cyano, formyl, carboxy, or alkoxycarbonyl, wherein (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_1-C_6)alkoxy, and 4- to 7-membered heterocycloalkyl are each optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy, or

two vicinal occurrences of R^1 taken together with the atoms to which they are attached form a fused 5- to 7-membered cycloalkyl or 5- to 7-membered heterocycloalkyl ring, either of which is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

Q is N or CR^{2c};

R^{2a}, R^{2b}, and R^{2c}, are each independently hydrogen, halo, cyano, or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

R^3 is (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

X and Z are independently NR^4, $C(R^5)_2$, or O;

R^4 and R^5 independently for each occurrence hydrogen or $(C_1\text{-}C_6)$alkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and $(C_1\text{-}C_6)$alkoxy;

L is $(C_1\text{-}C_6)$alkylene optionally substituted with one or more substituents independently selected from halo, hydroxy, $C_1\text{-}C_6)$alkoxy, and cyano;

W represents:

$–C(R^6)_2–C(R^7)_2–$,

$–C(R^7)_2–$,

$–O–C(R^8)_2–$,

$–C(R^8)_2–O–$,

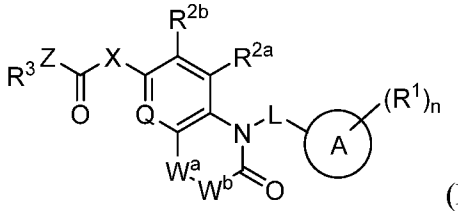
$–C(R^8)_2–NR^9–$,

$–N=C(R^{10})$ –, or

–O–; and

R^6, R^7, R^8, R^9 and R^{10} are independently for each occurrence hydrogen or $(C_1\text{-}C_6)$alkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and $(C_1\text{-}C_6)$alkoxy.:

Another aspect of the invention relates to a compound Formula (II):



(II),

or a pharmaceutically acceptable salt thereof,

wherein

A is $(C_6\text{-}C_{10})$aryl, 5- to 10-membered heteroaryl, $(C_3\text{-}C_8)$cycloalkyl, or 4- to 7-membered heterocycloalkyl;

n is 0, 1, 2, 3, 4, or 5;

R^1 is independently for each occurrence $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkynyl, $(C_2\text{-}C_6)$alkenyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_3\text{-}C_8)$cycloalkoxy, $(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, 4- to 7-membered heterocycloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, halo, cyano, amino, formyl, carboxy, or alkoxycarbonyl,

wherein (C_1-C_6)alkyl, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and 4- to 7-membered heterocycloalkyl are each optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, 4- to 7-membered heterocycloalkyl, 5- to 6-membered heteroaryl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)fluoroalkoxy, 5- to 6-membered heteroaryloxy, or

two vicinal occurrences of R^1 taken together with the atoms to which they are attached form a fused 5- to 7-membered cycloalkyl, 5- to 7-membered heterocycloalkyl ring, 5- to 6-membered heteroaryl ring or phenyl ring, any of which is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

Q is N or CR^{2c};

R^{2a}, R^{2b}, and R^{2c}, are each independently hydrogen, halo, cyano, (C_1-C_6)alkyl, or (C_3-C_8)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

R^3 is (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl), (C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkyl), or 4- to 7-membered heterocycloalkyl; each of which is optionally substituted with one or more substituents independently selected from halo, cyano, (C_1-C_6)haloalkyl, hydroxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and (C_1-C_6)alkoxy;

X and Z are independently NR^4, $C(R^5)_2$, or O;

R^4 and R^5 independently for each occurrence hydrogen or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy, or when Z is NR^4, R^3 and R^4 taken together with the nitrogen to which they are attached form a 4- to 7-member heterocycloalkyl optionally substituted with one or more (C_1-C_6)alkyl or halo;

L is (C_1-C_6)alkylene optionally substituted with one or more substituents independently selected from halo, hydroxy, C_1-C_6)alkoxy, and cyano;

W represents:

$–C(R^6)_2–C(R^7)_2–$,

$–C(R^7)_2–$,

–O–C(R^8)$_2$–,

–C(R^8)$_2$–O–,

–C(R^8)$_2$–NR^9–,

–N=C(R^{10}) –, or

–O–; and

R^6, R^7, R^8, R^9 and R^{10} are independently for each occurrence hydrogen, (C_1-C_6)alkyl,or NH_2, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, cyano, hydroxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and (C_1-C_6)alkoxy.

In other embodiments or of the compound of Formula (II),

A is (C_6-C_{10})aryl or 5- to 10-membered heteroaryl;

n is 0, 1, 2, 3, 4 or 5;

R^1 is independently for each occurrence (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, , 4- to 7-membered heterocycloalkyl, (C_1-C_6)alkoxy, halo, cyano, formyl, carboxy, or alkoxycarbonyl, wherein (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, 4- to 7-membered heterocycloalkyl, and (C_1-C_6)alkoxy are each optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy; or

two vicinal occurrences of R^1 taken together with the atoms to which they are attached form a fused 5- to 7-membered cycloalkyl or 5- to 7-membered heterocycloalkyl ring, either of which is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

Q is N or CR^{2c};

R^{2a}, R^{2b}, and R^{2c}, are each independently hydrogen, halo, cyano, or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

R^3 is (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

X and Z are independently NR^4, C(R^5)$_2$, or O;

R^4 and R^5 are independently for each occurrence hydrogen or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

L is (C_1-C_6)alkylene optionally substituted with one or more substituents independently selected from halo, hydroxy, (C_1-C_6)alkoxy, and cyano;

W^a–W^b represents:

–$C(R^6)_2$–$C(R^7)_2$–,

–O–$C(R^8)_2$–,

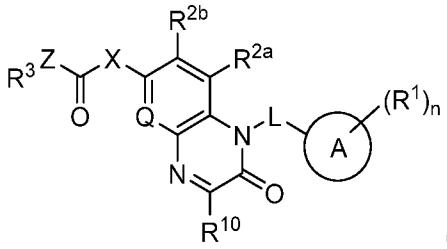
–$C(R^8)_2$–O–,

–$C(R^8)_2$–NR^9–, or

–N=$C(R^{10})$ –; and

R^6, R^7, R^8, R^9 and R^{10} are independently for each occurrence hydrogen or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy.

Yet another aspect of the invention relates to a compound of Formula (III):



(III),

or a pharmaceutically acceptable salt thereof,

A is (C_6-C_{10})aryl, 5- to 10-membered heteroaryl, (C_3-C_8)cycloalkyl, or 4- to 7-membered heterocycloalkyl;

n is 0, 1, 2, 3, 4, or 5;

R^1 is independently for each occurrence (C_1-C_6)alkyl, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy, (C_6-C_{10})aryl(C_1-C_6)alkyl, 4- to 7-membered heterocycloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo, cyano, amino, formyl, carboxy, or alkoxycarbonyl,

wherein (C_1-C_6)alkyl, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and 4- to 7-membered heterocycloalkyl are each optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, 4- to 7-membered heterocycloalkyl, 5- to 6-

membered heteroaryl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)fluoroalkoxy, 5- to 6-membered heteroaryloxy, or

two vicinal occurrences of R^1 taken together with the atoms to which they are attached form a fused 5- to 7-membered cycloalkyl, 5- to 7-membered heterocycloalkyl ring, 5- to 6-membered heteroaryl ring or phenyl ring, any of which is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

Q is N or CR^{2c};

R^{2a}, R^{2b}, and R^{2c}, are each independently hydrogen, halo, cyano, (C_1-C_6)alkyl, or (C_3-C_8)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

R^3 is (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl), (C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkyl), or 4- to 7-membered heterocycloalkyl; each of which is optionally substituted with one or more substituents independently selected from halo, cyano, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, hydroxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and (C_1-C_6)alkoxy;

X and Z are independently NR^4, $C(R^5)_2$, or O;

R^4 and R^5 independently for each occurrence hydrogen or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy, or when Z is NR^4, R^3 and R^4 taken together with the nitrogen to which they are attached form a 4- to 7-member heterocycloalkyl optionally substituted with one or more (C_1-C_6)alkyl or halo, or when Z is $C(R^5)_2$, R^3 and one R^5 taken together with the carbon to which they are attached form a 4, (C_3-C_8)cycloalkyl optionally substituted with one or more (C_1-C_6)alkyl or halo;

L is (C_1-C_6)alkylene optionally substituted with one or more substituents independently selected from halo, hydroxy, C_1-C_6)alkoxy, and cyano;

R^{10} is hydrogen, (C_1-C_6)alkyl,or NH_2, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, cyano, hydroxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and (C_1-C_6)alkoxy.

In some embodiments of the conmpound of Formula (III),

A is (C_6-C_{10})aryl or 5- to 10-membered heteroaryl;

n is 0, 1, 2, 3, 4 or 5;

R^1 is independently for each occurrence (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, 4- to 7-membered heterocycloalkyl, (C_1-C_6)alkoxy, halo, cyano, formyl, carboxy, or alkoxycarbonyl, wherein (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, 4- to 7-membered heterocycloalkyl, and (C_1-C_6)alkoxy are each optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy; or

two vicinal occurrences of R^1 taken together with the atoms to which they are attached form a fused 5- to 7-membered cycloalkyl or 5- to 7-membered heterocycloalkyl ring, either of which is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

Q is N or CR^{2c};

R^{2a}, R^{2b}, and R^{2c}, are each independently hydrogen, halo, cyano, (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

R^3 is (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

X and Z are independently NR^4, $C(R^5)_2$, or O;

R^4 and R^5 are independently for each occurrence hydrogen or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

L is (C_1-C_6)alkylene optionally substituted with one or more substituents independently selected from halo, hydroxy, C_1-C_6)alkoxy, and cyano; and

R^{10} is hydrogen or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy.

In certain embodiments, A is phenyl.

In certain embodiments, A is a 5- to 7-membered heteroaryl comprising 1 or 2 nitrogen atoms.

In certain embodiments, A is pyridyl or diazolyl. thiazolyl, pyrazinyl, pyrimidinyl, while in other embodiments, A is pyridyl or diazolyl.

In some embodiments, A is wherein A is isoquinolinyl or indazolyl.

In other embodiments, A is cyclopentyl, cyclohexyl, or tetrahydropyranyl.

In certain embodiments, R^1 is independently for each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, fluoro, chloro, or cyano, wherein (C_1-C_6)alkyl and (C_1-C_6)alkoxy are optionally substituted with one or more substituents independently selected from fluoro and hydroxyl.

In certain embodiments, at least one R^1 is fluoro, chloro, or cyano.

In certain embodiments, at least one R^1 is (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from hydroxyl and fluoro. In certain preferred embodiments, R^1 is 2,2,2-trifluoroethyl-1-hydroxyethyl. In other preferred embodiments, at least one R^1 is difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluropropyl, or 4,4,4-trifluorobutyl.

In certain embodiments, at least one R^1 is (C_1-C_6)alkoxy optionally substituted with at least one fluoro, preferably (C_1-C_3)alkoxy optionally substituted with at least one fluoro, more preferably difluoromethoxy or trifluoromethoxy. In other preferred embodiments, R^1 is methoxy or isopropoxy.

In certain embodiments, R^1 is methyl optionally substituted with hydroxy or one or more fluoro.

In certain embodiments, R^1 is (C_1-C_3)alkoxy optionally substituted with at least one fluoro.

In certain embodiments, at least one R^1 is (C_3-C_8)cycloalkyl, preferably cyclopropyl or cyclobutyl.

In certain embodiments, at least R^1 is (C_3-C_8)cycloalkoxy, preferably cyclopentyloxy, cyclohexyloxy.

In certain embodiments, R^1 is (C_2-C_6)alkynyl optionally substituted with hydroxy.

In certain embodiments, two vicinal occurrences of R^1 taken together with the atoms to which they are attached form a fused 5- to 7-membered cycloalkyl or 5- to 7-membered heterocycloalkyl ring, either of which is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy.

In certain embodiments, A is phenyl comprising two vicinal occurrences of R^1, wherein the two vicinal occurrences of R^1, taken together with the atoms to which they are attached, form a fused 5- to 7-membered cycloalkyl or 5- to 7-membered heterocycloalkyl ring.

In certain embodiments, n is 2.

In certain embodiments, n is 1.

In certain embodiments, n is 0.

In certain embodiments, Q is CR^{2c}.

In certain embodiments, Q is N.

In certain embodiments, R^{2a}, R^{2b}, and R^{2c} are each hydrogen.

In certain embodiments, at least one of R^{2a}, R^{2b}, and R^{2c} is fluoro, chloro, or cyano.

In certain embodiments, R^3 is (C_1-C_6)alkyl optionally substituted with hydroxy.

In certain preferred embodiments, R^3 is t-butyl.

In certain embodiments, R^3 is (C_3-C_8)cycloalkyl optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)fluoroalkyl, fluoro, or (C_1-C_6)alkoxy(C_1-C_6)alkyl. In more particular embodiments, the (C_3-C_8)cycloalkyl is cyclobutyl, cyclopentyl, cylohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl,bicycle[2.1.1]hexanyl, or bicyclo[3.1.0]hexanyl. Inb further particular embodiments, the (C_3-C_8)cycloalkyl is optionally substituted with one or more substituents selected from fluoro, trifluoromethyl, methoxymethyl, methyl, and hydroxyl.

In certain embodiments, R^3 is 4- to 7-membered heterocycloalkyl optionally substituted with one or more substituents selected from (C_1-C_6)alkyl, (C_1-C_6)fluoroalkyl, or fluoro. In more particular embodiments, the 4- to 7-membered heterocycloalkyl is etrahydropyranyl or oxetanyl.

In some embodiments, Z is NR^4, R^3 and R^4 taken together with the nitrogen to which they are attached form a 4- to 7-member heterocycloalkyl optionally substituted with one or more (C_1-C_6)alkyl or halo. In some embodiments, the 4- to 7 membered heterocycloalkyl is azetidine or pyrrolidine,

In certain embodiments, X is NR^4 or O.

In certain embodiments, X is NH.

In certain embodiments, Z is NR^4, or O.

In certain embodiments, Z is NH.

In certain embodiments, one and only one of X and Z is CH_2.

In certain embodiments, X and Z are each NH.

In certain embodiments, L is unsubstituted (C_1-C_6)alkylene.

In certain embodiments, L is (C_1-C_6)alkylene substituted with hydroxy.

In certain embodiments, L is (C_1-C_6)alkylene substituted with 1 to 3 halo atoms.

In certain embodiments, L is $–CH_2–$, $–$-$CH(CH_3)–$, $–CH(CH_2CH_3)–$, or $–CH(CH_2OH)–$.

In certain embodiments, $W^a–W^b$ represents:

$–C(R^6)_2–C(R^7)_2–$.

In certain embodiments, R^6 is $(C_1\text{-}C_6)$alkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and $(C_1\text{-}C_6)$alkoxy.

In certain embodiments, at least one R^7 is $(C_1\text{-}C_6)$alkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, $(C_1\text{-}C_6)$alkoxy, and cyano.

In certain embodiments, each R^6 and each R^7 is hydrogen.

In certain embodiments, $W^a–W^b$ represents:

$–O–C(R^8)_2–$.

In certain embodiments, R^8 is hydrogen.

In certain embodiments, one R^8 $(C_1\text{-}C_6)$alkyl, preferably methyl; and one R^8 is hydrogen.

In certain embodiments, $W^a–W^b$ represents:

$–C(R^8)_2–O–$, where each R8 is hydrogen.

In certain embodiments, $W^a–W^b$ represents:

$–C(R^8)_2–NR^9–$.

In certain embodiments, each R^8 is hydrogen.

In certain embodiments, R^9 is $(C_1\text{-}C_6)$alkyl, preferably methyl.

In certain embodiments, $W^a–W^b$ represents:

$–N=C(R^{10})–$.

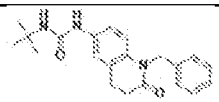
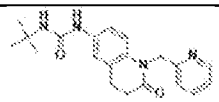
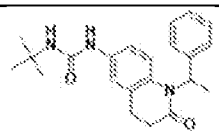
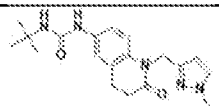
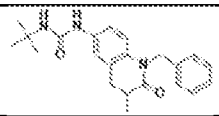
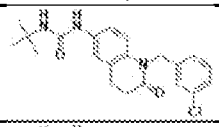
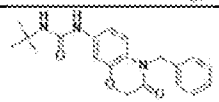
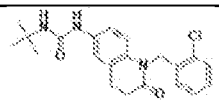
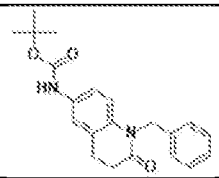
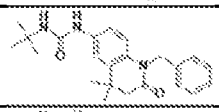
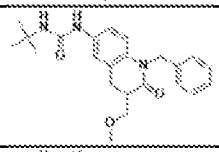
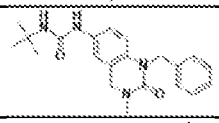
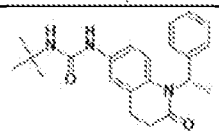
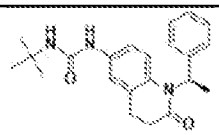
In certain embodiments, R^{10} is hydrogen.

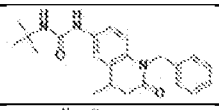
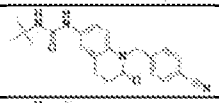
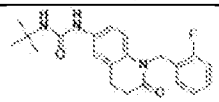
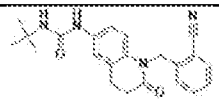
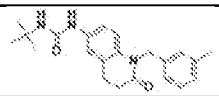
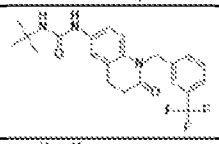
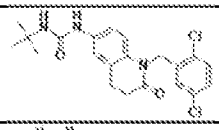
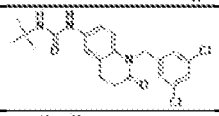
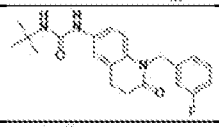
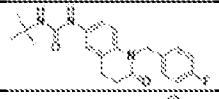
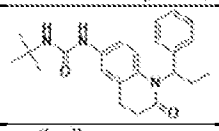
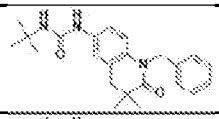
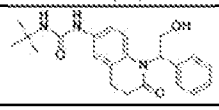
In certain embodiments, R^{10} is $(C_1\text{-}C_6)$alkyl.

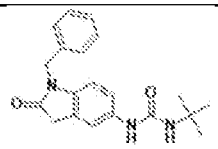
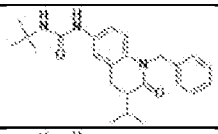
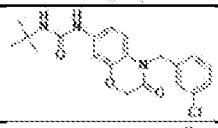
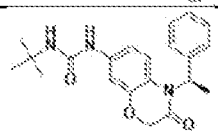
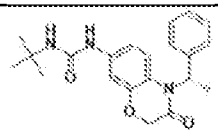
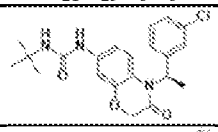
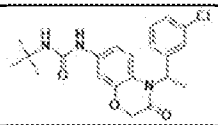
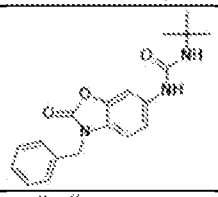
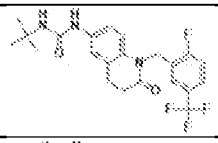
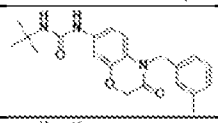
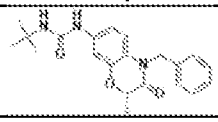
In certain embodiments, R^{10} is methyl.

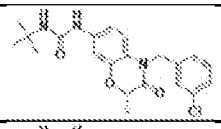
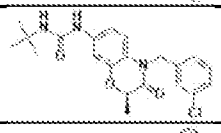
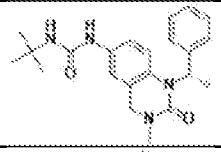
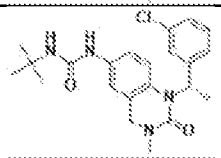
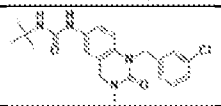
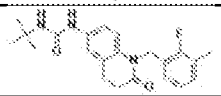
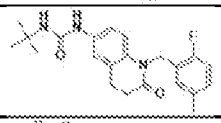
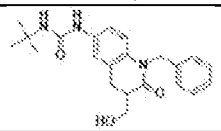
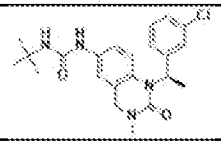
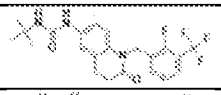
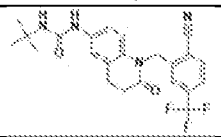
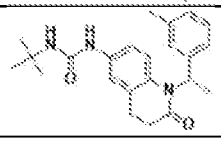
In certain embodiments, a compound is selected from Table 1:

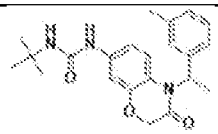
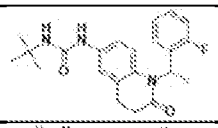
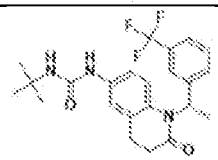
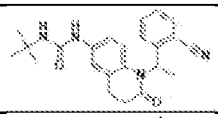
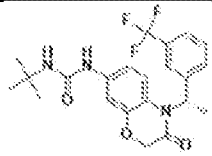
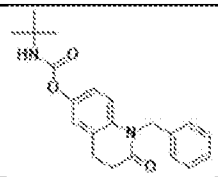
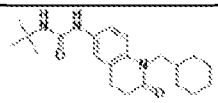
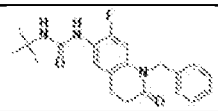
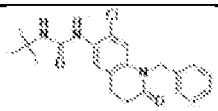
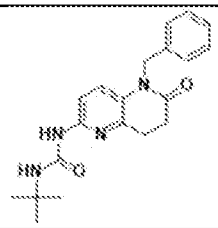
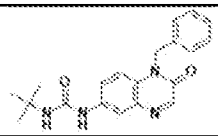
Table 1.

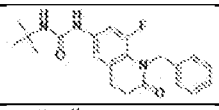
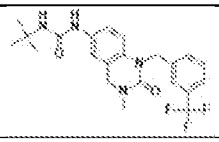
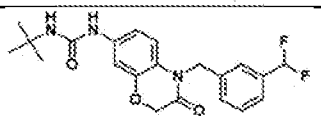
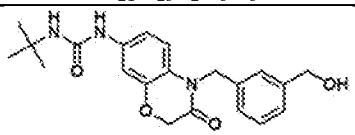
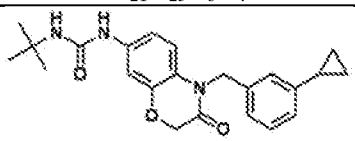
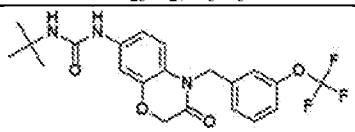
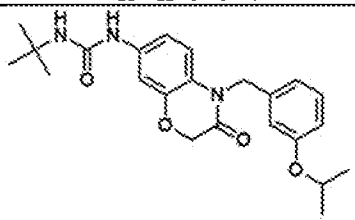
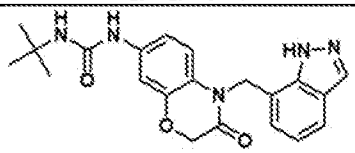
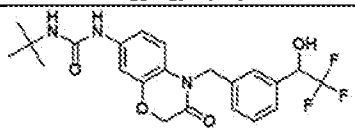
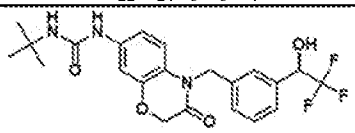
1		1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
2		1-(tert-butyl)-3-(2-oxo-1-(pyridin-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
3		1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
4		1-(tert-butyl)-3-(1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
5		1-(1-benzyl-3-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
6		1-(tert-butyl)-3-(1-(3-chlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
7		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
8		1-(tert-butyl)-3-(1-(2-chlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
9		tert-butyl (1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)carbamate
10		1-(1-benzyl-4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
11		1-(1-benzyl-3-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
12		1-(1-benzyl-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-3-(tert-butyl)urea
13		(S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
14		(R)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea

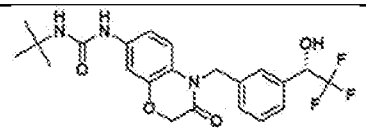
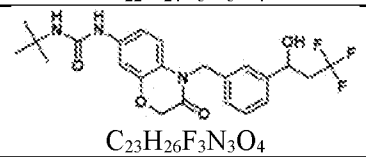
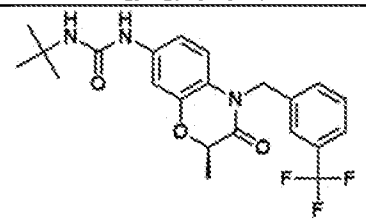
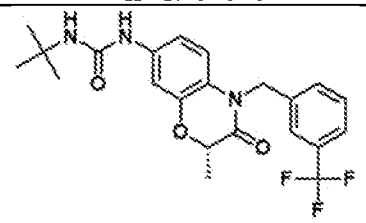
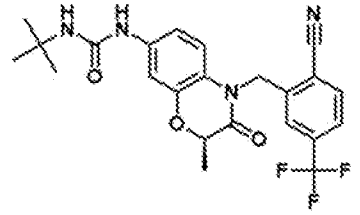
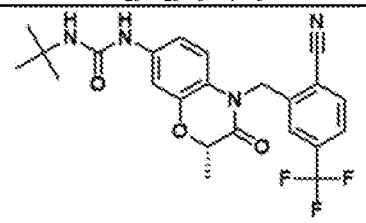
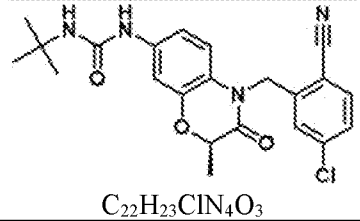
15		1-(1-benzyl-4-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
16		1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-hydroxy-2-methylbutan-2-yl)urea
17		1-(tert-butyl)-3-(1-(4-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
18		1-(tert-butyl)-3-(1-(3-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
19		1-(tert-butyl)-3-(1-(2-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
20		1-(tert-butyl)-3-(1-(2-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
21		1-(tert-butyl)-3-(1-(3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
22		1-(tert-butyl)-3-(1-(3-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
23		1-(tert-butyl)-3-(2-oxo-1-(3-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
24		1-(tert-butyl)-3-(1-(2,5-dichlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
25		1-(tert-butyl)-3-(1-(3,5-dichlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
26		1-(tert-butyl)-3-(1-(3-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
27		1-(tert-butyl)-3-(1-(4-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
28		1-(tert-butyl)-3-(2-oxo-1-(1-phenylpropyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
29		1-(1-benzyl-3,3-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
30		1-(tert-butyl)-3-(1-(2-hydroxy-1-phenylethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

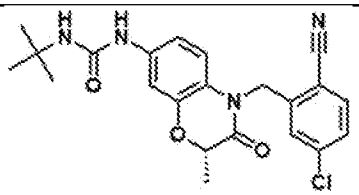
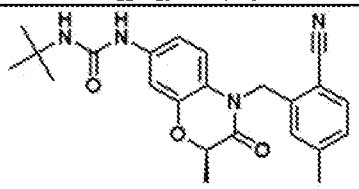
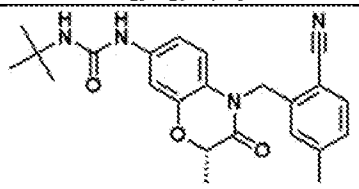
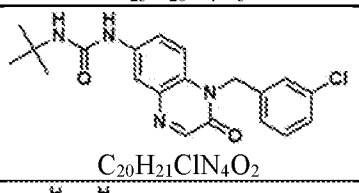
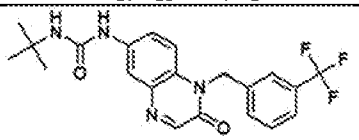
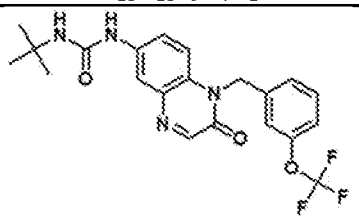
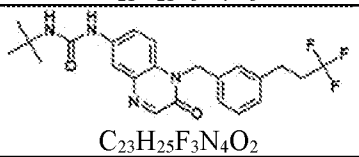
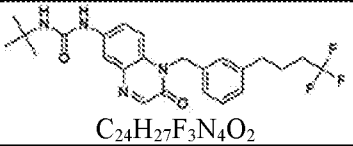
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32		1-(1-benzyl-3-isopropyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
33		1-(tert-butyl)-3-(4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
34		(R)-1-(tert-butyl)-3-(3-oxo-4-(1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
35	 $C_{21}H_{25}N_3O_3$	(S)-1-(tert-butyl)-3-(3-oxo-4-(1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
36		(R)-1-(tert-butyl)-3-(4-(1-(3-chlorophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
37		(S)-1-(tert-butyl)-3-(4-(1-(3-chlorophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
38		1-(3-benzyl-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-(tert-butyl)urea
39		1-(tert-butyl)-3-(1-(2-fluoro-5-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
40		1-(tert-butyl)-3-(4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
41		(R)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
42		(S)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

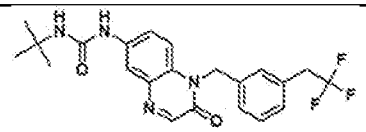
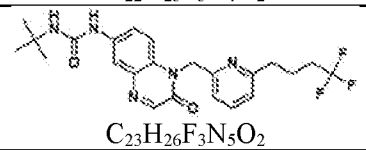
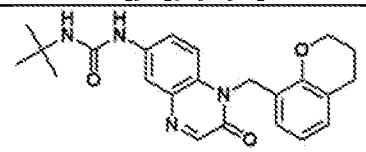
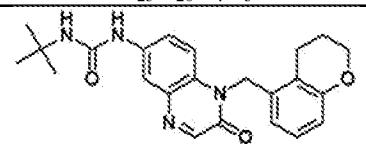
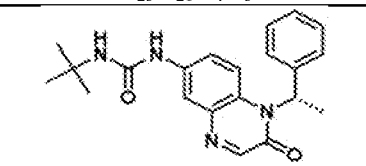
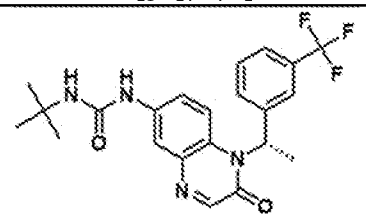
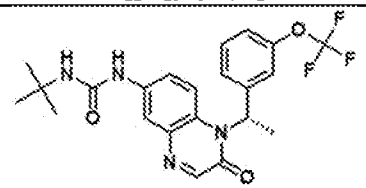
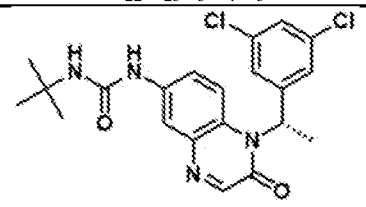
43		(S)-1-(tert-butyl)-3-(4-(3-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
44		(R)-1-(tert-butyl)-3-(4-(3-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
45		(S)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea
46		(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea
47		1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea
48		1-(tert-butyl)-3-(1-(2-fluoro-3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
49		1-(tert-butyl)-3-(1-(2-fluoro-5-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
50		1-(tert-butyl)-3-(3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
51		1-(1-benzyl-3-(hydroxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
52		(R)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea
53		1-(tert-butyl)-3-(1-(2-cyano-3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
54		1-(tert-butyl)-3-(1-(2-fluoro-3-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
55		1-(tert-butyl)-3-(1-(2-cyano-5-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
56		(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(m-tolyl)ethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea

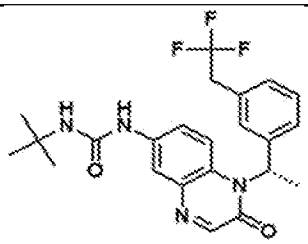
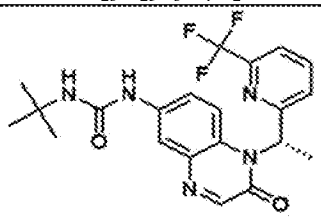
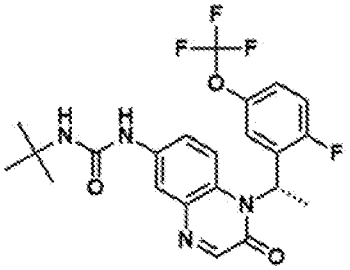
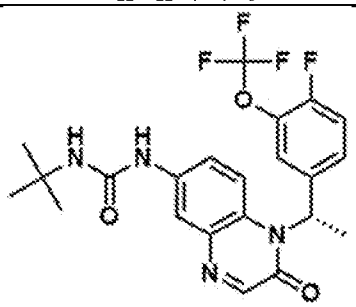
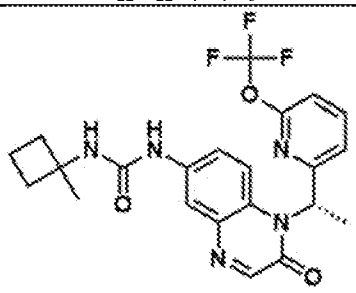
57		(S)-1-(tert-butyl)-3-(3-oxo-4-(1-(m-tolyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
58		(S)-1-(tert-butyl)-3-(1-(1-(2-fluorophenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
59		1-(tert-butyl)-3-(1-(2-cyano-3-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
60		(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
61		(S)-1-(tert-butyl)-3-(1-(1-(2-cyanophenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
62		(S)-1-(tert-butyl)-3-(3-oxo-4-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
63		1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl tert-butylcarbamate
64		1-(tert-butyl)-3-(1-(cyclohexylmethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
65		1-(1-benzyl-7-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
66		1-(1-benzyl-7-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
67		1-(5-benzyl-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)-3-(tert-butyl)urea
68		1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea

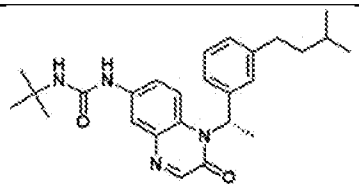
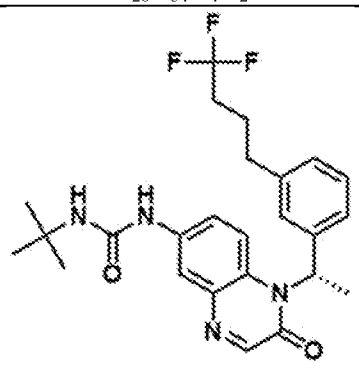
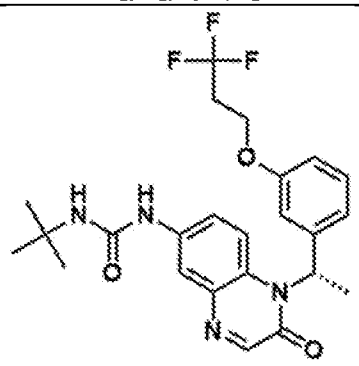
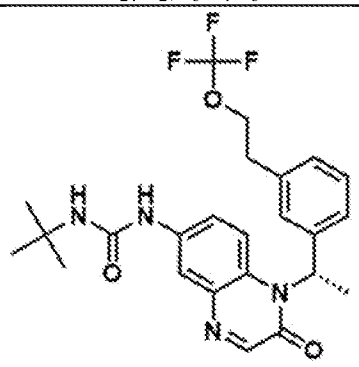
69		1-(1-benzyl-8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea; and
70		1-(tert-butyl)-3-(3-methyl-2-oxo-1-(3-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea
71	 $C_{21}H_{23}F_2N_3O_3$	1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
72	 $C_{21}H_{25}N_3O_4$	1-(tert-butyl)-3-(4-(3-(hydroxymethyl)benzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
73	 $C_{23}H_{27}N_3O_3$	1-(tert-butyl)-3-(4-(3-cyclopropylbenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
74	 $C_{21}H_{22}F_3N_3O_4$	1-(tert-butyl)-3-(3-oxo-4-(3-(trifluoromethoxy)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
75	 $C_{23}H_{29}N_3O_4$	1-(tert-butyl)-3-(4-(3-isopropoxybenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
76	 $C_{21}H_{23}N_5O_3$	1-(4-((1H-indazol-7-yl)methyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
77	 $C_{22}H_{24}F_3N_3O_4$	1-(tert-butyl)-3-(3-oxo-4-(3-(2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
78	 $C_{22}H_{24}F_3N_3O_4$	(R)-1-(tert-butyl)-3-(3-oxo-4-(3-(2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

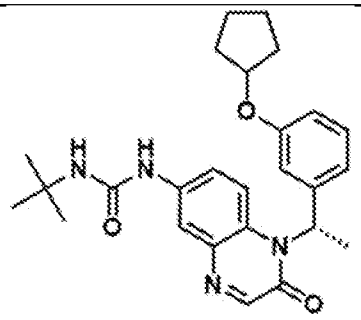
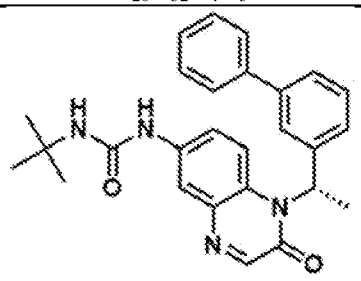
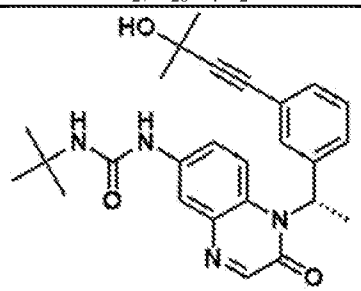
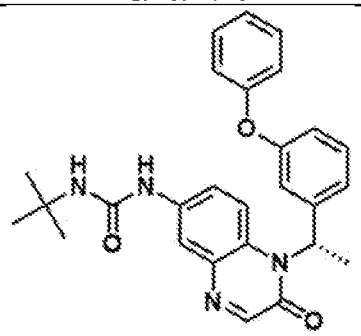
79	 $C_{22}H_{24}F_3N_3O_4$	(S)-1-(tert-butyl)-3-(3-oxo-4-(3-(2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
80	 $C_{23}H_{26}F_3N_3O_4$	1-(tert-butyl)-3-(3-oxo-4-(3-(3,3,3-trifluoro-1-hydroxypropyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
81	 $C_{22}H_{24}F_3N_3O_3$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
82	 $C_{22}H_{24}F_3N_3O_3$	(S)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
83	 $C_{23}H_{23}F_3N_4O_3$	(R)-1-(tert-butyl)-3-(4-(2-cyano-5-(trifluoromethyl)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
84	 $C_{23}H_{23}F_3N_4O_3$	(S)-1-(tert-butyl)-3-(4-(2-cyano-5-(trifluoromethyl)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
85	 $C_{22}H_{23}ClN_4O_3$	(R)-1-(tert-butyl)-3-(4-(5-chloro-2-cyanobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

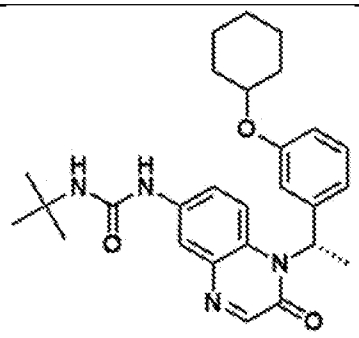
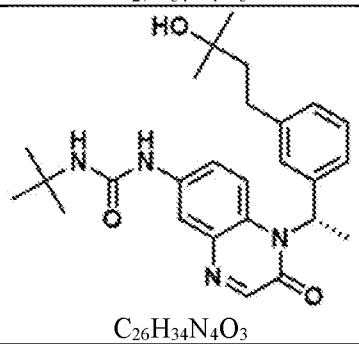
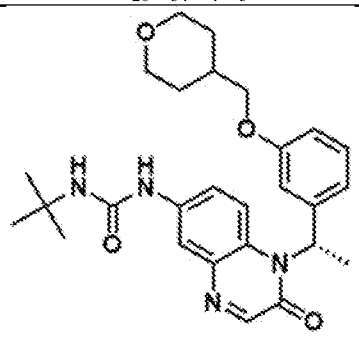
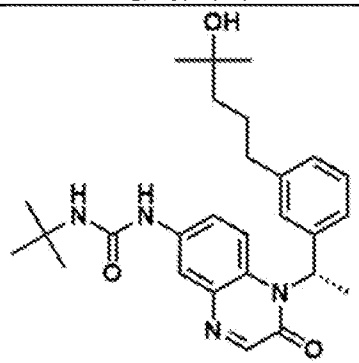
86	 $C_{22}H_{23}ClN_4O_3$	(S)-1-(tert-butyl)-3-(4-(5-chloro-2-cyanobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
87	 $C_{23}H_{26}N_4O_3$	(R)-1-(tert-butyl)-3-(4-(2-cyano-5-methylbenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
88	 $C_{23}H_{26}N_4O_3$	(S)-1-(tert-butyl)-3-(4-(2-cyano-5-methylbenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
89	 $C_{20}H_{21}ClN_4O_2$	1-(tert-butyl)-3-(1-(3-chlorobenzyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
90	 $C_{21}H_{21}F_3N_4O_2$	1-(tert-butyl)-3-(2-oxo-1-(3-(trifluoromethyl)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
91	 $C_{21}H_{21}F_3N_4O_3$	1-(tert-butyl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
92	 $C_{23}H_{25}F_3N_4O_2$	1-(tert-butyl)-3-(2-oxo-1-(3-(3,3,3-trifluoropropyl)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
93	 $C_{24}H_{27}F_3N_4O_2$	1-(tert-butyl)-3-(2-oxo-1-(3-(4,4,4-trifluorobutyl)benzyl)-1,2-dihydroquinoxalin-6-yl)urea

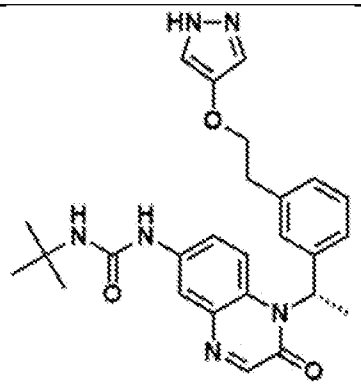
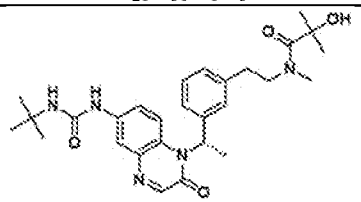
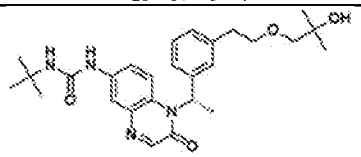
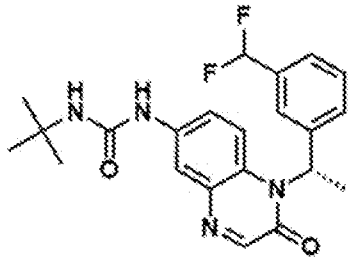
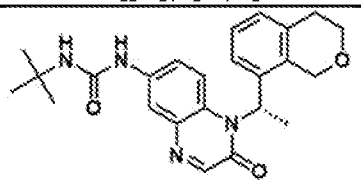
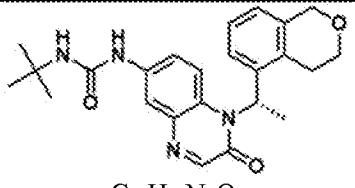
94	 $C_{22}H_{23}F_3N_4O_2$	1-(tert-butyl)-3-(2-oxo-1-(3-(2,2,2-trifluoroethyl)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
95	 $C_{23}H_{26}F_3N_5O_2$	1-(tert-butyl)-3-(2-oxo-1-((6-(4,4,4-trifluorobutyl)pyridin-2-yl)methyl)-1,2-dihydroquinoxalin-6-yl)urea
96	 $C_{23}H_{26}N_4O_3$	1-(tert-butyl)-3-(1-(chroman-8-ylmethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
97	 $C_{23}H_{26}N_4O_3$	1-(tert-butyl)-3-(1-(chroman-5-ylmethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
98	 $C_{21}H_{24}N_4O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea
99	 $C_{22}H_{23}F_3N_4O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
100	 $C_{22}H_{23}F_3N_4O_3$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
101	 $C_{21}H_{22}Cl_2N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3,5-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

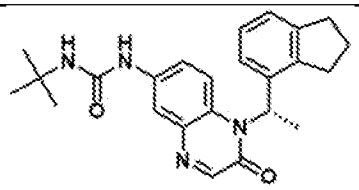
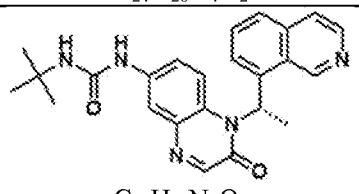
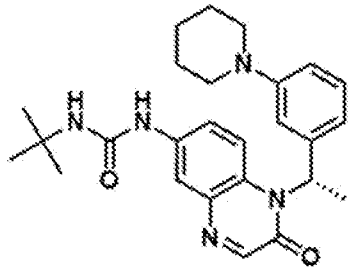
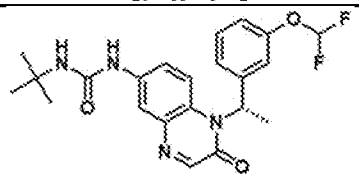
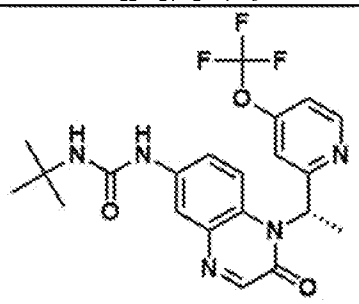
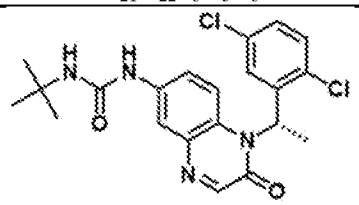
102	 $C_{23}H_{25}F_3N_4O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2,2,2-trifluoroethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
103	 $C_{21}H_{22}F_3N_5O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
104	 $C_{22}H_{22}F_4N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(2-fluoro-5-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
105	 $C_{22}H_{22}F_4N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(4-fluoro-3-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
106	 $C_{22}H_{22}F_3N_5O_3$	(S)-1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(6-(trifluoromethoxy)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

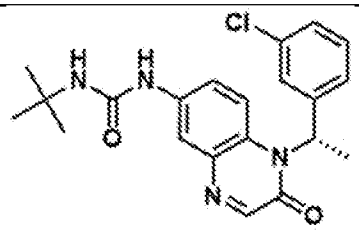
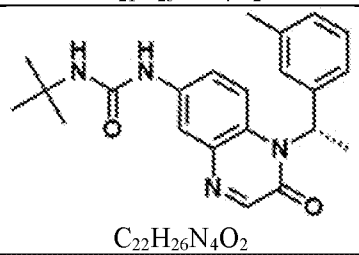
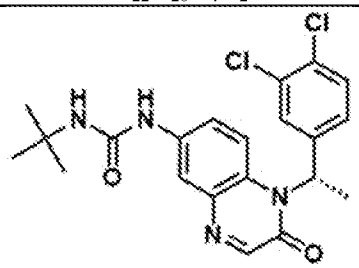
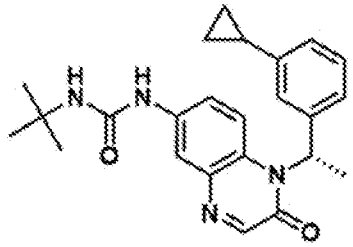
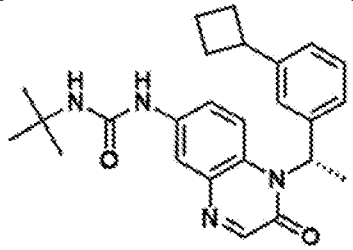
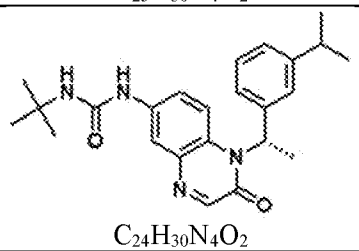
107	 $C_{26}H_{34}N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-isopentylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
108	 $C_{25}H_{29}F_3N_4O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(4,4,4-trifluorobutyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
109	 $C_{24}H_{27}F_3N_4O_3$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(3,3,3-trifluoropropoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
110	 $C_{24}H_{27}F_3N_4O_3$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2-(trifluoromethoxy)ethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

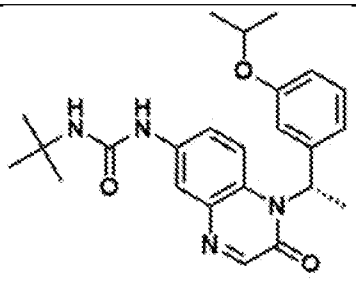
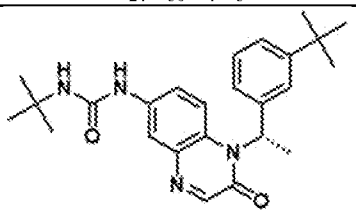
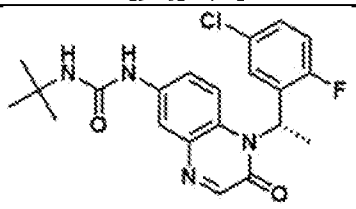
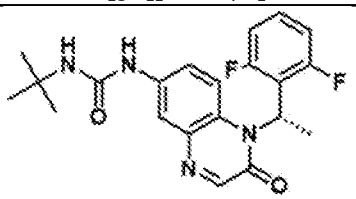
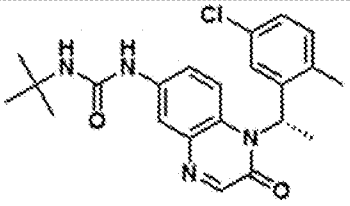
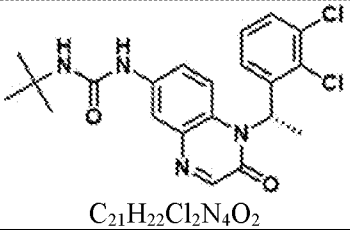
111	 $C_{26}H_{32}N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(3-(cyclopentyloxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
112	 $C_{27}H_{28}N_4O_2$	(S)-1-(1-(1-([1,1'-biphenyl]-3-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea
113	 $C_{26}H_{30}N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(3-(3-hydroxy-3-methylbut-1-yn-1-yl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
114	 $C_{27}H_{28}N_4O_3$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-phenoxyphenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

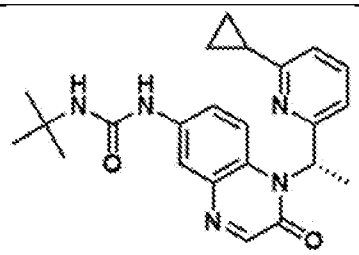
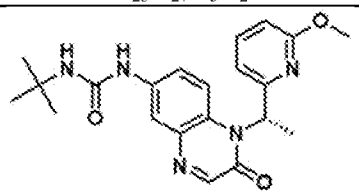
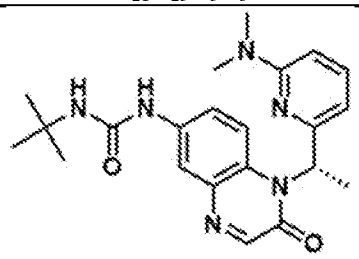
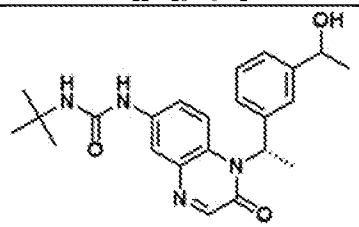
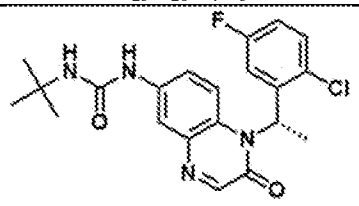
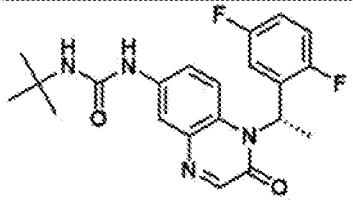
115	 $C_{27}H_{34}N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(3-(cyclohexyloxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
116	 $C_{26}H_{34}N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(3-(3-hydroxy-3-methylbutyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
117	 $C_{27}H_{34}N_4O_4$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
118	 $C_{27}H_{36}N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(3-(4-hydroxy-4-methylpentyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

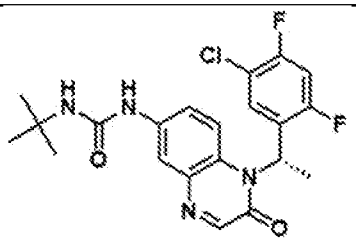
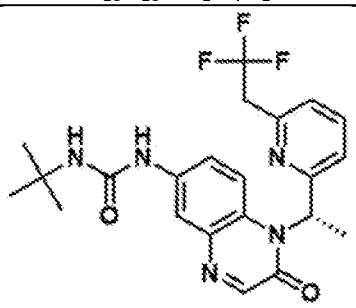
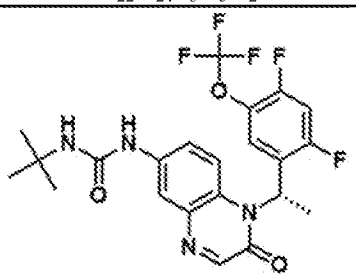
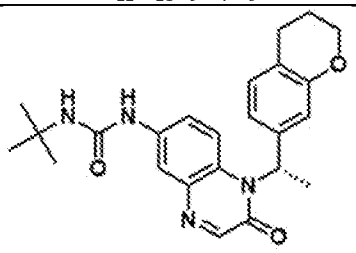
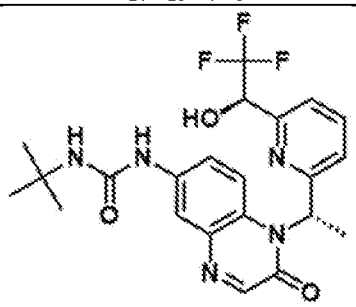
119	 $C_{26}H_{30}N_6O_3$	(S)-1-(1-(1-(3-(2-((1H-pyrazol-4-yl)oxy)ethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea
120	 $C_{28}H_{37}N_5O_4$	(S)-N-(3-(1-(6-(3-(tert-butyl)ureido)-2-oxoquinoxalin-1(2H)-yl)ethyl)phenethyl)-2-hydroxy-N,2-dimethylpropanamide
121	 $C_{27}H_{36}N_4O_4$	(S)-1-(tert-butyl)-3-(1-(1-(3-(2-(2-hydroxy-2-methylpropoxy)ethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
122	 $C_{22}H_{24}F_2N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-(difluoromethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
123	 $C_{24}H_{28}N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(isochroman-8-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
124	 $C_{24}H_{28}N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(isochroman-5-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

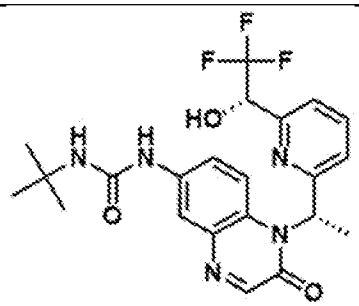
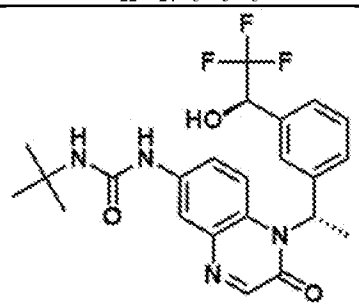
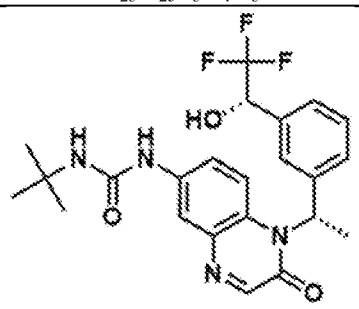
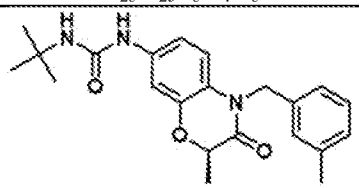
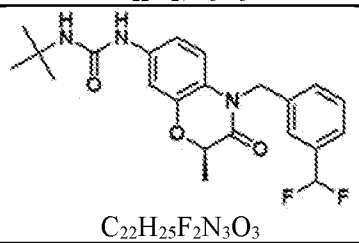
125	 $C_{24}H_{28}N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(2,3-dihydro-1H-inden-4-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
126	 $C_{24}H_{25}N_5O_2$	(S)-1-(tert-butyl)-3-(1-(1-(isoquinolin-8-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
127	 $C_{26}H_{33}N_5O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(piperidin-1-yl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
128	 $C_{22}H_{24}F_2N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(3-(difluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
129	 $C_{21}H_{22}F_3N_5O_3$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(4-(trifluoromethoxy)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
130	 $C_{21}H_{22}Cl_2N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(2,5-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

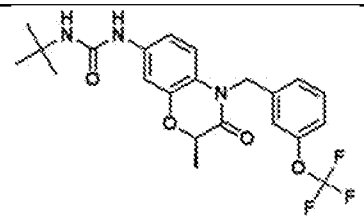
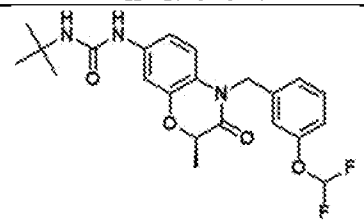
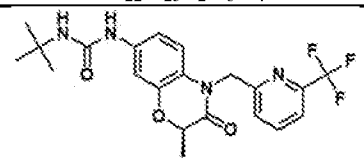
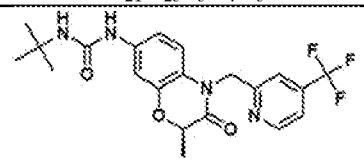
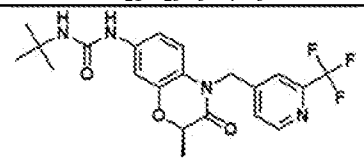
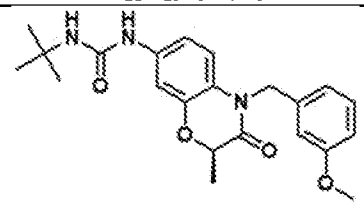
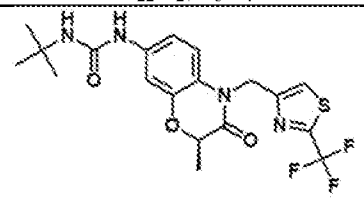
131	 $C_{21}H_{23}ClN_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
132	 $C_{22}H_{26}N_4O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(m-tolyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
133	 $C_{21}H_{22}Cl_2N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3,4-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
134	 $C_{24}H_{28}N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-cyclopropylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
135	 $C_{25}H_{30}N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-cyclobutylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
136	 $C_{24}H_{30}N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-isopropylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

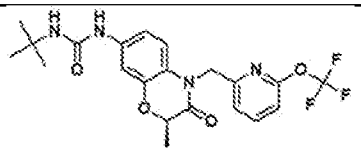
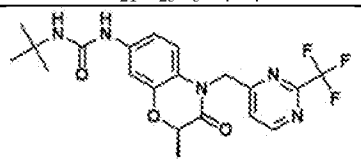
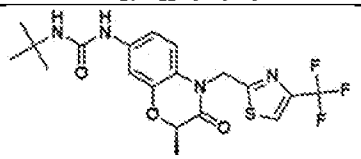
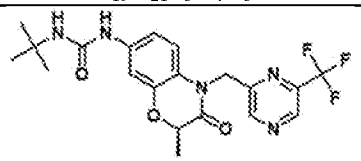
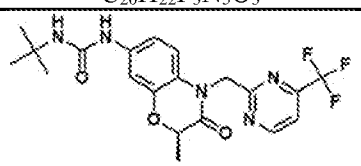
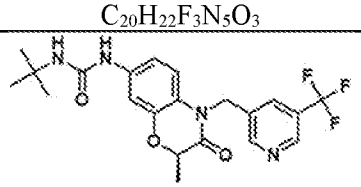
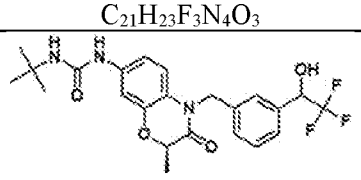
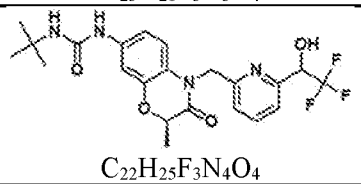
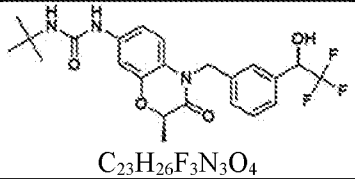
137	 $C_{24}H_{30}N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(3-isopropoxyphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
138	 $C_{25}H_{32}N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-(tert-butyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
139	 $C_{21}H_{22}ClFN_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(5-chloro-2-fluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
140	 $C_{21}H_{22}F_2N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(2,6-difluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
141	 $C_{22}H_{25}ClN_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(5-chloro-2-methylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
142	 $C_{21}H_{22}Cl_2N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(2,3-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

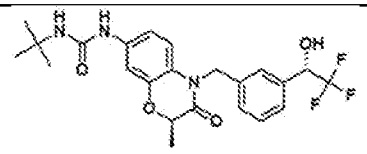
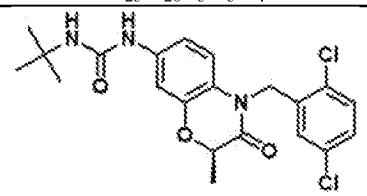
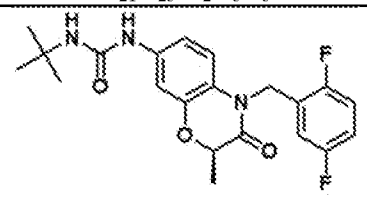
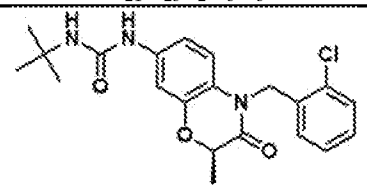
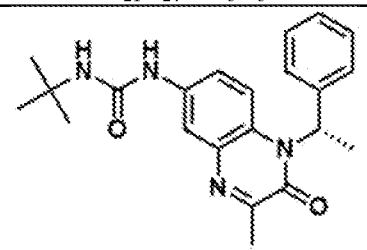
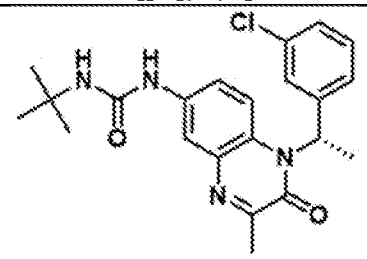
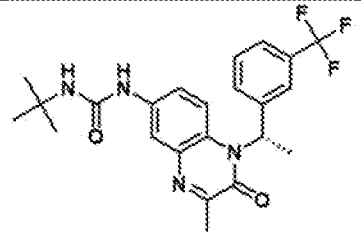
143	 $C_{23}H_{27}N_5O_2$	(S)-1-(tert-butyl)-3-(1-(1-(6-cyclopropylpyridin-2-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
144	 $C_{21}H_{25}N_5O_3$	(S)-1-(tert-butyl)-3-(1-(1-(6-methoxypyridin-2-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
145	 $C_{22}H_{28}N_6O_2$	(S)-1-(tert-butyl)-3-(1-(1-(6-(dimethylamino)pyridin-2-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
146	 $C_{23}H_{28}N_4O_3$	1-(tert-butyl)-3-(1-((1S)-1-(3-(1-hydroxyethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
147	 $C_{21}H_{22}ClFN_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(2-chloro-5-fluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
148	 $C_{21}H_{22}F_2N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(2,5-difluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

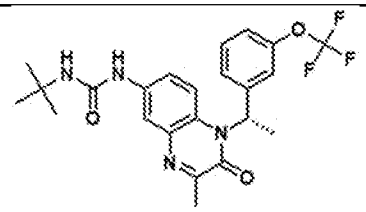
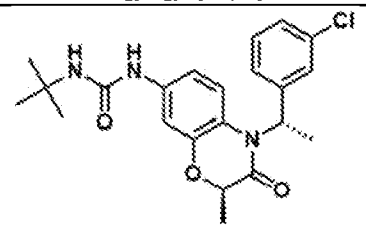
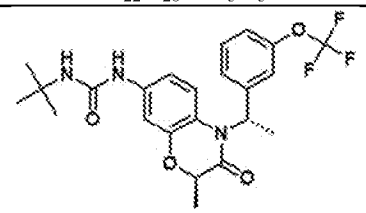
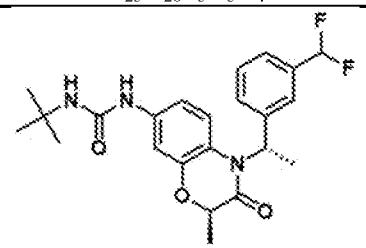
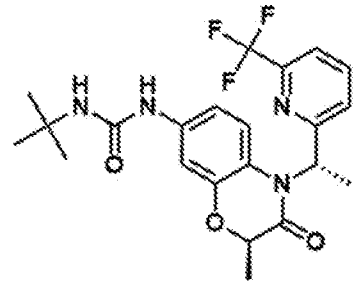
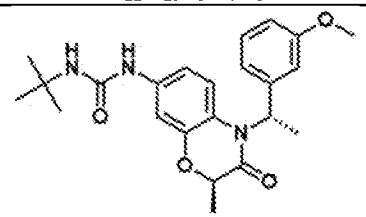
149	 $C_{21}H_{21}ClF_2N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(5-chloro-2,4-difluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
150	 $C_{22}H_{24}F_3N_5O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(6-(2,2,2-trifluoroethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
151	 $C_{22}H_{21}F_5N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(2,4-difluoro-5-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
152	 $C_{24}H_{28}N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(chroman-7-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
153	 $C_{22}H_{24}F_3N_5O_3$	1-(tert-butyl)-3-(2-oxo-1-((S)-1-(6-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

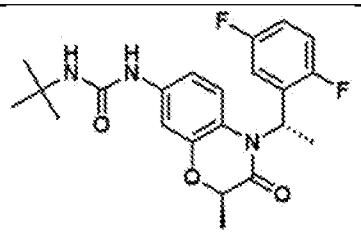
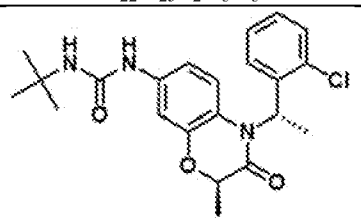
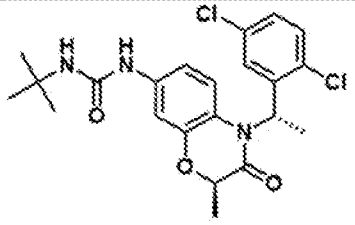
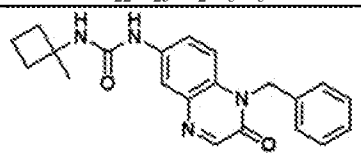
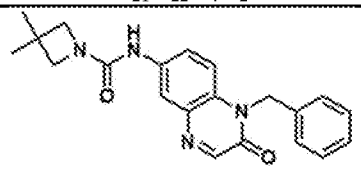
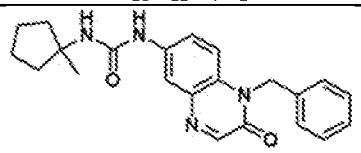
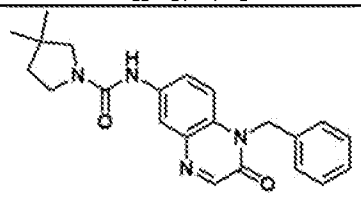
154	 $C_{22}H_{24}F_3N_5O_3$	1-(tert-butyl)-3-(2-oxo-1-((S)-1-(6-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
155	 $C_{23}H_{25}F_3N_4O_3$	1-(tert-butyl)-3-(2-oxo-1-((S)-1-(3-((R)-2,2,2-trifluoro-1-hydroxyethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
156	 $C_{23}H_{25}F_3N_4O_3$	1-(tert-butyl)-3-(2-oxo-1-((S)-1-(3-((S)-2,2,2-trifluoro-1-hydroxyethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
157	 $C_{22}H_{27}N_3O_3$	(R)-1-(tert-butyl)-3-(2-methyl-4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
158	 $C_{22}H_{25}F_2N_3O_3$	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

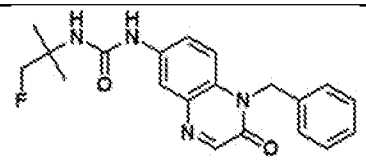
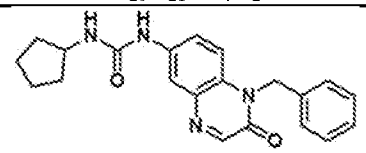
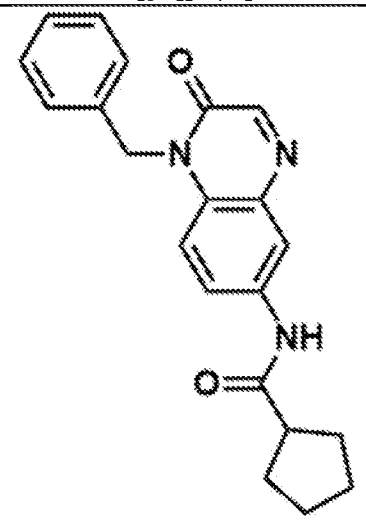
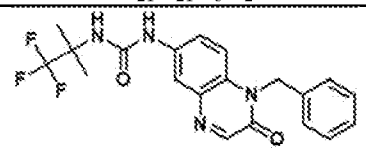
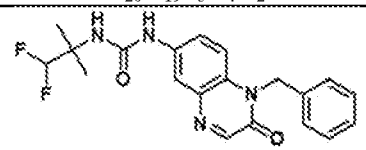
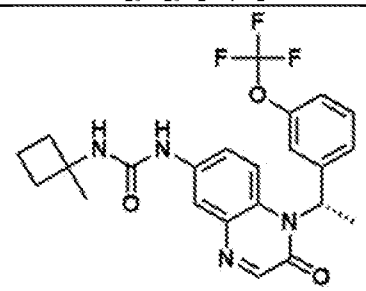
159	 $C_{22}H_{24}F_3N_3O_4$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-(3-(trifluoromethoxy)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
160	 $C_{22}H_{25}F_2N_3O_4$	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethoxy)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
161	 $C_{21}H_{23}F_3N_4O_3$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
162	 $C_{21}H_{23}F_3N_4O_3$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((4-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
163	 $C_{21}H_{23}F_3N_4O_3$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((2-(trifluoromethyl)pyridin-4-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
164	 $C_{22}H_{27}N_3O_4$	(R)-1-(tert-butyl)-3-(4-(3-methoxybenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
165	 $C_{19}H_{21}F_3N_4O_3S$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((2-(trifluoromethyl)thiazol-4-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

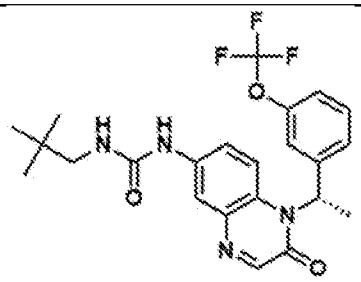
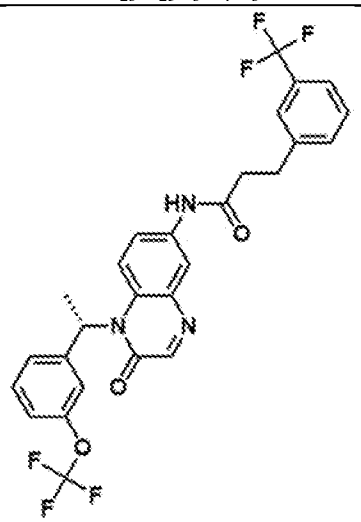
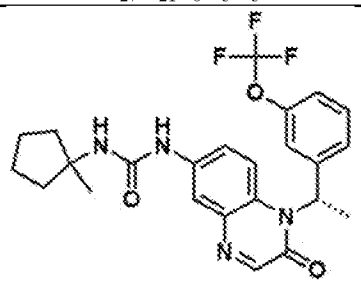
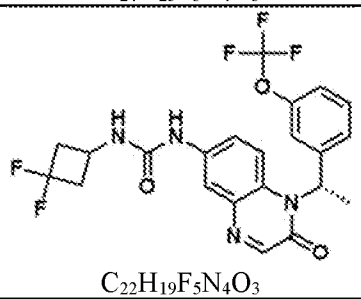
166	 $C_{21}H_{23}F_3N_4O_4$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethoxy)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
167	 $C_{20}H_{22}F_3N_5O_3$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((2-(trifluoromethyl)pyrimidin-4-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
168	 $C_{19}H_{21}F_3N_4O_3S$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((4-(trifluoromethyl)thiazol-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
169	 $C_{20}H_{22}F_3N_5O_3$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyrazin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
170	 $C_{20}H_{22}F_3N_5O_3$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((4-(trifluoromethyl)pyrimidin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
171	 $C_{21}H_{23}F_3N_4O_3$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((5-(trifluoromethyl)pyridin-3-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
172	 $C_{23}H_{26}F_3N_3O_4$	1-(tert-butyl)-3-((2R)-2-methyl-3-oxo-4-(3-(2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
173	 $C_{22}H_{25}F_3N_4O_4$	1-(tert-butyl)-3-((2R)-2-methyl-3-oxo-4-((6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
174	 $C_{23}H_{26}F_3N_3O_4$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-(3-((R)-2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

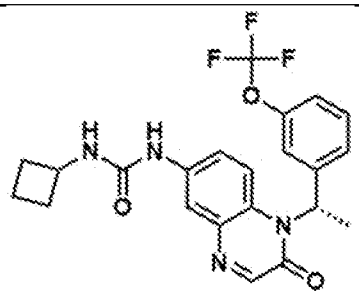
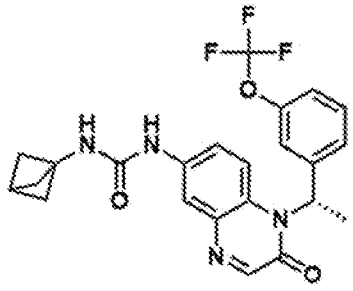
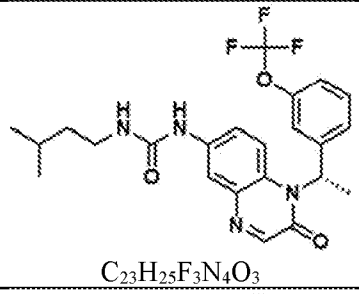
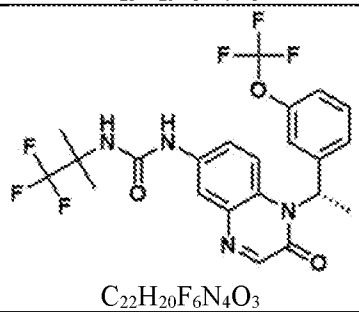
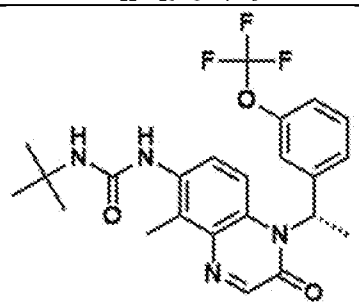
175	 $C_{23}H_{26}F_3N_3O_4$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-(3-((S)-2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
176	 $C_{21}H_{23}Cl_2N_3O_3$	(R)-1-(tert-butyl)-3-(4-(2,5-dichlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
177	 $C_{21}H_{23}F_2N_3O_3$	(R)-1-(tert-butyl)-3-(4-(2,5-difluorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
178	 $C_{21}H_{24}ClN_3O_3$	(R)-1-(tert-butyl)-3-(4-(2-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
179	 $C_{22}H_{26}N_4O_2$	(S)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea
180	 $C_{22}H_{25}ClN_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
181	 $C_{23}H_{25}F_3N_4O_2$	(S)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

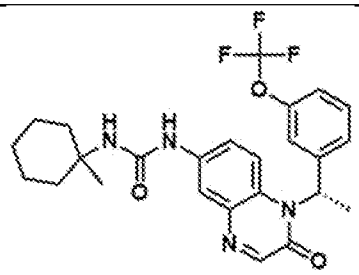
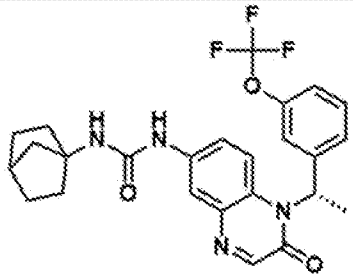
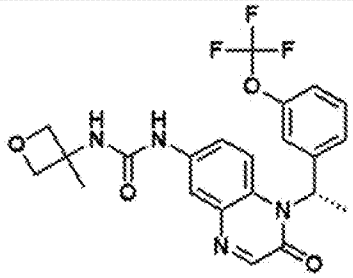
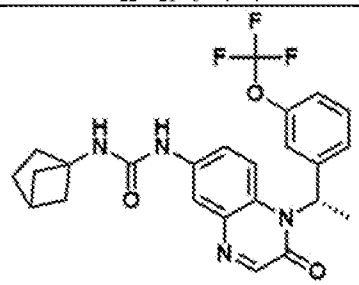
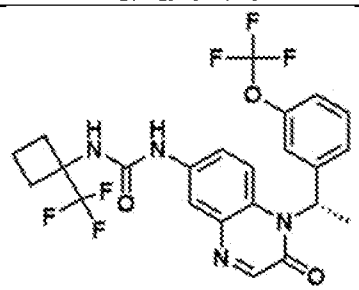
182	 $C_{23}H_{25}F_3N_4O_3$	(S)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
183	 $C_{22}H_{26}ClN_3O_3$	1-(tert-butyl)-3-((R)-4-((S)-1-(3-chlorophenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
184	 $C_{23}H_{26}F_3N_3O_4$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
185	 $C_{23}H_{27}F_2N_3O_3$	1-(tert-butyl)-3-((R)-4-((S)-1-(3-(difluoromethyl)phenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
186	 $C_{22}H_{25}F_3N_4O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
187	 $C_{23}H_{29}N_3O_4$	1-(tert-butyl)-3-((R)-4-((S)-1-(3-methoxyphenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

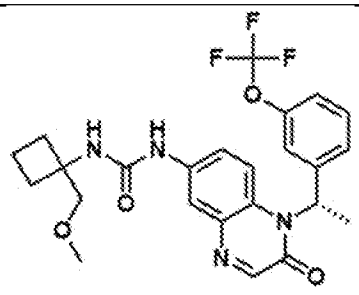
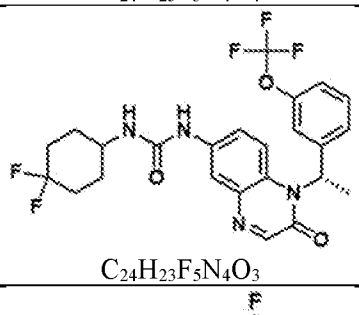
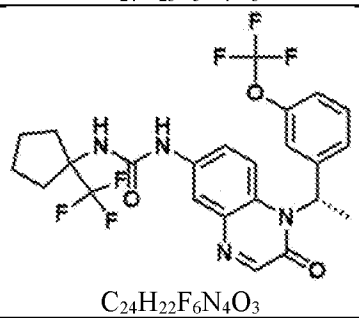
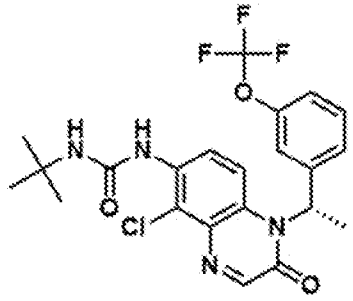
188	 $C_{22}H_{25}F_2N_3O_3$	1-(tert-butyl)-3-((R)-4-((S)-1-(2,5-difluorophenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
189	 $C_{22}H_{26}ClN_3O_3$	1-(tert-butyl)-3-((R)-4-((S)-1-(2-chlorophenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
190	 $C_{22}H_{25}Cl_2N_3O_3$	1-(tert-butyl)-3-((R)-4-((S)-1-(2,5-dichlorophenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
191	 $C_{21}H_{22}N_4O_2$	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1-methylcyclobutyl)urea
192	 $C_{21}H_{22}N_4O_2$	N-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3,3-dimethylazetidine-1-carboxamide
193	 $C_{22}H_{24}N_4O_2$	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1-methylcyclopentyl)urea
194	 $C_{22}H_{24}N_4O_2$	N-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3,3-dimethylpyrrolidine-1-carboxamide

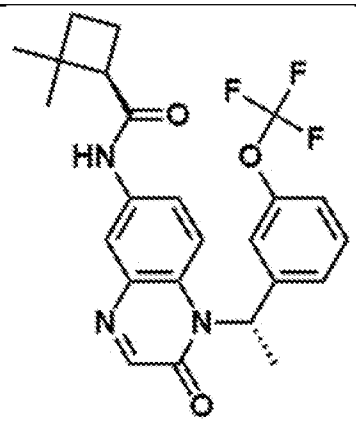
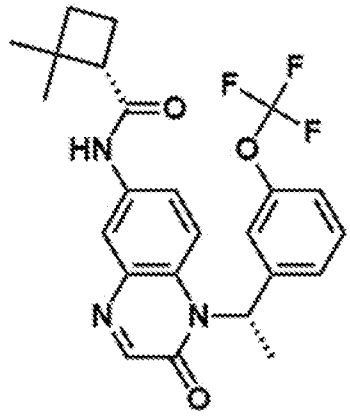
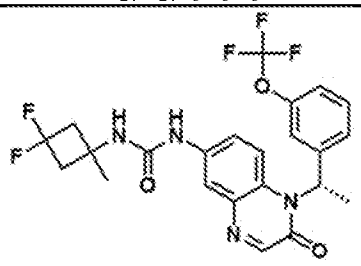
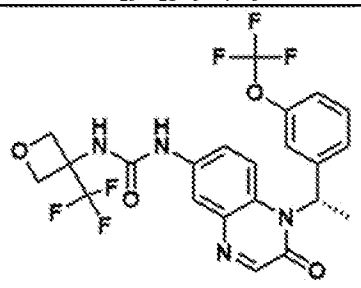
195	 $C_{20}H_{21}FN_4O_2$	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1-fluoro-2-methylpropan-2-yl)urea
196	 $C_{21}H_{22}N_4O_2$	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-cyclopentylurea
197	 $C_{21}H_{21}N_3O_2$	N-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)cyclopentanecarboxamide
198	 $C_{20}H_{19}F_3N_4O_2$	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1,1,1-trifluoro-2-methylpropan-2-yl)urea
199	 $C_{20}H_{20}F_2N_4O_2$	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1,1-difluoro-2-methylpropan-2-yl)urea
200	 $C_{23}H_{23}F_3N_4O_3$	(S)-1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

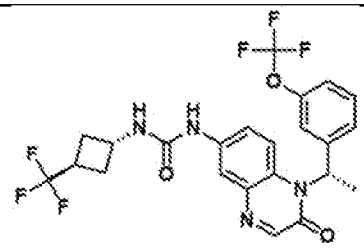
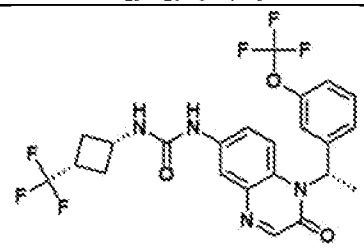
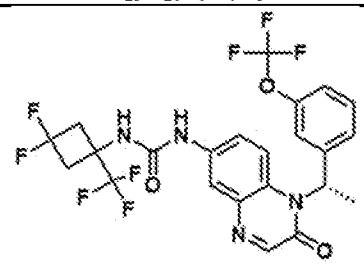
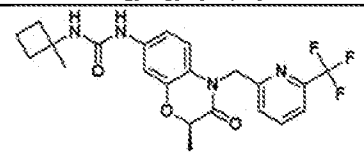
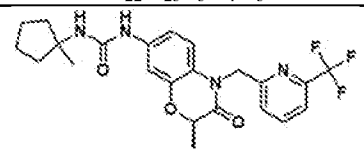
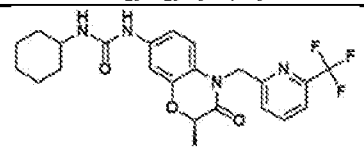
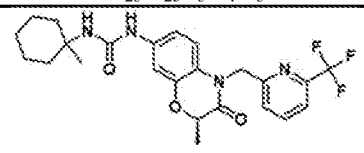
201	 $C_{23}H_{25}F_3N_4O_3$	(S)-1-neopentyl-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
202	 $C_{27}H_{21}F_6N_3O_3$	(S)-N-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)phenyl)propanamide
203	 $C_{24}H_{25}F_3N_4O_3$	(S)-1-(1-methylcyclopentyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
204	 $C_{22}H_{19}F_5N_4O_3$	(S)-1-(3,3-difluorocyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

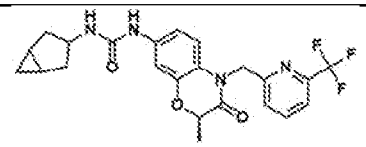
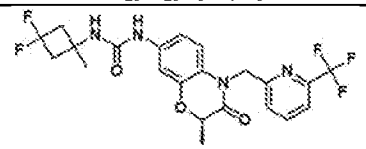
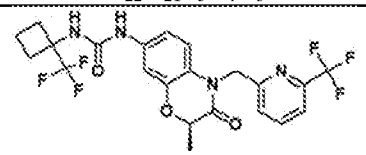
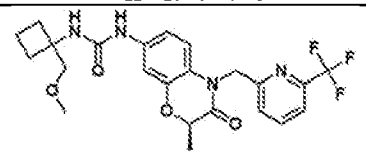
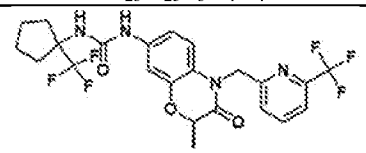
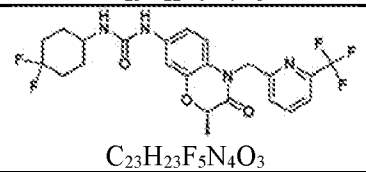
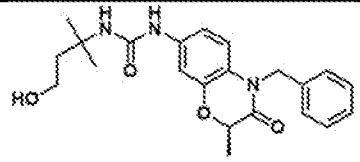
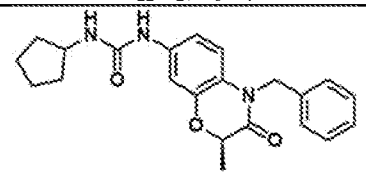
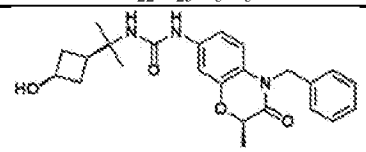
205	 $C_{22}H_{21}F_3N_4O_3$	(S)-1-cyclobutyl-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
206	 $C_{23}H_{21}F_3N_4O_3$	(S)-1-(bicyclo[1.1.1]pentan-1-yl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
207	 $C_{23}H_{25}F_3N_4O_3$	(S)-1-isopentyl-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
208	 $C_{22}H_{20}F_6N_4O_3$	(S)-1-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(1,1,1-trifluoro-2-methylpropan-2-yl)urea
209	 $C_{23}H_{25}F_3N_4O_3$	(S)-1-(tert-butyl)-3-(5-methyl-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

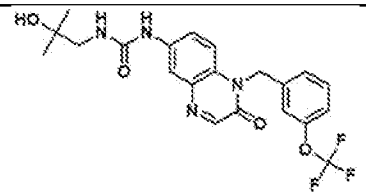
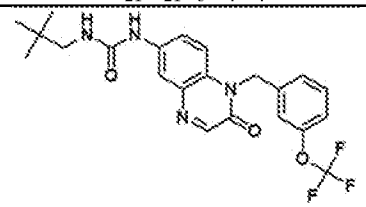
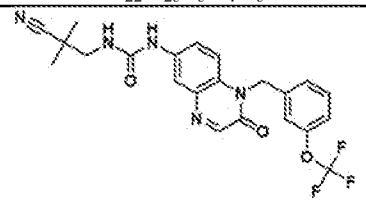
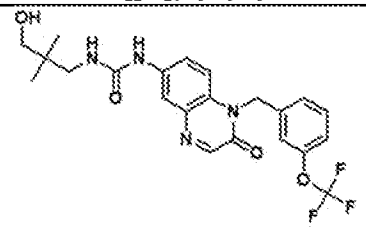
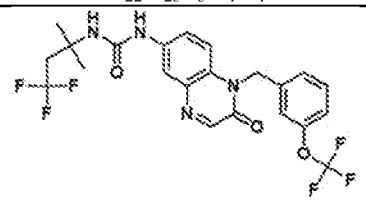
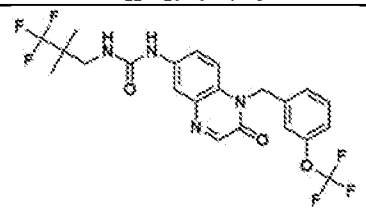
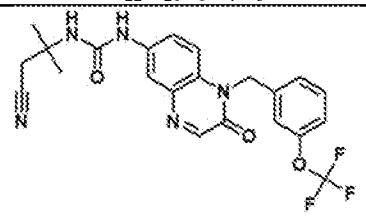
210	 $C_{25}H_{27}F_3N_4O_3$	(S)-1-(1-methylcyclohexyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
211	 $C_{25}H_{25}F_3N_4O_3$	(S)-1-(bicyclo[2.2.1]heptan-1-yl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
212	 $C_{22}H_{21}F_3N_4O_4$	(S)-1-(3-methyloxetan-3-yl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
213	 $C_{24}H_{23}F_3N_4O_3$	(S)-1-(bicyclo[2.1.1]hexan-1-yl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
214	 $C_{23}H_{20}F_6N_4O_3$	(S)-1-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(1-(trifluoromethyl)cyclobutyl)urea

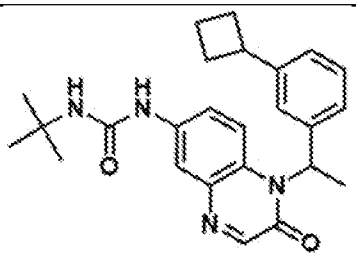
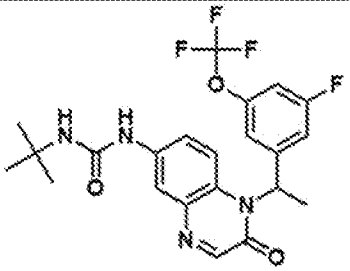
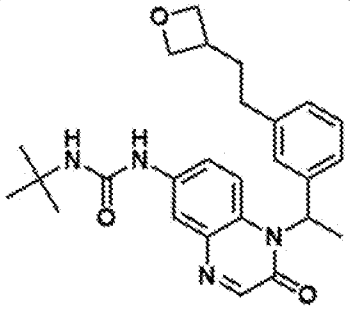
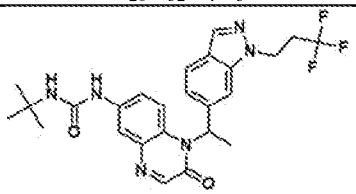
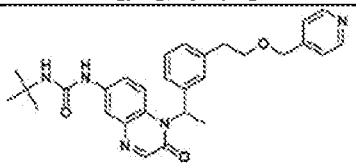
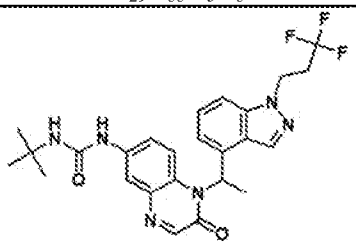
215	 $C_{24}H_{25}F_3N_4O_4$	(S)-1-(1-(methoxymethyl)cyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
216	 $C_{24}H_{23}F_5N_4O_3$	(S)-1-(4,4-difluorocyclohexyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
217	 $C_{24}H_{22}F_6N_4O_3$	(S)-1-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(1-(trifluoromethyl)cyclopentyl)urea
218	 $C_{22}H_{22}ClF_3N_4O_3$	(S)-1-(tert-butyl)-3-(5-chloro-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

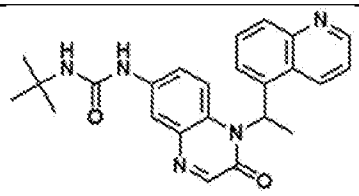
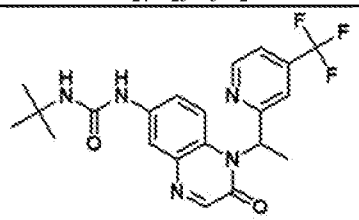
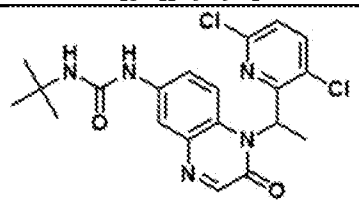
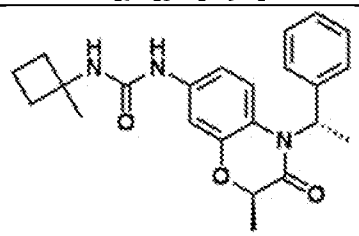
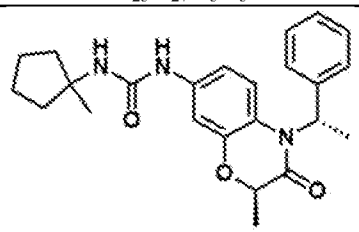
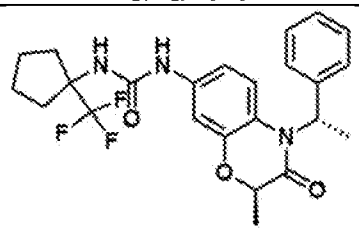
219	 $C_{24}H_{24}F_3N_3O_3$	(R)-2,2-dimethyl-N-(2-oxo-1-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)cyclobutane-1-carboxamide
220	 $C_{24}H_{24}F_3N_3O_3$	(S)-2,2-dimethyl-N-(2-oxo-1-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)cyclobutane-1-carboxamide
221	 $C_{23}H_{21}F_5N_4O_3$	(S)-1-(3,3-difluoro-1-methylcyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
222	 $C_{22}H_{18}F_6N_4O_4$	(S)-1-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)oxetan-3-yl)urea

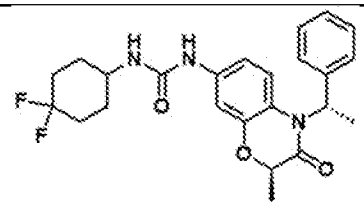
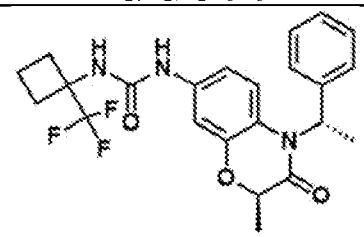
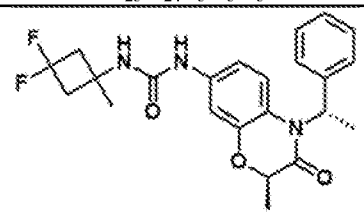
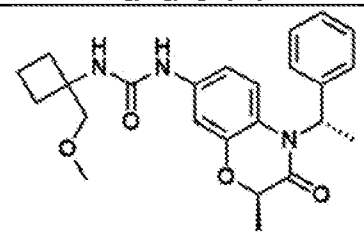
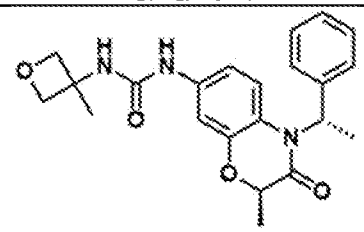
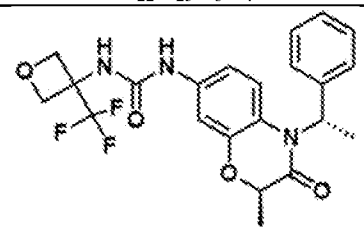
223	 $C_{23}H_{20}F_6N_4O_3$	1-(2-oxo-1-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-((1r,3S)-3-(trifluoromethyl)cyclobutyl)urea
224	 $C_{23}H_{20}F_6N_4O_3$	1-(2-oxo-1-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-((1s,3R)-3-(trifluoromethyl)cyclobutyl)urea
225	 $C_{23}H_{18}F_8N_4O_3$	(S)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
226	 $C_{22}H_{23}F_3N_4O_3$	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclobutyl)urea
227	 $C_{23}H_{25}F_3N_4O_3$	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea
228	 $C_{23}H_{25}F_3N_4O_3$	(R)-1-cyclohexyl-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
229	 $C_{24}H_{27}F_3N_4O_3$	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclohexyl)urea

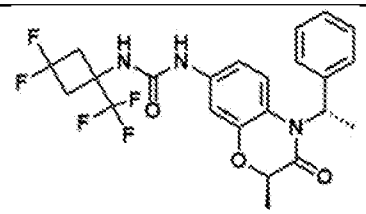
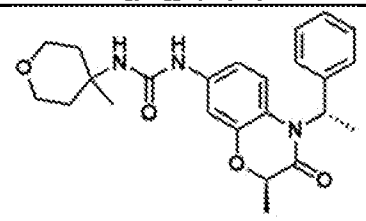
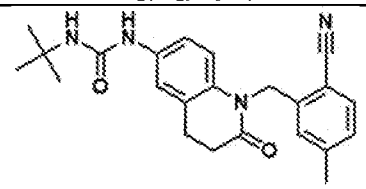
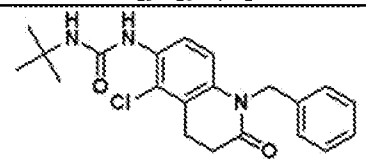
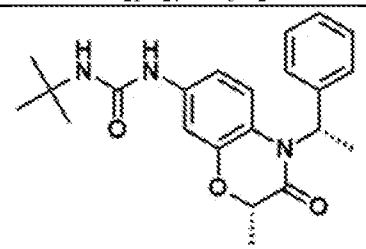
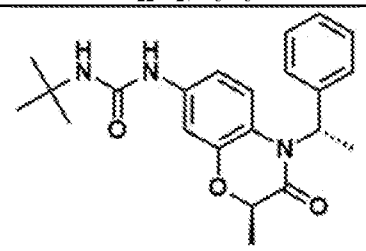
230	 $C_{23}H_{23}F_3N_4O_3$	1-(bicyclo[3.1.0]hexan-3-yl)-3-((R)-2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
231	 $C_{22}H_{21}F_5N_4O_3$	(R)-1-(3,3-difluoro-1-methylcyclobutyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
232	 $C_{22}H_{20}F_6N_4O_3$	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-(trifluoromethyl)cyclobutyl)urea
233	 $C_{23}H_{25}F_3N_4O_4$	(R)-1-(1-(methoxymethyl)cyclobutyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
234	 $C_{23}H_{22}F_6N_4O_3$	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-(trifluoromethyl)cyclopentyl)urea
235	 $C_{23}H_{23}F_5N_4O_3$	(R)-1-(4,4-difluorocyclohexyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
236	 $C_{22}H_{27}N_3O_4$	(R)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(4-hydroxy-2-methylbutan-2-yl)urea
237	 $C_{22}H_{25}N_3O_3$	(R)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-cyclopentylurea
238	 $C_{24}H_{29}N_3O_4$	1-((R)-4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(2-((1s,3S)-3-hydroxycyclobutyl)propan-2-yl)urea

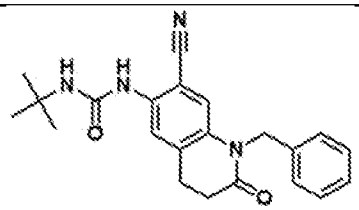
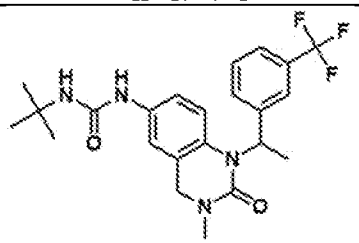
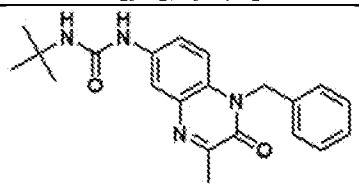
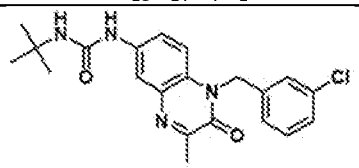
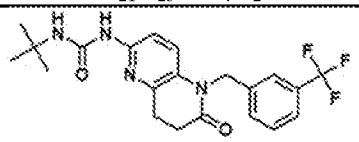
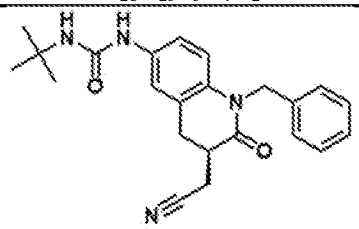
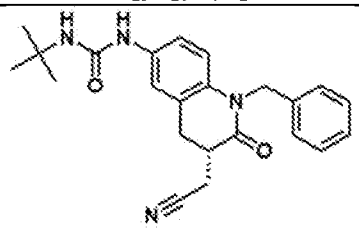
239	 $C_{21}H_{21}F_3N_4O_4$	1-(2-hydroxy-2-methylpropyl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
240	 $C_{22}H_{23}F_3N_4O_3$	1-neopentyl-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
241	 $C_{22}H_{20}F_3N_5O_3$	1-(2-cyano-2-methylpropyl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
242	 $C_{22}H_{23}F_3N_4O_4$	1-(3-hydroxy-2,2-dimethylpropyl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
243	 $C_{22}H_{20}F_6N_4O_3$	1-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)-3-(4,4,4-trifluoro-2-methylbutan-2-yl)urea
244	 $C_{22}H_{20}F_6N_4O_3$	1-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)-3-(3,3,3-trifluoro-2,2-dimethylpropyl)urea
245	 $C_{22}H_{20}F_3N_5O_3$	1-(1-cyano-2-methylpropan-2-yl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea

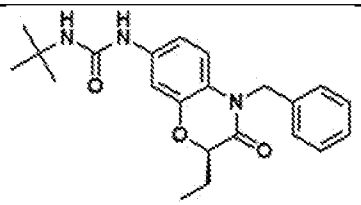
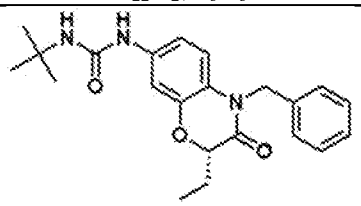
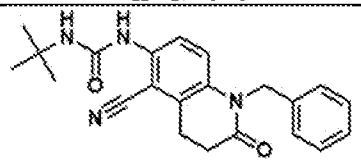
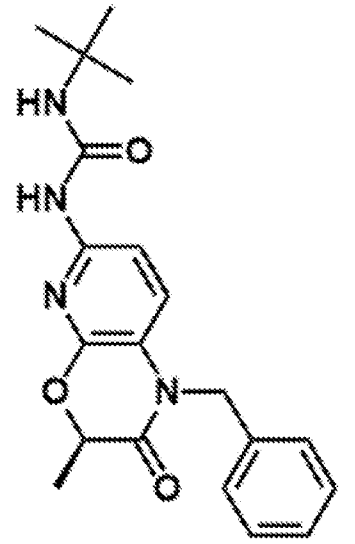
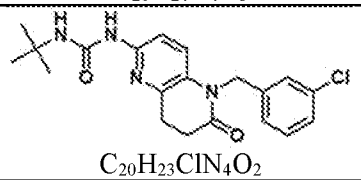
246	 $C_{25}H_{30}N_4O_2$	1-(tert-butyl)-3-(1-(1-(3-cyclobutylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
247	 $C_{22}H_{22}F_4N_4O_3$	1-(tert-butyl)-3-(1-(1-(3-fluoro-5-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
248	 $C_{26}H_{32}N_4O_3$	1-(tert-butyl)-3-(1-(1-(3-(2-(oxetan-3-yl)ethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
249	 $C_{25}H_{27}F_3N_6O_2$	1-(tert-butyl)-3-(2-oxo-1-(1-(1-(3,3,3-trifluoropropyl)-1H-indazol-6-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
250	 $C_{29}H_{33}N_5O_3$	1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2-(pyridin-4-ylmethoxy)ethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
251	 $C_{25}H_{27}F_3N_6O_2$	1-(tert-butyl)-3-(2-oxo-1-(1-(1-(3,3,3-trifluoropropyl)-1H-indazol-4-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

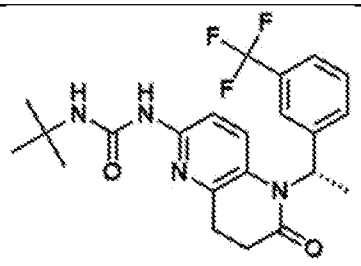
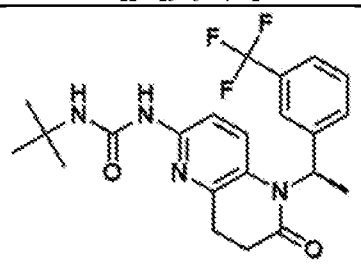
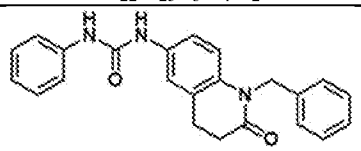
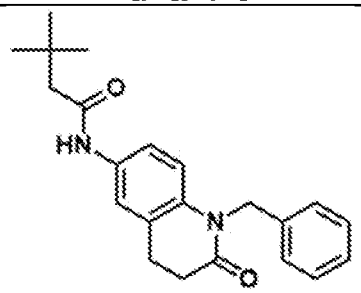
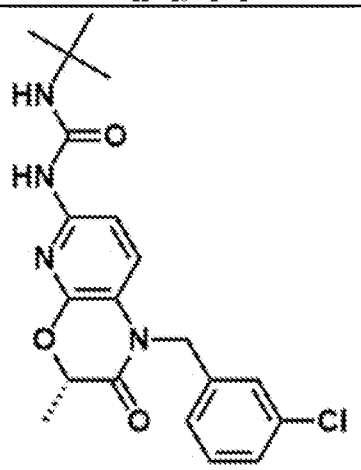
252	 $C_{24}H_{25}N_5O_2$	1-(tert-butyl)-3-(2-oxo-1-(1-(quinolin-5-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
253	 $C_{21}H_{22}F_3N_5O_2$	1-(tert-butyl)-3-(2-oxo-1-(1-(4-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
254	 $C_{20}H_{21}Cl_2N_5O_2$	1-(tert-butyl)-3-(1-(1-(3,6-dichloropyridin-2-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
255	 $C_{23}H_{27}N_3O_3$	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclobutyl)urea
256	 $C_{24}H_{29}N_3O_3$	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea
257	 $C_{24}H_{26}F_3N_3O_3$	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-(trifluoromethyl)cyclopentyl)urea

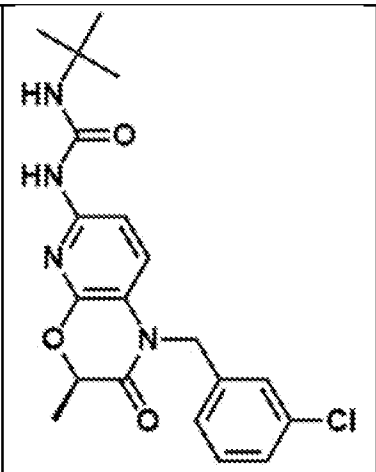
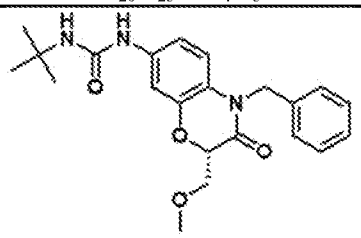
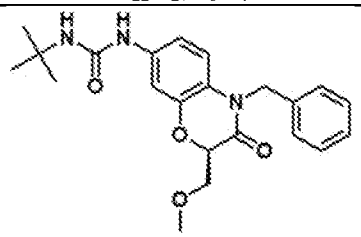
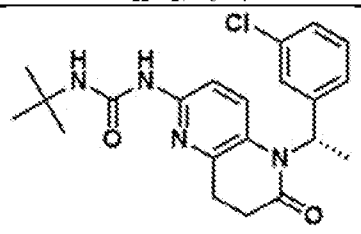
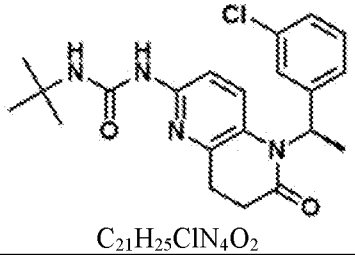
258	 $C_{24}H_{27}F_2N_3O_3$	1-(4,4-difluorocyclohexyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
259	 $C_{23}H_{24}F_3N_3O_3$	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-(trifluoromethyl)cyclobutyl)urea
260	 $C_{23}H_{25}F_2N_3O_3$	1-(3,3-difluoro-1-methylcyclobutyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
261	 $C_{24}H_{29}N_3O_4$	1-(1-(methoxymethyl)cyclobutyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
262	 $C_{22}H_{25}N_3O_4$	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(3-methyloxetan-3-yl)urea
263	 $C_{22}H_{22}F_3N_3O_4$	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(3-(trifluoromethyl)oxetan-3-yl)urea

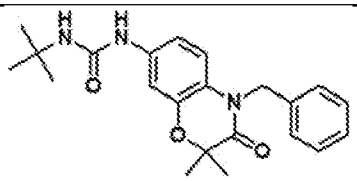
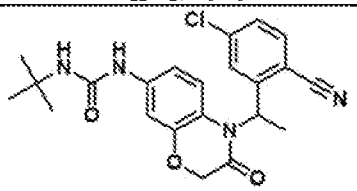
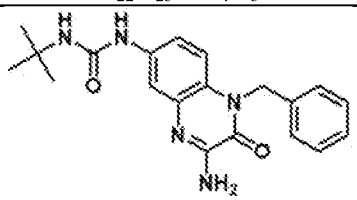
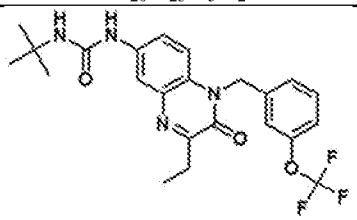
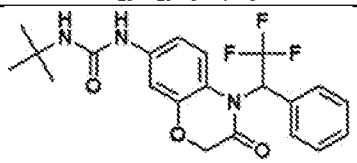
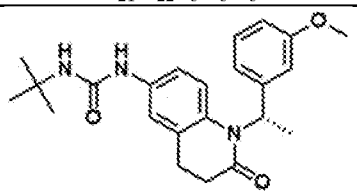
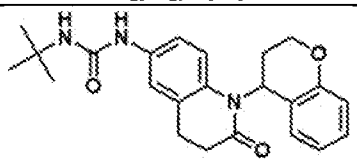
264	 $C_{23}H_{22}F_5N_3O_3$	1-(3,3-difluoro-1-(trifluoromethyl)cyclobutyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
265	 $C_{24}H_{29}N_3O_4$	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(4-methyltetrahydro-2H-pyran-4-yl)urea
266	 $C_{23}H_{26}N_4O_2$	1-(tert-butyl)-3-(1-(2-cyano-5-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
267	 $C_{21}H_{24}ClN_3O_2$	1-(1-benzyl-5-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
268	 $C_{22}H_{27}N_3O_3$	1-(tert-butyl)-3-((S)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
269	 $C_{22}H_{27}N_3O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

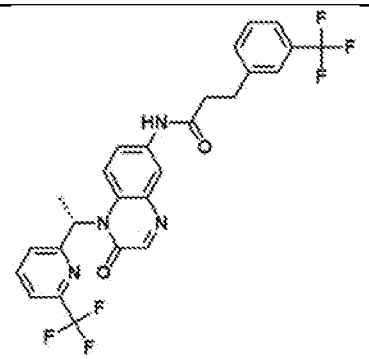
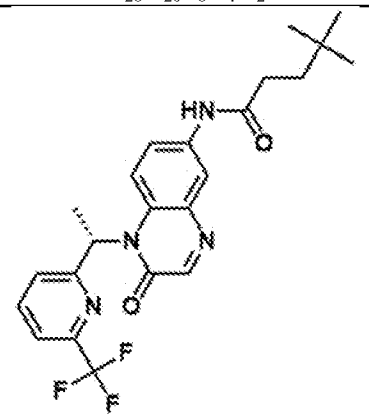
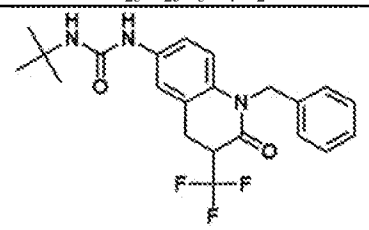
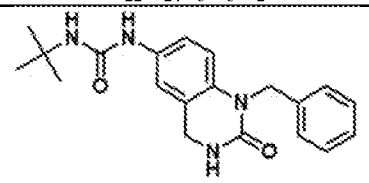
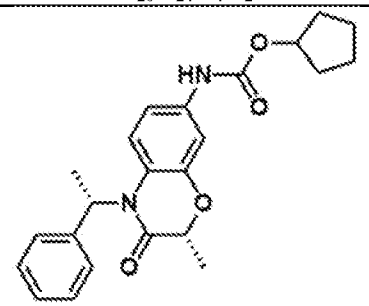
270	 $C_{22}H_{24}N_4O_2$	1-(1-benzyl-7-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
271	 $C_{23}H_{27}F_3N_4O_2$	1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea
272	 $C_{21}H_{24}N_4O_2$	1-(1-benzyl-3-methyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea
273	 $C_{21}H_{23}ClN_4O_2$	1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
274	 $C_{21}H_{23}F_3N_4O_2$	1-(tert-butyl)-3-(6-oxo-5-(3-(trifluoromethyl)benzyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea
275	 $C_{23}H_{26}N_4O_2$	(R)-1-(1-benzyl-3-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
276	 $C_{23}H_{26}N_4O_2$	(S)-1-(1-benzyl-3-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

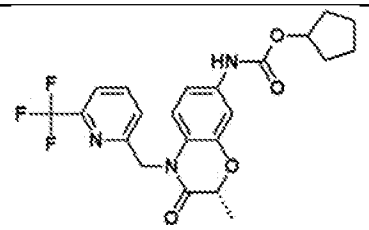
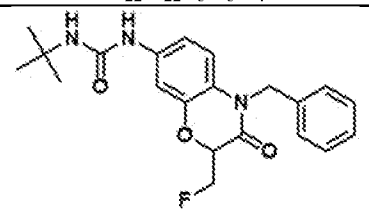
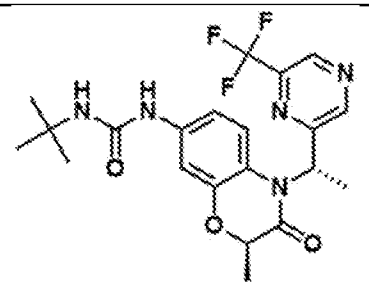
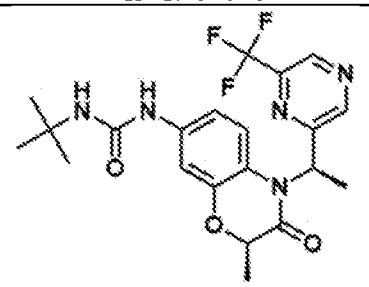
277	 $C_{22}H_{27}N_3O_3$	(R)-1-(4-benzyl-2-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
278	 $C_{22}H_{27}N_3O_3$	(S)-1-(4-benzyl-2-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
279	 $C_{22}H_{24}N_4O_2$	1-(1-benzyl-5-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
280	 $C_{20}H_{24}N_4O_3$	(R)-1-(1-benzyl-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea
281	 $C_{20}H_{23}ClN_4O_2$	1-(tert-butyl)-3-(5-(3-chlorobenzyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea

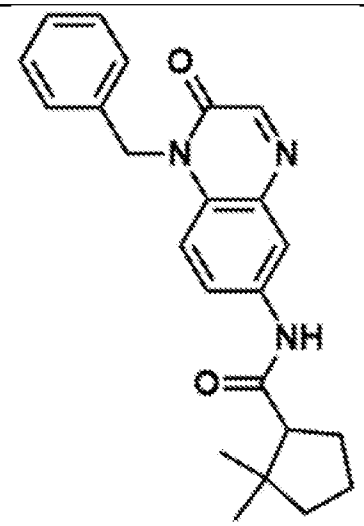
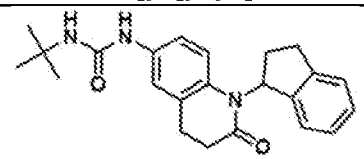
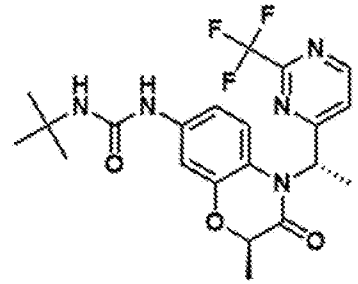
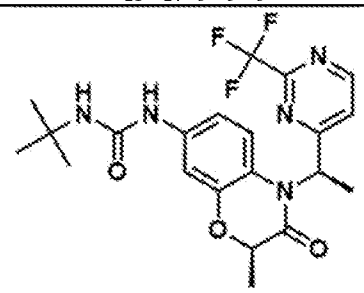
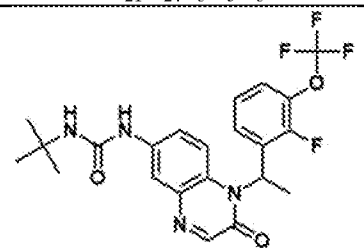
282	 $C_{22}H_{25}F_3N_4O_2$	(S)-1-(tert-butyl)-3-(6-oxo-5-(1-(3-(trifluoromethyl)phenyl)ethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea
283	 $C_{22}H_{25}F_3N_4O_2$	(R)-1-(tert-butyl)-3-(6-oxo-5-(1-(3-(trifluoromethyl)phenyl)ethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea
284	 $C_{23}H_{21}N_3O_2$	1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-phenylurea
285	 $C_{22}H_{26}N_2O_2$	N-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3,3-dimethylbutanamide
286	 $C_{20}H_{23}ClN_4O_3$	(S)-1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea

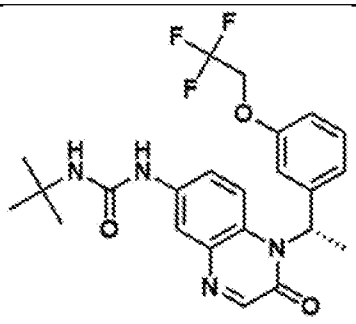
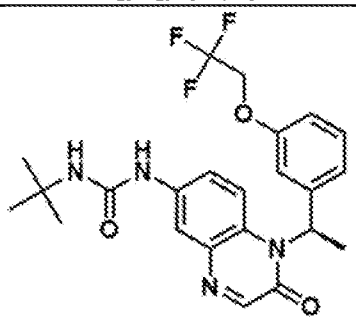
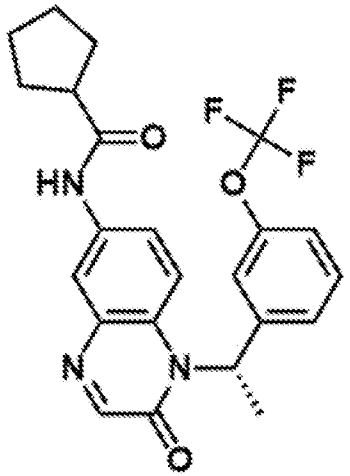
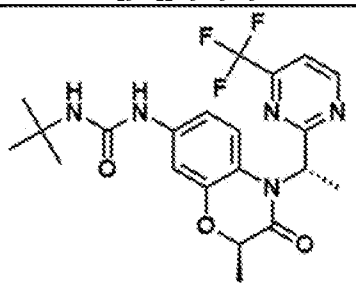
287	 $C_{20}H_{23}ClN_4O_3$	(R)-1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea
288	 $C_{22}H_{27}N_3O_4$	(S)-1-(4-benzyl-2-(methoxymethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
289	 $C_{22}H_{27}N_3O_4$	(R)-1-(4-benzyl-2-(methoxymethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
290	 $C_{21}H_{25}ClN_4O_2$	(S)-1-(tert-butyl)-3-(5-(1-(3-chlorophenyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea
291	 $C_{21}H_{25}ClN_4O_2$	(R)-1-(tert-butyl)-3-(5-(1-(3-chlorophenyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea

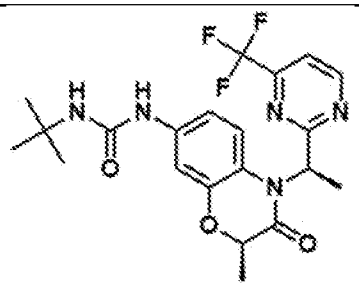
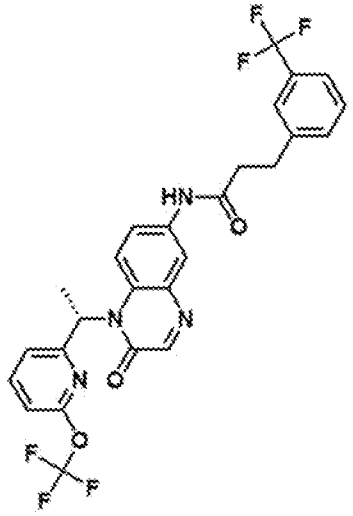
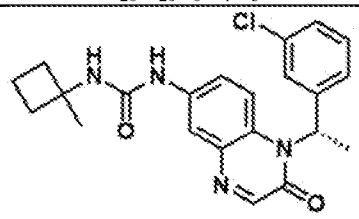
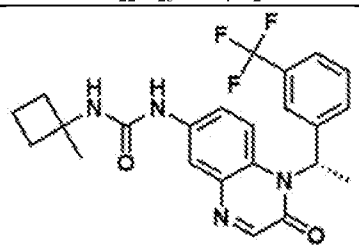
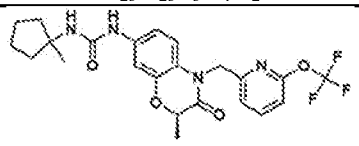
292	 $C_{22}H_{27}N_3O_3$	1-(4-benzyl-2,2-dimethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
293	 $C_{22}H_{23}ClN_4O_3$	1-(tert-butyl)-3-(4-(1-(5-chloro-2-cyanophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
294	 $C_{20}H_{23}N_5O_2$	1-(3-amino-1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea
295	 $C_{23}H_{25}F_3N_4O_3$	1-(tert-butyl)-3-(3-ethyl-2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
296	 $C_{21}H_{22}F_3N_3O_3$	1-(tert-butyl)-3-(3-oxo-4-(2,2,2-trifluoro-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
297	 $C_{23}H_{29}N_3O_3$	(S)-1-(tert-butyl)-3-(1-(1-(3-methoxyphenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
298	 $C_{23}H_{27}N_3O_3$	1-(tert-butyl)-3-(1-(chroman-4-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

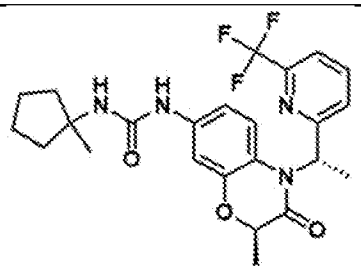
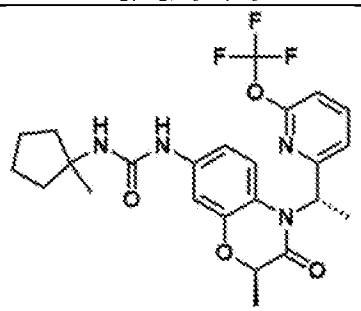
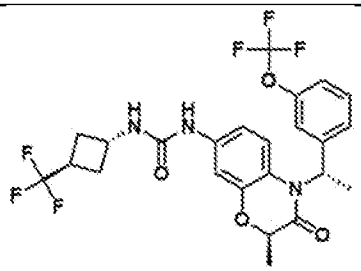
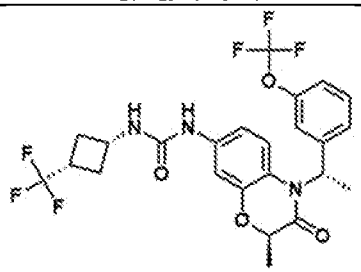
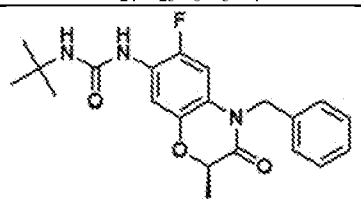
299	 $C_{26}H_{20}F_6N_4O_2$	(S)-N-(2-oxo-1-(1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)phenyl)propanamide
300	 $C_{23}H_{25}F_3N_4O_2$	(S)-4,4-dimethyl-N-(2-oxo-1-(1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)pentanamide
301	 $C_{22}H_{24}F_3N_3O_2$	1-(1-benzyl-2-oxo-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
302	 $C_{20}H_{24}N_4O_2$	1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-3-(tert-butyl)urea
303	 $C_{23}H_{26}N_2O_4$	cyclopentyl ((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)carbamate

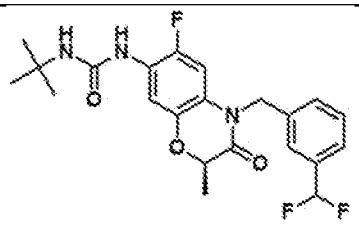
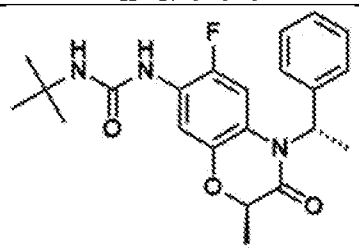
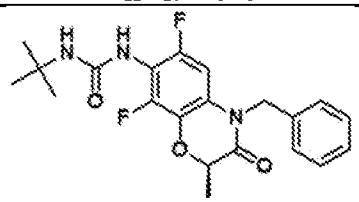
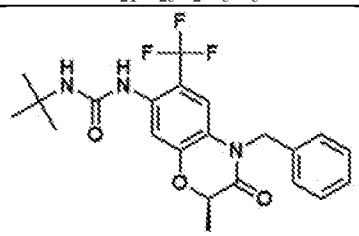
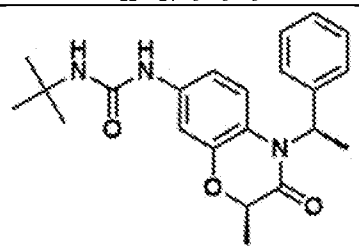
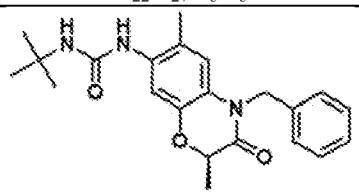
304	 $C_{22}H_{22}F_3N_3O_4$	cyclopentyl (R)-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)carbamate
305	 $C_{21}H_{24}FN_3O_3$	1-(4-benzyl-2-(fluoromethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
306	 $C_{21}H_{24}F_3N_5O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethyl)pyrazin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
307	 $C_{21}H_{24}F_3N_5O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-(6-(trifluoromethyl)pyrazin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

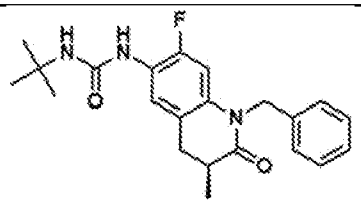
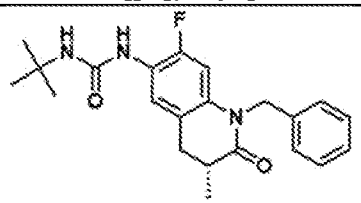
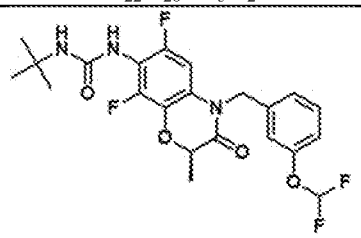
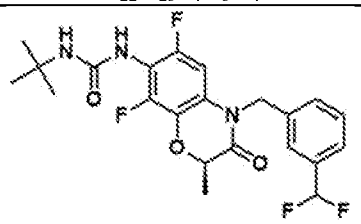
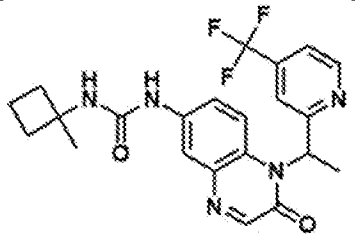
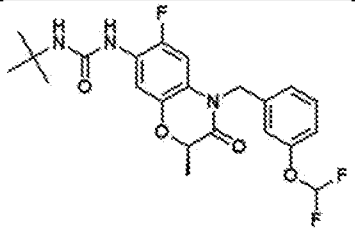
308	 $C_{23}H_{25}N_3O_2$	N-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-2,2-dimethylcyclopentane-1-carboxamide
309	 $C_{23}H_{27}N_3O_2$	1-(tert-butyl)-3-(1-(2,3-dihydro-1H-inden-1-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
310	 $C_{21}H_{24}F_3N_5O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(2-(trifluoromethyl)pyrimidin-4-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
311	 $C_{21}H_{24}F_3N_5O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-(2-(trifluoromethyl)pyrimidin-4-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
312	 $C_{22}H_{22}F_4N_4O_3$	1-(tert-butyl)-3-(1-(1-(2-fluoro-3-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

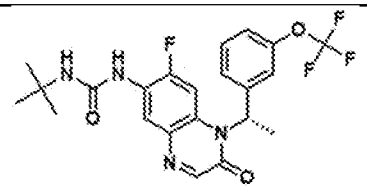
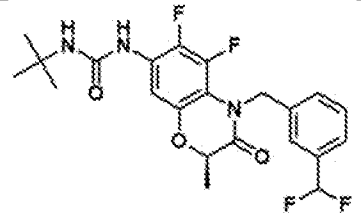
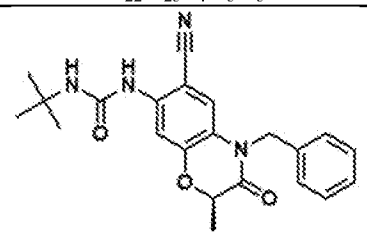
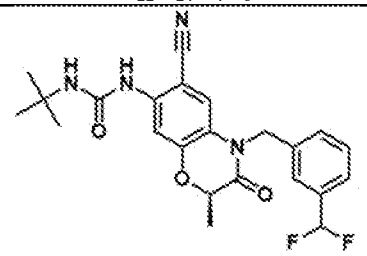
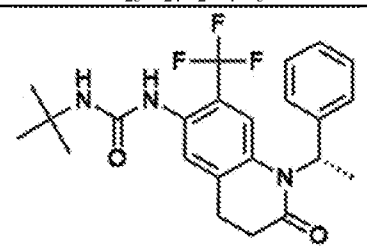
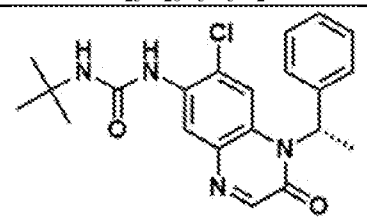
313	 $C_{23}H_{25}F_3N_4O_3$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
314	 $C_{23}H_{25}F_3N_4O_3$	(R)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
315	 $C_{23}H_{22}F_3N_3O_3$	(S)-N-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)cyclopentanecarboxamide
316	 $C_{21}H_{24}F_3N_5O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(4-(trifluoromethyl)pyrimidin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

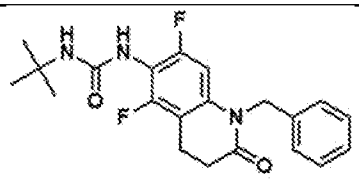
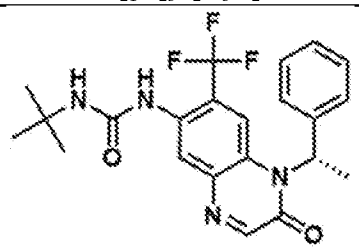
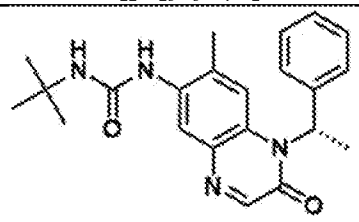
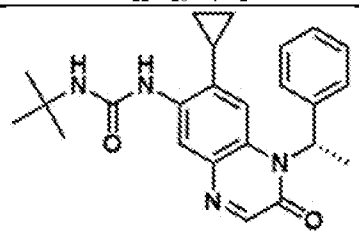
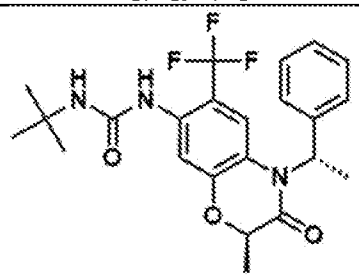
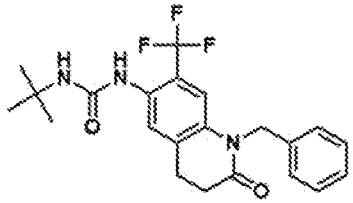
317	 $C_{21}H_{24}F_3N_5O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-(4-(trifluoromethyl)pyrimidin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
318	 $C_{26}H_{20}F_6N_4O_3$	(S)-N-(2-oxo-1-(1-(6-(trifluoromethoxy)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)phenyl)propanamide
319	 $C_{22}H_{23}ClN_4O_2$	(S)-1-(1-(1-(3-chlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1-methylcyclobutyl)urea
320	 $C_{23}H_{23}F_3N_4O_2$	(S)-1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
321	 $C_{23}H_{25}F_3N_4O_4$	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethoxy)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea

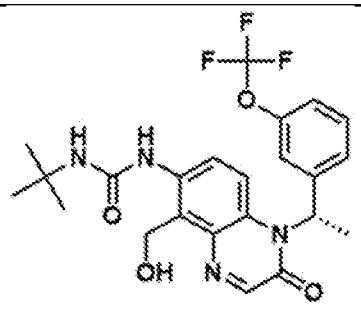
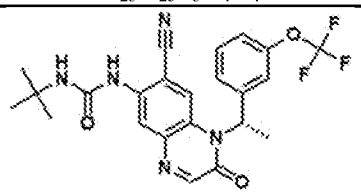
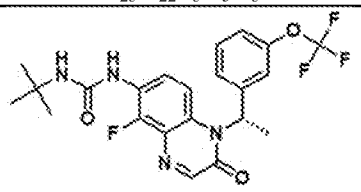
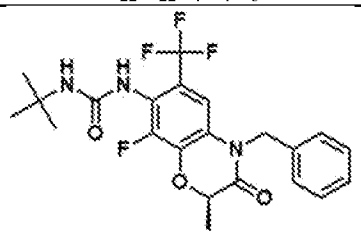
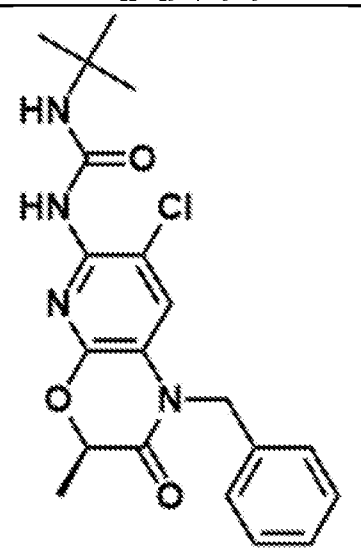
322	 $C_{24}H_{27}F_3N_4O_3$	1-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea
323	 $C_{24}H_{27}F_3N_4O_4$	1-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethoxy)pyridin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea
324	 $C_{24}H_{23}F_6N_3O_4$	1-((R)-2-methyl-3-oxo-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-((1r,3R)-3-(trifluoromethyl)cyclobutyl)urea
325	 $C_{24}H_{23}F_6N_3O_4$	1-((R)-2-methyl-3-oxo-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-((1s,3S)-3-(trifluoromethyl)cyclobutyl)urea
326	 $C_{21}H_{24}FN_3O_3$	(R)-1-(4-benzyl-6-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

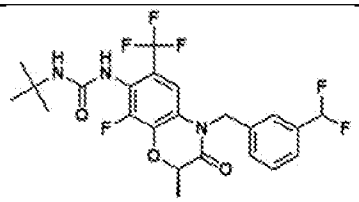
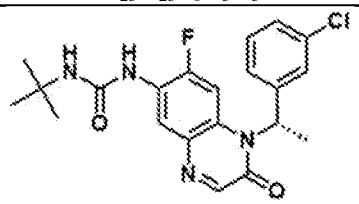
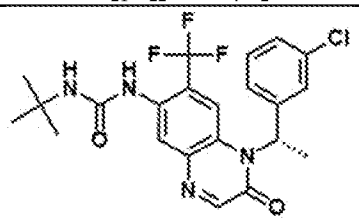
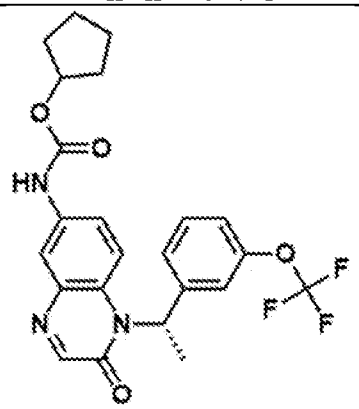
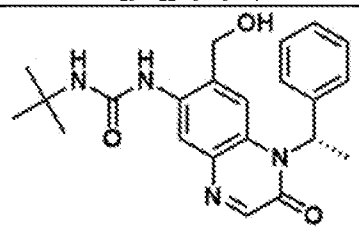
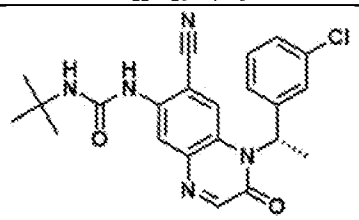
327	 $C_{22}H_{24}F_3N_3O_3$	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-6-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
328	 $C_{22}H_{26}FN_3O_3$	1-(tert-butyl)-3-((R)-6-fluoro-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
329	 $C_{21}H_{23}F_2N_3O_3$	(R)-1-(4-benzyl-6,8-difluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
330	 $C_{22}H_{24}F_3N_3O_3$	(R)-1-(4-benzyl-2-methyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
331	 $C_{22}H_{27}N_3O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
332	 $C_{22}H_{27}N_3O_3$	(R)-1-(4-benzyl-2,6-dimethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

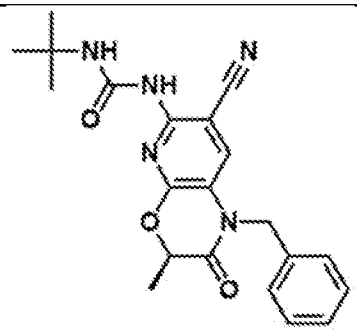
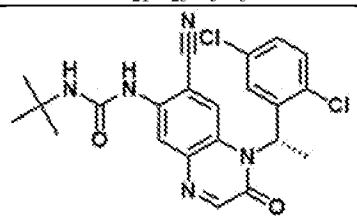
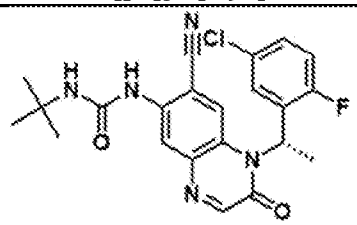
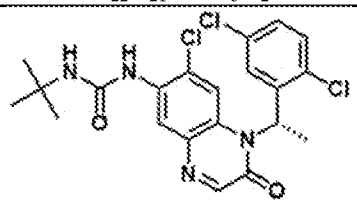
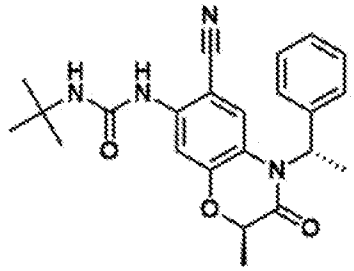
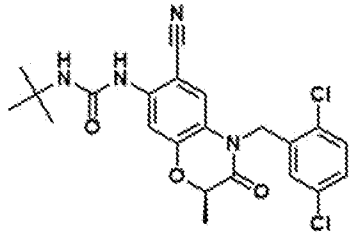
333	 $C_{22}H_{26}FN_3O_2$	(S)-1-(1-benzyl-7-fluoro-3-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
334	 $C_{22}H_{26}FN_3O_2$	(R)-1-(1-benzyl-7-fluoro-3-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
335	 $C_{22}H_{23}F_4N_3O_4$	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethoxy)benzyl)-6,8-difluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
336	 $C_{22}H_{23}F_4N_3O_3$	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-6,8-difluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
337	 $C_{22}H_{22}F_3N_5O_2$	1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(4-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
338	 $C_{22}H_{24}F_3N_3O_4$	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethoxy)benzyl)-6-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

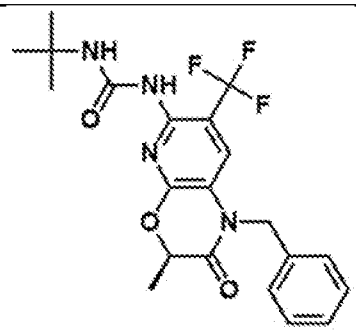
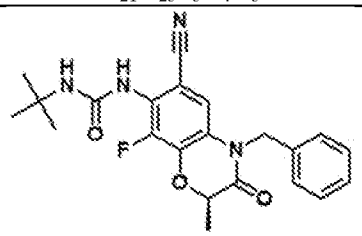
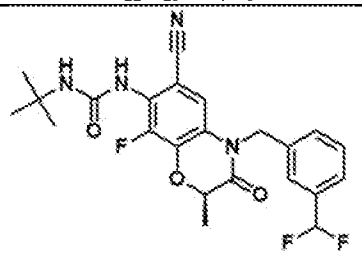
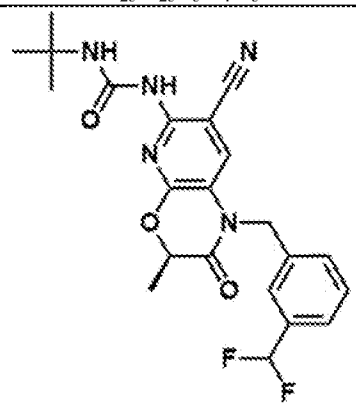
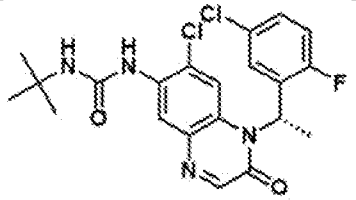
339	 $C_{22}H_{22}F_4N_4O_3$	(S)-1-(tert-butyl)-3-(7-fluoro-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
340	 $C_{22}H_{23}F_4N_3O_3$	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-5,6-difluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
341	 $C_{22}H_{24}N_4O_3$	(R)-1-(4-benzyl-6-cyano-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
342	 $C_{23}H_{24}F_2N_4O_3$	(R)-1-(tert-butyl)-3-(6-cyano-4-(3-(difluoromethyl)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
343	 $C_{23}H_{26}F_3N_3O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-7-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
344	 $C_{21}H_{23}ClN_4O_2$	(S)-1-(tert-butyl)-3-(7-chloro-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea

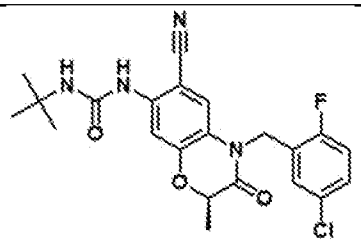
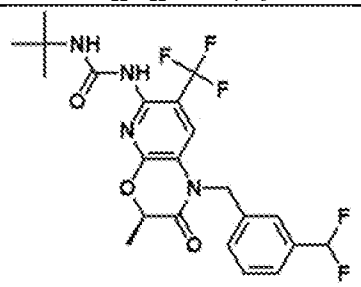
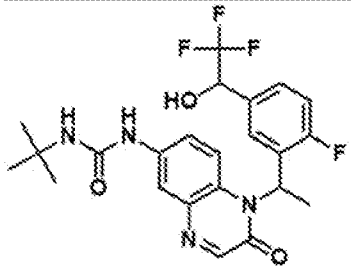
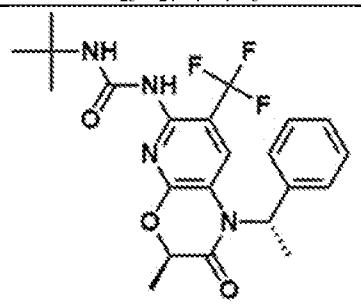
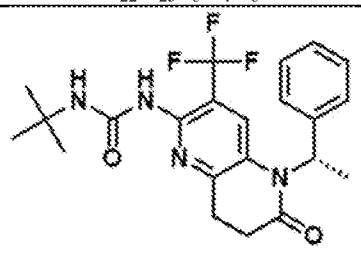
345	 $C_{21}H_{23}F_2N_3O_2$	1-(1-benzyl-5,7-difluoro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
346	 $C_{22}H_{23}F_3N_4O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-7-(trifluoromethyl)-1,2-dihydroquinoxalin-6-yl)urea
347	 $C_{22}H_{26}N_4O_2$	(S)-1-(tert-butyl)-3-(7-methyl-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea
348	 $C_{24}H_{28}N_4O_2$	(S)-1-(tert-butyl)-3-(7-cyclopropyl-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea
349	 $C_{23}H_{26}F_3N_3O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
350	 $C_{22}H_{24}F_3N_3O_2$	1-(1-benzyl-2-oxo-7-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

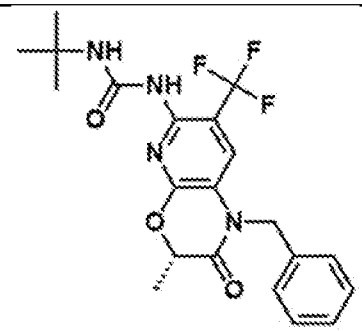
351	 $C_{23}H_{25}F_3N_4O_4$	(S)-1-(tert-butyl)-3-(5-(hydroxymethyl)-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
352	 $C_{23}H_{22}F_3N_5O_3$	(S)-1-(tert-butyl)-3-(7-cyano-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
353	 $C_{22}H_{22}F_4N_4O_3$	(S)-1-(tert-butyl)-3-(5-fluoro-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
354	 $C_{22}H_{23}F_4N_3O_3$	(R)-1-(4-benzyl-8-fluoro-2-methyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
355	 $C_{20}H_{23}ClN_4O_3$	(R)-1-(1-benzyl-7-chloro-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea

356	 $C_{23}H_{23}F_6N_3O_3$	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
357	 $C_{21}H_{22}ClFN_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-7-fluoro-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
358	 $C_{22}H_{22}ClF_3N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-2-oxo-7-(trifluoromethyl)-1,2-dihydroquinoxalin-6-yl)urea
359	 $C_{23}H_{22}F_3N_3O_4$	cyclopentyl (S)-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)carbamate
360	 $C_{22}H_{26}N_4O_3$	(S)-1-(tert-butyl)-3-(7-(hydroxymethyl)-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea
361	 $C_{22}H_{22}ClN_5O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-7-cyano-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

362	 $C_{21}H_{23}N_5O_3$	(R)-1-(1-benzyl-7-cyano-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea
363	 $C_{22}H_{21}Cl_2N_5O_2$	(S)-1-(tert-butyl)-3-(7-cyano-1-(1-(2,5-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
364	 $C_{22}H_{21}ClFN_5O_2$	(S)-1-(tert-butyl)-3-(1-(1-(5-chloro-2-fluorophenyl)ethyl)-7-cyano-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
365	 $C_{21}H_{21}Cl_3N_4O_2$	(S)-1-(tert-butyl)-3-(7-chloro-1-(1-(2,5-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
366	 $C_{23}H_{26}N_4O_3$	1-(tert-butyl)-3-((R)-6-cyano-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
367	 $C_{22}H_{22}Cl_2N_4O_3$	(R)-1-(tert-butyl)-3-(6-cyano-4-(2,5-dichlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

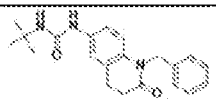
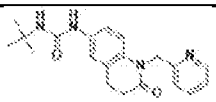
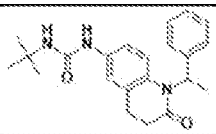
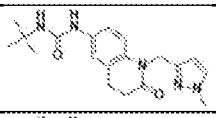
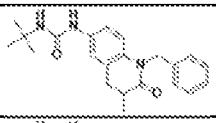
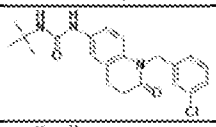
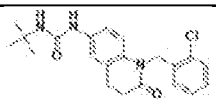
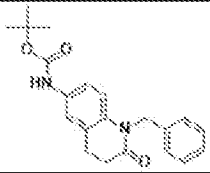
368	 $C_{21}H_{23}F_3N_4O_3$	(R)-1-(1-benzyl-3-methyl-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea
369	 $C_{22}H_{23}FN_4O_3$	(R)-1-(4-benzyl-6-cyano-8-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
370	 $C_{23}H_{23}F_3N_4O_3$	(R)-1-(tert-butyl)-3-(6-cyano-4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
371	 $C_{22}H_{23}F_2N_5O_3$	(R)-1-(tert-butyl)-3-(7-cyano-1-(3-(difluoromethyl)benzyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea
372	 $C_{21}H_{21}Cl_2FN_4O_2$	(S)-1-(tert-butyl)-3-(7-chloro-1-(1-(5-chloro-2-fluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

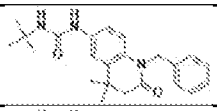
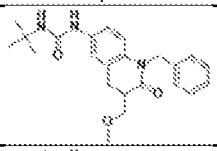
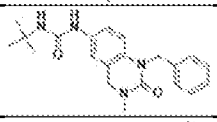
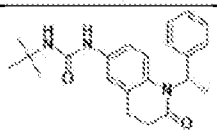
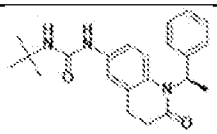
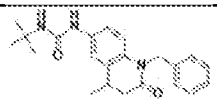
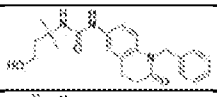
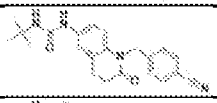
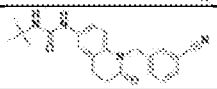
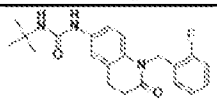
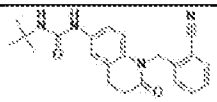
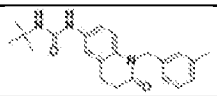
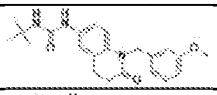
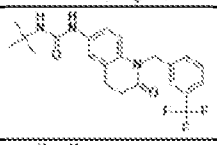
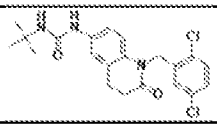
373	 $C_{22}H_{22}ClFN_4O_3$	(R)-1-(tert-butyl)-3-(4-(5-chloro-2-fluorobenzyl)-6-cyano-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
374	 $C_{22}H_{23}F_5N_4O_3$	(R)-1-(tert-butyl)-3-(1-(3-(difluoromethyl)benzyl)-3-methyl-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea
375	 $C_{23}H_{24}F_4N_4O_3$	1-(tert-butyl)-3-(1-(1-(2-fluoro-5-(2,2,2-trifluoro-1-hydroxyethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
376	 $C_{22}H_{25}F_3N_4O_3$	1-(tert-butyl)-3-((R)-3-methyl-2-oxo-1-((S)-1-phenylethyl)-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea
377	 $C_{22}H_{25}F_3N_4O_2$	(S)-1-(tert-butyl)-3-(6-oxo-5-(1-phenylethyl)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea

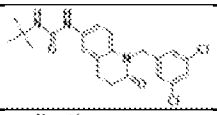
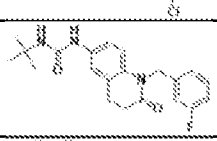
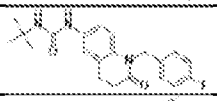
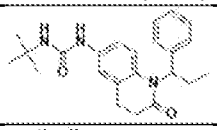
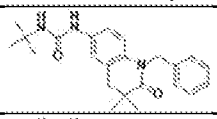
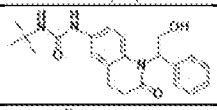
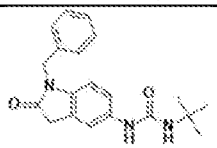
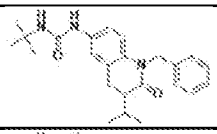
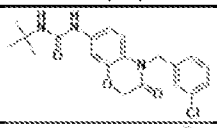
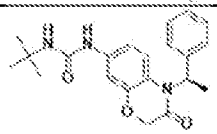
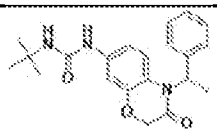
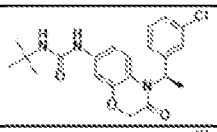
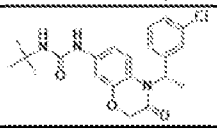
378	 $C_{21}H_{23}F_3N_4O_3$	(R)-1-(1-benzyl-3-methyl-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea

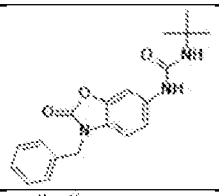
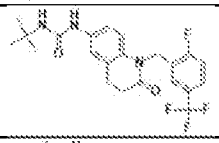
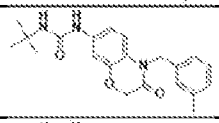
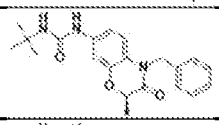
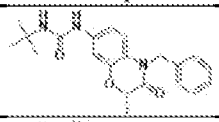
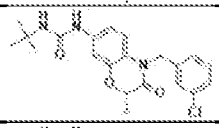
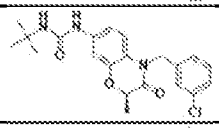
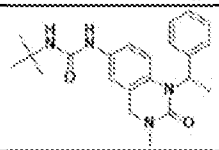
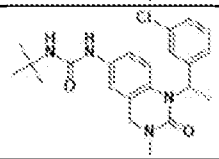
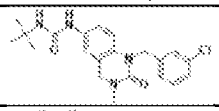
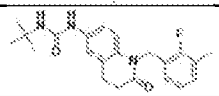
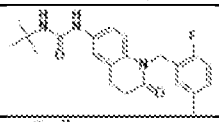
In certain embodiments, the compound is selected from Table 2.

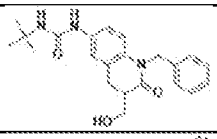
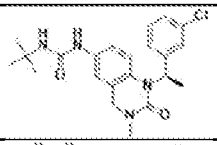
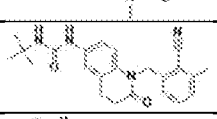
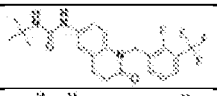
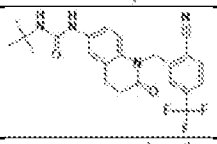
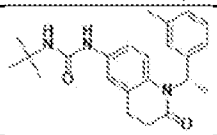
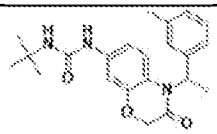
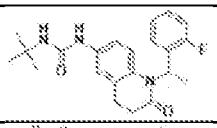
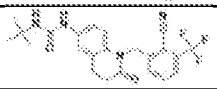
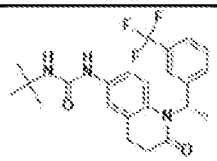
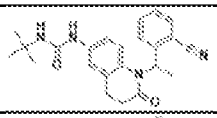
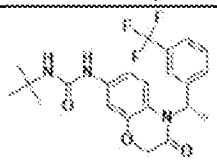
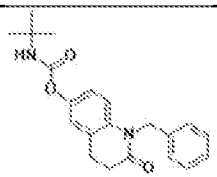
Table 2.

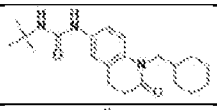
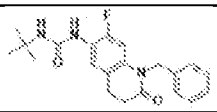
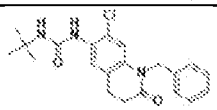
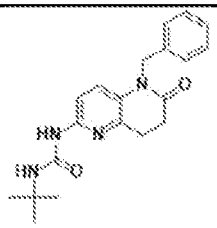
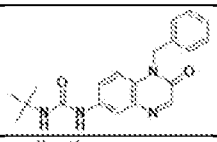
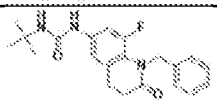
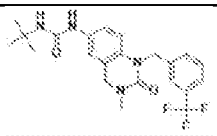
1		1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
2		1-(tert-butyl)-3-(2-oxo-1-(pyridin-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
3		1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
4		1-(tert-butyl)-3-(1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
5		1-(1-benzyl-3-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
6		1-(tert-butyl)-3-(1-(3-chlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
7		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
8		1-(tert-butyl)-3-(1-(2-chlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
9		tert-butyl (1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)carbamate

10		1-(1-benzyl-4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
11		1-(1-benzyl-3-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
12		1-(1-benzyl-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-3-(tert-butyl)urea
13		(S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
14		(R)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
15		1-(1-benzyl-4-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
16		1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-hydroxy-2-methylbutan-2-yl)urea
17		1-(tert-butyl)-3-(1-(4-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
18		1-(tert-butyl)-3-(1-(3-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
19		1-(tert-butyl)-3-(1-(2-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
20		1-(tert-butyl)-3-(1-(2-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
21		1-(tert-butyl)-3-(1-(3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
22		1-(tert-butyl)-3-(1-(3-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
23		1-(tert-butyl)-3-(2-oxo-1-(3-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
24		1-(tert-butyl)-3-(1-(2,5-dichlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

25		1-(tert-butyl)-3-(1-(3,5-dichlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
26		1-(tert-butyl)-3-(1-(3-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
27		1-(tert-butyl)-3-(1-(4-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
28		1-(tert-butyl)-3-(2-oxo-1-(1-phenylpropyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
29		1-(1-benzyl-3,3-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
30		1-(tert-butyl)-3-(1-(2-hydroxy-1-phenylethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
31		1-(1-benzyl-2-oxoindolin-5-yl)-3-(tert-butyl)urea
32		1-(1-benzyl-3-isopropyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
33		1-(tert-butyl)-3-(4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
34		(R)-1-(tert-butyl)-3-(3-oxo-4-(1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
35	 $C_{21}H_{25}N_3O_3$	(S)-1-(tert-butyl)-3-(3-oxo-4-(1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
36		(R)-1-(tert-butyl)-3-(4-(1-(3-chlorophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
37		(S)-1-(tert-butyl)-3-(4-(1-(3-chlorophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

38		1-(3-benzyl-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-(tert-butyl)urea
39		1-(tert-butyl)-3-(1-(2-fluoro-5-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
40		1-(tert-butyl)-3-(4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
41		(R)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
42		(S)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
43		(S)-1-(tert-butyl)-3-(4-(3-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
44		(R)-1-(tert-butyl)-3-(4-(3-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
45		(S)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea
46		(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea
47		1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea
48		1-(tert-butyl)-3-(1-(2-fluoro-3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
49		1-(tert-butyl)-3-(1-(2-fluoro-5-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
50		1-(tert-butyl)-3-(3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

51		1-(1-benzyl-3-(hydroxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
52		(R)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea
53		1-(tert-butyl)-3-(1-(2-cyano-3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
54		1-(tert-butyl)-3-(1-(2-fluoro-3-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
55		1-(tert-butyl)-3-(1-(2-cyano-5-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
56		(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(m-tolyl)ethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
57		(S)-1-(tert-butyl)-3-(3-oxo-4-(1-(m-tolyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
58		(S)-1-(tert-butyl)-3-(1-(1-(2-fluorophenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
59		1-(tert-butyl)-3-(1-(2-cyano-3-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
60		(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
61		(S)-1-(tert-butyl)-3-(1-(1-(2-cyanophenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
62		(S)-1-(tert-butyl)-3-(3-oxo-4-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
63		1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl tert-butylcarbamate

64		1-(tert-butyl)-3-(1-(cyclohexylmethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
65		1-(1-benzyl-7-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
66		1-(1-benzyl-7-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
67		1-(5-benzyl-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)-3-(tert-butyl)urea
68		1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea
69		1-(1-benzyl-8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea; and
70		1-(tert-butyl)-3-(3-methyl-2-oxo-1-(3-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea

or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compounds are atropisomers. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds produced by the replacement of a hydrogen with deuterium or tritium, or of a carbon with a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention. For example, in the case of variable R^1, the (C_1-C_4)alkyl or the -O-(C_1-C_4)alkyl can be suitably deuterated (*e.g.*, $-CD_3$, $-OCD_3$).

Any compound of the invention can also be radiolabed for the preparation of a radiopharmaceutical agent.

Methods of Treatment

One aspect of the invention provides methods of inhibiting a thyroid stimulating hormone receptor, comnprising administering to a subject in need thereof a therapeutically effective amount of a compound described herein.

Another aspect of the invention comprises treating or preventing a thyroid disease, comnprising administering to a subject in need thereof a therapeutically effective amount of a compound described herein.

In certain embodiments, the subject has Graves' disease.

In certain embodiments, the subject has Graves' ophthalmopathy.

In certain embodiments, the subject has Graves' dermopathy.

In certain embodiments, the subject has thyroid cancer.

While not being bound by theory, TSHR in thyroid cells, and likely in fibroblasts and adipocytes in the supporting tissue behind the eye (in the retro-orbital space), also are stimulated by TSHR-stimulating antibodies (TSAbs), resulting in Graves' disease. Graves' disease, which is an autoimmune disease that occurs in 1% of the US population, has two important clinical components: 1) hyperthyroidism from stimulation of TSHR on thyroid cells and 2) Graves' orbitopathy (or Graves' ophthalmopathy or thyroid eye disease), which appears to result from stimulation of TSHR on retro-orbital fibroblasts and/or adipocytes.

Hyperthyroidism, in particular Graves' hyperthyroidism, is a hypermetabolic state that affects virtually every tissue/cell in the body and can lead to, in particular, cardiovascular dysfunction and death.

Graves' ophthalmopathy, also known as Graves' orbitopathy, occurs in 80% of Graves' hyperthyroid patients as diagnosed by computerized tomographic scan. Symptoms range from mild to moderate to severe to sight-threatening. Protrusion of the eyeball (proptosis) and varying degrees of extra-ocular muscle weakness or paralysis leading to double vision (diplopia) can be disfiguring and incapacitating.

Graves dermopathy, also known as Pretibial myxedema, thyroid dermopathy, Jadassohn-Dössekker disease or Myxoedema tuberosum, is an infiltrative dermopathy, resulting as a complication of Graves' disease, with an incidence rate of about 1-5% in patients. The disease usually presents itself as a waxy, discolored induration of the skin on the anterior aspect of the lower legs.

In certain embodiments, a disease that can be treated o prevented by TSHR antagonists is thyroid cancer.While not being bound by theory, TSHR is expressed in thyroid cancer cells and regulates the growth, proliferation and metastatic potential of thyroid cancer cells.

The thyroid gland is, as is well known, one site of metabolic control within the body. Cancer of the thyroid gland is not particularly common, but the high rate of disease re-occurrence necessitates long-term surveillance. Usually, during treatment for cancer of the thyroid, the majority of the thyroid tumor is removed, but a small amount often remains that must be treated by radioactive iodide therapy. Indeed, thyroid cancer is characterized by a high likelihood of relapses in up to 30% of patients, even after successful therapy.

In rare cases, the TSHR contains a hereditary mutation that makes it more active than the normal TSHR, resulting in hereditary non-immune hyperthyroidism. TSHR antagonists could be effective treatment for these patients also.

A “TSHR antagonist” as described herein blocks or inhibits the action of the agonists (TSH or thyroid-stimulating antibodies for TSHR. Small-molecule ligands for the TSHR (antagonists) typically bind to an intra-membrane domain of the receptor, and act by inducing a conformational change rather than simply competing for TSH binding to its extracellular site on the receptor.

In certain embodiments, the antagonists may be selective antagonists for TSHR (i.e, the compounds do not activate or modulate other hormone receptors, particularly luteinizing hormone/chorionic gonadotropin receptor (LHCGR) and follicle-stimulating hormone receptor (FSHR)).

In certain embodiments, the antagonists disclosed herein may be used for treating hyperthyroidism in a subject. For example, the antagonists may inhibit mutant TSHRs with higher than normal basal signaling activities (CAMs) that cause an unusual form of hyperthyroidism. In another example, the antagonists may inhibit stimulation by antibodies found in Graves' disease, which is the most common form of hyperthyroidism.

In certain embodiments, the TSHR antagonists are useful for treating TSHR-mediated thyroid cancer or hyperthyroidism by blocking TSHR-stimulating antibodies (TSAbs) in Graves' hyperthyroidism.

In certain embodiments, the compound is administered orally to the subject.

In certain embodiments, the compound is administered parenterally to the subject.

In certain embodiments, the disease is prevented. In other embodiments, the disease is treated.

Pharmaceutical Compositions, Routes of Administration, and Dosing

In certain embodiments, the invention is directed to a pharmaceutical composition, comprising a compound of the invention, e.g. a compound of Formula (1), and a pharmaceutically acceptable carrier.

In certain embodiments, the invention is directed to a pharmaceutical composition, comprising a compound of any of the disclosed embodiments, and a pharmaceutically acceptable carrier.

In certain embodiments, the invention is directed to a pharmaceutical composition, comprising a compound of Table 1 or 2, and a pharmaceutically acceptable carrier.

In certain embodiments, the pharmaceutical composition comprises a plurality of compounds of the invention and a pharmaceutically acceptable carrier.

In certain embodiments, a pharmaceutical composition of the invention further comprises at least one additional pharmaceutically active agent other than a compound of the invention. The at least one additional pharmaceutically active agent can be an agent useful in the treatment of ischemia-reperfusion injury.

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

As stated above, an "effective amount" refers to any amount that is sufficient to achieve a desired biological effect. Combined with the teachings provided herein, by choosing among the various active compounds and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned which does not cause substantial unwanted toxicity and yet is effective to treat the particular subject. The effective amount for any particular application can vary depending on such factors as the disease or condition being treated, the particular compound of the invention being administered, the size of the subject, or the severity of the disease or condition. One of ordinary skill in the art can empirically determine the effective amount of a particular compound of the invention and/or other therapeutic agent without necessitating undue experimentation. A maximum dose may be used,

that is, the highest safe dose according to some medical judgment. Multiple doses per day may be contemplated to achieve appropriate systemic levels of compounds. Appropriate systemic levels can be determined by, for example, measurement of the patient's peak or sustained plasma level of the drug. "Dose" and "dosage" are used interchangeably herein.

In certain embodiments, intravenous administration of a compound may typically be from 0.1 mg/kg/day to 20 mg/kg/day. In one embodiment, intravenous administration of a compound may typically be from 0.1 mg/kg/day to 2 mg/kg/day. In one embodiment, intravenous administration of a compound may typically be from 0.5 mg/kg/day to 5 mg/kg/day. In one embodiment, intravenous administration of a compound may typically be from 1 mg/kg/day to 20 mg/kg/day. In one embodiment, intravenous administration of a compound may typically be from 1 mg/kg/day to 10 mg/kg/day.

Generally, daily oral doses of a compound will be, for human subjects, from about 0.01 milligrams/kg per day to 1000 milligrams/kg per day. It is expected that oral doses in the range of 0.5 to 50 milligrams/kg, in one or more administrations per day, will yield therapeutic results. Dosage may be adjusted appropriately to achieve desired drug levels, local or systemic, depending upon the mode of administration. For example, it is expected that intravenous administration would be from one order to several orders of magnitude lower dose per day. In the event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Multiple doses per day are contemplated to achieve appropriate systemic levels of the compound.

For any compound described herein the therapeutically effective amount can be initially determined from animal models. A therapeutically effective dose can also be determined from human data for compounds which have been tested in humans and for compounds which are known to exhibit similar pharmacological activities, such as other related active agents. Higher doses may be required for parenteral administration. The applied dose can be adjusted based on the relative bioavailability and potency of the administered compound. Adjusting the dose to achieve maximal efficacy based on the methods described above and other methods as are well-known in the art is well within the capabilities of the ordinarily skilled artisan.

The formulations of the invention can be administered in pharmaceutically acceptable solutions, which may routinely contain pharmaceutically acceptable concentrations of salt,

buffering agents, preservatives, compatible carriers, adjuvants, and optionally other therapeutic ingredients.

For use in therapy, an effective amount of the compound can be administered to a subject by any mode that delivers the compound to the desired surface. Administering a pharmaceutical composition may be accomplished by any means known to the skilled artisan. Routes of administration include but are not limited to intravenous, intramuscular, intraperitoneal, intravesical (urinary bladder), oral, subcutaneous, direct injection (for example, into a tumor or abscess), mucosal (e.g., topical to eye), inhalation, and topical.

For intravenous and other parenteral routes of administration, a compound of the invention can be formulated as a lyophilized preparation, as a lyophilized preparation of liposome-intercalated or -encapsulated active compound, as a lipid complex in aqueous suspension, or as a salt complex. Lyophilized formulations are generally reconstituted in suitable aqueous solution, e.g., in sterile water or saline, shortly prior to administration.

For oral administration, the compounds can be formulated readily by combining the active compound(s) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject to be treated. Pharmaceutical preparations for oral use can be obtained as solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Optionally the oral formulations may also be formulated in saline or buffers, e.g., EDTA for neutralizing internal acid conditions or may be administered without any carriers.

Also specifically contemplated are oral dosage forms of the above component or components. The component or components may be chemically modified so that oral delivery of the derivative is efficacious. Generally, the chemical modification contemplated is the

attachment of at least one moiety to the component molecule itself, where said moiety permits (a) inhibition of acid hydrolysis; and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the component or components and increase in circulation time in the body. Examples of such moieties include: polyethylene glycol, copolymers of ethylene glycol and propylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone and polyproline. Abuchowski and Davis, "Soluble Polymer-Enzyme Adducts", In: Enzymes as Drugs, Hocenberg and Roberts, eds., Wiley-Interscience, New York, N.Y., pp. 367-383 (1981); Newmark et al., *J Appl Biochem* 4:185-9 (1982). Other polymers that could be used are poly-1,3-dioxolane and poly-1,3,6-tioxocane. For pharmaceutical usage, as indicated above, polyethylene glycol moieties are suitable.

For the component (or derivative) the location of release may be the stomach, the small intestine (the duodenum, the jejunum, or the ileum), or the large intestine. One skilled in the art has available formulations which will not dissolve in the stomach, yet will release the material in the duodenum or elsewhere in the intestine. Preferably, the release will avoid the deleterious effects of the stomach environment, either by protection of the compound of the invention (or derivative) or by release of the biologically active material beyond the stomach environment, such as in the intestine.

To ensure full gastric resistance a coating impermeable to at least pH 5.0 is essential. Examples of the more common inert ingredients that are used as enteric coatings are cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP), HPMCP 50, HPMCP 55, polyvinyl acetate phthalate (PVAP), Eudragit L30D, Aquateric, cellulose acetate phthalate (CAP), Eudragit L, Eudragit S, and shellac. These coatings may be used as mixed films.

A coating or mixture of coatings can also be used on tablets, which are not intended for protection against the stomach. This can include sugar coatings, or coatings which make the tablet easier to swallow. Capsules may consist of a hard shell (such as gelatin) for delivery of dry therapeutic (e.g., powder); for liquid forms, a soft gelatin shell may be used. The shell material of cachets could be thick starch or other edible paper. For pills, lozenges, molded tablets or tablet triturates, moist massing techniques can be used.

The therapeutic can be included in the formulation as fine multi-particulates in the form of granules or pellets of particle size about 1 mm. The formulation of the material for capsule

administration could also be as a powder, lightly compressed plugs or even as tablets. The therapeutic could be prepared by compression.

Colorants and flavoring agents may all be included. For example, the compound of the invention (or derivative) may be formulated (such as by liposome or microsphere encapsulation) and then further contained within an edible product, such as a refrigerated beverage containing colorants and flavoring agents.

One may dilute or increase the volume of the therapeutic with an inert material. These diluents could include carbohydrates, especially mannitol, α-lactose, anhydrous lactose, cellulose, sucrose, modified dextrans and starch. Certain inorganic salts may also be used as fillers including calcium triphosphate, magnesium carbonate and sodium chloride. Some commercially available diluents are Fast-Flo, Emdex, STA-Rx 1500, Emcompress and Avicell.

Disintegrants may be included in the formulation of the therapeutic into a solid dosage form. Materials used as disintegrates include but are not limited to starch, including the commercial disintegrant based on starch, Explotab. Sodium starch glycolate, Amberlite, sodium carboxymethylcellulose, ultramylopectin, sodium alginate, gelatin, orange peel, acid carboxymethyl cellulose, natural sponge and bentonite may all be used. Another form of the disintegrants are the insoluble cationic exchange resins. Powdered gums may be used as disintegrants and as binders and these can include powdered gums such as agar, Karaya or tragacanth. Alginic acid and its sodium salt are also useful as disintegrants.

Binders may be used to hold the therapeutic agent together to form a hard tablet and include materials from natural products such as acacia, tragacanth, starch and gelatin. Others include methyl cellulose (MC), ethyl cellulose (EC) and carboxymethyl cellulose (CMC). Polyvinyl pyrrolidone (PVP) and hydroxypropylmethyl cellulose (HPMC) could both be used in alcoholic solutions to granulate the therapeutic.

An anti-frictional agent may be included in the formulation of the therapeutic to prevent sticking during the formulation process. Lubricants may be used as a layer between the therapeutic and the die wall, and these can include but are not limited to; stearic acid including its magnesium and calcium salts, polytetrafluoroethylene (PTFE), liquid paraffin, vegetable oils and waxes. Soluble lubricants may also be used such as sodium lauryl sulfate, magnesium lauryl sulfate, polyethylene glycol of various molecular weights, Carbowax 4000 and 6000.

Glidants that might improve the flow properties of the drug during formulation and to aid rearrangement during compression might be added. The glidants may include starch, talc, pyrogenic silica and hydrated silicoaluminate.

To aid dissolution of the therapeutic into the aqueous environment a surfactant might be added as a wetting agent. Surfactants may include anionic detergents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents which can be used and can include benzalkonium chloride and benzethonium chloride. Potential non-ionic detergents that could be included in the formulation as surfactants include lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50 and 60, glycerol monostearate, polysorbate 40, 60, 65 and 80, sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. These surfactants could be present in the formulation of the compound of the invention or derivative either alone or as a mixture in different ratios.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Microspheres formulated for oral administration may also be used. Such microspheres have been well defined in the art. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For topical administration, the compound may be formulated as solutions, gels, ointments, creams, suspensions, etc. as are well-known in the art. Systemic formulations include those designed for administration by injection, e.g., subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal oral or pulmonary administration.

For administration by inhalation, compounds for use according to the present invention may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane,

trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

Also contemplated herein is pulmonary delivery of the compounds disclosed herein (or salts thereof). The compound is delivered to the lungs of a mammal while inhaling and traverses across the lung epithelial lining to the blood stream. Other reports of inhaled molecules include Adjei et al., *Pharm Res* 7:565-569 (1990); Adjei et al., *Int J Pharmaceutics* 63:135-144 (1990) (leuprolide acetate); Braquet et al., *J Cardiovasc Pharmacol* 13(suppl. 5):143-146 (1989) (endothelin-1); Hubbard et al., *Annal Int Med* 3:206-212 (1989) (α1-antitrypsin); Smith et al., 1989, *J Clin Invest* 84:1145-1146 (a-1-proteinase); Oswein et al., 1990, "Aerosolization of Proteins", Proceedings of Symposium on Respiratory Drug Delivery II, Keystone, Colorado, March, (recombinant human growth hormone); Debs et al., 1988, *J Immunol* 140:3482-3488 (interferon-gamma and tumor necrosis factor alpha) and Platz et al., U.S. Pat. No. 5,284,656 (granulocyte colony stimulating factor; incorporated by reference). A method and composition for pulmonary delivery of drugs for systemic effect is described in U.S. Pat. No. 5,451,569 (incorporated by reference), issued Sep. 19, 1995 to Wong et al.

Contemplated for use in the practice of this invention are mechanical devices designed for pulmonary delivery of therapeutic products, including but not limited to nebulizers, metered dose inhalers, and powder inhalers, all of which are familiar to those skilled in the art.

Some specific examples of commercially available devices suitable for the practice of this invention are the Ultravent nebulizer, manufactured by Mallinckrodt, Inc., St. Louis, Mo.; the Acorn II nebulizer, manufactured by Marquest Medical Products, Englewood, Colo.; the Ventolin metered dose inhaler, manufactured by Glaxo Inc., Research Triangle Park, North Carolina; and the Spinhaler powder inhaler, manufactured by Fisons Corp., Bedford, Mass.

All such devices require the use of formulations suitable for the dispensing of the compounds of the invention. Typically, each formulation is specific to the type of device employed and may involve the use of an appropriate propellant material, in addition to the usual diluents, adjuvants and/or carriers useful in therapy. Also, the use of liposomes, microcapsules or microspheres, inclusion complexes, or other types of carriers is contemplated. Chemically

modified compound of the invention may also be prepared in different formulations depending on the type of chemical modification or the type of device employed.

Formulations suitable for use with a nebulizer, either jet or ultrasonic, will typically comprise a compound of the invention (or derivative) dissolved in water at a concentration of about 0.1 to 25 mg of biologically active compound of the invention per mL of solution. The formulation may also include a buffer and a simple sugar (e.g., for inhibitor stabilization and regulation of osmotic pressure). The nebulizer formulation may also contain a surfactant, to reduce or prevent surface induced aggregation of the compound of the invention caused by atomization of the solution in forming the aerosol.

Formulations for use with a metered-dose inhaler device will generally comprise a finely divided powder containing the compound of the invention (or derivative) suspended in a propellant with the aid of a surfactant. The propellant may be any conventional material employed for this purpose, such as a chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol, and 1,1,1,2-tetrafluoroethane, or combinations thereof. Suitable surfactants include sorbitan trioleate and soya lecithin. Oleic acid may also be useful as a surfactant.

Formulations for dispensing from a powder inhaler device will comprise a finely divided dry powder containing a compound of the invention (or derivative) and may also include a bulking agent, such as lactose, sorbitol, sucrose, or mannitol in amounts which facilitate dispersal of the powder from the device, e.g., 50 to 90% by weight of the formulation. The compound of the invention (or derivative) should advantageously be prepared in particulate form with an average particle size of less than 10 micrometers (μm), most preferably 0.5 to 5 μm, for most effective delivery to the deep lung.

Nasal delivery of a pharmaceutical composition of the present invention is also contemplated. Nasal delivery allows the passage of a pharmaceutical composition of the present invention to the blood stream directly after administering the therapeutic product to the nose, without the necessity for deposition of the product in the lung. Formulations for nasal delivery include those with dextran or cyclodextran.

For nasal administration, a useful device is a small, hard bottle to which a metered dose sprayer is attached. In one embodiment, the metered dose is delivered by drawing the

pharmaceutical composition of the present invention solution into a chamber of defined volume, which chamber has an aperture dimensioned to aerosolize and aerosol formulation by forming a spray when a liquid in the chamber is compressed. The chamber is compressed to administer the pharmaceutical composition of the present invention. In a specific embodiment, the chamber is a piston arrangement. Such devices are commercially available.

Alternatively, a plastic squeeze bottle with an aperture or opening dimensioned to aerosolize an aerosol formulation by forming a spray when squeezed is used. The opening is usually found in the top of the bottle, and the top is generally tapered to partially fit in the nasal passages for efficient administration of the aerosol formulation. Preferably, the nasal inhaler will provide a metered amount of the aerosol formulation, for administration of a measured dose of the drug.

The compounds, when it is desirable to deliver them systemically, may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethylcellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active compounds may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal or vaginal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described above, a compound may also be formulated as a depot preparation. Such long acting formulations may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Suitable liquid or solid pharmaceutical preparation forms are, for example, aqueous or saline solutions for inhalation, microencapsulated, encochleated, coated onto microscopic gold particles, contained in liposomes, nebulized, aerosols, pellets for implantation into the skin, or dried onto a sharp object to be scratched into the skin. The pharmaceutical compositions also include granules, powders, tablets, coated tablets, (micro)capsules, suppositories, syrups, emulsions, suspensions, creams, drops or preparations with protracted release of active compounds, in whose preparation excipients and additives and/or auxiliaries such as disintegrants, binders, coating agents, swelling agents, lubricants, flavorings, sweeteners or solubilizers are customarily used as described above. The pharmaceutical compositions are suitable for use in a variety of drug delivery systems. For a brief review of methods for drug delivery, see Langer R, *Science* 249:1527-33 (1990).

The compound of the invention and optionally other therapeutics may be administered *per se* (neat) or in the form of a pharmaceutically acceptable salt or cocrystal. When used in medicine the salts or cocrystals should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts or cocrystals may conveniently be used to prepare pharmaceutically acceptable salts or cocrystals thereof. Such salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluene sulphonic, tartaric, citric, methane sulphonic, formic, malonic, succinic, naphthalene-2-sulphonic, and benzene sulphonic. Also, such salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts of the carboxylic acid group.

Suitable buffering agents include: acetic acid and a salt (1-2% w/v); citric acid and a salt (1-3% w/v); boric acid and a salt (0.5-2.5% w/v); and phosphoric acid and a salt (0.8-2% w/v).

Suitable preservatives include benzalkonium chloride (0.003-0.03% w/v); chlorobutanol (0.3-0.9% w/v); parabens (0.01-0.25% w/v) and thimerosal (0.004-0.02% w/v).

Pharmaceutical compositions of the invention contain an effective amount of a compound as described herein and optionally therapeutic agents included in a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" means one or more compatible solid or liquid filler, diluents or encapsulating substances which are suitable for administration to a human or other vertebrate animal. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions also are capable of being commingled with the compounds of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficiency.

The therapeutic agent(s), including specifically but not limited to a compound of the invention, may be provided in particles. Particles as used herein means nanoparticles or microparticles (or in some instances larger particles) which can consist in whole or in part of the compound of the invention or the other therapeutic agent(s) as described herein. The particles may contain the therapeutic agent(s) in a core surrounded by a coating, including, but not limited to, an enteric coating. The therapeutic agent(s) also may be dispersed throughout the particles. The therapeutic agent(s) also may be adsorbed into the particles. The particles may be of any order release kinetics, including zero-order release, first-order release, second-order release, delayed release, sustained release, immediate release, and any combination thereof, etc. The particle may include, in addition to the therapeutic agent(s), any of those materials routinely used in the art of pharmacy and medicine, including, but not limited to, erodible, nonerodible, biodegradable, or nonbiodegradable material or combinations thereof. The particles may be microcapsules which contain the compound of the invention in a solution or in a semi-solid state. The particles may be of virtually any shape.

Both non-biodegradable and biodegradable polymeric materials can be used in the manufacture of particles for delivering the therapeutic agent(s). Such polymers may be natural or synthetic polymers. The polymer is selected based on the period of time over which release is desired. Bioadhesive polymers of particular interest include bioerodible hydrogels described in Sawhney H S et al. (1993) *Macromolecules* 26:581-7, the teachings of which are incorporated herein. These include polyhyaluronic acids, casein, gelatin, glutin, polyanhydrides, polyacrylic

acid, alginate, chitosan, poly(methyl methacrylates), poly(ethyl methacrylates), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecyl acrylate).

The therapeutic agent(s) may be contained in controlled release systems. The term "controlled release" is intended to refer to any drug-containing formulation in which the manner and profile of drug release from the formulation are controlled. This refers to immediate as well as non-immediate release formulations, with non-immediate release formulations including but not limited to sustained release and delayed release formulations. The term "sustained release" (also referred to as "extended release") is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that preferably, although not necessarily, results in substantially constant blood levels of a drug over an extended time period. The term "delayed release" is used in its conventional sense to refer to a drug formulation in which there is a time delay between administration of the formulation and the release of the drug there from. "Delayed release" may or may not involve gradual release of drug over an extended period of time, and thus may or may not be "sustained release."

Use of a long-term sustained release implant may be particularly suitable for treatment of chronic conditions. "Long-term" release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 7 days, and preferably 30-60 days. Long-term sustained release implants are well-known to those of ordinary skill in the art and include some of the release systems described above.

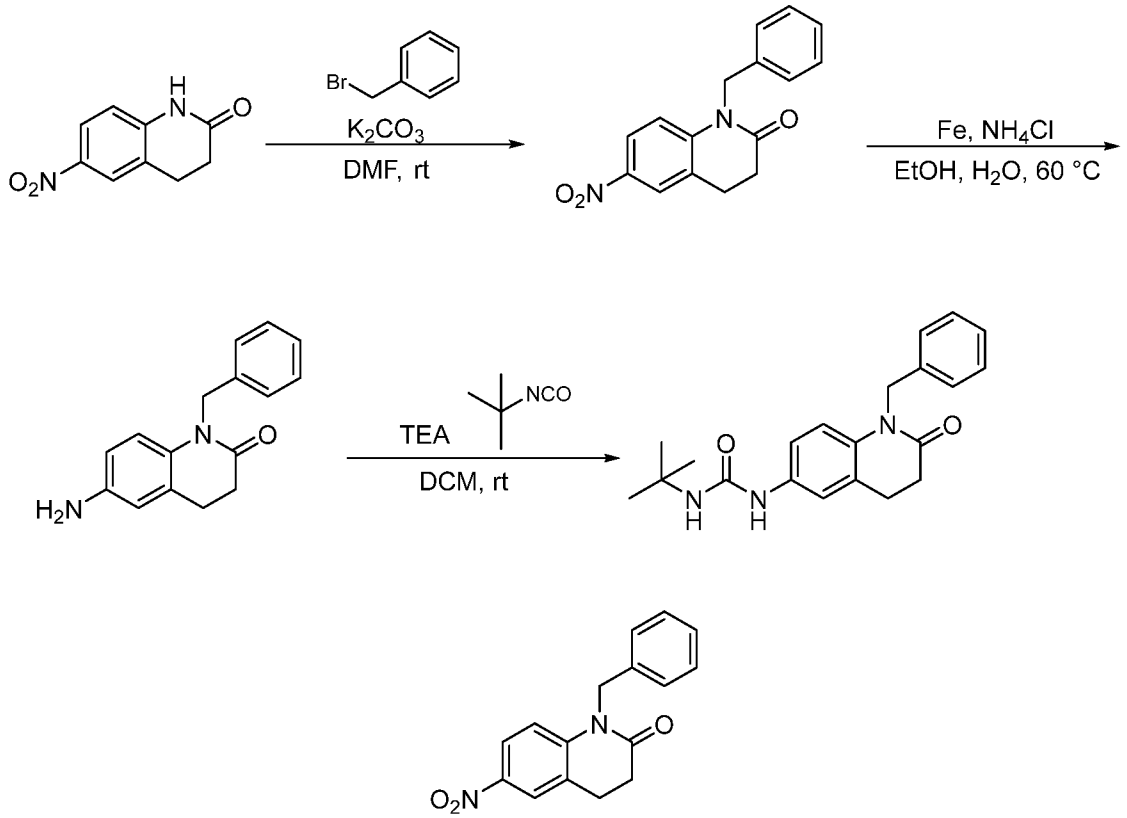
It will be understood by one of ordinary skill in the relevant arts that other suitable modifications and adaptations to the compositions and methods described herein are readily apparent from the description of the invention contained herein in view of information known to the ordinarily skilled artisan, and may be made without departing from the scope of the invention or any embodiment thereof. Having now described the present invention in detail, the same will be more clearly understood by reference to the following examples, which are included herewith for purposes of illustration only and are not intended to be limiting of the invention.

EXAMPLES

The invention is further described in the following examples, which do not limit the scope of the invention described in the claims.

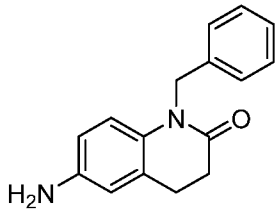
Example 1: 1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

Synthetic Scheme



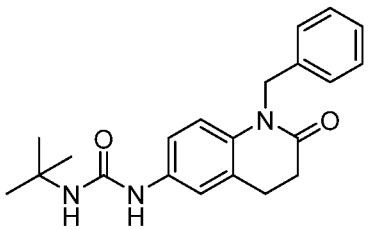
1-benzyl-6-nitro-3,4-dihydroquinolin-2(1H)-one

To a solution of 6-nitro-3,4-dihydroquinolin-2(1H)-one (1 g, 5.204 mmol, 1 equiv) in DMF (20 mL) was added K_2CO_3 (2.154 g, 15.611 mmol, 3 equiv) and (bromomethyl)benzene (979 mg, 5.724 mmol, 1.1 equiv). The resulting mixture was stirred for 16 h at rt. The mixture was diuted with EtOAc (100 mL), washed with water (3 x 50 mL), brine (2 x 50 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 1-benzyl-6-nitro-3,4-dihydroquinolin-2(1H)-one (500 mg, 34.04%) as a white solid.



6-amino-1-benzyl-3,4-dihydroquinolin-2(1H)-one

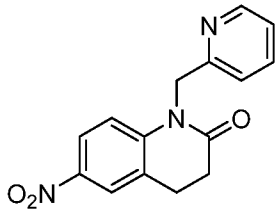
To a solution of 1-benzyl-6-nitro-3,4-dihydroquinolin-2(1H)-one (0.45 g, 1.590 mmol, 1 equiv) in EtOH (10 mL) and H_2O (2.5 mL) was added Fe (888.0 mg, 15.90 mmol, 10 equiv) and NH_4Cl (850.5 mg, 15.90 mmol, 10 equiv).The resulting mixture was stirred for 2 h at 60 °C and stirred until the starting material was totally consumed by TLC. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 6-amino-1-benzyl-3,4-dihydroquinolin-2(1H)-one (350 mg, 87.28%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{16}N_2O$: 252.13 m/z, found 253.10 $[M+H]^+$.



1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

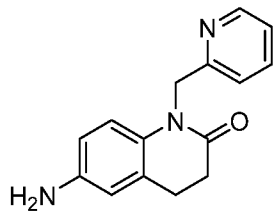
To a solution of 6-amino-1-benzyl-3,4-dihydroquinolin-2(1H)-one (150 mg, 0.594 mmol, 1 equiv) in DCM (8 mL) was added TEA (179.9 mg, 1.782 mmol, 3 equiv) and 2-isocyanato-2-methylpropane (176.65 mg, 1.782 mmol, 3 equiv). The resulting mixture was stirred for 16 h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 53% B in 9 min, 53% B; Wave Length: 254/220 nm; RT1(min): 8.52; Number Of Runs: 0) to afford 1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea (60.2 mg, 28.94%) as an off-white solid. MS (ESI): mass calcd. For $C_{21}H_{25}N_3O_2$, 351.19 m/z, found 352.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.08 (s, 1H), 7.26 – 7.34 (m, 3H), 7.16 – 7.25 (m, 3H), 6.95 (dd, J = 8.8, 2.5 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 5.90 (s, 1H), 5.09 (s, 2H), 2.87 (dd, J = 8.7, 5.9 Hz, 2H), 2.64 (dd, J = 8.7, 5.9 Hz, 2H), 1.26 (s, 9H).

Example 2: 1-(tert-butyl)-3-(2-oxo-1-(pyridin-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea



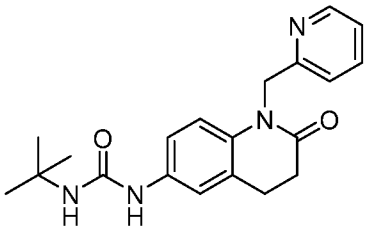
6-nitro-1-(pyridin-2-ylmethyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of 6-nitro-3,4-dihydro-1H-quinolin-2-one (500 mg, 2.602 mmol, 1 equiv) in DMF (10 mL) was added K_2CO_3 (1078.7 mg, 7.805 mmol, 3 equiv) and 2-(bromomethyl)pyridine (492.3 mg, 2.862 mmol, 1 equiv). The resulting mixture was stirred for 16 h at rt. The mixture was diuted with EtOAc (100 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 6-nitro-1-(pyridin-2-ylmethyl)-3,4-dihydroquinolin-2(1H)-one (500 mg, 63.20%) as a white solid. MS (ESI): mass calcd. for $C_{15}H_{13}N_3O_3$ 283.10 m/z, found 284.05 $[M+H]^+$.



6-amino-1-(pyridin-2-ylmethyl)-3,4-dihydroquinolin-2-one

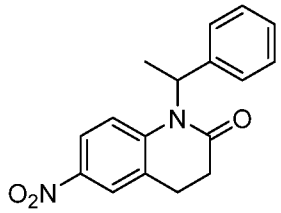
To a solution of 6-nitro-1-(pyridin-2-ylmethyl)-3,4-dihydroquinolin-2-one (440 mg, 1.553 mmol, 1 equiv) in EtOH (10 mL) and H_2O (2.5 mL) was added Fe (867.3 mg, 15.532 mmol, 10 equiv) and NH_4Cl (830.8 mg, 15.530 mmol, 10 equiv). The resulting mixture was stirred for 2 h at 60 °C. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 6-amino-1-(pyridin-2-ylmethyl)-3,4-dihydroquinolin-2-one (200 mg, 46.52%) as a yellow solid. MS (ESI): mass calcd. for $C_{15}H_{15}N_3O$, 253.12 m/z, found 254.15 $[M+H]^+$.



1-(tert-butyl)-3-(2-oxo-1-(pyridin-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a solution of 6-amino-1-(pyridin-2-ylmethyl)-3,4-dihydroquinolin-2(1H)-one (200 mg, 0.793 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (234.8 mg, 2.369 mmol, 3 equiv) and TEA (79.9 mg, 0.790 mmol, 1 equiv). The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 22% B to 34% B in 10.5 min; Wave Length: 254/220 nm; RT1(min): 11.3; Number Of Runs: 4) to afford 1-(tert-butyl)-3-(2-oxo-1-(pyridin-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea (83.1 mg, 29.82%) as a white solid. MS (ESI): mass calcd. for $C_{20}H_{24}N_4O_2$, 352.19 m/z, found 353.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.52 (d, J = 4.8 Hz, 1H), 8.11 (d, J = 3.5 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.34 (s, 1H), 7.25 (q, J = 5.1 Hz, 1H), 7.21 – 7.21 (m, 1H), 6.97 (d, J = 8.8 Hz, 1H), 6.69 – 6.78 (m, 1H), 5.92 (s, 1H), 5.13 (s, 2H), 2.89 (d, J = 8.0 Hz, 2H), 2.64 (d, J = 8.4 Hz, 2H), 1.26 (s, 9H).

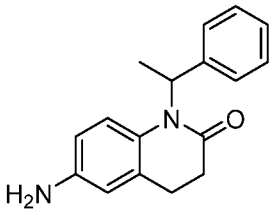
Example 3: 1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea



6-nitro-1-(1-phenylethyl)-3,4-dihydroquinolin-2-one

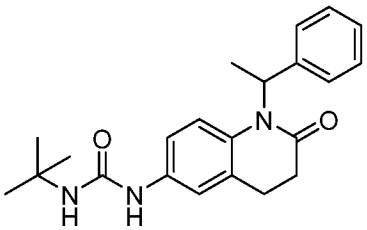
To a solution of 6-nitro-3,4-dihydro-1H-quinolin-2-one (500 mg, 2.602 mmol, 1 equiv) in DMF (10 mL) was added K_2CO_3 (1078.7 mg, 7.805 mmol, 3 equiv) and (1-bromoethyl)benzene (529.6 mg, 2.862 mmol, 1 equiv). The resulting mixture was stirred for 16 h at rt. The mixture

was diuted with EtOAc (100 mL), washed with water (3 x 50 mL), brine (2 x 50 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 6-nitro-1-(1-phenylethyl)-3,4-dihydroquinolin-2-one (400 mg, 45.17%) as a white solid.MS (ESI): mass calcd. for $C_{17}H_{16}N_2O_3$ 296.12 m/z, found 297.05 $[M+H]^+$.



6-amino-1-(1-phenylethyl)-3,4-dihydroquinolin-2-one

To a solution of 6-nitro-1-(1-phenylethyl)-3,4-dihydroquinolin-2-one (400 mg, 1.350 mmol, 1 equiv) in EtOH (10 mL) and H_2O (2.5 mL) was added Fe (753.8 mg, 13.499 mmol, 10 equiv) and NH_4Cl (722.0 mg, 13.499 mmol, 10 equiv). The resulting mixture was stirred for 2 h at 60 °C. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 6-amino-1-(1-phenylethyl)-3,4-dihydroquinolin-2-one (200 mg, 55.63%) as a white solid.

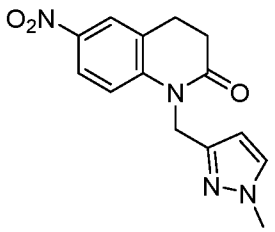


1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a solution of 6-amino-1-(1-phenylethyl)-3,4-dihydroquinolin-2-one (200 mg, 0.751 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (223.3 mg, 2.253 mmol, 3 equiv) and TEA (75.9 mg, 0.751 mmol, 1 equiv).The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel

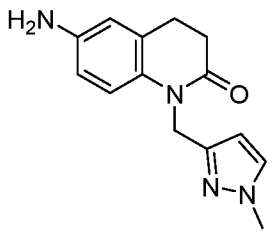
column, eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 38% B to 50% B in 10.5 min; Wave Length: 254/220 nm; RT1(min): 10.7; Number Of Runs: 3) to afford 1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea (57.7 mg, 21.02%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_2$, 365.21 m/z, found 366.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.18 – 7.39 (m, 6H), 6.81 (d, J = 8.8 Hz, 1H), 6.42 – 6.52 (m, 1H), 6.15 (d, J = 8.0 Hz, 1H), 5.91 (s, 1H), 2.80 (d, J = 5.6 Hz, 2H), 2.54 – 2.70 (m, 2H), 1.67 (t, J = 5.7 Hz, 3H), 1.24 (dd, J = 4.1, 2.2 Hz, 9H).

Example 4: 1-(tert-butyl)-3-(1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea



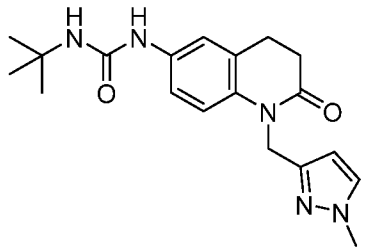
1-[(1-methylpyrazol-3-yl)methyl]-6-nitro-3,4-dihydroquinolin-2-one

To a solution of 6-nitro-3,4-dihydro-1H-quinolin-2-one (500 mg, 2.602 mmol, 1 equiv) in DMF (10 mL) was added K_2CO_3 (1086.6 mg, 7.805 mmol, 3 equiv) and 3-(bromomethyl)-1-methylpyrazole (500.9 mg, 2.862 mmol, 1.1 equiv). The resulting mixture was stirred for 16 h at rt. The mixture was diuted with EtOAc (100 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 1-[(1-methylpyrazol-3-yl)methyl]-6-nitro-3,4-dihydroquinolin-2-one (500 mg, 46.59%) as a white solid. MS (ESI): mass calcd. for $C_{14}H_{14}N_4O_3$: 286.11 m/z, found 287.00 $[M+H]^+$.



6-amino-1-[(1-methylpyrazol-3-yl)methyl]-3,4-dihydroquinolin-2-one

To a solution of 6-nitro-1-(1H-pyrazol-3-ylmethyl)-3,4-dihydroquinolin-2-one (300 mg, 1.102 mmol, 1 equiv) in EtOH (10 mL) and H_2O (2.5 mL) was added Fe (615.3 mg, 11.019 mmol, 10 equiv) and NH_4Cl (589.3 mg, 11.019 mmol, 10 equiv).The resulting mixture was stirred for 2 h at 60 °C and stirred until the starting material was totally consumed by TLC. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 6-amino-1-[(1-methylpyrazol-3-yl)methyl]-3,4-dihydroquinolin-2-one (101 mg, 36.03%) as a yellow solid.



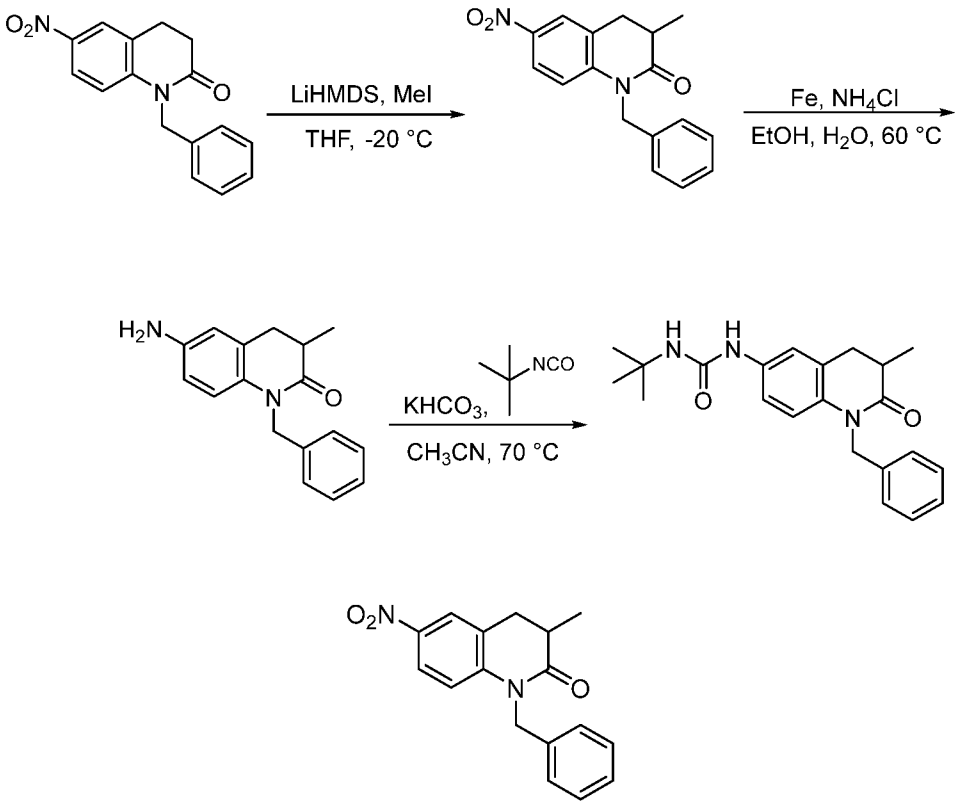
1-(tert-butyl)-3-(1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a solution of 6-amino-1-[(1-methylpyrazol-3-yl)methyl]-3,4-dihydroquinolin-2-one (50 mg, 0.195 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (58.0 mg, 0.585 mmol, 3 equiv) and TEA (19.7 mg, 0.195 mmol, 1 equiv).The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9; Number Of Runs: 0) to afford 1-(tert-butyl)-3-(1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea (9.0 mg, 12.23%) as a white solid. MS (ESI): mass calcd. for $C_{19}H_{25}N_5O_2$, 355.20 m/z, found 356.10 $[M+H]^+$. ^1H NMR (300

MHz, DMSO-d_6) δ 8.10 (d, J = 5.2 Hz, 1H), 7.48 – 7.62 (m, 1H), 7.29 (s, 1H), 7.01 (s, 2H), 5.85 – 6.04 (m, 2H), 4.95 (s, 2H), 3.78 – 3.82 (m, 3H), 2.81 (s, 2H), 2.51 (s, 2H), 1.17 – 1.37 (m, 9H).

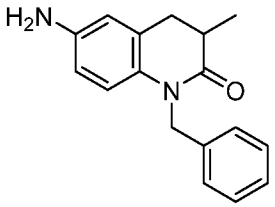
Example 5: 1-(1-benzyl-3-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

Synthetic Scheme



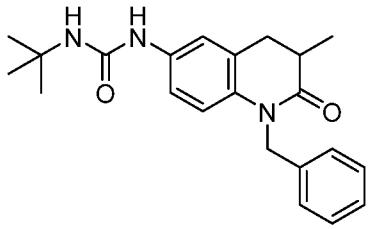
1-benzyl-3-methyl-6-nitro-3,4-dihydroquinolin-2(1H)-one

To a solution of 1-benzyl-6-nitro-3,4-dihydroquinolin-2(1H)-one (1 g, 3.54 mmol, 1 equiv) in THF (70 mL) was added 2M LiHMDS (in THF) (2.3 mL, 4.60 mmol, 1.3 equiv) at -20 °C under N_2. The resulting mixture was stirred 30 min at -20 °C. The reaction mixture was added MeI (653.6 mg, 4.60 mmol, 1.3 equiv) at -20 °C. The resulting mixture was stirred 30 min at -20 °C and then stirred 16 h at rt. The reaction mixture was quenched by water (50 mL) and extracted with EA (3 x 70 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE /EA (3:1) to afford 1-benzyl-3-methyl-6-nitro-3,4-dihydroquinolin-2(1H)-one (0.3 g, 28.59%) as a white solid.



6-amino-1-benzyl-3-methyl-3,4-dihydroquinolin-2(1H)-one

To a solution of 1-benzyl-3-methyl-6-nitro-3,4-dihydroquinolin-2(1H)-one (0.28 g, 0.944 mmol, 1 equiv) in EtOH (10 mL) and H_2O (2.5 mL) was added Fe (527.7 mg, 9.44 mmol, 10 equiv) and NH_4Cl (504.9 mg, 9.76 mmol, 10 equiv). The resulting mixture was stirred for 2 h at 60 °C and stirred until the starting material was totally consumed by TLC. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 3-((6-amino-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)benzonitrile (160 mg, 46.37%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{18}N_2O$: 266.14 m/z, found 267.20 $[M+H]^+$.

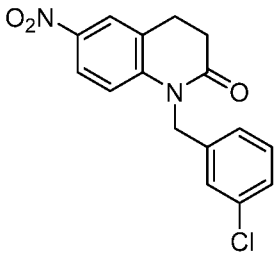


1-(tert-butyl)-3-(1-(3-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a solution of 6-amino-1-benzyl-3-methyl-3,4-dihydroquinolin-2(1H)-one (150 mg, 0.563 mmol, 1 equiv) in CH_3CN (5 mL) was added 2-isocyanato-2-methylpropane (167.48 mg, 1.689 mmol, 3 equiv) and $KHCO_3$ (112.7 mg, 1.126 mmol, 2 equiv). The resulting mixture was stirred for overnight at 70 °C. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9; Number Of Runs: 0) to afford 1-(tert-butyl)-3-(1-(3-

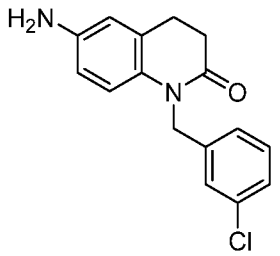
cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea (18.1 mg, 8.78%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_2$: 365.21 m/z, found 366.10 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.26 – 7.31 (m, 2H), 7.12 – 7.23 (m, 3H), 6.82 (d, *J* = 8.7 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 6.25 – 6.54 (m, 1H), 5.19 (d, *J* = 16.3 Hz, 1H), 5.05 (d, *J* = 16.0 Hz, 1H), 2.94 (d, *J* = 11.6 Hz, 1H), 2.58 – 2.81 (m, 2H), 1.33 (s, 9H), 1.30 (d, *J* = 6.2 Hz, 3H).

Example 6: 1-(tert-butyl)-3-(1-(3-chlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea



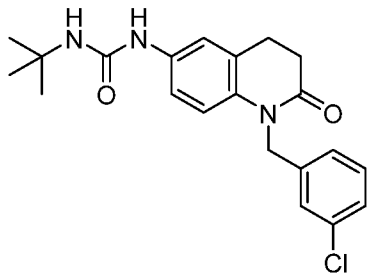
1-(3-chlorobenzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one

To a solution of 6-nitro-3,4-dihydro-1H-quinolin-2-one (500 mg, 2.602 mmol, 1 equiv) in dimethylformamide (10 mL) was added 1-(bromomethyl)-3-chlorobenzene (801.93 mg, 3.903 mmol, 1.5 equiv) and potassium methaneperoxoate potassium (724.41 mg, 5.204 mmol, 2.0 equiv) at rt. The mixture was stirred for overnight at rt. The reaction mixture was quenched by water (30 mL) and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EA (3:1) to afford 1-(3-chlorobenzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (700 mg, 88.29%) as a white solid. MS (ESI): mass calcd. $C_{16}H_{13}ClN_2O_3$: for 316.06 m/z, found 317.10$[M+H]^+$.



6-amino-1-(3-chlorobenzyl)-3,4-dihydroquinolin-2(1H)-one

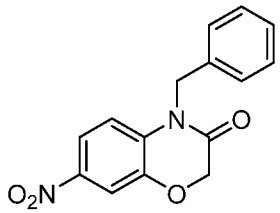
To a solution of 1-(3-chlorobenzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (700 mg, 2.210 mmol, 1 equiv) in EtOH (5 mL)/H_2O (0.5 mL) was added Fe (1.2 g, 22.1 mmol, 10 equiv) and NH_4Cl (1.2 g, 22.100 mmol, 10 equiv) at rt. The mixture was stirred for 2 h at 60 °C. The reaction mixture was quenched by water (30 mL) and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EA (2:1) to afford 6-amino-1-(3-chlorobenzyl)-3,4-dihydroquinolin-2(1H)-one (600 mg, 94.68%) as a brown solid. MS (ESI): mass calcd. $C_{16}H_{15}ClN_2O$: for 286.09 m/z, found 287.10$[M+H]^+$.



1-(tert-butyl)-3-(1-(3-chlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

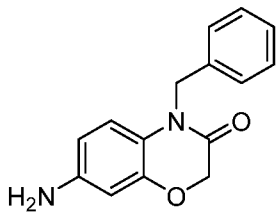
A solution of 6-amino-1-(3-chlorobenzyl)-3,4-dihydroquinolin-2(1H)-one (50 mg, 0.174 mmol, 1 equiv) in DCM (3 mL) was added TEA (35.29 mg, 0.348 mmol, 2.0 equiv) and 2-isocyanato-2-methylpropane (20.74 mg, 0.209 mmol, 1.2 equiv) at 0 °C. The resulting mixture was stirred for 16 h at rt. The reaction mixture was quenched by water (20 mL). The resulting mixture was extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (2:1) to afford 1-(tert-butyl)-3-(1-(3-chlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea (30.4 mg, 45.11%) as white solid. MS (ESI): mass calcd. $C_{21}H_{24}ClN_3O_2$ for : 385.16 m/z, found 386.1 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.24 – 7.40 (m, 4H), 7.15 – 7.18 (m, 1H), 6.96 – 7.01 (m, 1H), 6.75 – 6.80 (m, 1H), 5.92 (s, 1H), 5.10 (s, 2H), 2.85 – 2.92 (m, 2H), 2.61 – 2.70 (m, 2H), 1.27 (s, 9H).

Example 7: 1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea



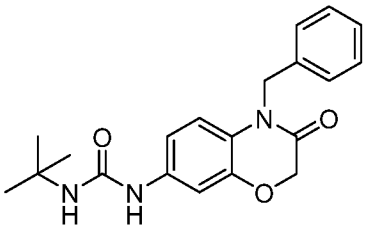
4-benzyl-7-nitro-2H-1,4-benzoxazin-3-one

To a solution of 7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (400 mg, 2.060 mmol, 1 equiv) in DMF (10 mL) was added K_2CO_3 (860.4 mg, 6.181 mmol, 3 equiv) and benzyl bromide (387.6 mg, 2.266 mmol, 1.1 equiv). The resulting mixture was stirred for 16 h at rt. The mixture was diuted with EtOAc (100 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 4-benzyl-7-nitro-2H-1,4-benzoxazin-3-one (500 mg, 72.97%) as a yellow solid. MS (ESI): mass calcd. for $C_{15}H_{12}N_2O_4$ 284.08 m/z, found 285.05 $[M+H]^+$.



7-amino-4-benzyl-2H-1,4-benzoxazin-3-one

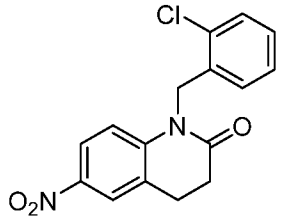
To a solution of 4-benzyl-7-nitro-2H-1,4-benzoxazin-3-one (500 mg, 1.759 mmol, 1 equiv) in EtOH (10 mL) and H_2O (2.5 mL) was added Fe (982.2 mg, 17.589 mmol, 10 equiv) and NH_4Cl (940.8 mg, 17.589 mmol, 10 equiv). The resulting mixture was stirred for 2 h at 60 °C. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 7-amino-4-benzyl-2H-1,4-benzoxazin-3-one (200 mg, 44.72%) as a yellow solid. MS (ESI): mass calcd. for $C_{15}H_{14}N_2O_2$, 254.11 m/z, found 255.05 $[M+H]^+$.



1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

To a solution of 7-amino-4-benzyl-2H-1,4-benzoxazin-3-one (150 mg, 0.590 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (175.4 mg, 1.770 mmol, 3 equiv) and TEA (59.6 mg, 0.590 mmol, 1 equiv). The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9; Number Of Runs: 0) to afford 1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea (56.8 mg, 27.14%) as a white solid. MS (ESI): mass calcd. for $C_{20}H_{23}N_3O_3$, 353.17 m/z, found 354.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.17 – 7.41 (m, 7H), 6.86 (dd, J = 8.6, 2.1 Hz, 1H), 6.71 – 6.82 (m, 1H), 5.93 (s, 1H), 5.11 (s, 2H), 4.74 (d, J = 2.1 Hz, 2H), 1.26 (d, J = 2.1 Hz, 9H).

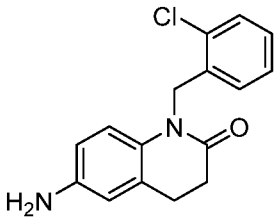
Example 8: 1-(tert-butyl)-3-(1-(2-chlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea



1-(2-chlorobenzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one

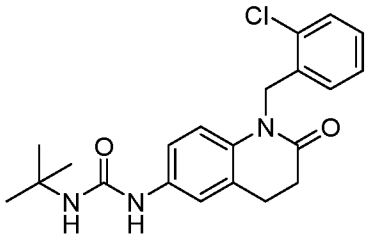
To a solution of 6-nitro-3,4-dihydroquinolin-2(1H)-one (500 mg, 2.602 mmol, 1 equiv) in DMF (10 mL) was added K_2CO_3 (1086.6 mg, 7.805 mmol, 3 equiv) and 1-(bromomethyl)-2-chlorobenzene (583.64 mg, 2.862 mmol, 1.1 equiv). The resulting mixture was stirred for 16 h at

rt. The mixture was diuted with EtOAc (50 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 1-(2-chlorobenzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (400 mg, 48.54%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{13}ClN_2O_3$: 316.06 m/z, found 317.00 $[M+H]^+$.



6-amino-1-(2-chlorobenzyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of 1-(2-chlorobenzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (400 mg, 1.263 mmol, 1 equiv) in EtOH (10 mL) and H_2O (2.5 mL) was added Fe (705.3 mg, 12.63 mmol, 10 equiv) and NH_4Cl (675.6 mg, 12.63 mmol, 10 equiv).The resulting mixture was stirred for 2 h at 60 °C and stirred until the starting material was totally consumed by TLC. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 6-amino-1-(2-chlorobenzyl)-3,4-dihydroquinolin-2(1H)-one (0.3 g, 82.87%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{15}ClN_2O$: 286.09 m/z, found 287.00 $[M+H]^+$.



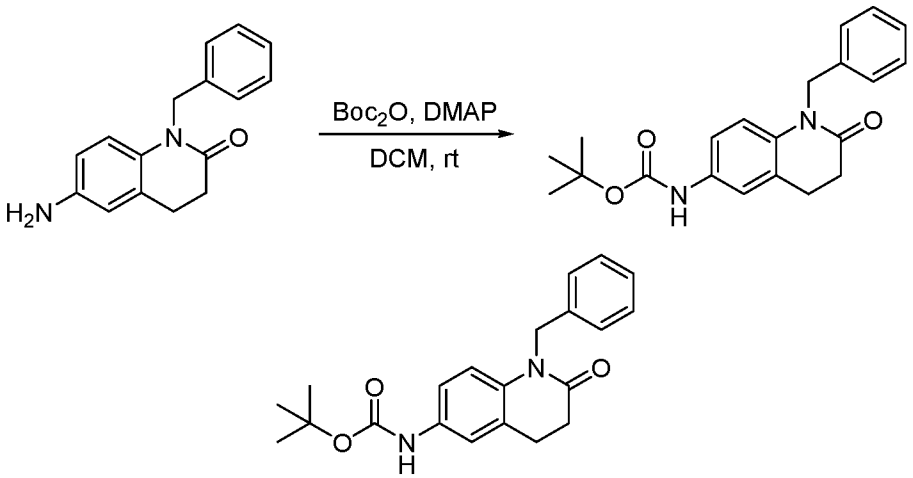
1-(tert-butyl)-3-(1-(2-chlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a solution of 6-amino-1-(2-chlorobenzyl)-3,4-dihydroquinolin-2(1H)-one (100 mg, 0.349 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (103.9 mg, 1.048 mmol, 3 equiv) and TEA (105.8 mg, 1.048 mmol, 3 equiv). The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous

Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9; Number Of Runs: 0) to afford 1-(tert-butyl)-3-(1-(2-chlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea (39.7 mg, 29.40%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{24}ClN_3O_2$: 385.16 m/z, found 386.05 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.47 – 7.56 (m, 1H), 7.35 – 7.42 (m, 1H), 7.26 (d, J = 8.7 Hz, 2H), 6.92 – 7.01 (m, 2H), 6.47 – 6.62 (m, 1H), 5.91 (s, 1H), 5.07 (s, 2H), 2.88 – 2.96 (m, 2H), 2.63 – 2.72 (m, 2H), 1.25 (s, 9H).

Example 9: tert-butyl (1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)carbamate

Synthetic Scheme



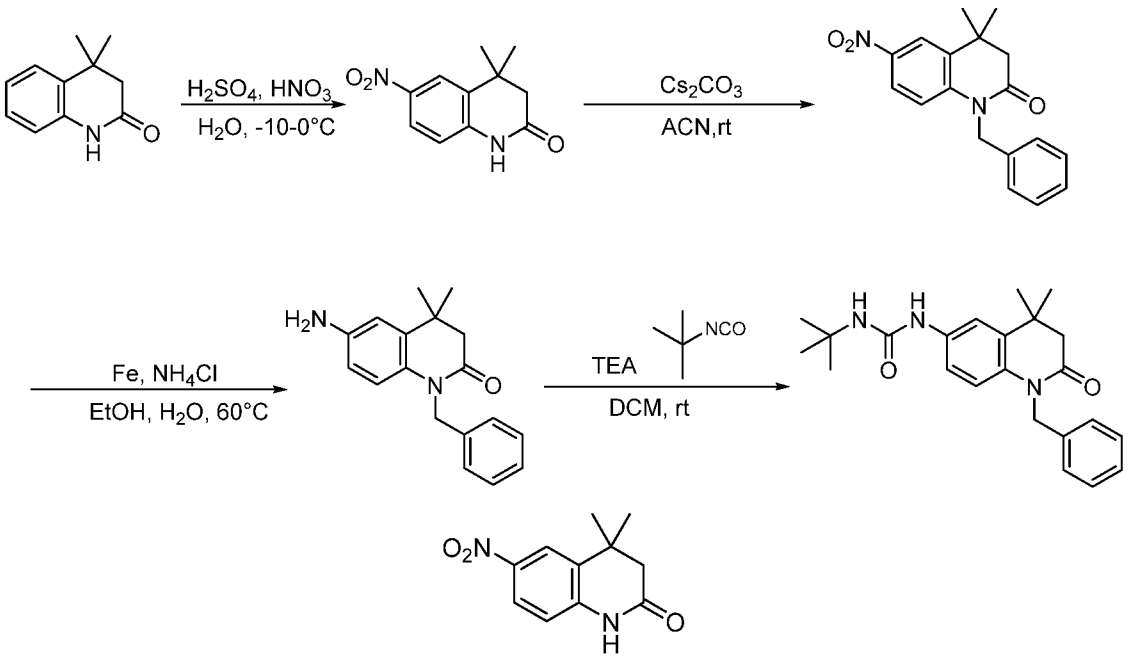
tert-butyl (1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)carbamate

To a solution of 6-amino-1-benzyl-3,4-dihydroquinolin-2(1H)-one (100 mg, 0.396 mmol, 1 equiv) in DCM (6 mL) was added Boc2O (129.7 mg, 0.594 mmol, 1.5 equiv) and DMAP (72.6 mg, 0.594 mmol, 1.5 equiv). The resulting mixture was stirred for 5 h at rt. The mixture was diuted with DCM (30 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 45% B in 9 min,

45% B; Wave Length: 254/220 nm; RT1(min): 8.6; Number Of Runs: 0) to afford tert-butyl (1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)carbamate (19.4 mg, 10.21%) as a yellow solid. MS (ESI): mass calcd. for $C_{21}H_{24}N_2O_3$: 352.18 m/z, found 353.10 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.21 (s, 1H), 7.39 – 7.16 (m, 6H), 7.10 (dd, J = 9.0, 2.4 Hz, 1H), 6.82 (d, J = 8.8 Hz, 1H), 5.11 (s, 2H), 2.88 (t, J = 7.2 Hz, 2H), 2.66 (dd, J = 8.7, 6.0 Hz, 2H), 1.45 (s, 9H).

Example 10: 1-(1-benzyl-4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

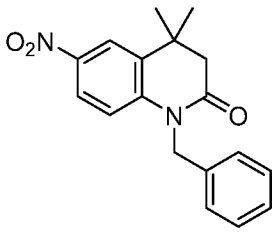
Synthetic Scheme



4,4-dimethyl-6-nitro-3,4-dihydroquinolin-2(1H)-one

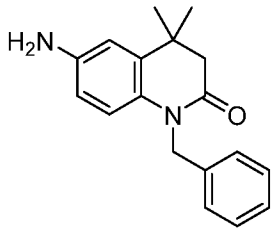
To a solution of 4,4-dimethyl-3,4-dihydroquinolin-2(1H)-one (0.4 g, 2.28 mmol, 1 equiv) in H_2O (2 mL) and H_2SO_4 (9 mL) was added HNO_3 (0.3 mL) at -10 °C. The reaction was stirred for 2 h at -10-0 °C. The reaction mixture was quenched by water. The mixture was acidified pH = 7 with $NaHCO_3$ (*aq.*) and then extracted with EA (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE /EA

(3:1) to afford 4,4-dimethyl-6-nitro-3,4-dihydroquinolin-2(1H)-one (0.3 g, 59.76%) as a white solid. MS (ESI): mass calcd. for $C_{11}H_{12}N_2O_3$, 220.08 m/z, found 221.10 [M+H]+ .



1-benzyl-4,4-dimethyl-6-nitro-3,4-dihydroquinolin-2(1H)-one

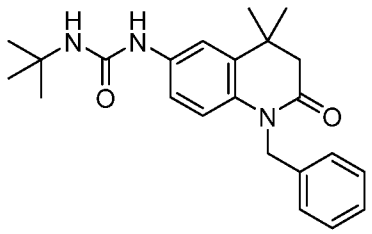
To a solution of 4,4-dimethyl-6-nitro-3,4-dihydroquinolin-2(1H)-one (280 mg, 1.270 mmol, 1 equiv) in CH_3CN (10 mL) was added Cs_2CO_3 (828.3 mg, 2.542 mmol, 2.0 equiv) and (bromomethyl)benzene (238.9 mg, 1.397 mmol, 1.1 equiv). The resulting mixture was stirred for 16 h at rt. The mixture was diuted with EtOAc (50 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 1-benzyl-4,4-dimethyl-6-nitro-3,4-dihydroquinolin-2(1H)-one (300 mg, 76.14%) as a white solid. MS (ESI): mass calcd. for $C_{18}H_{18}N_2O_3$: 310.13 m/z, found 311.25 [M+H]+.



6-amino-1-benzyl-4,4-dimethyl-3,4-dihydroquinolin-2(1H)-one

To a solution of 1-benzyl-4,4-dimethyl-6-nitro-3,4-dihydroquinolin-2(1H)-one (280 mg, 0.902 mmol, 1 equiv) in EtOH (10 mL) and H_2O (2.5 mL) was added Fe (503.9 mg, 9.02 mmol, 10 equiv) and NH_4Cl (482.5 mg, 9.02 mmol, 10 equiv). The resulting mixture was stirred for 2 h at 60 °C and stirred until the starting material was totally consumed by TLC. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1)

to afford 6-amino-1-benzyl-4,4-dimethyl-3,4-dihydroquinolin-2(1H)-one (100 mg, 39.68%) as a yellow solid. MS (ESI): mass calcd. for $C_{18}H_{20}N_2O$: 280.16 m/z, found 281.20 $[M+H]^+$.

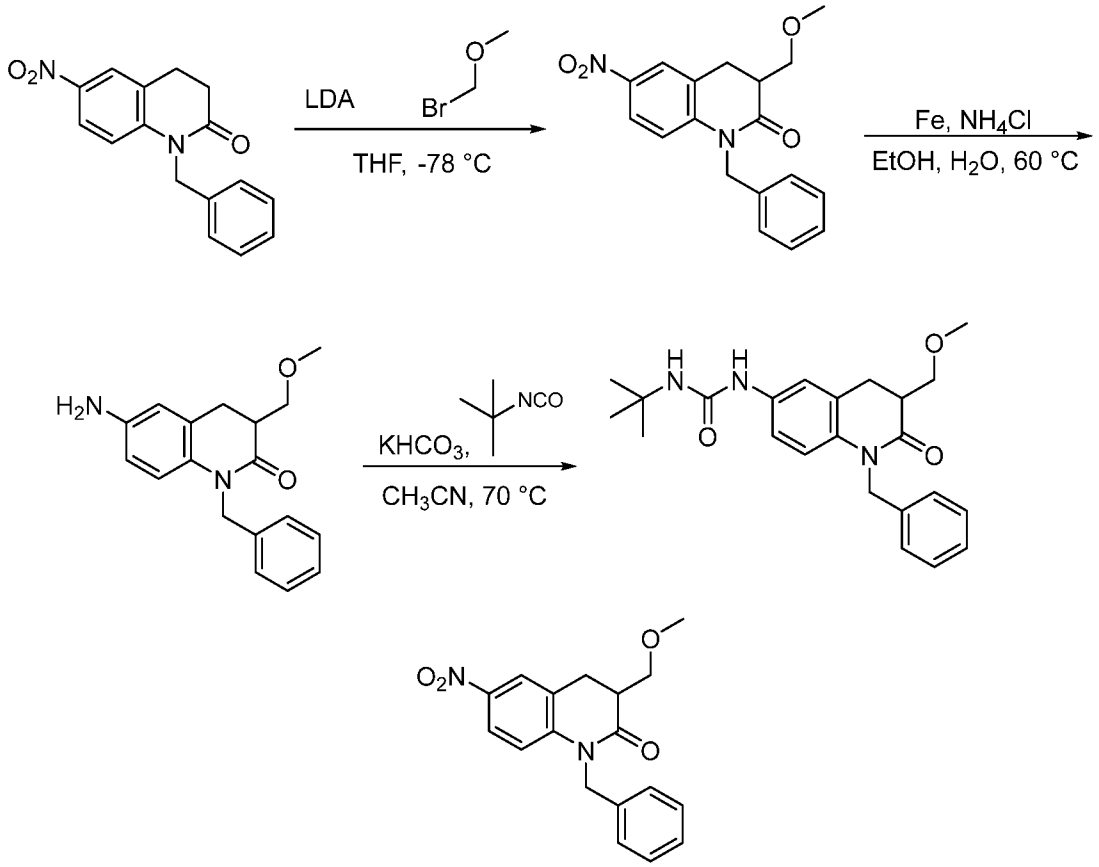


1-(1-benzyl-4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

To a solution of 6-amino-1-benzyl-4,4-dimethyl-3,4-dihydroquinolin-2(1H)-one (100 mg, 0.357 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (106.1 mg, 1.07 mmol, 3 equiv) and TEA (108.1 mg, 1.07 mmol, 3 equiv). The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep C18 OBD Column, 30*50 mm, 5μm 13nm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 45% B in 9 min, 45% B; Wave Length: 254/220 nm; RT1(min): 8.9; Number Of Runs: 0) to afford 1-(1-benzyl-4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea (51.0 mg, 37.50%) as a white solid. MS (ESI): mass calcd. for $C_{23}H_{29}N_3O_2$: 379.23 m/z, found 380.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.16 (s, 1H),7.38 (s, 1H),7.20 - 7.31 (m, 5H),7.02 (s, 1H), 6.86 (s, 1H), 5.88 (s, 1H), 5.13 (s, 2H), 2.50 - 2.55 (s, 2H), 1.26 (s, 9H), 1.22 (s, 6H).

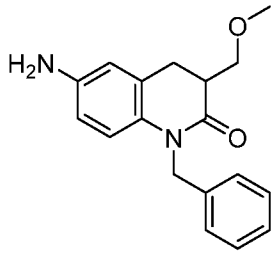
Example 11: 1-(1-benzyl-3-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

Synthetic Scheme



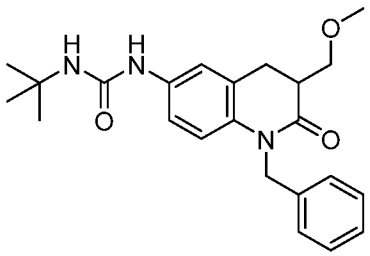
1-benzyl-3-(methoxymethyl)-6-nitro-3,4-dihydroquinolin-2-one

To a solution of 1-benzyl-6-nitro-3,4-dihydroquinolin-2-one (1.3 g, 4.605 mmol, 1 equiv) in THF (40 mL) was added 2M LDA (in THF) (3.5 mL, 0.74 g, 6.907 mmol, 1.5 equiv) at -78 °C under N_2. The resulting mixture was stirred 30 min at -78 °C. The reaction mixture was added bromo(methoxy)methane (1.15 g, 9.203 mmol, 2.00 equiv) at -78 °C. The resulting mixture was stirred for 1 h at -78 °C and 16 h at rt. The reaction mixture was quenched by NH_4Cl (*aq.*) and extracted with EA (3 x 50 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 1-benzyl-3-(methoxymethyl)-6-nitro-3,4-dihydroquinolin-2-one (400 mg, 12.30%) as a yellow solid. MS (ESI): mass calcd. for $C_{18}H_{18}N_2O_4$, 326.13 m/z, found 327.05 $[M+H]^+$.



6-amino-1-benzyl-3-(methoxymethyl)-3,4-dihydroquinolin-2-one

To a solution of 1-benzyl-3-(methoxymethyl)-6-nitro-3,4-dihydroquinolin-2-one (300 mg, 0.919 mmol, 1 equiv) in EtOH (10 mL) and H_2O (2.5 mL) was added Fe (513.3 mg, 9.193 mmol, 10 equiv) and NH_4Cl (491.7 mg, 9.193 mmol, 10 equiv). The resulting mixture was stirred for 2 h at 60 °C. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 6-amino-1-benzyl-3-(methoxymethyl)-3,4-dihydroquinolin-2-one (200 mg, 26.38%) as a yellow solid. MS (ESI): mass calcd. for $C_{18}H_{20}N_2O_2$, 296.15 m/z, found 297.10 $[M+H]^+$.



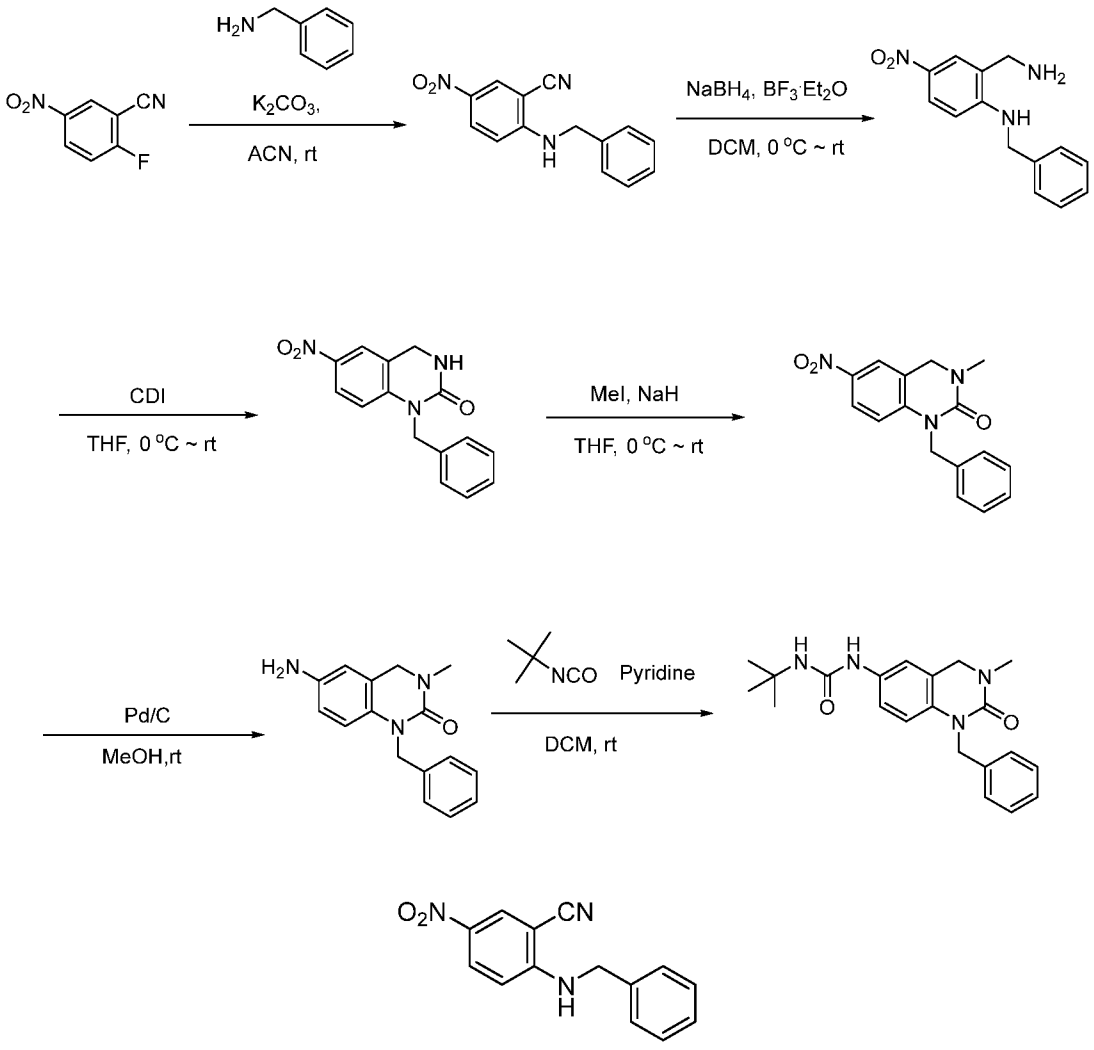
1-(1-benzyl-3-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

To a solution of 6-amino-1-benzyl-3-(methoxymethyl)-3,4-dihydroquinolin-2-one (100 mg, 0.337 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (100.3 mg, 1.012 mmol, 3 equiv) and TEA (102.4 mg, 1.012 mmol, 3 equiv).The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length:

254/220 nm; RT1(min): 8.9; Number Of Runs: 0) to afford 1-(1-benzyl-3-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea (12.1 mg, 8.95%) as a white solid. MS (ESI): mass calcd. for $C_{23}H_{29}N_3O_3$, 395.22 m/z, found 396.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.01 (s, 1H), 7.19 (d, J = 5.5 Hz, 3H), 7.04 – 7.17 (m, 3H), 6.90 (d, J = 8.7 Hz, 1H), 6.66 (d, J = 9.1 Hz, 1H), 5.83 (s, 1H), 4.99 (s, 2H), 3.53 – 3.64 (m, 1H), 3.46 (t, J = 8.2 Hz, 1H), 3.20 (d, J = 1.7 Hz, 3H), 2.60 – 2.95 (m, 3H), 1.16 (d, J = 1.7 Hz, 9H).

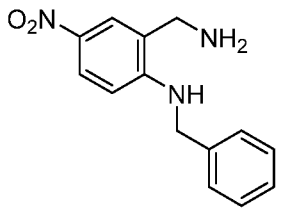
Example 12: 1-(1-benzyl-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-3-(tert-butyl)urea

Synthetic Scheme



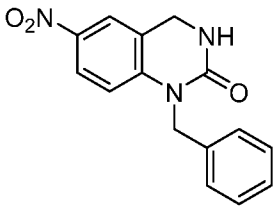
2-(benzylamino)-5-nitrobenzonitrile

To a solution of 2-fluoro-5-nitrobenzonitrile (5 g, 30.100 mmol, 1 equiv) in ACN (100 mL) was added benzylamine (4.84 g, 45.150 mmol, 1.5 equiv) and K_2CO_3 (8.32 g, 60.200 mmol, 2 equiv). The reaction was stirred at rt for 1 hour. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 2-(benzylamino)-5-nitrobenzonitrile (6.875 g, 90.18%) as a yellow solid. MS(ESI): mass calcd. for $C_{14}H_{11}N_3O_2$: 253.26 m/z, found 254.00$[M+H]^+$.



2-(aminomethyl)-N-benzyl-4-nitroaniline

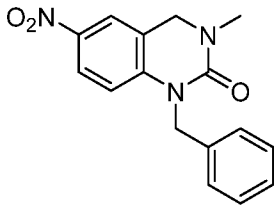
To a solution of 2-(benzylamino)-5-nitrobenzonitrile (400 mg, 1.579 mmol, 1 equiv) in THF (20 mL) was added $NaBH_4$ (238.99 mg, 6.316 mmol, 4 equiv) and Boron trifluoride diethyl etherate (896.66 mg, 6.316 mmol, 4 equiv). The reaction was stirred at 0 °C for 0.5h. The reaction was quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with DCM/MeOH (0-30%) to give 2-(aminomethyl)-N-benzyl-4-nitroaniline (41 mg, 10.09%) as a yellow solid. MS (ESI): mass calcd for $C_{14}H_{15}N_3O_2$: 257.29 m/z, found 258.10 $[M+H]^+$.



1-benzyl-6-nitro-3,4-dihydroquinazolin-2(1H)-one

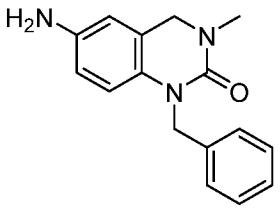
To a solution of 2-(aminomethyl)-N-benzyl-4-nitroaniline (260 mg, 1.011 mmol, 1 equiv) in THF (20 mL) was added CDI (163.86 mg, 1.011 mmol, 1 equiv) at 0 °C. The reaction was stirred at rt for 15 min. To the above mixture was added CDI (327.71 mg, 2.022 mmol, 2 equiv) dropwise at 0 °C. The resulting mixture was stirred for additional 15 min at rt. After the final reaction mixture was stirred for 18 h at 70 °C. Quenched with water (10 mL) and extracted with

EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-benzyl-6-nitro-3,4-dihydroquinazolin-2-one (198 mg, 69.17%) as a white solid. MS (ESI): mass calcd. for $C_{15}H_{13}N_3O_3$: 283.29 m/z, found 284.05 $[M+H]^+$.



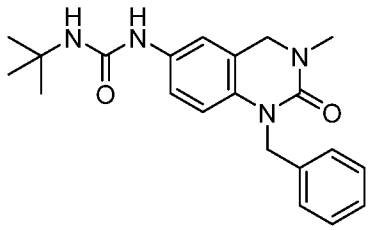
1-benzyl-3-methyl-6-nitro-3,4-dihydroquinazolin-2(1H)-one

To a solution of 1-benzyl-6-nitro-3,4-dihydroquinazolin-2-one (184 mg, 0.650 mmol, 1 equiv) in THF (20 mL) was added NaH (23.38 mg, 0.975 mmol, 1.5 equiv) at 0°C. The reaction was stirred at 0°C for 30 min. To the above mixture was added MeI (184.38 mg, 1.300 mmol, 2 equiv) dropwise at 0 °C. The final reaction mixture was stirred for 1h at rt. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-benzyl-3-methyl-6-nitro-4H-quinazolin-2-one (122 mg, 63.18%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{15}N_3O_3$: 297.31 m/z, found 298.00 $[M+H]^+$.



6-amino-1-benzyl-3-methyl-3,4-dihydroquinazolin-2(1H)-one

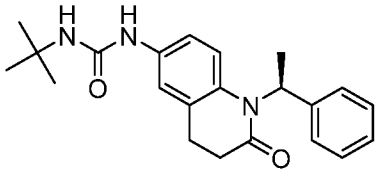
To a solution of 1-benzyl-3-methyl-6-nitro-4H-quinazolin-2-one (122 mg, 0.410 mmol, 1 equiv) in MeOH (10 mL) was added Pd/C (10%, 122 mg) at rt. The mixture was hydrogenated at room temperature under 30 psi of hydrogen pressure for 1h. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 10 mL). The filtrate was concentrated under reduced pressure. This resulted in 6-amino-1-benzyl-3-methyl-4H-quinazolin-2-one (110 mg, 100.28%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{17}N_3O$: 267.33 m/z, found 268.20 $[M+H]^+$.



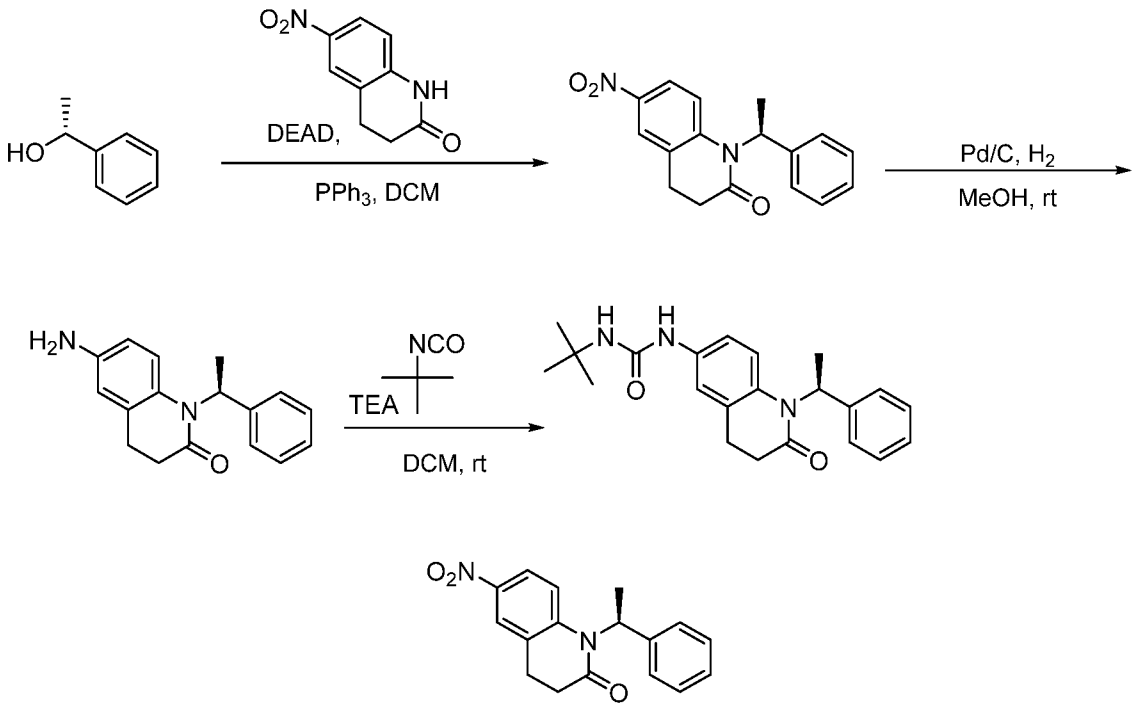
1-(1-benzyl-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-3-(tert-butyl)urea

To a solution of 6-amino-1-benzyl-3-methyl-4H-quinazolin-2-one (100 mg, 0.374 mmol, 1 equiv) in DCM (10 mL, 157.306 mmol, 420.53 equiv) was added 2-isocyanato-2-methylpropane (370.82 mg, 3.740 mmol, 10 equiv) and Pyridine (295.89 mg, 3.740 mmol, 10 equiv). The reaction was stirred at rt for 3 days. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC using a YMC-Actus Triart C18, 30*150 mm, 5μm column (eluent: 36% to 56% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 1-(1-benzyl-3-methyl-2-oxo-4H-quinazolin-6-yl)-3-tert-butylurea (23.2 mg, 16.92%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{26}N_4O_2$:366.47 m/z, found:367.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 7.90 – 8.21 (m, 1H), 7.18 – 7.39 (m, 6H), 6.80 – 7.00 (m, 1H), 6.44 – 6.68 (m, 1H), 5.72 – 5.99 (m, 1H), 4.90 – 5.20 (m, 2H), 4.28 – 4.51 (m, 2H), 2.80 – 3.01 (m, 3H), 1.20 – 1.31 (m, 9H).

Example 13: (S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea

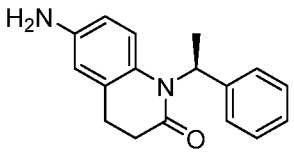


Synthetic Scheme



(S)-6-nitro-1-(1-phenylethyl)-3,4-dihydroquinolin-2(1H)-one

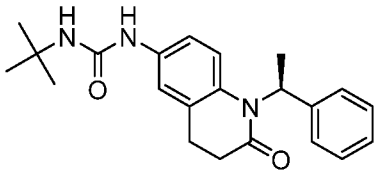
To a solution of (R)-1-phenylethanol (1 g, 8.186 mmol, 1 equiv) in DCM (30 mL) was added 6-nitro-3,4-dihydro-1H-quinolin-2-one (1.57 g, 8.186 mmol, 1 equiv) and PPh_3 (2.15 g, 8.186 mmol, 1 equiv). DEAD (1.43 g, 8.211 mmol, 1 equiv) was added the mixture at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 16 h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford (S)-6-nitro-1-(1-phenylethyl)-3,4-dihydroquinolin-2(1H)-one (300 mg, 11.61%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{16}N_2O_3$, 296.12 m/z, found 297.15 $[M+H]^+$.



(S)-6-amino-1-(1-phenylethyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of (S)-6-nitro-1-(1-phenylethyl)-3,4-dihydroquinolin-2(1H)-one (280 mg, 0.945 mmol, 1 equiv) in MeOH (10 mL) was added Pd/C (30 mg). The reaction mixture was then stirred for 1 h under hydrogen atmosphere (balloon). The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to afford (S)-6-amino-1-(1-

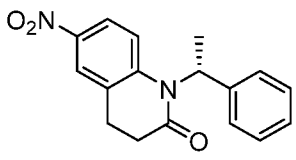
phenylethyl)-3,4-dihydroquinolin-2(1H)-one (220 mg, 86.81%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{18}N_2O$, 266.14 m/z, found 267.15 $[M+H]^+$.



(S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a stirred solution of (S)-6-amino-1-(1-phenylethyl)-3,4-dihydroquinolin-2(1H)-one (200 mg, 0.751 mmol, 1 equiv) in DCM (10.00 mL) was added 2-isocyanato-2-methylpropane (372.2 mg, 3.755 mmol, 5 equiv) and TEA (227.9 mg, 2.253 mmol, 3 equiv) stirred overnight at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8; Number Of Runs: 0) to afford (S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea (73.9 mg, 26.88%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_2$, 365.21 m/z, found 366.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.18 – 7.39 (m, 6H), 6.81 (d, J = 8.8 Hz, 1H), 6.42 – 6.52 (m, 1H), 6.15 (d, J = 8.0 Hz, 1H), 5.91 (s, 1H), 2.80 (d, J = 5.6 Hz, 2H), 2.54 – 2.70 (m, 2H), 1.67 (t, J = 5.7 Hz, 3H), 1.24 (dd, J = 4.1, 2.2 Hz, 9H).

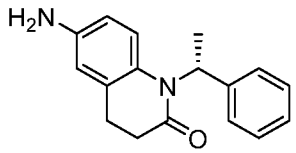
Example 14: (R)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea



(R)-6-nitro-1-(1-phenylethyl)-3,4-dihydroquinolin-2(1H)-one

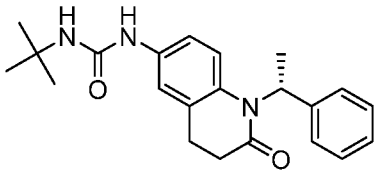
To a solution of (S)-1-phenylethanol (1 g, 8.186 mmol, 1 equiv) in DCM (30 mL) was added 6-nitro-3,4-dihydro-1H-quinolin-2-one (1.57 g, 8.186 mmol, 1 equiv) and PPh_3 (2.15 g,

8.186 mmol, 1 equiv). DEAD (1.43 g, 8.211 mmol, 1 equiv) was added the mixture at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 16 h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford (R)-6-nitro-1-(1-phenylethyl)-3,4-dihydroquinolin-2(1H)-one (300 mg, 11.61%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{16}N_2O_3$, 296.12 m/z, found 297.15 $[M+H]^+$.



(R)-6-amino-1-(1-phenylethyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of (R)-6-nitro-1-(1-phenylethyl)-3,4-dihydroquinolin-2(1H)-one (280 mg, 0.945 mmol, 1 equiv) in MeOH (10 mL) was added Pd/C (30 mg). The reaction mixture was then stirred for 1 h under hydrogen atmosphere (balloon). The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to afford (R)-6-amino-1-(1-phenylethyl)-3,4-dihydroquinolin-2(1H)-one (220 mg, 86.81%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{18}N_2O$, 266.14 m/z, found 267.15 $[M+H]^+$.

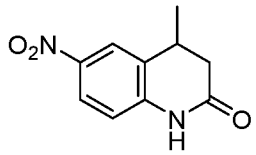


(R)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a stirred solution of (R)-6-amino-1-(1-phenylethyl)-3,4-dihydroquinolin-2(1H)-one (200 mg, 0.751 mmol, 1 equiv) in DCM (10.00 mL) was added 2-isocyanato-2-methylpropane (372.2 mg, 3.755 mmol, 5 equiv) and TEA (227.9 mg, 2.253 mmol, 3 equiv) stirred overnight at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm;

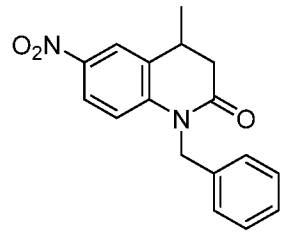
RT1(min): 8.9; Number Of Runs: 0) to afford 3-tert-butyl-1-{2-oxo-1-[(1R)-1-phenylethyl]-3,4-dihydroquinolin-6-yl}urea (70 mg, 25.46%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_2$, 365.21 m/z, found 366.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.18 – 7.39 (m, 6H), 6.81 (d, J = 8.8 Hz, 1H), 6.42 – 6.52 (m, 1H), 6.15 (d, J = 8.0 Hz, 1H), 5.91 (s, 1H), 2.80 (d, J = 5.6 Hz, 2H), 2.54 – 2.70 (m, 2H), 1.67 (t, J = 5.7 Hz, 3H), 1.24 (dd, J = 4.1, 2.2 Hz, 9H).

Example 15: 1-(1-benzyl-4-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea



4-methyl-6-nitro-3,4-dihydroquinolin-2(1H)-one

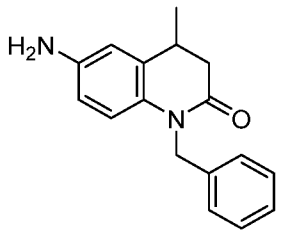
To a solution of 4-methyl-3,4-dihydroquinolin-2(1H)-one (0.4 g, 2.48 mmol, 1 equiv) in H_2O (2 mL) and H_2SO_4 (9 mL) was added HNO_3 (0.3 mL) at -10 °C. The reaction was stirred for 2 h at -10-0 °C. The reaction mixture was quenched by water. The mixture was acidified pH = 7 with $NaHCO_3$ (*aq.*) and then extracted with EA (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE /EA (3:1) to afford 4-methyl-6-nitro-3,4-dihydroquinolin-2(1H)-one (0.28 g, 54.79%) as a white solid. MS (ESI): mass calcd. for $C_{10}H_{10}N_2O_3$, 206.07 m/z, found 207.05 $[M+H]^+$.



1-benzyl-4-methyl-6-nitro-3,4-dihydroquinolin-2(1H)-one

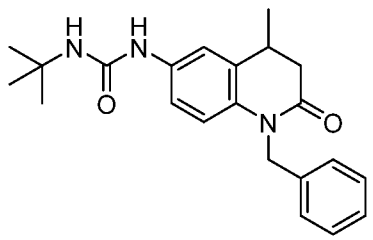
To a solution of 4-methyl-6-nitro-3,4-dihydroquinolin-2(1H)-one (260 mg, 1.260 mmol, 1 equiv) in DMF (10 mL) was added K_2CO_3 (522.0 mg, 3.782 mmol, 3 equiv) and (bromomethyl)benzene (237.1 mg, 1.386 mmol, 1.1 equiv). The resulting mixture was stirred for 16 h at rt. The mixture was diuted with EtOAc (50 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by

silica gel column, eluted with PE / EA (3:1) to afford 1-benzyl-4-methyl-6-nitro-3,4-dihydroquinolin-2(1H)-one (200 mg, 53.62%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{16}N_2O_3$: 296.12 m/z, found 297.05 $[M+H]^+$.



6-amino-1-benzyl-4-methyl-3,4-dihydroquinolin-2(1H)-one

To a solution of 1-benzyl-4-methyl-6-nitro-3,4-dihydroquinolin-2(1H)-one (180 mg, 0.607 mmol, 1 equiv) in EtOH (10 mL) and H_2O (2.5 mL) was added Fe (339.3 mg, 6.07 mmol, 10 equiv) and NH_4Cl (324.7 mg, 6.07 mmol, 10 equiv). The resulting mixture was stirred for 2 h at 60 °C and stirred until the starting material was totally consumed by TLC. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 6-amino-1-benzyl-4-methyl-3,4-dihydroquinolin-2(1H)-one (120 mg, 74.07%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{18}N_2O$: 266.14 m/z, found 267.15 $[M+H]^+$.



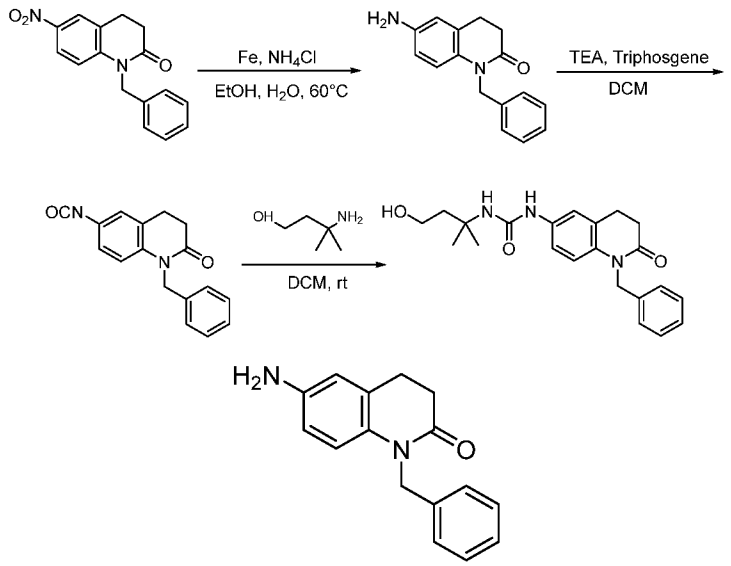
1-(1-benzyl-4-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

To a solution of 6-amino-1-benzyl-4-methyl-3,4-dihydroquinolin-2(1H)-one (120 mg, 0.451 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (133.9 mg, 1.351 mmol, 3 equiv) and TEA (136.4 mg, 1.351 mmol, 3 equiv). The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18

Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9; Number Of Runs: 0) to afford 1-(1-benzyl-4-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea (47.9 mg, 44.35%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_2$: 365.21 m/z, found 366.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.21 – 7.32 (m, 6H), 6.99 (dd, J = 8.8, 2.4 Hz, 1H), 6.82 (d, J = 8.8 Hz, 1H), 5.90 (s, 1H), 5.05 – 5.17 (m, 2H), 2.90 – 3.13 (m, 1H), 2.68 – 2.86 (m, 1H), 2.33 – 2.50 (m, 1H), 1.26 (s, 9H), 1.18 (d, J = 6.9 Hz, 3H).

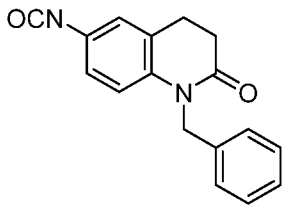
Example 16: 1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-hydroxy-2-methylbutan-2-yl)urea

Synthetic Scheme



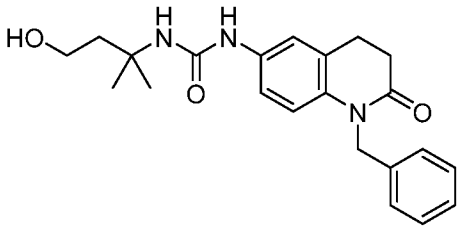
6-amino-1-benzyl-3,4-dihydroquinolin-2(1H)-one

A solution of 1-benzyl-6-nitro-3,4-dihydroquinolin-2-one (400 mg, 1.417 mmol, 1 equiv) in EtOH (10 mL) and H_2O (2 mL) was treated with Fe (791.29 mg, 14.170 mmol, 10 equiv) and NH_4Cl (757.92 mg, 14.170 mmol, 10 equiv) for 2 h at 60 °C.The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (5%-11%) to afford 6-amino-1-benzyl-3,4-dihydroquinolin-2-one (320 mg, 89.51%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{16}N_2O$, 252.13m/z, found 253.25 $[M+H]^+$.



1-benzyl-6-isocyanato-3,4-dihydroquinolin-2(1H)-one

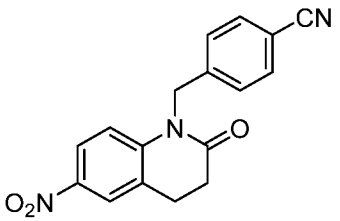
To a stirred solution of 6-amino-1-benzyl-3,4-dihydroquinolin-2-one (180 mg, 0.713 mmol, 1 equiv) in anhydrous DCM (5 mL) was added TEA (216.57 mg, 2.139 mmol, 3 equiv) and Triphosgene (105.84 mg, 0.356 mmol, 0.5 equiv) at 0 °C, and stirred for 2 h at rt. After completion of reaction to afford 1-benzyl-6-isocyanato-3,4-dihydroquinolin-2-one as a crude. MS (ESI): mass calcd. for $C_{17}H_{14}N_2O_2$, 278.11m/z, found 279.05 [M+H]+



1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-hydroxy-2-methylbutan-2-yl)urea

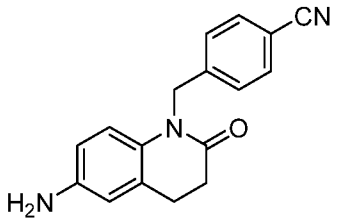
To a stirred solution of 1-benzyl-6-isocyanato-3,4-dihydroquinolin-2-one (crude) in anhydrous DCM (5 mL) was added 3-amino-3-methylbutan-1-ol (220.3 mg, 2.139 mmol, 3 equiv) was added at 0 °C. The resulting mixture was stirred for 1 h at rt. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product was purified by HPLC with the following conditions Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 21% B to 41% B in 10 min, 41% B; Wave Length: 254/220 nm; RT1(min): 10; Number Of Runs: 0; to afford 1-(1-benzyl-2-oxo-3,4-dihydroquinolin-6-yl)-3-(4-hydroxy-2-methylbutan-2-yl)urea (23.3 mg, 16.47%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_3$: 381.21 m/z, found 382.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.39 – 7.12 (m, 6H), 6.96 (dd, J = 8.8, 2.5 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 5.93 (s, 1H), 5.10 (s, 2H), 4.39 (t, J = 4.9 Hz, 1H), 3.48 (td, J = 7.1, 4.7 Hz, 2H), 2.88 (dd, J = 8.8, 5.8 Hz, 2H), 2.65 (dd, J = 8.8, 5.8 Hz, 2H), 1.79 (t, J = 7.2 Hz, 2H), 1.25 (s, 6H).

Example 17: 1-(tert-butyl)-3-(1-(4-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea



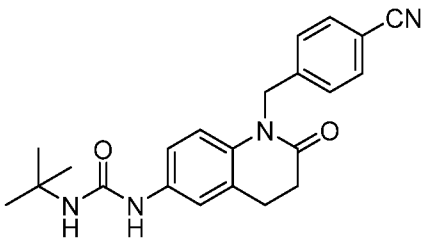
4-((6-nitro-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)benzonitrile

To a solution of 6-nitro-3,4-dihydroquinolin-2(1H)-one (500 mg, 2.602 mmol, 1 equiv) in DMF (10 mL) was added K_2CO_3 (1086.6 mg, 7.805 mmol, 3 equiv) and 4-(bromomethyl)benzonitrile (558.09 mg, 2.862 mmol, 1.1 equiv). The resulting mixture was stirred for 16 h at rt. The mixture was diuted with EtOAc (50 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 4-((6-nitro-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)benzonitrile (400 mg, 50.00%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{13}N_3O_3$: 307.10 m/z, found 308.15 $[M+H]^+$.



4-((6-amino-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)benzonitrile

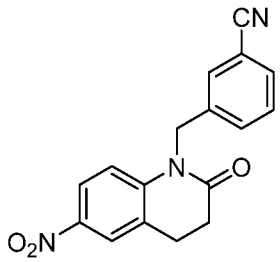
To a solution of 4-((6-nitro-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)benzonitrile (300 mg, 0.976 mmol, 1 equiv) in EtOH (10 mL) and H_2O (2.5 mL) was added Fe (545.1 mg, 9.76 mmol, 10 equiv) and NH_4Cl (522.1 mg, 9.76 mmol, 10 equiv).The resulting mixture was stirred for 2 h at 60 °C and stirred until the starting material was totally consumed by TLC. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 4-((6-amino-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)benzonitrile (108 mg, 40.05%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{15}N_3O$: 277.12 m/z, found 278.25 $[M+H]^+$.



1-(tert-butyl)-3-(1-(4-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a solution of 4-((6-amino-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)benzonitrile (80 mg, 0.288 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (85.8 mg, 0.865 mmol, 3 equiv) and TEA (87.4 mg, 0.865 mmol, 3 equiv). The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 45% B in 10.5 min; Wave Length: 220 nm; RT1(min): 12; Number Of Runs: 1) to afford 1-(tert-butyl)-3-(1-(4-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea (38.9 mg, 36.02%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{24}N_4O$: 376.19 m/z, found 377.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.75 – 7.81 (m, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 2.4 Hz, 1H), 6.97 (dd, J = 8.8, 2.5 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.92 (s, 1H), 5.18 (s, 2H), 2.86 – 2.94 (m, 2H), 2.63 – 2.71 (m, 2H), 1.26 (s, 9H).

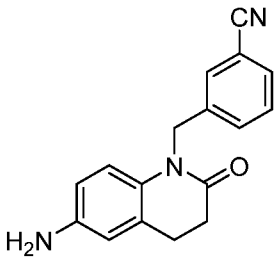
Example 18: 1-(tert-butyl)-3-(1-(3-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea



3-((6-nitro-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)benzonitrile

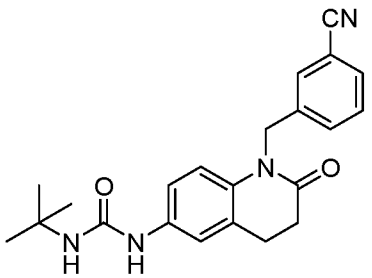
To a solution of 6-nitro-3,4-dihydroquinolin-2(1H)-one (500 mg, 2.602 mmol, 1 equiv) in DMF (10 mL) was added K_2CO_3 (1086.6 mg, 7.805 mmol, 3 equiv) and 3-

(bromomethyl)benzonitrile (558.09 mg, 2.862 mmol, 1.1 equiv). The resulting mixture was stirred for 16 h at rt. The mixture was diuted with EtOAc (50 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 3-((6-nitro-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)benzonitrile (350 mg, 43.75%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{13}N_3O_3$: 307.10 m/z, found 308.05 $[M+H]^+$.



3-((6-amino-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)benzonitrile

To a solution of 3-((6-nitro-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)benzonitrile (300 mg, 0.976 mmol, 1 equiv) in EtOH (10 mL) and H_2O (2.5 mL) was added Fe (545.1 mg, 9.76 mmol, 10 equiv) and NH_4Cl (522.1 mg, 9.76 mmol, 10 equiv).The resulting mixture was stirred for 2 h at 60 °C and stirred until the starting material was totally consumed by TLC. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 3-((6-amino-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)benzonitrile (120 mg, 44.44%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{15}N_3O$: 277.12 m/z, found 278.20 $[M+H]^+$.

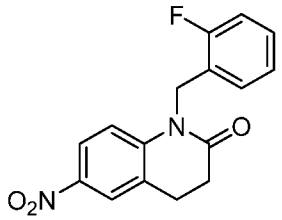


1-(tert-butyl)-3-(1-(3-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a solution of 3-((6-amino-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)benzonitrile (80 mg, 0.288 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (85.8

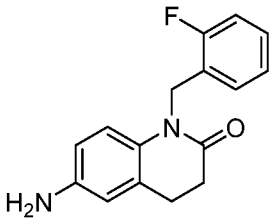
mg, 0.865 mmol, 3 equiv) and TEA (87.4 mg, 0.865 mmol, 3 equiv). The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 45% B in 10.5 min; Wave Length: 220 nm; RT1(min): 12; Number Of Runs: 1) to afford 1-(tert-butyl)-3-(1-(3-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea (47.9 mg, 44.35%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{24}N_4O$: 376.19 m/z, found 377.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.67 – 7.75 (m, 2H), 7.48 – 7.58 (m, 2H), 7.33 (d, J = 2.4 Hz, 1H), 6.98 (dd, J = 8.8, 2.5 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 5.92 (s, 1H), 5.14 (s, 2H), 2.86 – 2.94 (m, 2H), 2.64 – 2.72 (m, 2H), 1.26 (s, 9H).

Example 1: 3-tert-butyl-1-{1-[(2-fluorophenyl)methyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea



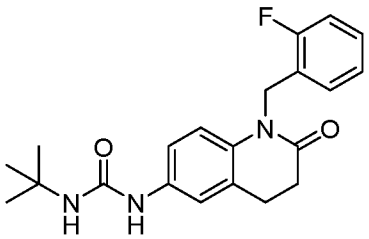
1-[(2-fluorophenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one

To a solution of 6-nitro-3,4-dihydro-1H-quinolin-2-one (2 g, 10.407 mmol, 1 equiv) and 1-(bromomethyl)-2-fluorobenzene (3147.60 mg, 16.651 mmol, 1.6 equiv) in dimethylformamide (20 mL) was added K_2CO_3 (4346.47 mg, 31.221 mmol, 3 equiv). The reaction was stirred at rt for 3h. Quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-[(2-fluorophenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one (2.06 g, 65.92%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{13}FN_2O_3$: 300.09 m/z, found 301.05$[M+H]^+$.



6-amino-1-[(2-fluorophenyl)methyl]-3,4-dihydroquinolin-2-one

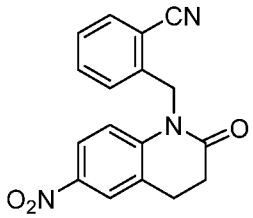
To a solution of 1-[(2-fluorophenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one (1 g, 3.330 mmol, 1 equiv) in EA (35 mL) was added Pd/C (1 g). The resulting mixture was stirred for 1 h at room temperature under hydrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was filtered, the filter cake was washed with EA (3 x 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-1-[(2-fluorophenyl)methyl]-3,4-dihydroquinolin-2-one (990 mg, 109.98%) as a white solid. MS (ESI): mass calcd for $C_{16}H_{15}FN_2O$: 270.12 m/z, found 271.10$[M+H]^+$.



3-tert-butyl-1-{1-[(2-fluorophenyl)methyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea

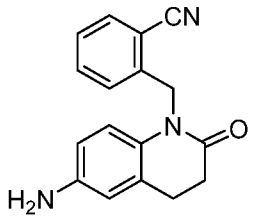
To a solution of 6-amino-1-[(2-fluorophenyl)methyl]-3,4-dihydroquinolin-2-one (980 mg, 3.626 mmol, 1 equiv) in DCM/toluene (10 mL, 2/1) was added 2-isocyanato-2-methylpropane (1077.9 mg, 10.873 mmol, 3.00 equiv) The reaction was stirred at 90 °C for 1h. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC using aXBridge Prep OBD C18 Column 150 mm x 30 mm x 5 μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH4HCO3) to afford the title compound 3-tert-butyl-1-{1-[(2-fluorophenyl)methyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea (412.3 mg, 30.33%) as a white solid. LC/MS (ESI): mass calcd. for $C_{21}H_{24}FN_3O_2$:369.19 m/z, found:370.05 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.35 (m, 1H), 7.23 - 7.32 (m, 2H), 7.00 -7.09(m, 3H), 6.73 (m, 1H), 5.93 (s, 1H), 5.12 (s, 2H), 2.89 (m, 2H), 2.66 (m, 2H), 1.27 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ-118.31.

Example 20: 1-(tert-butyl)-3-(1-(2-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea



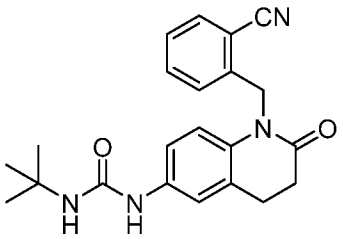
2-((6-nitro-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)benzonitrile

To a stirred solution of 6-nitro-3,4-dihydro-1H-quinolin-2-one (400 mg, 2.081 mmol, 1 equiv) in DMF (10 mL) was added 2-(bromomethyl)benzonitrile (612.09 mg, 3.122 mmol, 1.5 equiv) and potassium methaneperoxoate potassium (869.29 mg, 6.243 mmol, 3 equiv) at rt and stirred for overnight. The reaction progress was monitored by LCMS. The resulting mixture was extracted with brine (1 x 30 mL). The combined organic layers were washed with EA (3 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (3:1) to afford 2-[(6-nitro-2-oxo-3,4-dihydroquinolin-1-yl)methyl]benzonitrile (447 mg, 70.0%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{13}N_3O_3$: 307.10 m/z, found 308.10 $[M+H]^+$.



2-((6-amino-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)benzonitrile

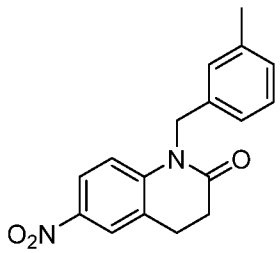
To a stirred solution of 2-[(6-nitro-2-oxo-3,4-dihydroquinolin-1-yl)methyl]benzonitrile (400 mg, 1.302 mmol, 1 equiv) in ethyl alcohol (10 mL) and water (2 mL) was added iron (726.89 mg, 13.020 mmol, 10 equiv) and NH_4Cl (696.24 mg, 13.020 mmol, 10 equiv) and stirred for 1 h at 60 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with PE/EA (2:1) to afford 2-((6-amino-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)benzonitrile (280 mg, 77.57%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{15}N_3O$: 277.12 m/z, found 278.05 $[M+H]^+$.



1-(tert-butyl)-3-(1-(2-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

A solution of 2-((6-amino-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)benzonitrile (150 mg, 0.541 mmol, 1 equiv) in DCM (5 mL) was add TEA (164.20 mg, 1.623 mmol, 3 equiv) and 2-isocyanato-2-methylpropane (214.48 mg, 2.164 mmol, 4 equiv) at 0 °C. The resulting mixture was stirred for 1 h at rt. The resulting mixture was concentrated under reduced pressure. The crude product was purified by HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9; Number Of Runs: 0; to afford 3-tert-butyl-1-{1-[(2-cyanophenyl)methyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea (69.2 mg, 33.91%) as a white solid. MS (ESI):mass calcd. for $C_{22}H_{24}N_4O_2$: 376.19 m/z, found 377.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.86 (dd, J = 7.7, 1.3 Hz, 1H), 7.61 (td, J = 7.7, 1.4 Hz, 1H), 7.44 (td, J = 7.6, 1.2 Hz, 1H), 7.37 (d, J = 2.4 Hz, 1H), 7.25 – 7.18 (m, 1H), 7.00 (dd, J = 8.7, 2.5 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 5.94 (s, 1H), 5.25 (s, 2H), 2.93 (dd, J = 8.7, 5.8 Hz, 2H), 2.67 (dd, J = 8.7, 5.8 Hz, 2H), 1.27 (s, 9H).

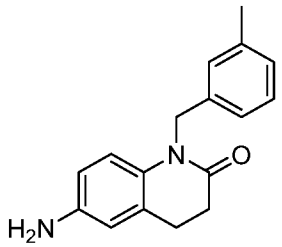
Example 21: 1-(tert-butyl)-3-(1-(3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea



6-amino-1-[(3-methylphenyl)methyl]-3,4-dihydroquinolin-2-one

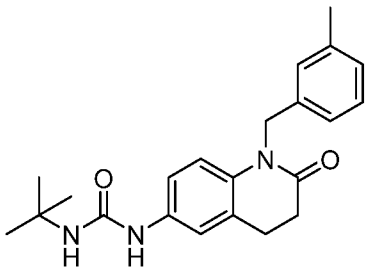
To a solution of 6-nitro-3,4-dihydro-1H-quinolin-2-one (500 mg, 2.602 mmol, 1 equiv) in DMF (8 mL) was added K_2CO_3 (1086.6 mg, 7.862 mmol, 3 equiv) and 1-(bromomethyl)-3-

methylbenzene (529.6 mg, 2.862 mmol, 1.1 equiv). The resulting mixture was stirred for 16 h at rt. The mixture was diuted with EtOAc (100 mL), washed with water (3 x 50 mL), brine (2 x 50 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 1-[(3-methylphenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one (500 mg, 64.44%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{16}N_2O_3$ 296.12 m/z, found 297.00 $[M+H]^+$.



6-amino-1-(1-phenylpropyl)-3,4-dihydroquinolin-2-one

To a solution of 1-[(3-methylphenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one (500 mg, 1.687 mmol, 1 equiv) in EtOH (10 mL) and H2O (2.5 mL) was added Fe (942.2 mg, 16.873 mmol, 10 equiv) and NH_4Cl (902.5 mg, 16.873 mmol, 10 equiv). The resulting mixture was stirred for 2 h at 60 °C. The mixture was diuted with EtOAc (100 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 6-amino-1-[(3-methylphenyl)methyl]-3,4-dihydroquinolin-2-one (400 mg, 88.46%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{18}N_2O$ 266.14 m/z, found 267.10 $[M+H]^+$.

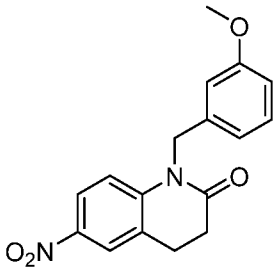


1-(tert-butyl)-3-(1-(3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a solution of 6-amino-1-[(3-methylphenyl)methyl]-3,4-dihydroquinolin-2-one (400 mg, 1.502 mmol, 1 equiv) in DCM (10 mL) was added 2-isocyanato-2-methylpropane (446.6 mg, 4.506 mmol, 3 equiv) and TEA (455.9 mg, 4.505 mmol, 3 equiv). The resulting mixture was

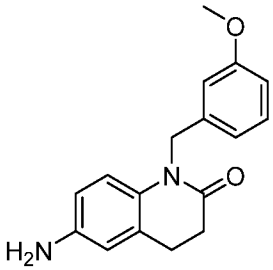
stirred for overnight at rt. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 38% B to 60% B in 10 min, 60% B; Wave Length: 254/220 nm; RT1(min): 10; Number Of Runs: 0) to afford 1-(tert-butyl)-3-(1-(3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea (282.3 mg, 51.15%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_2$, 365.21 m/z, found 366.05 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.11 (s, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 6.92 – 7.09 (m, 4H), 6.76 (d, J = 8.8 Hz, 1H), 5.92 (s, 1H), 5.05 (s, 2H), 2.87 (dd, J = 8.8, 5.8 Hz, 2H), 2.64 (dd, J = 8.7, 5.8 Hz, 2H), 2.25 (s, 3H), 1.27 (s, 9H).

Example 22: 1-(tert-butyl)-3-(1-(3-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea



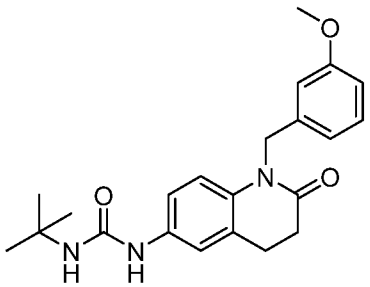
1-[(3-methoxyphenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one

To a solution of 6-nitro-3,4-dihydro-1H-quinolin-2-one (500 mg, 2.602 mmol, 1 equiv) in DMF (8 mL) was added K_2CO_3 (1078.7 mg, 7.862 mmol, 3 equiv) and 1-(bromomethyl)-3-methoxybenzene (575.4 mg, 2.862 mmol, 1.1 equiv). The resulting mixture was stirred for 16 h at rt. The mixture was diuted with EtOAc (100 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 1-[(3-methoxyphenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one (500 mg, 60.71%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{16}N_2O_4$ 312.11 m/z, found 313.05 $[M+H]^+$.



6-amino-1-(1-phenylpropyl)-3,4-dihydroquinolin-2-one

To a solution of 1-[(3-methoxyphenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one (500 mg, 1.601 mmol, 1 equiv) in EtOH (10 mL) and H_2O (2.5 mL) was added Fe (894.0 mg, 16.009 mmol, 10 equiv) and NH_4Cl (856.3 mg, 16.009 mmol, 10 equiv). The resulting mixture was stirred for 2 h at 60 °C. The mixture was diuted with EtOAc (100 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 6-amino-1-[(3-methoxyphenyl)methyl]-3,4-dihydroquinolin-2-one (400 mg, 88.33%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{18}N_2O_2$ 282.14 m/z, found 283.10 $[M+H]^+$.

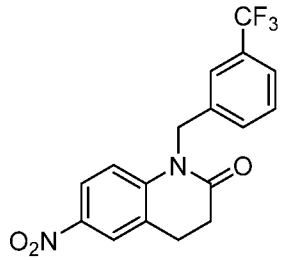


1-(tert-butyl)-3-(1-(3-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a solution of 6-amino-1-[(3-methoxyphenyl)methyl]-3,4-dihydroquinolin-2-one (400 mg, 1.417 mmol, 1 equiv) in DCM (10 mL) was added 2-isocyanato-2-methylpropane (421.3 mg, 4.250 mmol, 3 equiv) and TEA (430.0 mg, 4.250 mmol, 3 equiv). The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 50% B in 9 min, 50% B; Wave Length:

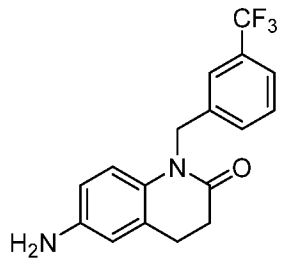
254/220 nm; RT1(min): 8.6; Number Of Runs: 0) to afford 1-(tert-butyl)-3-(1-(3-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea (85.3 mg, 15.75%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_3$, 381.21 m/z, found 382.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.11 (s, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.16 – 7.25 (m, 1H), 6.97 (dd, J = 8.7, 2.5 Hz, 1H), 6.71 – 6.82 (m, 4H), 5.92 (s, 1H), 5.06 (s, 2H), 3.70 (s, 3H), 2.87 (dd, J = 8.8, 5.8 Hz, 2H), 2.64 (dd, J = 8.7, 5.8 Hz, 2H), 1.26 (s, 9H).

Example 23: 1-(tert-butyl)-3-(2-oxo-1-(3-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea



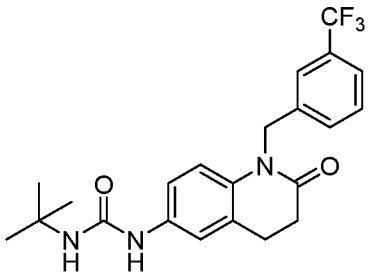
6-nitro-1-(3-(trifluoromethyl)benzyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of 6-nitro-3,4-dihydro-1H-quinolin-2-one (500 mg, 2.602 mmol, 1 equiv) in DMF (8 mL) was added K_2CO_3 (1086.6 mg, 7.862 mmol, 3 equiv) and 1-(bromomethyl)-3-(trifluoromethyl)benzene (684.1 mg, 2.862 mmol, 1.1 equiv). The resulting mixture was placed at rt and stirred overnight until the starting material was totally consumed by LCMS, The mixture was diuted with EtOAc (100 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (PE/EA=3:1r) to afford 6-nitro-1-{[3-(trifluoromethyl)phenyl]methyl}-3,4-dihydroquinolin-2-one (500 mg, 54.86%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{13}F_3N_2O_3$ 350.09 m/z, found 350.95 $[M+H]^+$.



6-amino-1-(3-(trifluoromethyl)benzyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of 6-nitro-1-{[3-(trifluoromethyl)phenyl]methyl}-3,4-dihydroquinolin-2-one (500 mg, 1.427 mmol, 1 equiv) in EtOH (10 mL) and H_2O (2.5 mL) was added Fe (797.1 mg, 14.274 mmol, 10 equiv) and NH_4Cl (763.4 mg, 14.274 mmol, 10 equiv). The resulting mixture was stirred 30 min at 60 °C until the starting material was totally consumed by LCMS, The mixture was diuted with EtOAc (100 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (PE/EA=2:1) to afford 6-amino-1-{[3-(trifluoromethyl)phenyl]methyl}-3,4-dihydroquinolin-2-one (300 mg, 64.88%) as a yellow solid.MS (ESI): mass calcd. for $C_{17}H_{15}F_3N_2O$ 320.11 m/z, found 321.05 [M+H]+.

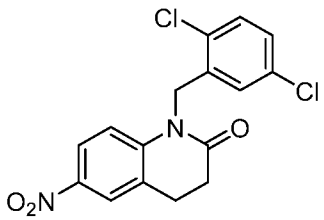


1-(tert-butyl)-3-(2-oxo-1-(3-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a solution of 6-amino-1-{[3-(trifluoromethyl)phenyl]methyl}-3,4-dihydroquinolin-2-one (300 mg, 0.937 mmol, 1 equiv) in DCM (10 mL) was added 2-isocyanato-2-methylpropane (278.5 mg, 2.810 mmol, 3 equiv) and TEA (284.3 mg, 2.810 mmol, 3 equiv).The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water and extracted with EA (3*20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 100 mg crude product as a white solid.The compound was separated by preparative HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 45% B in 10 min, 45% B; Wave Length: 254/220 nm; RT1(min): 8.9; Number Of Runs: 0) to afford 3-tert-butyl-1-(2-oxo-1-{[3-(trifluoromethyl)phenyl]methyl}-3,4-dihydroquinolin-6-yl)urea (125.4 mg, 31.80%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{24}F_3N_3O_2$, 419.18 m/z, found 419.95 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.45 – 7.63 (m, 4H), 7.34 (d, J =

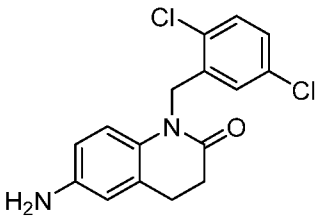
2.4 Hz, 1H), 7.00 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 5.93 (s, 1H), 5.20 (s, 2H), 2.89 (dd, *J* = 8.8, 5.7 Hz, 2H), 2.67 (dd, *J* = 8.6, 5.8 Hz, 2H), 1.27 (s, 9H).

Example 24: 3-tert-butyl-1-{1-[(2,5-dichlorophenyl)methyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea



1-[(2,5-dichlorophenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one

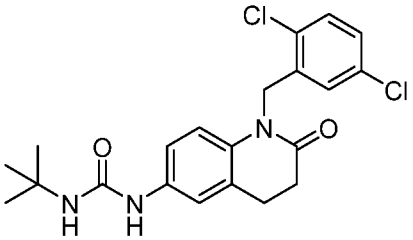
To a stirred solution of 6-nitro-3,4-dihydro-1H-quinolin-2-one (500 mg, 2.602 mmol, 1 equiv) in DMF (10 mL) was added 2-(bromomethyl)-1,4-dichlorobenzene (936.34 mg, 3.903 mmol, 1.5 equiv) and potassium carbonate (724.41 mg, 5.204 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The final reaction mixture was stirred for 3 h at room temperature. The reaction was monitored by LCMS. The resulting mixture was quenched with water (20 mL) and extracted with EA (3 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford 1-[(2,5-dichlorophenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one (500 mg, 54.72%) as a white solid. LC/MS: mass calcd. for $C_{16}H_{12}Cl_2N_2O_3$: 350.02 m/z, found:350.90 $[M+H]^+$



6-amino-1-[(2,5-dichlorophenyl)methyl]-3,4-dihydroquinolin-2-one

To a stirred solution of 1-[(2,5-dichlorophenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one (500 mg, 1.424 mmol, 1 equiv) in EtOH/H_2O (10 mL, 10/1) was added Fe (795.11 mg, 14.240 mmol, 10 equiv) and NH_4Cl (761.58 mg, 14.240 mmol, 10 equiv) at room temperature under nitrogen

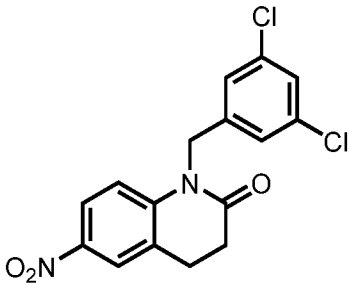
atmosphere. The final reaction mixture was stirred for 2 h at 60°C. The reaction was quenched with water at rt. After filtration, the filter cake was washed with EA (3 x 20 mL). The filtrate was added water (20 mL) and extracted with EA (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford 6-amino-1-[(2,5-dichlorophenyl)methyl]-3,4-dihydroquinolin-2-one (280 mg, 61.23%) as a white solid. LC/MS: mass calcd. for $C_{16}H_{14}Cl_2N_2O$: 320.05 m/z, found:320.95 $[M+H]^+$.



3-tert-butyl-1-{1-[(2,5-dichlorophenyl)methyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea

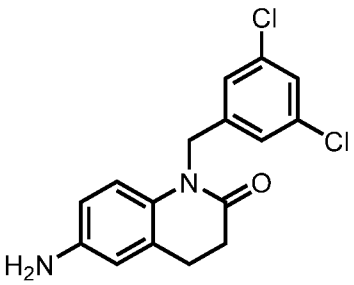
To a stirred solution of 6-amino-1-[(2,5-dichlorophenyl)methyl]-3,4-dihydroquinolin-2-one (140 mg, 0.436 mmol, 1 equiv) and 2-isocyanato-2-methylpropane (129.63 mg, 1.308 mmol, 3 equiv) in DCM (10 mL) was added TEA (132.32 mg, 1.308 mmol, 3 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 day at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by Prep-HPLC to afford 3-tert-butyl-1-{1-[(2,5-dichlorophenyl)methyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea (20.8 mg, 11.34%) as a white solid. LC/MS: mass calcd for $C_{21}H_{23}Cl_2N_3O_2$: 419.12 m/z, found:420.05 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.40 - 7.37 (m, 2H), 7.01 - 6.95 (m, 2H), 6.60 (d, J = 8.4 Hz, 1H), 5.94 (s, 1H), 5.05 (s, 2H), 2.94 - 2.90 (m, 2H), 2.72 - 2.69 (m, 2H), 1.27 (s, 9H).

Example 25: 1-(tert-butyl)-3-(1-(3,5-dichlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl) urea



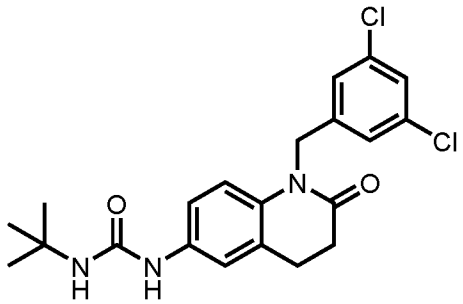
1-(3,5-dichlorobenzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one

To a mixture of 6-nitro-3,4-dihydro-1H-quinolin-2-one (400 mg, 2.081 mmol, 1 equiv) and K_2CO_3 (869.29 mg, 6.243 mmol, 3 equiv) in DMF (20 mL) was added 1-(bromomethyl)-3,5-dichlorobenzene (749.07 mg, 3.122 mmol, 1.5 equiv). The reaction was stirred at rt for 2 hours. Quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-[(3,5-dichlorophenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one (647 mg, 88.51%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{12}Cl_2N_2O_3$: 351.18m/z, found 350.95 $[M+H]^+$.



6-amino-1-(3,5-dichlorobenzyl)-3,4-dihydroquinolin-2(1H)-one

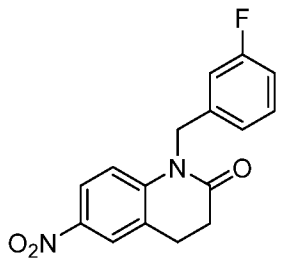
To a solution of 1-[(3,5-dichlorophenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one (500 mg, 1.424 mmol, 1 equiv) in MeOH/H_2O (11 mL, 10/1) was added Fe (397.55 mg, 7.120 mmol, 5 equiv) and NH_4Cl (380.79 mg, 7.120 mmol, 5 equiv). The reaction was stirred at 80 °C for 1 hours. After filtration, the filter cake was washed with EA (3 x 10 mL). The filtrate was added water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The resulting mixture was concentrated under vacuum. This resulted in 6-amino-1-[(3,5-dichlorophenyl)methyl]-3,4-dihydroquinolin-2-one (418 mg, 91.40%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{14}Cl_2N_2O$: 321.20 m/z, found 320.95 $[M+H]^+$.



1-(tert-butyl)-3-(1-(3,5-dichlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a solution of 6-amino-1-[(3,5-dichlorophenyl)methyl]-3,4-dihydroquinolin-2-one (100 mg, 0.311 mmol, 1 equiv) in DCM (10 mL) was added 2-isocyanato-2-methylpropane (92.59 mg, 0.933 mmol, 3 equiv) and TEA (94.51 mg, 0.933 mmol, 3 equiv) at 0 °C. The reaction was stirred at rt for 2 days. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC using a XBridge Shield RP18 OBD Column, 30*150 mm, 5μm column (eluent: 45% to 67% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-{1-[(3,5-dichlorophenyl)methyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea (20 mg, 15.28%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{23}Cl_2N_3O_2$:420.33 m/z, found:420.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 8.04 – 8.23 (m, 1H), 7.39 – 7.49 (m, 1H), 7.22 – 7.39 (m, 3H), 6.94 – 7.11 (m, 1H), 6.65 – 6.88 (m, 1H), 5.80 – 6.01 (m, 1H), 5.00 – 5.21 (m, 2H), 2.81 – 2.98 (m, 2H), 2.60 – 2.78 (m, 2H), 1.25 – 1.33 (m, 9H).

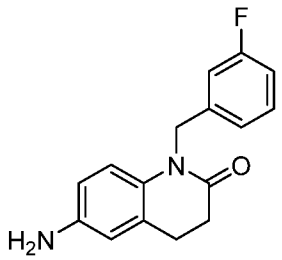
Example 26: 1-(tert-butyl)-3-(1-(3-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea



1-(3-fluorobenzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one

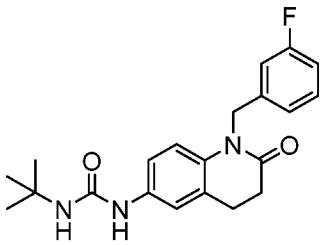
To a solution of 6-nitro-3,4-dihydro-1H-quinolin-2-one (500 mg, 2.602 mmol, 1 equiv) in DMF (20 mL) was added K_2CO_3 (1086.62 mg, 7.806 mmol, 3 equiv) and (bromomethyl)-3-fluorobenzene (737.72 mg, 3.903 mmol, 1.5 equiv) at rt. The final reaction mixture was stirred

for 1h at rt. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-[(3-fluorophenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one (163 mg, 20.86%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{13}FN_2O_3$: 300.29 m/z, found 301.00 $[M+H]^+$.



6-amino-1-(3-fluorobenzyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of 1-[(3-fluorophenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one (155 mg, 0.516 mmol, 1 equiv) in MeOH/H_2O (22 mL, 10/1) was added Fe (144.13 mg, 2.580 mmol, 5 equiv) and NH_4Cl (138.05 mg, 2.580 mmol, 5 equiv). The reaction was stirred at 80 °C for 1 hour. The resulting mixture was filtered, the filter cake was washed with EA (3 x 20 mL). The filtrate was concentrated under reduced pressure. The residue was added water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-1-[(3-fluorophenyl)methyl]-3,4-dihydroquinolin-2-one hydrochloride (100 mg, 63.15%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{15}FN_2O$: 270.31m/z, found 271.15 $[M+H]^+$.

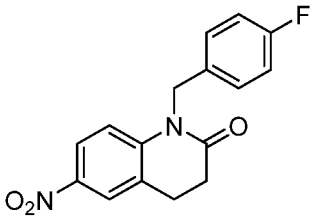


1-(tert-butyl)-3-(1-(3-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a solution of 6-amino-1-[(3-fluorophenyl)methyl]-3,4-dihydroquinolin-2-one (90 mg, 0.333 mmol, 1 equiv) in DCM (10 mL) was added 2-isocyanato-2-methylpropane (99.02 mg, 0.999 mmol, 3 equiv) and Pyridine (79.01 mg, 0.999 mmol, 3 equiv). The reaction was stirred at

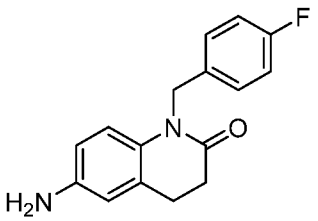
rt for 3 days. Quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-{1-[(3-fluorophenyl)methyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea (20.7 mg, 16.83%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{24}FN_3O_2$:369.44 m/z, found:370.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 7.96 – 8.19 (m, 1H), 7.30 – 7.40 (m, 2H), 6.93 – 7.19 (m, 4H), 6.69 – 6.81 (m, 1H), 5.80 – 6.00 (m, 1H), 4.98 – 5.29 (m, 2H), 2.81 – 2.94 (m, 2H), 2.60 – 2.71 (m, 2H), 1.19 – 1.29 (m, 9H). ^{19}F NMR (376 MHz, DMSO) δ (ppm): -113.2050.

Example 27: 1-(tert-butyl)-3-(1-(4-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea



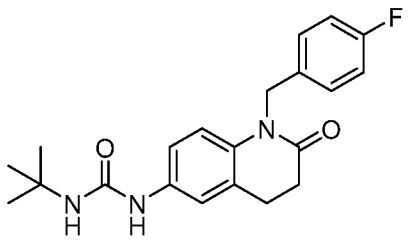
1-(4-fluorobenzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one

To a solution of 6-nitro-3,4-dihydro-1H-quinolin-2-one (500 mg, 2.602 mmol, 1 equiv) and K_2CO_3 (1086.62 mg, 7.806 mmol, 3 equiv) in DMF (10 mL) was added 1-(bromomethyl)-4-fluorobenzene (737.78 mg, 3.903 mmol, 1.5 equiv). The reaction was stirred at rt for 2 hours. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-[(4-fluorophenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one (630 mg, 80.64%) as a yellow solid. MS(ESI): mass calcd. for $C_{16}H_{13}FN_2O_3$: 300.29 m/z, found 301.00 $[M+H]^+$.



6-amino-1-(4-fluorobenzyl)-3,4-dihydroquinolin-2(1H)-one

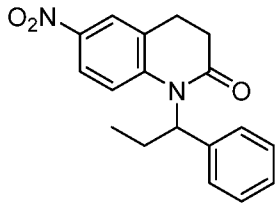
To a solution of 1-[(4-fluorophenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one (400 mg, 1.332 mmol, 1 equiv) in MeOH/H_2O (22 mL, 10/1) was added Fe (371.94 mg, 6.660 mmol, 5 equiv) and NH_4Cl (356.26 mg, 6.660 mmol, 5 equiv). The reaction was stirred for 1 hour at 80 °C. The reaction was quenched with water at rt. After filtration, the filter cake was washed with EA (3 x 20 mL). The filtrate was added water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The resulting mixture was concentrated under vacuum. This resulted in 6-amino-1-[(4-fluorophenyl)methyl]-3,4-dihydroquinolin-2-one (325 mg, 90.26%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{15}FN_2O$: 270.31m/z, found 271.05 $[M+H]^+$.



1-(tert-butyl)-3-(1-(4-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

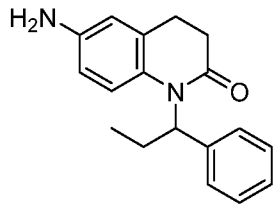
To a solution of 6-amino-1-[(4-fluorophenyl)methyl]-3,4-dihydroquinolin-2-one (150 mg, 0.555 mmol, 1 equiv) in DCM (20 mL) was added 2-isocyanato-2-methylpropane (165.03 mg, 1.665 mmol, 3 equiv) and Pyridine (131.68 mg, 1.665 mmol, 3 equiv). The reaction was stirred at rt for 3 days. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-{1-[(4-fluorophenyl)methyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea (5.3 mg, 2.59%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{24}FN_3O_2$:369.44 m/z, found:370.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.11 – 7.40 (m, 3H), 6.96 – 7.11 (m, 3H), 6.81– 6.91 (m, 1H), 5.10– 5.22 (m, 2H), 2.82 – 3.03 (m, 2H), 2.59 – 2.82 (m, 2H), 1.29 – 1.41 (m, 9H). ^{19}F NMR (376 MHz, DMSO) δ (ppm): -117.9957.

Example 28: 1-(tert-butyl)-3-(2-oxo-1-(1-phenylpropyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea



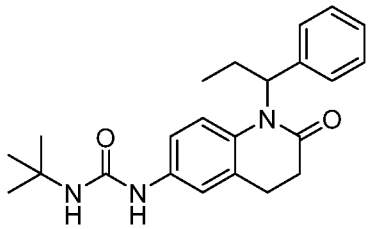
6-nitro-1-(1-phenylpropyl)-3,4-dihydroquinolin-2-one

To a solution of 6-nitro-3,4-dihydro-1H-quinolin-2-one (400 mg, 2.081 mmol, 1 equiv) in DMF (8 mL) was added K_2CO_3 (863.0 mg, 6.244 mmol, 3 equiv) and (1-bromopropyl)benzene (455.8 mg, 2.289 mmol, 1.1 equiv). The resulting mixture was stirred for 16 h at rt. The mixture was diuted with EtOAc (100 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 6-nitro-1-(1-phenylpropyl)-3,4-dihydroquinolin-2-one (150 mg, 22.24%) as a yellow solid. MS (ESI): mass calcd. for $C_{18}H_{18}N_2O_3$ 310.13 m/z, found 311.25 $[M+H]^+$.



6-amino-1-(1-phenylpropyl)-3,4-dihydroquinolin-2-one

To a solution of 6-nitro-1-(1-phenylpropyl)-3,4-dihydroquinolin-2-one (130 mg, 0.419 mmol, 1 equiv) in EtOH (8 mL) and H_2O (2 mL) was added Fe (233.9 mg, 4.189 mmol, 10 equiv) and NH_4Cl (224.0 mg, 4.189 mmol, 10 equiv). The resulting mixture was stirred for 2 h at 60 °C. The mixture was diuted with EtOAc (100 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 6-amino-1-(1-phenylpropyl)-3,4-dihydroquinolin-2-one (100 mg, 85.15%) as a yellow solid.MS (ESI): mass calcd. for $C_{18}H_{20}N_2O$ 280.16 m/z, found 281.10 $[M+H]^+$.

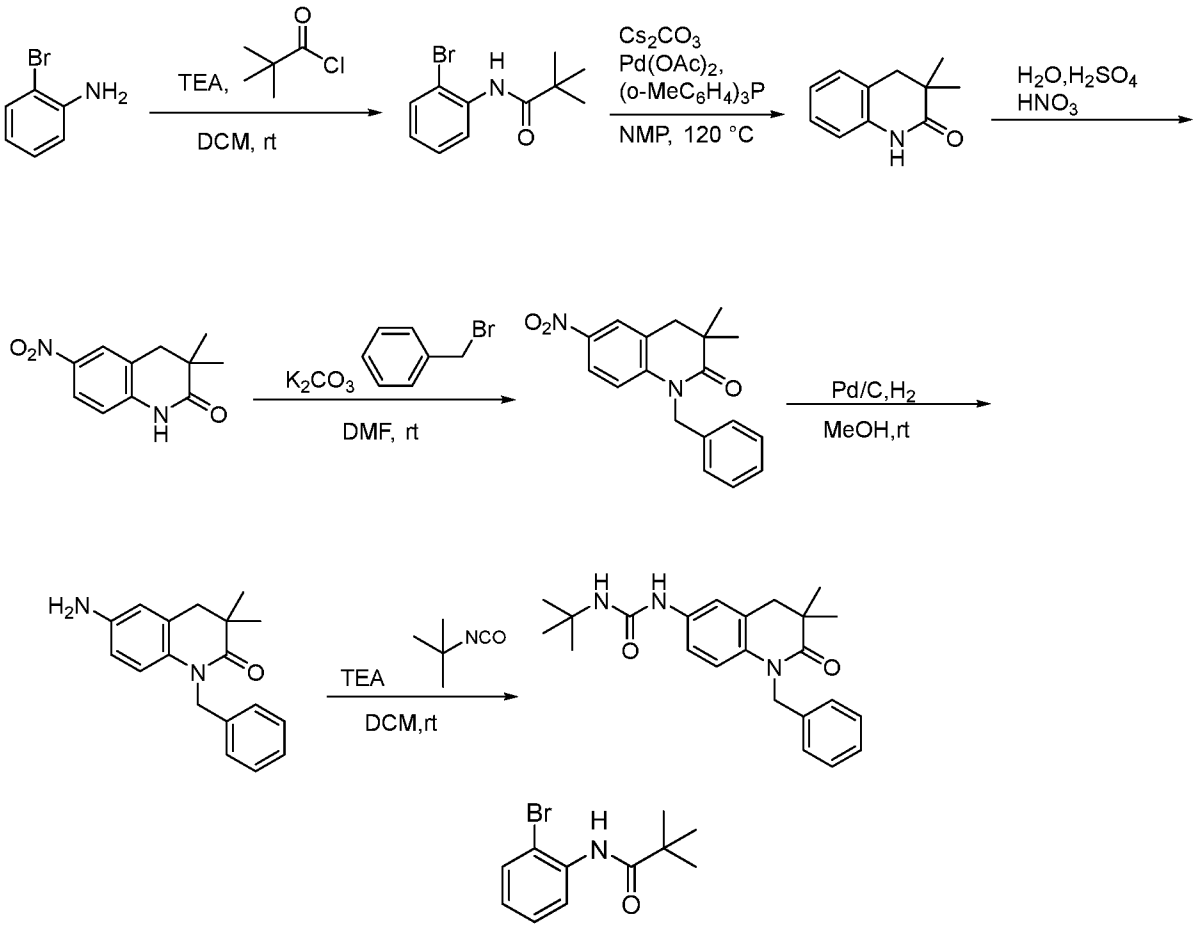


1-(tert-butyl)-3-(2-oxo-1-(1-phenylpropyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a solution of 6-amino-1-(1-phenylpropyl)-3,4-dihydroquinolin-2-one (100 mg, 1.502 mmol, 1 equiv) in DCM (8 mL) was added 2-isocyanato-2-methylpropane (106.0 mg, 1.070 mmol, 3 equiv) and TEA (108.2 mg, 1.070 mmol, 3 equiv). The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column eluted with PE / EA (2:1) & Prep-HPLC (Column: Aeris PEPTIDE 5um XB-C18 Axia, 21.2 mm X 250 mm, 5 μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 39% B to 61% B in 10.5 min; Wave Length: 220 nm; RT1(min): 7.9; Number Of Runs: 2) to afford 1-(tert-butyl)-3-(2-oxo-1-(1-phenylpropyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea (29.8 mg, 21.98%) as a white solid. MS (ESI): mass calcd. for $C_{23}H_{29}N_3O_2$, 379.23 m/z, found 380.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.20 – 7.41 (m, 6H), 6.81 (dd, J = 8.8, 2.5 Hz, 1H), 6.49 (d, J = 8.8 Hz, 1H), 5.95 (d, J = 13.1 Hz, 2H), 2.74 – 2.92 (m, 2H), 2.56 – 2.74 (m, 2H), 2.31 – 2.40 (m, 1H), 2.04 – 2.22 (m, 1H), 1.25 (s, 9H), 0.77 (t, J = 7.2 Hz, 3H).

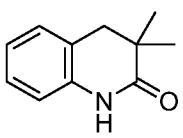
Example 29: 1-(1-benzyl-3,3-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

Synthetic Scheme



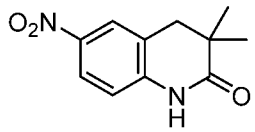
N-(2-bromophenyl)pivalamide

To a stirred solution of O-bromoaniline (3 g, 17.439 mmol, 1 equiv) in anhydrous DCM (50 mL) was added triethylamine (2.29 g, 22.671 mmol, 1.3 equiv) followed by 2,2-dimethylpropanoyl chloride (2.10 g, 17.439 mmol, 1 equiv) at 0 °C. The reaction mixture was stirred for 16 h at rt. After completion of reaction, the reaction mixture was quenched by addition of water (50 mL). The aqueous layer was extracted with DCM (50 mL). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude product which was further purified by silica gel column, eluted with PE / EA (3:1) to afford desired compound N-(2-bromophenyl)-2,2-dimethylpropanamide (2.7 g, 60.44%) as a yellow solid. MS (ESI): mass calcd. for $C_{11}H_{14}BrNO$: 255.03 m/z, found 256.05 $[M+H]^+$.



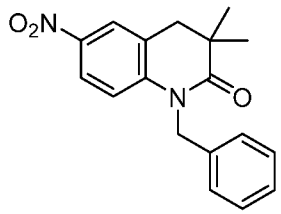
3,3-dimethyl-3,4-dihydroquinolin-2(1H)-one

To a stirred solution of N-(2-bromophenyl)-2,2-dimethylpropanamide (400 mg, 1.562 mmol, 1 equiv) in NMP (20 mL, 207.398 mmol, 132.81 equiv) was added Cs_2CO_3 (1.02 g, 3.124 mmol, 2 equiv), tris(4-methylphenyl)phosphane (95.06 mg, 0.312 mmol, 0.2 equiv), $Pd(OAc)_2$ (35.06 mg, 0.156 mmol, 0.1 equiv) and TBHP (42.22 mg, 0.469 mmol, 0.3 equiv) at rt and stirred for overnight at 140 °C under N_2. The reaction mixture was concentrated under reduced pressure to give crude product which was further purified by silica, gel column PE / EA (3:1) to afford desired compound 3,3-dimethyl-1,4-dihydroquinolin-2-one (0.2 g, 73.26%). MS (ESI): mass calcd. for $C_{11}H_{13}NO$: 175.10 m/z, found 176.25 $[M+H]^+$.



3,3-dimethyl-6-nitro-3,4-dihydroquinolin-2(1H)-one

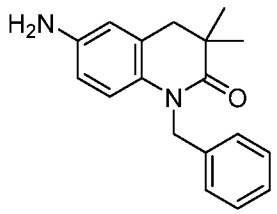
To a solution of 3,3-dimethyl-3,4-dihydroquinolin-2(1H)-one (0.2 g, 1.14 mmol, 1 equiv) in H_2O (2 mL) and H_2SO_4 (9 mL) was added HNO_3 (0.2 mL) at -10 °C. The reaction was stirred for 2 h at -10-0 °C. The reaction mixture was quenched by water. The mixture was acidified pH = 7 with $NaHCO_3$ (*aq.*) and then extracted with EA (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE /EA (3:1) to afford 3,3-dimethyl-6-nitro-3,4-dihydroquinolin-2(1H)-one (0.15 g, 60.0%) as a white solid. MS (ESI): mass calcd. for $C_{11}H_{12}N_2O_3$, 220.08 m/z, found 221.05 [M+H]+ .



1-benzyl-3,3-dimethyl-6-nitro-3,4-dihydroquinolin-2(1H)-one

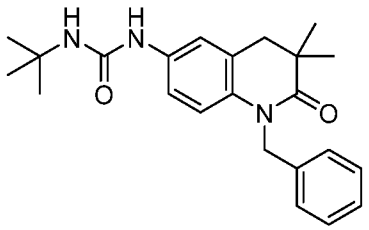
To a stirred solution of 3,3-dimethyl-6-nitro-1,4-dihydroquinolin-2-one (150 mg, 0.681 mmol, 1 equiv) in DMF (3 mL) was added K_2CO_3 (322.39 mg, 2.316 mmol, 3 equiv) and benzyl bromide (158.43 mg, 0.926 mmol, 1.2 equiv) at rt and stirred for overnight. The resulting mixture was extracted with EA (3 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to yield a crude product which was directly

purified by silica gel column, eluted with PE /EA (3:1) to afford 1-benzyl-3,3-dimethyl-6-nitro-3,4-dihydroquinolin-2(1H)-one (150 mg, 71.09%) as a white solid. MS (ESI): mass calcd. for $C_{18}H_{18}N_2O_3$: 310.13 m/z, found 311.10 $[M+H]^+$.



6-amino-1-benzyl-3,3-dimethyl-3,4-dihydroquinolin-2(1H)-one

To a solution of 1-benzyl-3,3-dimethyl-6-nitro-3,4-dihydroquinolin-2(1H)-one (130 mg, 0.419 mmol, 1 equiv) in 10 mL MeOH was added Pd/C (30 mg) under nitrogen atmosphere. The mixture was hydrogenated at room temperature for 50 min under hydrogen atmosphere using a hydrogen balloon, then filtered through a Celite pad and concentrated under reduced pressure to afford 6-amino-1-benzyl-3,3-dimethyl-4H-quinolin-2-one (100 mg, 85.15%) as a white solid. MS (ESI): mass calcd. for $C_{18}H_{20}N_2O$: 280.16 m/z, found 281.25 $[M+H]^+$.



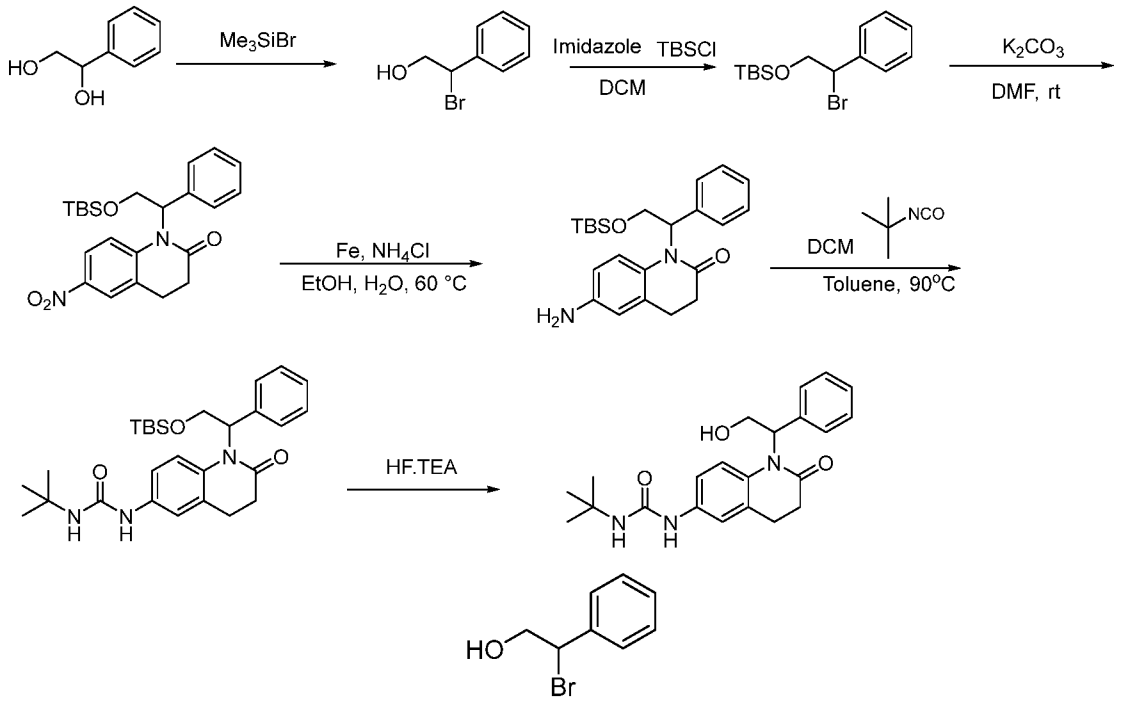
1-(1-benzyl-3,3-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

To a stirred solution of 6-amino-1-benzyl-3,3-dimethyl-4H-quinolin-2-one (50 mg, 0.178 mmol, 1 equiv) in anhydrous DCM (5 mL) was added TEA (54.14 mg, 0.534 mmol, 3 equiv) 2-isocyanato-2-methylpropane (70.72 mg, 0.712 mmol, 4 equiv) at 0 °C, and stirred for overnight at rt. After completion of reaction, the reaction mixture was concentrated under reduced pressure to give crude product which was further purified by HPLC with the following conditions Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 44% B to 60% B in 8.5 min; Wave Length: 220 nm; RT1(min): 6.9; Number Of Runs: 3; to afford 1-(1-benzyl-3,3-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea (5.6 mg, 8.26%) as a white solid. MS (ESI):mass calcd. for $C_{23}H_{29}N_3O_2$: 379.23 m/z, found 380.20 $[M+H]^+$. ^1H NMR

(300 MHz, Methanol-d_4) δ 7.18 – 7.34 (m, 6H), 7.01 – 7.04 (m, 1H), 6.82 (d, J = 8.7 Hz, 1H), 5.16 (s, 2H), 2.84 (s, 2H), 1.36 (s, 9H), 1.23 (s, 6H).

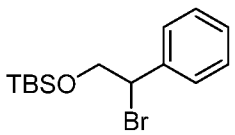
Example 30: 1-(tert-butyl)-3-(1-(2-hydroxy-1-phenylethyl)-2-oxo-1,2,3,4-tetrahydroquinoli n-6-yl)urea

Synthetic Scheme



2-bromo-2-phenylethan-1-ol

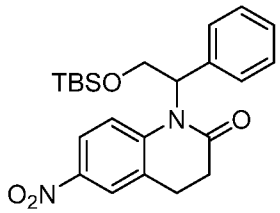
Into a 40 mL round-bottom flask was added 2-bromo-2-phenylethan-1-ol (3 g, 21.713 mmol, 1 equiv) and bromotrimethylsilane (3.66 g, 23.884 mmol, 1.1 equiv) at rt. The resulting mixture was stirred for additional overnight at rt. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE /EA (5:1) afford 2-bromo-2-phenylethanol (2.7 g, 61.85%) as a yellow semi-solid.



(2-bromo-2-phenylethoxy)(tert-butyl)dimethylsilane

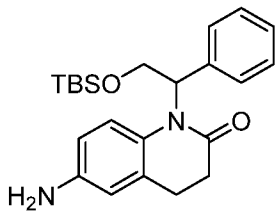
To a stirred solution of 2-bromo-2-phenylethanol (1.4 g, 6.963 mmol, 1 equiv) in anhydrous DCM (30 mL) was added t-butyldimethylchlorosilane (2.10 g, 13.926 mmol, 2

equiv) and Imidazole (1.42 g, 20.889 mmol, 3 equiv) at rt and stirred for 1 h. The reaction progress was monitored by TLC. The residue was purified by silica gel column chromatography, eluted with EA (35%-58%) to afford (2-bromo-2-phenylethoxy)(tert-butyl)dimethylsilane (1.2 g, 54.65%) as a yellow semi-solid.



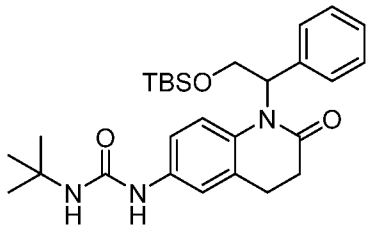
1-(2-((tert-butyldimethylsilyl)oxy)-1-phenylethyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one

To a stirred solution of (2-bromo-2-phenylethoxy)(tert-butyl)dimethylsilane (500 mg, 1.586 mmol, 1 equiv) in dimethylformamide (10 mL) was added 6-nitro-3,4-dihydro-1H-quinolin-2-one (274.25 mg, 1.427 mmol, 0.9 equiv) and Cs_2CO_3 (1549.92 mg, 4.758 mmol, 3 equiv) at rt and stirred for overnight. The reaction progress was monitored by LCMS. The resulting mixture was extracted with EA (3 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (3:1) to afford 1-(2-((tert-butyldimethylsilyl)oxy)-1-phenylethyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (350 mg, 51.74%) as a yellow solid. MS (ESI): mass calcd. for $C_{23}H_{30}N_2O_4Si$: 426.20 m/z, found 427.15 $[M+H]^+$.



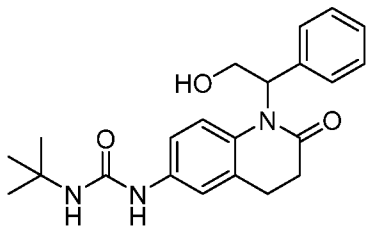
6-amino-1-(2-((tert-butyldimethylsilyl)oxy)-1-phenylethyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of 1-(2-((tert-butyldimethylsilyl)oxy)-1-phenylethyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (80 mg, 0.188 mmol, 1 equiv) in 10 mL MeOH was added Pd/C (10%, 50 mg) under nitrogen atmosphere in a 50 mL. The mixture was hydrogenated at room temperature for 1 h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure to afford 6-amino-1-(2-((tert-butyldimethylsilyl)oxy)-1-phenylethyl)-3,4-dihydroquinolin-2(1H)-one (75 mg, 100.0%) as a white solid. MS (ESI): mass calcd. for $C_{23}H_{32}N_2O_2S$: 396.22 m/z, found 397.30 $[M+H]^+$.



1-(tert-butyl)-3-(1-(2-((tert-butyldimethylsilyl)oxy)-1-phenylethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

o a stirred solution of 6-amino-1-(2-((tert-butyldimethylsilyl)oxy)-1-phenylethyl)-3,4-dihydroquinolin-2(1H)-one (100 mg, 0.252 mmol, 1 equiv) in DCM (10 mL) was added 2-isocyanato-2-methylpropane (74.99 mg, 0.756 mmol, 3 equiv) and toluene (5 mL, 46.993 mmol, 186.38 equiv) at rt and stirred for overnight at 90 °C. The reaction progress was monitored by LCMS. After completion of reaction, the reaction mixture was concentrated under reduced pressure to give crude product. MS (ESI): mass calcd. for $C_{28}H_{41}N_3O_3Si$: 495.29 m/z, found 496.30 $[M+H]^+$.



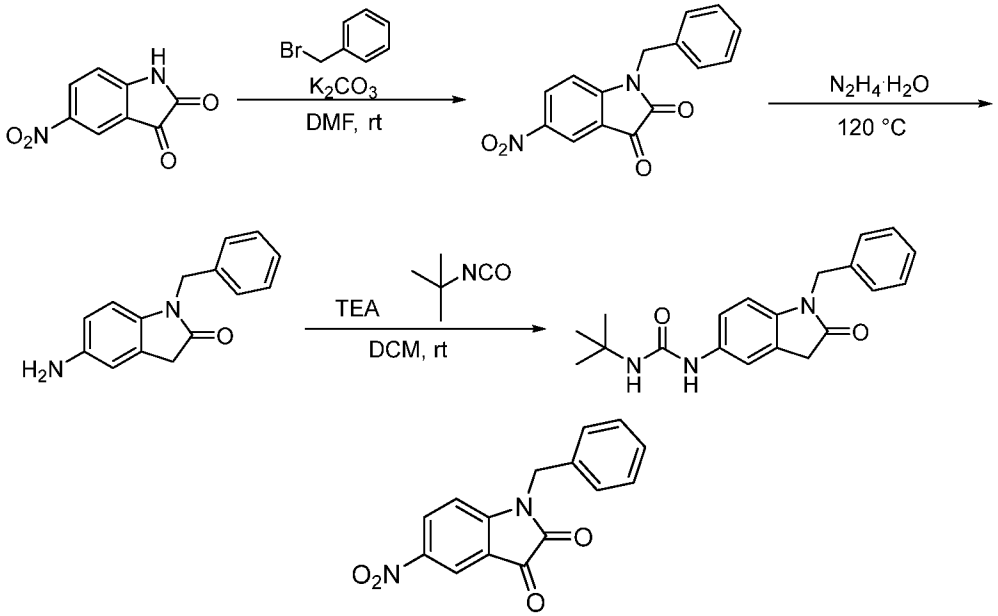
1-(tert-butyl)-3-(1-(2-hydroxy-1-phenylethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a stirred solution of 1-(tert-butyl)-3-(1-(2-((tert-butyldimethylsilyl)oxy)-1-phenylethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea (crude) in tetrahydrofuran (5 mL) was added Triethylamine trihydrofluoride (300 mg) and stirred for 2 h at 60 °C. The reaction progress was monitored by LCMS. After completion of reaction, the reaction mixture was concentrated under reduced pressure to give crude product which was further purified by HPLC with the following conditions Column: Xselect CSH F-Phenyl OBD column, 19*250 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 45% B to 75% B in 7 min, 75% B; Wave Length: 254/220 nm; RT1(min): 6.4; Number Of Runs: 0 to afford 3-tert-butyl-1-[1-(2-hydroxy-1-phenylethyl)-2-oxo-3,4-dihydroquinolin-6-yl]urea (4 mg, 10.30%) as a white solid. MS (ESI):mass calcd. for $C_{22}H_{27}N_3O_3$: 381.21 m/z, found 382.20 [M+H]+. ^1H NMR (300 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.33 (d, J = 4.0 Hz, 5H), 7.25 (q, J = 4.2 Hz, 1H), 6.87 (dd, J = 8.8, 2.5 Hz, 1H), 6.60 (d, J = 8.8

Hz, 1H), 5.89 (d, *J* = 13.5 Hz, 1H), 5.71 (d, *J* = 7.1 Hz, 1H), 5.01 (t, *J* = 5.5 Hz, 1H), 4.26 (dt, *J* = 11.4, 6.0 Hz, 1H), 4.07 (dt, *J* = 11.1, 6.1 Hz, 1H), 2.93 – 2.77 (m, 2H), 2.58 (q, *J* = 6.5 Hz, 2H), 1.26 (s, 9H).

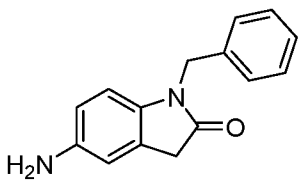
Example 31: 1-(1-benzyl-2-oxo-3H-indol-5-yl)-3-tert-butylurea

Synthetic Scheme



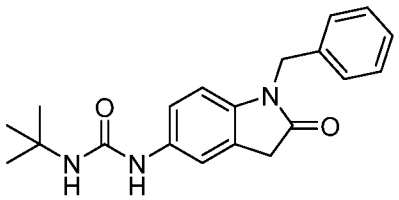
1-benzyl-5-nitroindole-2,3-dione

To a solution of 1H-indole-2,3-dione, 5-nitro (1 g, 5.205 mmol, 1 equiv) and benzyl bromide (979.24 mg, 5.726 mmol, 1.1 equiv) in dimethylformamide (10 mL) was added K_2CO_3 (1438.66 mg, 10.41 mmol, 2 equiv). The reaction was stirred at rt for 3h. Quenched with water (40 mL) and extracted with EA (3 x 40 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-benzyl-5-nitroindole-2,3-dione (665 mg, 45.27%) as a white solid. MS (ESI): mass calcd for $C_{15}H_{10}N_2O_4$: 282.06 m/z, found 283.15$[M+H]^+$.



benzyl-5-nitro-3H-indol-2-one

To a solution of 1-benzyl-5-nitroindole-2,3-dione (500 mg, 1.771 mmol, 1 equiv) in Hydrazinium hydroxide solution (5 mL) was stirred at 120 °C for 3h. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to 1-benzyl-5-nitro-3H-indol-2-one (437 mg, 91.96%) as a black solid. MS (ESI): mass calcd for $C_{15}H_{14}N_2O$: 238.11 m/z, found 239.15$[M+H]^+$.

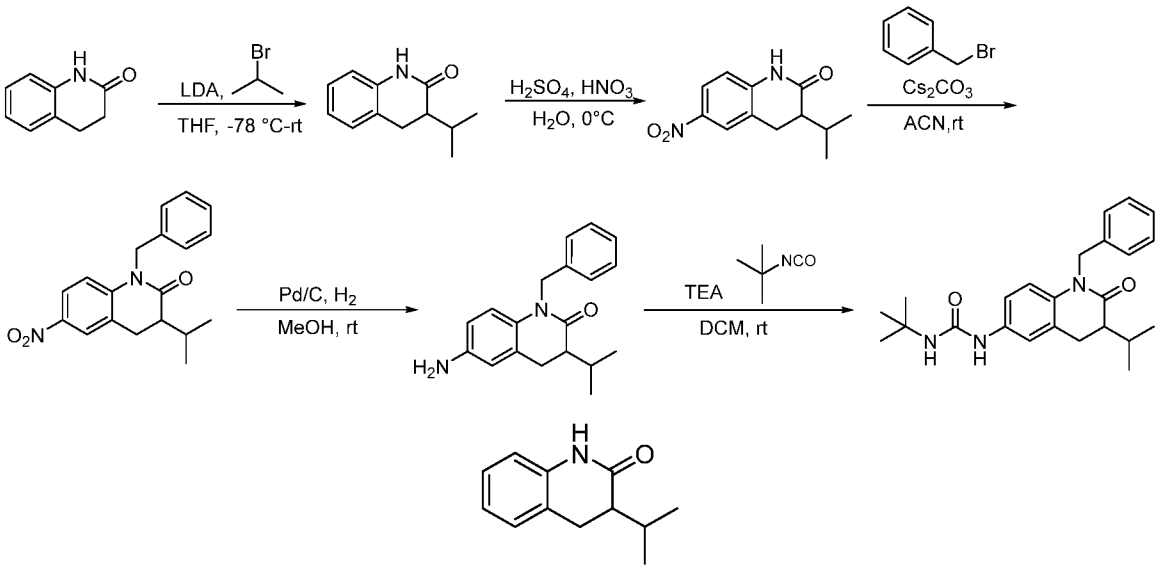


1-(1-benzyl-2-oxo-3H-indol-5-yl)-3-tert-butylurea

To a solution of 5-amino-1-benzyl-3H-indol-2-one (200 mg, 0.839 mmol, 1 equiv) and 2-isocyanato-2-methylpropane (124.2 mg, 1.253 mmol, 1.49 equiv) in DCM (2 mL) was added TEA (253.2 mg, 2.502 mmol, 2.98 equiv). The reaction was stirred at rt for 16h. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column 150 mm x 30 mm x 5 μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 1-(1-benzyl-2-oxo-3H-indol-5-yl)-3-tert-butylurea (26.3 mg, 9.27%) as a white solid. LC/MS (ESI): mass calcd. for $C_{20}H_{23}N_3O_2$:337.18 m/z, found:338.00 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 8.08 (s, 1H), 7.42 (m, 1H), 7.23-7.34 (m, 5H), 7.02 (m, 1H), 6.70 (m, 1H), 5.88 (s, 1H), 4.84 (s, 2H), 3.63 (s, 2H), 1.27 (s, 9H).

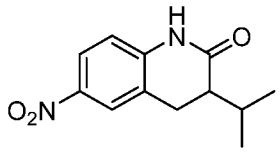
Example 32: 1-(1-benzyl-3-isopropyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

Synthetic Scheme



3-isopropyl-3,4-dihydroquinolin-2(1H)-one

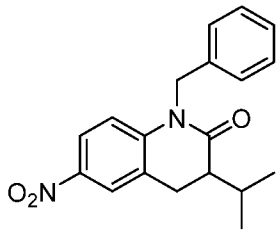
To a solution of 3,4-dihydro-1H-quinolin-2-one (2 g, 13.589 mmol, 1 equiv) in THF (70 mL) was added 2M LDA (in THF) (17 mL) at -78 °C under N_2. The resulting mixture was stirred 30 min at -78 °C. The reaction mixture was added 2-bromopropane (2.01 g, 16.343 mmol, 1.2 equiv) at -78 °C. The resulting mixture was stirred 30 min at -78 °C and then stirred 16 h at rt. The reaction mixture was quenched by water (50 mL) and extracted with EA (3 x 70 mL).The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE /EA (3:1) to afford 3-isopropyl-3,4-dihydro-1H-quinolin-2-one (1 g, 21.98%) as a white solid. MS (ESI): mass calcd. for $C_{12}H_{15}NO$, 189.12 m/z, found 190.30 $[M+H]^+$.



3-isopropyl-7-nitro-3,4-dihydroquinolin-2(1H)-one

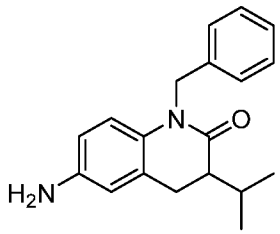
To a solution of 3-isopropyl-3,4-dihydro-1H-quinolin-2-one (510 mg, 2.695 mmol, 1 equiv) in H_2O (2 mL) and H_2SO_4 (9 mL) was added HNO_3 (0.2 mL)at -10 °C. The resulting mixture was stirred at -10 °C until the starting material was totally consumed by LCMS. The reaction mixture was quenched by water. The mixture was acidified pH = 7 with $NaHCO_3$ (*aq.*) and then extracted with EA (3 x 50 mL). The combined organic extracts were washed with brine

(50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE /EA (3:1) to afford 3-isopropyl-7-nitro-3,4-dihydro-1H-quinolin-2-one (200 mg, 24.28%) as a white solid. MS (ESI): mass calcd. for $C_{12}H_{14}N_2O_3$, 234.10 m/z, found 235.05 $[M+H]^+$.



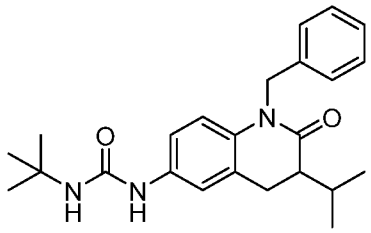
1-benzyl-3-isopropyl-7-nitro-3,4-dihydroquinolin-2(1H)-one

To a solution of 3-isopropyl-7-nitro-3,4-dihydro-1H-quinolin-2-one (140 mg, 0.598 mmol, 1 equiv) in DMF (5 mL) was added K_2CO_3 (247.7 mg, 1.793 mmol, 3 equiv) and benzyl bromide (112.4 mg, 0.657 mmol, 1.1 equiv). The resulting mixture was stirred 16 h at rt. The mixture was diuted with EtOAc (100 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE /EA (3:1) to afford 1-benzyl-3-isopropyl-7-nitro-3,4-dihydroquinolin-2(1H)-one (100 mg, 49.05%) as a yellow solid. MS (ESI): mass calcd. for $C_{19}H_{20}N_2O_3$ 324.15 m/z, found 325.05 $[M+H]^+$.



7-amino-1-benzyl-3-isopropyl-3,4-dihydroquinolin-2(1H)-one

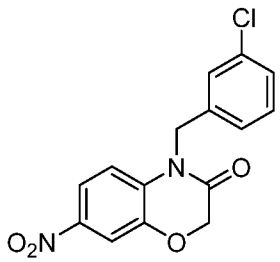
To a solution of 1-benzyl-3-isopropyl-7-nitro-3,4-dihydroquinolin-2(1H)-one (140 mg, 0.432 mmol, 1 equiv) in MeOH (10 mL) was added Pd/C (30 mg). The reaction mixture was then stirred for 1 h under hydrogen atmosphere (balloon). The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to afford 7-amino-1-benzyl-3-isopropyl-3,4-dihydroquinolin-2(1H)-one (100 mg, 77.79%) as a yellow solid. MS (ESI): mass calcd. for $C_{19}H_{22}N_2O$, 294.17 m/z, found 295.10 [M+H].



1-(1-benzyl-3-isopropyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

To a solution of 7-amino-1-benzyl-3-isopropyl-3,4-dihydroquinolin-2(1H)-one (100 mg, 0.340 mmol, 1 equiv) in DCM (5 mL) was added TEA (103.1 mg, 1.019 mmol, 3 equiv) and 2-isocyanato-2-methylpropane (101.0 mg, 1.019 mmol, 3 equiv). The resulting mixture was stirred for 16 h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column eluted with PE / EA (2:1) & Prep-HPLC (Column: XSelect CSH Fluoro Phenyl, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 31% B to 46% B in 10.5 min; Wave Length: 220 nm; RT1(min): 11.2; Number Of Runs: 7) to afford 1-(1-benzyl-3-isopropyl-2-oxo-3,4-dihydroquinolin-6-yl)-3-tert-butylurea (3.3 mg, 2.46%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{31}N_3O_2$, 393.24 m/z, found 394.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.11 (s, 1H), 7.13 – 7.37 (m, 6H), 6.96 (dd, J = 8.6, 2.4 Hz, 1H), 6.76 (d, J = 8.7 Hz, 1H), 5.93 (s, 1H), 5.09 (d, J = 3.5 Hz, 2H), 2.92 (dd, J = 15.7, 5.3 Hz, 1H), 2.77 (dd, J = 15.7, 8.1 Hz, 1H), 2.36 (q, J = 6.9 Hz, 1H), 1.98 (p, J = 6.4 Hz, 1H), 1.26 (s, 9H), 0.94 (dd, J = 17.0, 6.7 Hz, 6H).

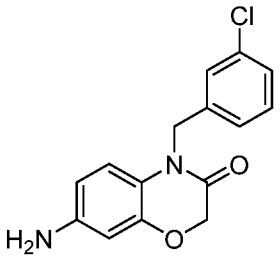
Example 33: 3-tert-butyl-1-{4-[(3-chlorophenyl)methyl]-3-oxo-2H-1,4-benzoxazin-7-yl}urea



4-[(3-chlorophenyl)methyl]-7-nitro-2H-1,4-benzoxazin-3-one

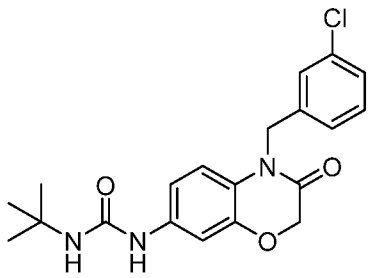
To a solution of 7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (500 mg, 2.575 mmol, 1 equiv) and 1-(bromomethyl)-3-chlorobenzene (794 mg, 3.863 mmol, 1.5 equiv) in

dimethylformamide (10 mL) was added Cs_2CO_3 (2.538 g, 7.766 mmol, 3.02 equiv). The reaction was stirred at rt for 3h. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 4-[(3-chlorophenyl)methyl]-7-nitro-2H-1,4-benzoxazin-3-one (203 mg, 24.73%) as a white solid. MS (ESI): mass calcd for $C_{15}H_{11}ClN_2O_4$: 318.04 m/z, found 319.00$[M+H]^+$.



7-amino-4-[(3E)-4-chloro-2-methylidenebut-3-en-1-yl]-2H-1,4-benzoxazin-3-one

To a mixture of 4-[(3-chlorophenyl)methyl]-7-nitro-2H-1,4-benzoxazin-3-one (700 mg, 2.196 mmol, 1 equiv) and NH_4Cl (1.17g, 21.960 mmol, 10 equiv) in ethyl alcohol/ water (10 mL, 10/1) was added Fe (1.23 g, 21.960 mmol, 10 equiv). The reaction was stirred at 60 °C for 6h. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-amino-4-[(3E)-4-chloro-2-methylidenebut-3-en-1-yl]-2H-1,4-benzoxazin-3-one (183 mg, 31.48%) as a white solid. MS (ESI): mass calcd for $C_{15}H_{13}ClN_2O_2$: 288.07m/z, found 289.00$[M+H]^+$.



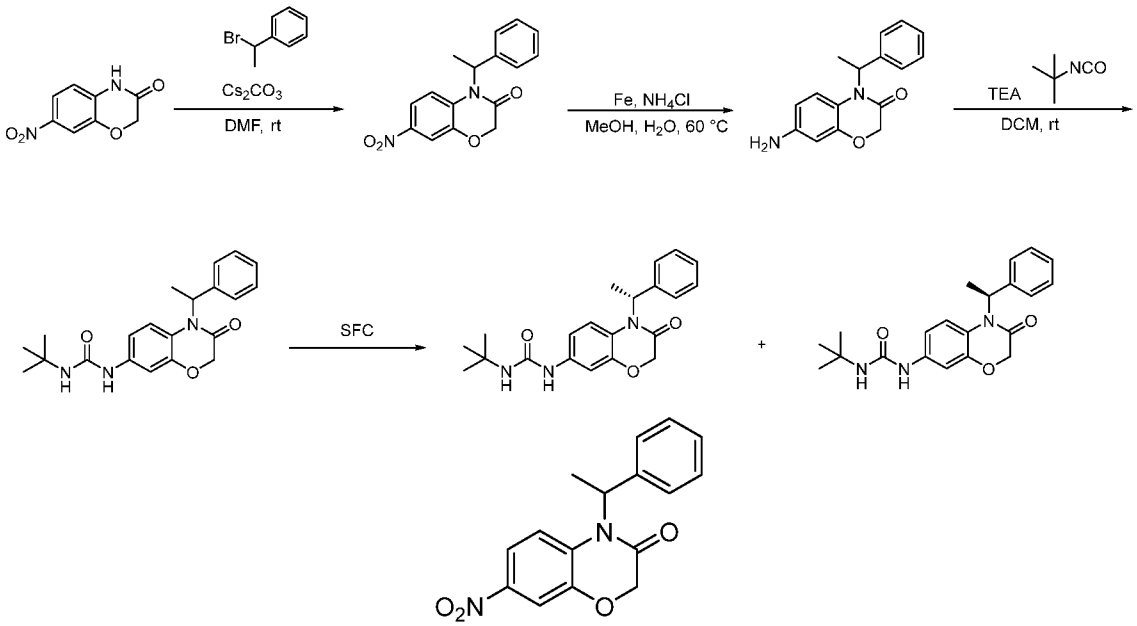
3-tert-butyl-1-{4-[(3-chlorophenyl)methyl]-3-oxo-2H-1,4-benzoxazin-7-yl}urea

To a solution of 7-amino-4-[(3-chlorophenyl)methyl]-2H-1,4-benzoxazin-3-one (200 mg, 0.693 mmol, 1 equiv) and 2-isocyanato-2-methylpropane (103.00 mg, 1.039 mmol, 1.5 equiv) in DCM (2 mL) was added TEA (210.29 mg, 2.079 mmol, 3 equiv). The reaction was stirred at rt for 3h. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts

were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column 150 mm x 30 mm x 5 μm (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-{4-[(3-chlorophenyl)methyl]-3-oxo-2H-1,4-benzoxazin-7-yl}urea (45.7 mg, 16.97%). LC/MS (ESI): mass calcd. for $C_{20}H_{22}ClN_3O_3$:387.13 m/z, found:387.95 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 7.29 – 7.41 (m, 3H), 7.22 (m, 2H), 6.86-6.85 (m, 2H), 5.94 (s, 1H), 5.11 (s, 2H), 4.76 (s, 2H), 1.26 (s, 9H).

Example 34 and Example 35: (R)-1-(tert-butyl)-3-(3-oxo-4-(1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea and (S)-1-(tert-butyl)-3-(3-oxo-4-(1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

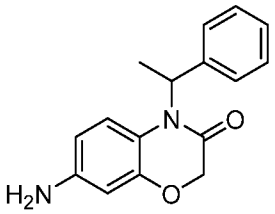
Synthetic Scheme



7-nitro-4-(1-phenylethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

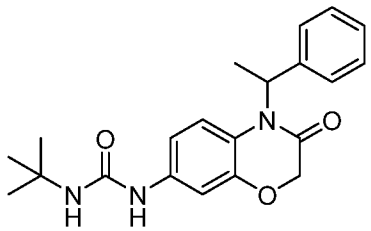
To a solution of 7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (500 mg, 2.575 mmol, 1 equiv) in DMF (20 mL) was added Cs_2CO_3 (1683.41 mg, 5.150 mmol, 2 equiv) and (1-bromoethyl)benzene (714.92 mg, 3.863 mmol, 1.5 equiv). The reaction was stirred at rt for 3 hours. Quenched with water (25 mL) and extracted with EA (3 x 25 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-nitro-4-(1-

phenylethyl)-2H-1,4-benzoxazin-3-one (564 mg, 73.42%) as a yellow liquid. MS (ESI): mass calcd. for $C_{16}H_{14}N_2O_4$: 298.30m/z, found 299.00 $[M+H]^+$.



7-amino-4-(1-phenylethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

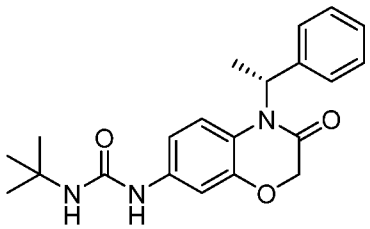
To a solution of 6-nitro-1-(1-phenylethyl)-3,4-dihydroquinolin-2-one (560 mg, 1.890 mmol, 1 equiv) in MeOH/H_2O (22 mL, 10:1) was added Fe (527.68 mg, 9.450 mmol, 5 equiv) and NH_4Cl (505.43 mg, 9.450 mmol, 5 equiv). The reaction was stirred at 80 °C for 1 hour. The reaction was quenched with water at rt. The resulting mixture was filtered, the filter cake was washed with EA (3 x 10 mL). The filtrate was added water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-1-(1-phenylethyl)-3,4-dihydroquinolin-2-one (382 mg, 75.89%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{16}N_2O_2$: 268.32m/z, found 269.15 $[M+H]^+$.

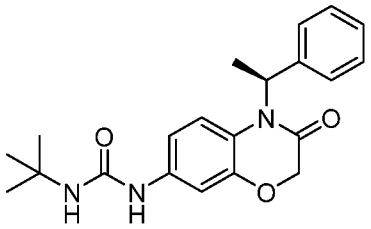


1-(tert-butyl)-3-(3-oxo-4-(1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a solution of 6-amino-1-[(3-fluorophenyl)methyl]-3,4-dihydroquinolin-2-one (380 mg, 1.406 mmol, 1 equiv) in DCM (15 mL) was added 2-isocyanato-2-methylpropane (557.45 mg, 5.624 mmol, 4 equiv) and TEA (426.77 mg, 4.218 mmol, 3 equiv) at 0 °C. The reaction was stirred at rt for 1 days. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-{1-[(3-fluorophenyl)methyl]-2-oxo-3,4-dihydroquinolin-

6-yl}urea (120 mg, 23.11%) .LC/MS (ESI): mass calcd. for $C_{21}H_{25}N_3O_3$:367.45 m/z, found:368.00 $[M+H]^+$.

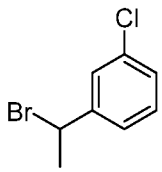




(R)-1-(tert-butyl)-3-(3-oxo-4-(1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea and (S)-1-(tert-butyl)-3-(3-oxo-4-(1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

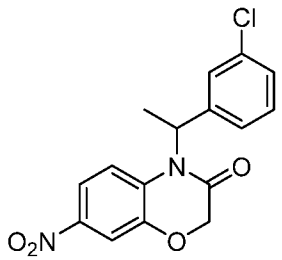
A sample of 3-tert-butyl-1-[3-oxo-4-(1-phenylethyl)-2H-1,4-benzoxazin-7-yl]urea (120 mg) was separated by chiral-HPLC using a CHIRAL ART Amylose-SA, 2*25 cm, 5 μm column (eluent: 30% to 30% (v/v) Hex(0.5% 2M NH_3-MeOH) and EtOH) to yield first enantiomer 3-tert-butyl-1-{3-oxo-4-[(1R)-1-phenylethyl]-2H-1,4-benzoxazin-7-yl}urea (37.1 mg) as a white solid. MS(ESI): mass calcd. for $C_{21}H_{25}N_3O_3$: 367.45, found: 368.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.99 – 8.31 (m, 1H), 7.11 – 7.44 (m, 6H), 6.43 – 6.67 (m, 2H), 6.04 – 6.24 (m, 1H), 5.80 – 5.98 (m, 1H), 4.55 – 4.80 (m, 2H), 1.67 – 1.80 (m, 3H), 1.22 – 1.31 (m, 9H). And to yield second enantiomer 3-tert-butyl-1-{3-oxo-4-[(1S)-1-phenylethyl]-2H-1,4-benzoxazin-7-yl}urea (22.7 mg) as a white solid. MS(ESI): mass calcd. for $C_{21}H_{25}N_3O_3$: 367.45, found: 368.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.10 – 8.26 (m, 1H), 7.17 – 7.40 (m, 6H), 6.45 – 6.70 (m, 2H), 6.02 – 6.21 (m, 1H), 5.85 – 6.00 (m, 1H), 4.60 – 4.70 (m, 2H), 1.70 – 1.80 (m, 3H), 1.20 – 1.30 (m, 9H).

Example 36 and Example 37: (R)-1-(tert-butyl)-3-(4-(1-(3-chlorophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea and (S)-1-(tert-butyl)-3-(4-(1-(3-chlorophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea



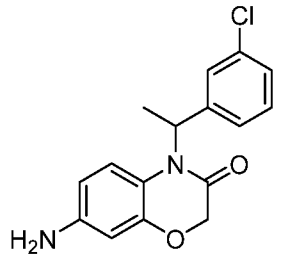
1-(1-bromoethyl)-3-chlorobenzene

To a solution of 1-(3-chlorophenyl)ethanol (1.5 g, 9.578 mmol, 1 equiv) in Et2O (10 mL) was added PBr_3 (5.19 g, 19.156 mmol, 2 equiv) at 0 °C. The reaction was stirred at rt for 2 hours. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. This resulted in 1-(1-bromoethyl)-3-chlorobenzene (762 mg, 36.24%) as a white oil. MS (ESI): mass calcd. for C_8H_8BrCl: 219.51 m/z, found 220.95 $[M+H]^+$.



4-(1-(3-chlorophenyl)ethyl)-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

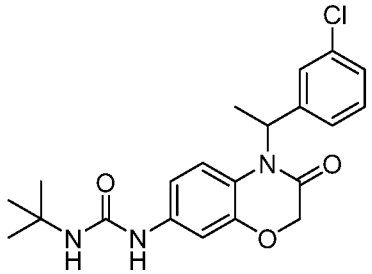
To a solution of 7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (500 mg, 2.575 mmol, 1 equiv) in DMF (15 mL) was added Cs_2CO_3 (1683.4 mg, 5.151 mmol, 2 equiv) and 1-(1-bromoethyl)-3-chlorobenzene (565.2 mg, 2.575 mmol, 1 equiv). The final reaction mixture was stirred for 2 hours at rt. Quenched with water (25 mL) and extracted with EA (3 x 25 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 4-[1-(3-chlorophenyl)ethyl]-7-nitro-2H-1,4-benzoxazin-3-one (560 mg, 73.40%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{13}ClN_2O_4$: 332.74 m/z, found 333.00 $[M+H]^+$.



7-amino-4-(1-(3-chlorophenyl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

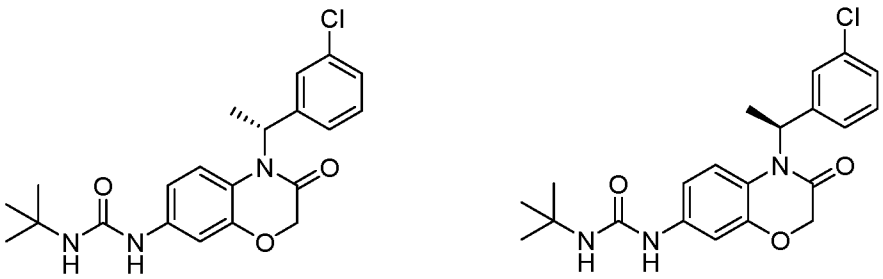
To a solution of 1-[1-(3-chlorophenyl)ethyl]-6-nitro-3,4-dihydroquinolin-2-one (560 mg, 1.693 mmol, 1 equiv) in MeOH/H_2O (22 mL, 10:1) was added Fe (472.73 mg, 8.465 mmol, 5 equiv) and NH_4Cl (452.80 mg, 8.465 mmol, 5 equiv). The reaction was stirred at 80 °C for 1 hour. The reaction was stirred for 1 hour at 80 °C. The reaction was quenched with water at rt. After filtration, the filter cake was washed with EA (3 x 20 mL). The filtrate was added water

(20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-1-[1-(3-chlorophenyl)ethyl]-3,4-dihydroquinolin-2-one (470 mg, 92.29%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{15}ClN_2O_2$: 302.76 m/z, found:303.00 $[M+H]^+$.



1-(tert-butyl)-3-(4-(1-(3-chlorophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

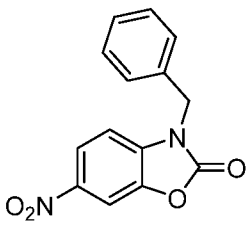
To a solution of 6-amino-1-[1-(3-chlorophenyl)ethyl]-3,4-dihydroquinolin-2-one (470 mg, 1.563 mmol, 1 equiv) in DCM (15 mL) was added 2-isocyanato-2-methylpropane (619.60 mg, 6.252 mmol, 4 equiv) and TEA (474.36 mg, 4.689 mmol, 3 equiv) at 0 °C. The reaction was stirred at rt for 1 day. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC using a YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm column (eluent: 49% to 69% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-{1-[1-(3-chlorophenyl)ethyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea (470 mg, 74.8%) as a white solid. MS (ESI): mass calcd for $C_{21}H_{24}ClN_3O_3$:401.89 m/z, found:402.00 [M+H]+.



(R)-1-(tert-butyl)-3-(4-(1-(3-chlorophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea and (S)-1-(tert-butyl)-3-(4-(1-(3-chlorophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

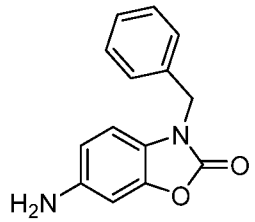
A sample of 3-tert-butyl-1-{4-[1-(3-chlorophenyl)ethyl]-3-oxo-2H-1,4-benzoxazin-7-yl}urea (200 mg) was separated by chiral-HPLC using a CHIRALPAK IG, 2*25 cm, 5 μm column (eluent: 30% to 30% (v/v) Hex(0.5% 2M NH_3-MeOH) and EtOH) to yield first enantiomer example 3-tert-butyl-1-{4-[(1R)-1-(3-chlorophenyl)ethyl]-3-oxo-2H-1,4-benzoxazin-7-yl}urea (48.0 mg) as a white solid. LC/MS: mass calcd. for $C_{21}H_{24}ClN_3O_3$: 401.89, found:402.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.10 – 8.30 (m, 1H), 7.30 – 7.44 (m, 3H), 7.20 – 7.30 (m, 2H), 6.51 – 6.72 (m, 2H), 5.99 – 6.16 (m, 1H), 5.81 – 5.99 (m, 1H), 4.59 – 4.78 (m, 2H), 1.68 – 1.78 (m, 3H), 1.24 – 1.29 (m, 9H). And to yield second enantiomer example 3-tert-butyl-1-{4-[(1S)-1-(3-chlorophenyl)ethyl]-3-oxo-2H-1,4-benzoxazin-7-yl}urea (26.2 mg) as a white solid. MS(ESI): mass calcd. for $C_{21}H_{24}ClN_3O_3$: 401.89, found:402.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.96 – 8.35 (m, 1H), 7.30 – 7.49 (m, 4H), 6.65 – 6.75 (m, 1H), 6.48 – 6.51 (m, 1H), 6.00 – 6.17 (m, 1H), 5.81 – 6.00 (m, 1H), 4.60 – 4.80 (m, 2H), 1.68 – 1.81 (m, 3H), 1.18 – 1.44 (m, 9H).

Example 38: 1-(3-benzyl-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-(tert-butyl)urea



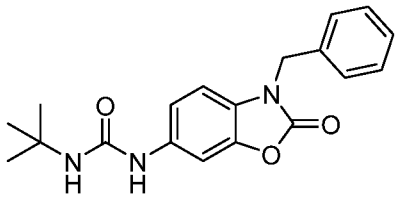
3-benzyl-6-nitrobenzo[d]oxazol-2(3H)-one

To a solution of 6-nitrobenzo[d]oxazol-2(3H)-one (300 mg, 1.666 mmol, 1 equiv) in CH_3CN (6 mL) was added KI (276.49 mg, 1.666 mmol, 1 equiv), K_2CO_3 (788.35 mg, 5.664 mmol, 3.4 equiv) and benzyl bromide (112.4 mg, 0.657 mmol, 1.1 equiv). The resulting mixture was stirred for 5 h at 60 °C. The mixture was diuted with EtOAc (100 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE /EA (3:1) to afford 3-benzyl-6-nitrobenzo[d]oxazol-2(3H)-one (300 mg, 66.65%) as a yellow solid. MS (ESI): mass calcd. for $C_{14}H_{10}N_2O_4$ 270.06 m/z, found 271.05 $[M+H]^+$.



6-amino-3-benzylbenzo[d]oxazol-2(3H)-one

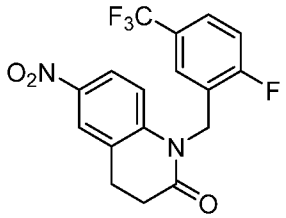
To a solution of 3-benzyl-6-nitrobenzo[d]oxazol-2(3H)-one (200 mg, 0.740 mmol, 1 equiv) in MeOH (10 mL) was added Pd/C (50 mg). The reaction mixture was then stirred for 1 h under hydrogen atmosphere (balloon). The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to afford 6-amino-3-benzylbenzo[d]oxazol-2(3H)-one (150 mg, 84.36%) as a white solid. MS (ESI): mass calcd. for $C_{14}H_{12}N_2O_2$, 240.09 m/z, found 241.20 $[M+H]^+$.



1-(3-benzyl-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-(tert-butyl)urea

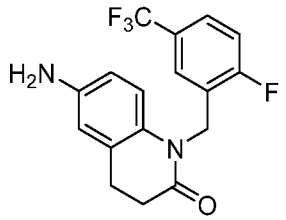
To a solution of 6-amino-3-benzylbenzo[d]oxazol-2(3H)-one (100 mg, 0.416 mmol, 1 equiv) in DCM (8 mL) was added TEA (126.3 mg, 1.249 mmol, 3 equiv) and 2-isocyanato-2-methylpropane (123.7 mg, 1.249 mmol, 3 equiv). The resulting mixture was stirred for 16 h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9; Number Of Runs: 0) to afford 1-(3-benzyl-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-(tert-butyl)urea (12.8 mg, 9.03%) as a off-white solid. MS (ESI): mass calcd. for $C_{19}H_{21}N_3O_3$, 339.16 m/z, found 340.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.61 (d, J = 1.9 Hz, 1H), 7.27 – 7.39 (m, 5H), 7.01 (d, J = 8.5 Hz, 1H), 6.89 (dd, J = 8.5, 2.0 Hz, 1H), 5.95 (s, 1H), 4.99 (s, 2H), 1.27 (s, 9H).

Example 39: 1-(tert-butyl)-3-(1-(2-fluoro-5-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea



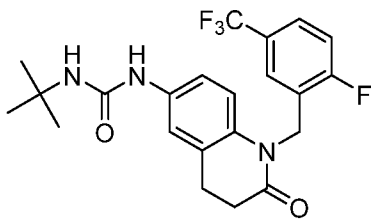
1-(2-fluoro-5-(trifluoromethyl)benzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one

To a solution of 6-nitro-3,4-dihydroquinolin-2(1H)-one (500 mg, 2.602 mmol, 1 equiv) in DMF (10 mL) was added Cs_2CO_3 (1.695 g, 5.20 mmol, 2 equiv) and 2-(bromomethyl)-1-fluoro-4-(trifluoromethyl)benzene (735.1 mg, 2.860 mmol, 1.1 equiv). The resulting mixture was stirred for 16 h at rt. The mixture was diuted with EtOAc (100 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 7-nitro-4-(3-(trifluoromethyl)benzyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (533.4 mg, 55.66%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{12}F_4N_2O_3$: 368.08 m/z, found 369.10 $[M+H]^+$.



6-amino-1-(2-fluoro-5-(trifluoromethyl)benzyl)-3,4-dihydroquinolin-2(1H)-one

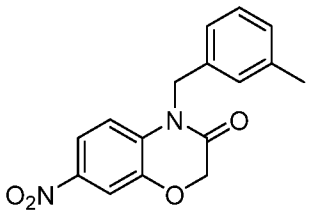
To a solution of 7-nitro-4-(3-(trifluoromethyl)benzyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (200 mg, 0.543 mmol, 1 equiv) in MeOH (10 mL) was added Pd/C (50 mg). The reaction mixture was then stirred for 1 h under hydrogen atmosphere (balloon). The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to afford 6-amino-1-(2-fluoro-5-(trifluoromethyl)benzyl)-3,4-dihydroquinolin-2(1H)-one (130 mg, 71.0%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{14}F_4N_2O$, 338.10 m/z, found 339.05 $[M+H]^+$.



1-(tert-butyl)-3-(1-(2-fluoro-5-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a stirred solution of 6-amino-1-(2-fluoro-5-(trifluoromethyl)benzyl)-3,4-dihydroquinolin-2(1H)-one (130 mg, 0.384 mmol, 1 equiv) in DCM (6 mL) & toluene (2 mL) was added 2-isocyanato-2-methylpropane (114.34 mg, 1.153 mmol, 3 equiv) stirred 16 h at 90 °C. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 45% B in 9 min, 45% B; Wave Length: 254/220 nm; RT1(min): 8.9; Number Of Runs: 0) to afford 1-(tert-butyl)-3-(1-(2-fluoro-5-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea (22.5 mg, 13.39%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{23}F4N_3O_2$, 437.17 m/z, found 438.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.66 – 7.78 (m, 1H), 7.48 (d, J = 9.3 Hz, 1H), 7.29 – 7.41 (m, 2H), 7.03 (dd, J = 8.7, 2.5 Hz, 1H), 6.81 (d, J= 8.8 Hz, 1H), 5.94 (s, 1H), 5.18 (s, 2H), 2.81 – 2.96 (m, 2H), 2.60 – 2.71 (m, 2H), 1.26 (s, 9H).

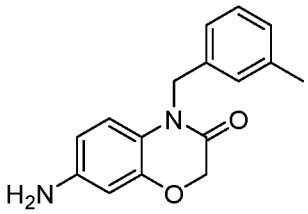
Example 40: 1-(tert-butyl)-3-(4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea



4-(3-methylbenzyl)-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

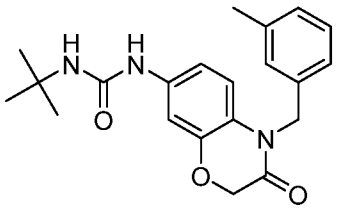
To a stirred solution of 7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (500 mg, 2.575 mmol, 1 equiv) in anhydrous dimethylformamide (10 mL) was added 1-(bromomethyl)-3-methylbenzene (619.59 mg, 3.348 mmol, 1.3 equiv) and Cs_2CO_3 (2.52 g, 7.725 mmol, 3 equiv) at rt and stirred for overnight. The reaction progress was monitored by LCMS. After completion of reaction, the resulting mixture was extracted with EA (3 x 30 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous Na_2SO_4. After

filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EA=3:1) to afford 4-[(3-methylphenyl)methyl]-7-nitro-2H-1,4-benzoxazin-3-one (750 mg, 97.63%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{14}N_2O_4$: 298.10 m/z, found 299.05 $[M+H]^+$.



7-amino-4-(3-methylbenzyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of 4-[(3-methylphenyl)methyl]-7-nitro-2H-1,4-benzoxazin-3-one (300 mg, 1.006 mmol, 1 equiv) in 20 mL MeOH was added Pd/C (10%, 150mg) under nitrogen atmosphere in a 50 mL bar. The mixture was hydrogenated at room temperature for 30 min under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 7-amino-4-[(3-methylphenyl)methyl]-2H-1,4-benzoxazin-3-one (250 mg, 92.65%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{16}N_2O_2$: 268.12 m/z, found 269.10 $[M+H]^+$.



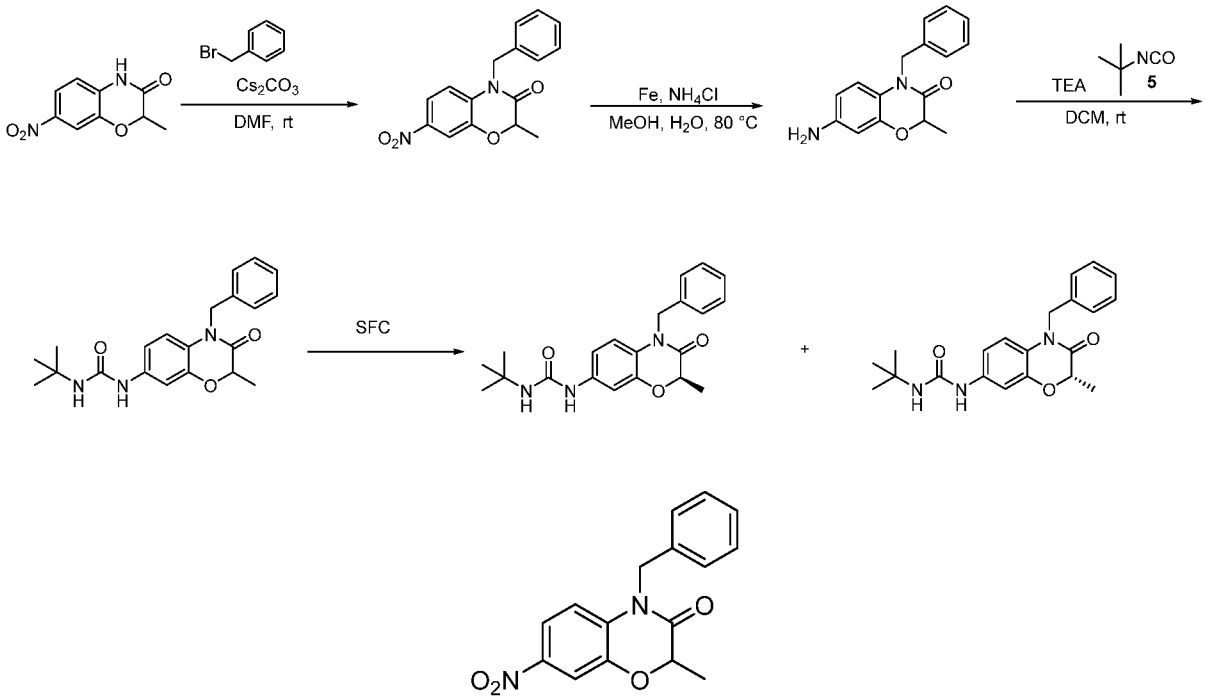
1-(tert-butyl)-3-(4-(3-methylb enzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a stirred solution of 7-amino-4-[(3-methylphenyl)methyl]-2H-1,4-benzoxazin-3-one (50 mg, 0.186 mmol, 1 equiv) in DCM (5 mL) and Toluene (2.5 mL) was added 2-isocyanato-2-methylpropane (55.42 mg, 0.558 mmol, 3 equiv) at 90 °C and stirred for overnight. The reaction progress was monitored by TLC. After completion of reaction, the reaction mixture was concentrated under reduced pressure to give crude product which was further purified by HPLC with the following conditions Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9; Number Of Runs: 0 to afford 3-tert-butyl-1-{4-[(3-methylphenyl)methyl]-3-oxo-2H-1,4-benzoxazin-7-yl}urea (2.6 mg, 3.74%) as a white solid. MS (ESI):mass calcd. for C21H25N3O3:

367.19 m/z, found 368.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.19 (d, J = 6.2 Hz, 2H), 7.06 (d, J = 7.3 Hz, 3H), 6.85 (d, J = 8.6 Hz, 1H), 6.75 (d, J = 8.8 Hz, 1H), 5.93 (s, 1H), 5.06 (s, 2H), 4.74 (s, 2H), 2.27 (s, 3H), 1.26 (s, 9H).

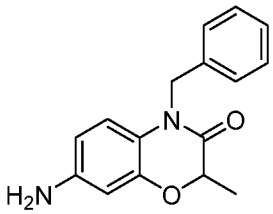
Example 41 and Example 42: (R)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea and (S)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

Synthetic Scheme



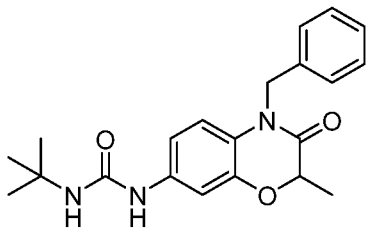
4-benzyl-2-methyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of 2-methyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (300 mg, 1.441 mmol, 1 equiv) in DMF (10 mL) was added Cs_2CO_3 (941.99 mg, 2.882 mmol, 2 equiv) and benzyl bromide (369.72 mg, 2.162 mmol, 1.5 equiv). The reaction was stirred at rt for 1 hour. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 4-benzyl-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (377 mg, 87.70%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{14}N_2O_4$: 298.30m/z, found 299.00 $[M+H]^+$.



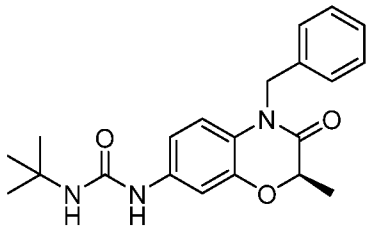
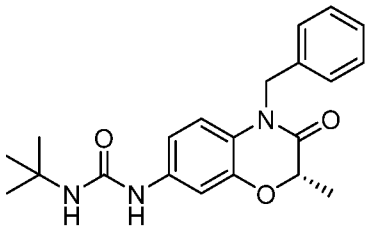
7-amino-4-benzyl-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of 6-nitro-1-(1-phenylethyl)-3,4-dihydroquinolin-2-one (560 mg, 1.890 mmol, 1 equiv) in MeOH/H_2O (22 mL, 10:1) was added Fe (527.68 mg, 9.450 mmol, 5 equiv) and NH_4Cl (505.43 mg, 9.450 mmol, 5 equiv). The reaction was stirred at 80 °C for 1 hour. The reaction was quenched with water at rt. After filtration, the filter cake was washed with EA (3 x 10 mL). The filtrate was added water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-amino-4-benzyl-2-methyl-2H-1,4-benzoxazin-3-one (530 mg, 99.87%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{16}N_2O_2$: 268.32m/z, found 269.05 [M+H]+.



1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

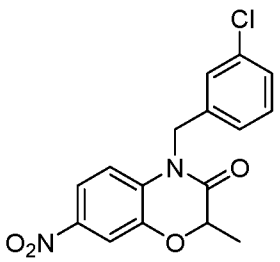
To a solution of 7-amino-4-benzyl-2-methyl-2H-1,4-benzoxazin-3-one (540 mg, 2.013 mmol, 1 equiv) in DCM/Toluene (15 mL, 2:1) was added 2-isocyanato-2-methylpropane (798.04 mg, 8.052 mmol, 4 equiv). The reaction was stirred at 90 °C for 2 hours. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-(4-benzyl-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl)-3-tert-butylurea (498 mg, 67.34%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{25}N_3O_3$:367.45 m/z, found:368.10 $[M+H]^+$.

(R)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea and (S)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

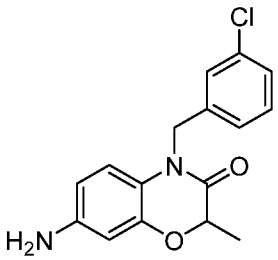
A sample of 1-(4-benzyl-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl)-3-tert-butylurea (200 mg) was separted by chiral-HPLC using a CHIRALPAK IE, 2*25 cm, 5 μm column (eluent: 15% to 15% (v/v) Hex(0.5% 2M NH_3-MeOH) and EtOH) to yield first enantiomer example 1-[(2R)-4-benzyl-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]-3-tert-butylurea (29.8 mg) as a white solid. MS(ESI): mass calcd. for $C_{21}H_{25}N_3O_3$: 367.45, found: 368.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.14 – 8.32 (m, 1H), 7.15 – 7.45 (m, 6H), 6.68 – 6.98 (m, 2H), 5.79 – 6.09 (m, 1H), 5.00 – 5.17 (m, 2H), 4.70 – 4.90 (m, 1H), 1.43 – 1.65 (m, 3H), 1.18 – 1.31 (m, 9H). And to yield second enantiomer example 1-[(2S)-4-benzyl-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]-3-tert-butylurea (25.5 mg) as a white solid. MS(ESI): mass calcd. for $C_{21}H_{25}N_3O_3$: 367.45, found: 368.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.08 – 8.31 (m, 1H), 7.30 – 7.39 (m, 2H), 7.18 – 7.30 (m, 4H), 6.71 – 6.92 (m, 2H), 5.75 – 6.07 (m, 1H), 5.01 – 5.19 (m, 2H), 4.72 – 4.87 (m, 1H), 1.42 – 1.53 (m, 3H), 1.21 – 1.33 (m, 9H).

Example 43 and Example 44: (R)-1-(tert-butyl)-3-(4-(3-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea and (S)-1-(tert-butyl)-3-(4-(3-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea



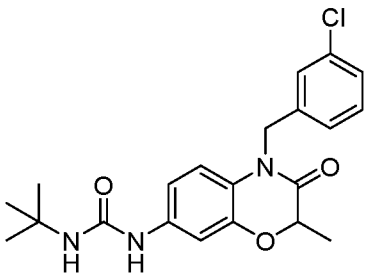
4-(3-chlorobenzyl)-2-methyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of 2-methyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (500 mg, 2.402 mmol, 1 equiv) in DMF (10 mL) was added Cs_2CO_3 (1569.98 mg, 4.804 mmol, 2 equiv) and 1-(bromomethyl)-3-chlorobenzene (740.30 mg, 3.603 mmol, 1.5 equiv). The reaction was stirred at rt for 1 hour. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 4-[(3-chlorophenyl)methyl]-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (790 mg, 98.85%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{13}ClN_2O_4$: 332.74 m/z, found 332.95 $[M+H]^+$.



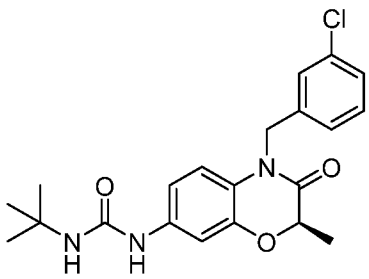
7-amino-4-(3-chlorobenzyl)-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

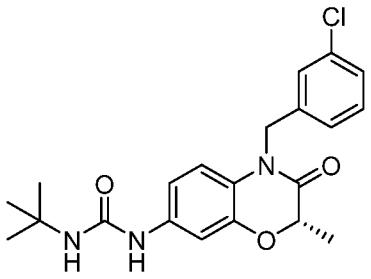
To a solution of 4-[(3-chlorophenyl)methyl]-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (570 mg, 1.713 mmol, 1 equiv) in EtOH (20 mL) was added $SnCl_2$ (1641.36 mg, 8.565 mmol, 5 equiv). The reaction was stirred at 60 °C for 1 hour. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-amino-4-[(3-chlorophenyl)methyl]-2-methyl-2H-1,4-benzoxazin-3-one (500 mg, 96.41%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{15}ClN_2O_2$: 302.76m/z, found 302.95 $[M+H]^+$.



1-(tert-butyl)-3-(4-(3-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a solution of 7-amino-4-[(3-chlorophenyl)methyl]-2-methyl-2H-1,4-benzoxazin-3-one (500 mg, 1.651 mmol, 1 equiv) in DCM/Toluene (25 mL, 2:1) was added 2-isocyanato-2-methylpropane (654.86 mg, 6.604 mmol, 4 equiv). The reaction was stirred at 90 °C for 2 hours. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 3-tert-butyl-1-{4-[(3-chlorophenyl)methyl]-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl}urea (170 mg, 25.61%) as a white solid. LC/MS (ESI): mass calcd. For $C_{21}H_{24}ClN_3O_3$: 401.89 m/z, found:402.05 $[M+H]^+$.

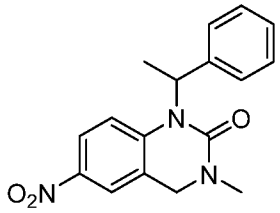




(R)-1-(tert-butyl)-3-(4-(3-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea and (S)-1-(tert-butyl)-3-(4-(3-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

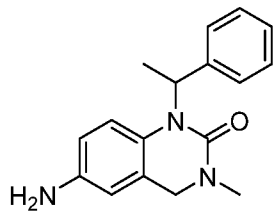
A sample of 3-tert-butyl-1-{2-methyl-4-[(3-methylphenyl)methyl]-3-oxo-2H-1,4-benzoxazin-7-yl}urea (170 mg) was separated by chiral-HPLC using a CHIRALPAK IE, 2*25 cm, 5 μm column (eluent: 20% to 20% (v/v) Hex(0.5% 2M NH_3-MeOH) and EtOH) to yield first enantiomer example 3-tert-butyl-1-[(2R)-2-methyl-4-[(3-methylphenyl)methyl]-3-oxo-2H-1,4-benzoxazin-7-yl]urea (23 mg) as a white solid. MS(ESI): mass calcd. for $C_{21}H_{24}ClN_3O_3$: 401.89, found: 402.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.93 – 8.31 (m, 1H), 7.29 – 7.44 (m, 3H), 7.13 – 7.29 (m, 2H), 6.68 – 6.99 (m, 2H), 5.84 – 6.08 (m, 1H), 4.97 – 5.21 (m, 2H), 4.71 – 4.89 (m, 1H), 1.40 – 1.58 (m, 3H), 1.21 – 1.30 (m, 9H). And to yield second enantiomer example 3-tert-butyl-1-[(2S)-2-methyl-4-[(3-methylphenyl)methyl]-3-oxo-2H-1,4-benzoxazin-7-yl]urea (24.5 mg) as a white solid. MS(ESI): mass calcd. for $C_{21}H_{24}ClN_3O_3$: 401.89, found: 402.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.00 – 8.32 (m, 1H), 7.30 – 7.49 (m, 3H), 7.19 – 7.30 (m, 2H), 6.70 – 6.92 (m, 2H), 5.81 – 6.06 (m, 1H), 5.00 – 5.21 (m, 2H), 4.66 – 4.91 (m, 1H), 1.43 – 1.54 (m, 3H), 1.25 – 1.30 (m, 9H).

Example 45 and Example 45: 3-tert-butyl-1-{3-methyl-2-oxo-1-[(1S)-1-phenylethyl]-4H-quinazolin-6-yl}urea and 3-tert-butyl-1-{3-methyl-2-oxo-1-[(1R)-1-phenylethyl]-4H-quinazolin-6-yl}urea



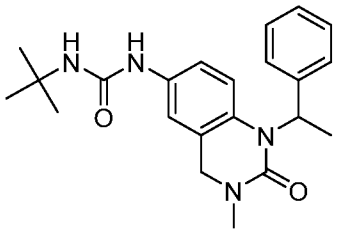
3-methyl-6-nitro-1-(1-phenylethyl)-4H-quinazolin-2-one

To a solution of 3-methyl-6-nitro-1,4-dihydroquinazolin-2-one (600 mg, 2.896 mmol, 1 equiv) and (1-bromoethyl)benzene (800 mg, 4.323 mmol, 1.49 equiv) in dimethylformamide (30 mL) was added Cs_2CO_3 (2802.47 mg, 8.575 mmol, 2.96 equiv). The reaction was stirred at rt for 3h. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 3-methyl-6-nitro-1-(1-phenylethyl)-4H-quinazolin-2-one (765 mg, 84.85%) as a white solid. MS (ESI): mass calcd for $C_{17}H_{19}N_3O_2$: 311.13 m/z, found 312.20$[M+H]^+$.



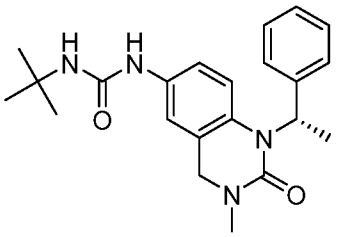
6-amino-3-methyl-1-(1-phenylethyl)-4H-quinazolin-2-one

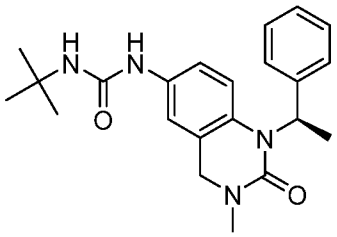
To a solution of 3-methyl-6-nitro-1-(1-phenylethyl)-4H-quinazolin-2-one (755 mg, 2.425 mmol, 1 equiv) in ethyl alcohol/ water (10 mL, 10/1) was added iron (1354.24 mg, 24.250 mmol, 10 equiv) and NH_4Cl (1297.13 mg, 24.250 mmol, 10 equiv). The reaction was stirred at 80 °C for 3h. Quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to 6-amino-3-methyl-1-(1-phenylethyl)-4H-quinazolin-2-one (200 mg, 29.31%) as a white solid. MS (ESI): mass calcd for$C_{17}H_{19}N_3O$: 281.15m/z, found 282.20 $[M+H]^+$.



1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea

To a solution of 6-amino-3-methyl-1-(1-phenylethyl)-4H-quinazolin-2-one (190 mg, 0.675 mmol, 1 equiv) in DCM/toluene (5 mL2/1) was added2-isocyanato-2-methylpropane (220.64 mg, 2.226 mmol, 3.30 equiv) The reaction was stirred at 90°C for 3h. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 3-tert-butyl-1-{3-methyl-2-oxo-1-[(1R)-1-phenylethyl]-4H-quinazolin-6-yl}urea (178 mg, 69.3%) as a white solidLC/MS (ESI): mass calcd. for $C_{22}H_{28}N_4O_2$:380.22 m/z, found:381.10 $[M+H]^+$.



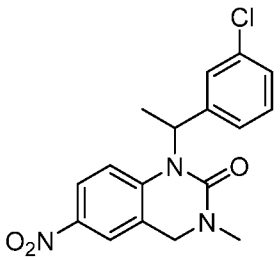


(S)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea and (R)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea.

A sample of 1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea (170 mg) was separated by chiral-HPLC using a (R, R)-WHELK-O1-Kromasil 2.11*25 cm, 5 μm column (eluent: MtBE(0.5% 2M NH_3-MeOH)--HPLC and Hex(EtOH--HPLC) to yield first example cyclopentyl 3-tert-butyl-1-{3-methyl-2-oxo-1-[(1R)-1-phenylethyl]-4H-quinazolin-6-yl}urea (26.6 mg). LC/MS (ESI): mass calcd. for $C_{22}H_{28}N_4O_2$:380.22 m/z, found:381.05 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 8.05 (s, 1H), 7.26 – 7.37 (m, 5H), 6.80 (m, 1H), 6.37 (m, 1H), 5.92 (m, 2H), 4.32 (m, 2H), 2.92 (s, 3H), 1.74 (m, 3H), 1.19-1.25 (s, 10H). And to yield second enantiomer example cyclopentyl 3-tert-butyl-1-{3-methyl-2-oxo-1-[(1S)-1-phenylethyl]-4H-quinazolin-6-yl}urea (41.6 mg). LC/MS (ESI): mass calcd. for $C_{22}H_{28}N_4O_2$:380.22 m/z, found:381.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6)

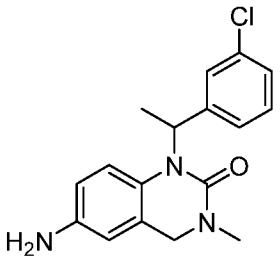
δ 8.05 (s, 1H), 7.26 – 7.37 (m, 5H), 6.80 (m, 1H), 6.37 (m, 1H), 5.92 (m, 2H), 4.32 (m, 2H), 2.92 (s, 3H), 1.74 (m, 3H), 1.19-1.25 (m, 10H).

Example 46 and Example 52: (S)-1-(tert-butyl)-3-(1-(1-(4-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea and (R)-1-(tert-butyl)-3-(1-(1-(4-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea



1-(1-(3-chlorophenyl)ethyl)-3-methyl-6-nitro-3,4-dihydroquinazolin-2(1H)-one

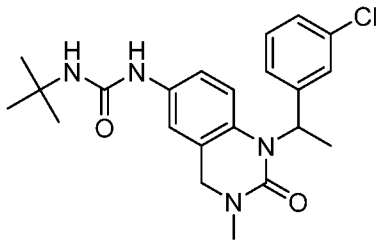
To a stirred mixture of 3-methyl-6-nitro-1,4-dihydroquinazolin-2-one (500 mg, 2.413 mmol, 1 equiv) and Cs_2CO_3 (1.57 g, 4.826 mmol, 2 equiv) in DMF (10 mL) was added 1-(1-bromoethyl)-3-chlorobenzene (635.68 mg, 2.896 mmol, 1.2 equiv) in portions at 25°C under air atmosphere. The resulting mixture was stirred for 2h at room temperature. Desired product could be detected by LCMS. The mixture was diluted with water (50 mL). The resulting mixture was extracted with EA (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 1-(1-(3-chlorophenyl)ethyl)-3-methyl-6-nitro-3,4-dihydroquinazolin-2(1H)-one (640 mg, 76.70%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{16}ClN_3O_3$: 345.09 m/z, found 345.78 $[M+H]^+$.



6-amino-1-(1-(3-chlorophenyl)ethyl)-3-methyl-3,4-dihydroquinazolin-2(1H)-one

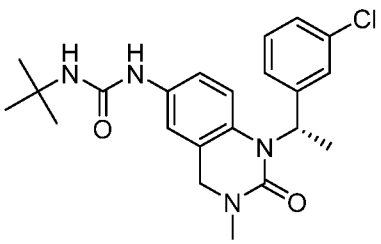
To a stirred mixture of 1-(1-(3-chlorophenyl)ethyl)-3-methyl-6-nitro-3,4-dihydroquinazolin-2(1H)-one (630 mg, 1.822 mmol, 1 equiv) and Fe (1017.48 mg, 18.220 mmol, 10 equiv) in EtOH (8 mL) and H_2O (0.8 mL) was added NH_4Cl (974.57 mg, 18.220 mmol, 10

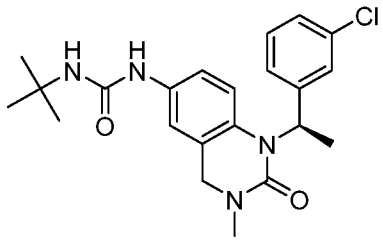
equiv) in portions at 70 degrees C under air atmosphere. The resulting mixture was stirred for 2h at room temperature. Desired product could be detected by LCMS. The mixture was diluted with water (100 mL). The resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 6-amino-1-(1-(3-chlorophenyl)ethyl)-3-methyl-3,4-dihydroquinazolin-2(1H)-one (240 mg, 41.71%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{16}ClN_3O$: 315.11 m/z, found 315.80 $[M+H]^+$.



1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea

To a stirred mixture of 6-amino-1-(1-(3-chlorophenyl)ethyl)-3-methyl-3,4-dihydroquinazolin-2(1H)-one(242 mg, 0.766 mmol, 1 equiv) and 2-isocyanato-2-methylpropane (151.93 mg, 1.532 mmol, 2 equiv) in DCM (5 mL) was added TEA (232.63 mg, 2.298 mmol, 3 equiv) at 25 degrees C under air atmosphere. The resulting mixture was stirred for 2h at room temperature. Desired product could be detected by LCMS. The mixture was diluted with water (30 mL). The resulting mixture was extracted with EA (3 x 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea (110 mg, 34.60%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{27}ClN_4O_2$: 414.18 m/z, found 414.93[M+H] $^+$

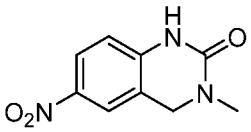




(S)-1-(tert-butyl)-3-(1-(1-(4-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea and (R)-1-(tert-butyl)-3-(1-(1-(4-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea

The 1-(tert-butyl)-3-(1-(1-(4-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea (110 mg) was separated by chiral-HPLC using a CHIRALPAK ID, 2*25 cm, 5 μm column (eluent: 10% to 10% (v/v) : EtOH--HPLC and Hex(0.5% 2M NH_3-MeOH) to yield first enantiomer example (R)-1-(tert-butyl)-3-(1-(1-(4-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea (24.4 mg, 7.57%) as a white solid. LC/MS: mass calcd for $C_{22}H_{27}ClN_4O_2$: 414.18, found: 415.00 $[M+H]^+$. ^{1}H-NMR (300 MHz, DMSO-d6) δ 8.07 (s, 1H), 7.32 – 7.39 (m, 1H), 7.20 – 7.30 (m, 4H), 6.80 – 6.92 (m, 1H), 6.39 (d, J = 8.8 Hz, 1H), 5.75 – 5.96 (m, 2H), 4.32 (s, 2H), 2.92 (s, 3H), 1.74 (d, J = 7.1 Hz, 3H), 1.26 (s, 9H). And to yield second enantiomer example (S)-1-(tert-butyl)-3-(1-(1-(4-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea (16.4 mg, 5.19%) as a white soild. LC/MS: mass calcd. for $C_{22}H_{27}ClN_4O_2$: 414.18, found: 415.00 $[M+H]^+$. ^{1}H-NMR (300 MHz, DMSO-d6) δ 8.07 (s, 1H), 7.20 – 7.42 (m, 5H), 6.81 – 6.91 (m, 1H), 6.38 (d, *J* = 8.8 Hz, 1H), 5.78 – 5.96 (m, 2H), 4.32 (s, 2H), 2.91 (s, 3H), 1.73 (d, J = 7.1 Hz, 3H), 1.25 (s, 9H).

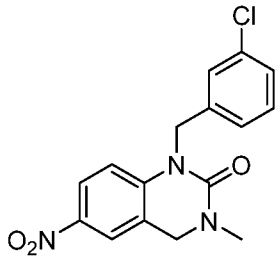
Example 47: 1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea



3-methyl-6-nitro-3,4-dihydroquinazolin-2(1H)-one

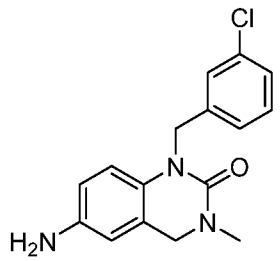
To a stirred mixture of 3-methyl-1,4-dihydroquinazolin-2-one (1 g, 6.166 mmol, 1 equiv) in H_2SO_4 (30 mL) was added KNO_3 (0.50 g, 4.933 mmol, 0.8 equiv) in portions at 0°C under air atmosphere. The resulting mixture was stirred for 2h at room temperature. Desired product could be detected by LCMS. The mixture was diluted with water (100 mL). The resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 3-methyl-6-

nitro-3,4-dihydroquinazolin-2(1H)-one (400 mg, 31.31%) as a white solid. MS (ESI): mass calcd. for $C_9H_9N_3O_3$: 207.06 m/z, found 208.19 $[M+H]^+$.



1-(3-chlorobenzyl)-3-methyl-6-nitro-3,4-dihydroquinazolin-2(1H)-one

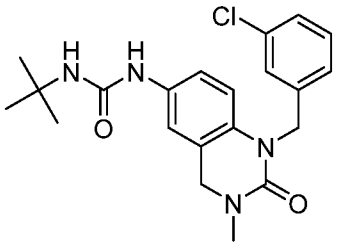
To a stirred mixture of 3-methyl-6-nitro-3,4-dihydroquinazolin-2(1H)-one (300 mg, 1.448 mmol, 1 equiv) and 1-(bromomethyl)-3-chlorobenzene (357.03 mg, 1.738 mmol, 1.2 equiv) in DMF (5 mL) was added Cs_2CO_3 (1419.69 mg, 4.344 mmol, 3 equiv) in portions at 25 degrees C under air atmosphere. The resulting mixture was stirred for 2h at room temperature. Desired product could be detected by LCMS. The mixture was diluted with water (50 mL). The resulting mixture was extracted with EA (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 1-(3-chlorobenzyl)-3-methyl-6-nitro-3,4-dihydroquinazolin-2(1H)-one (400 mg, 83.27%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{14}ClN_3O_3$: 331.07 m/z, found 331.76 $[M+H]^+$.



6-amino-1-(3-chlorobenzyl)-3-methyl-3,4-dihydroquinazolin-2(1H)-one

To a stirred mixture of 1-(3-chlorobenzyl)-3-methyl-6-nitro-3,4-dihydroquinazolin-2(1H)-one (395 mg, 1.191 mmol, 1 equiv) and Fe (664.90 mg, 11.910 mmol, 10 equiv) in EtOH (5 mL) and H_2O (0.5 mL) was added NH_4Cl (636.86 mg, 11.910 mmol, 10 equiv) in portions at 25 degrees C under air atmosphere. The resulting mixture was stirred for 2h at 60 degrees C. Desired product could be detected by LCMS. The mixture was diluted with water (50 mL). The resulting mixture was extracted with EA (3 x 50 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel

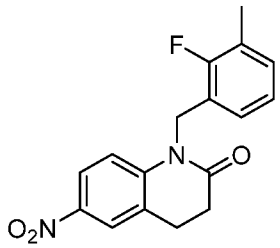
column chromatography, eluted with PE / EA (1:1) to afford 6-amino-1-(3-chlorobenzyl)-3-methyl-3,4-dihydroquinazolin-2(1H)-one (160 mg, 44.53%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{16}ClN_3O$: 301.10 m/z, found 301.77[M +H] $^+$.



1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea

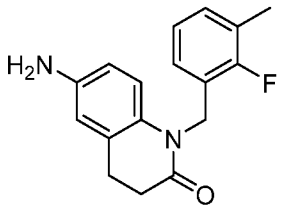
To a stirred mixture of 6-amino-1-(3-chlorobenzyl)-3-methyl-3,4-dihydroquinazolin-2(1H)-one (150 mg, 0.497 mmol, 1 equiv) and 2-isocyanato-2-methylpropane (98.55 mg, 0.994 mmol, 2 equiv) in dichloromethane (1 mL) was added TEA (150.90 mg, 1.491 mmol, 3 equiv) dropwise at 0 degrees C under air atmosphere. The resulting mixture was stirred for 2h at room temperature. Desired product could be detected by LCMS. The mixture was diluted with water (30 mL). The resulting mixture was extracted with EA (3 x 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford the 1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea(31.9 mg, 15.65%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{25}ClN_4O_2$: 400.17 m/z, found 401.00[M +H]$^+$. ^{1}H-NMR (300 MHz, DMSO-d6) δ 8.11 (s, 1H), 7.22 – 7.40 (m, 4H), 7.18 (d, J = 7.4 Hz, 1H), 6.90 – 6.99 (m, 1H), 6.56 (d, J = 8.7 Hz, 1H), 5.91 (s, 1H), 5.02 (s, 2H), 4.42 (s, 2H), 2.95 (s, 3H), 1.26 (s, 9H).

Example 48: 1-(tert-butyl)-3-(1-(2-fluoro-3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea



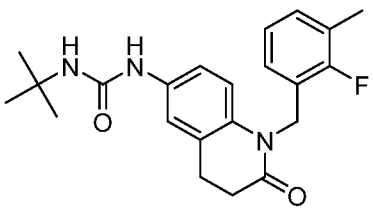
1-(2-fluoro-3-methylbenzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one

To a stirred solution of 6-nitro-3,4-dihydro-1H-quinolin-2-one (300 mg, 1.561 mmol, 1 equiv) in DMF (5 mL) was added 1-(bromomethyl)-2-fluoro-3-methylbenzene (412.08 mg, 2.029 mmol, 1.3 equiv) and Cs_2CO_3 (1.53 g, 4.683 mmol, 3 equiv) at rt and stirred for overnight. After completion of reaction, the resulting mixture was extracted with EA (3 x 30 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (3:1) to afford 1-(2-fluoro-3-methylbenzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (420 mg, 85.60%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{15}FN_2O_3$: 314.11 m/z, found 315.05 $[M+H]^+$.



6-amino-1-(2-fluoro-3-methylbenzyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of 1-(2-fluoro-3-methylbenzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (200 mg, 0.636 mmol, 1 equiv) in 20 mL MeOH was added Pd/C (30 mg) under nitrogen atmosphere. The mixture was hydrogenated at room temperature for 50 min under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure to afford 6-amino-1-(2-fluoro-3-methylbenzyl)-3,4-dihydroquinolin-2(1H)-one (160 mg, 88.44%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{17}FN_2O$: 284.13 m/z, found 285.10 $[M+H]^+$.

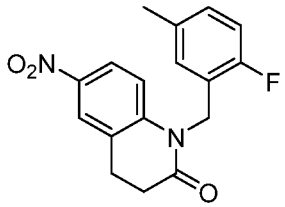


1-(tert-butyl)-3-(1-(2-fluoro-3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a stirred solution of 6-amino-1-[(2-fluoro-3-methylphenyl)methyl]-3,4-dihydroquinolin-2-one (80 mg, 0.281 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (139.46 mg, 1.405 mmol, 5 equiv) and Et_3N (85.41 mg, 0.843 mmol, 3 equiv) at rt and stirred for overnight. The reaction progress was monitored by LCMS. After completion of reaction, the reaction mixture was concentrated under reduced pressure to give crude product

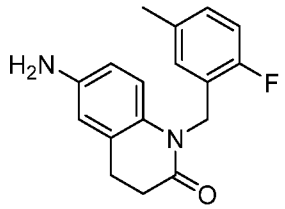
which was further purified by Prep-HPLC with the following conditions Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9; Number Of Runs: 0 to afford 3-tert-butyl-1-{1-[(2-fluoro-3-methylphenyl)methyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea (29.0 mg, 26.78%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{26}FN_3O_2$: 383.20 m/z, found 384.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.15 (t, J = 7.3 Hz, 1H), 6.92 – 7.04 (m, 2H), 6.76 – 6.88 (m, 1H), 6.71 (d, J = 8.7 Hz, 1H), 5.93 (s, 1H), 5.09 (s, 2H), 2.89 (dd, J = 8.7, 5.8 Hz, 2H), 2.65 (dd, J = 8.7, 5.8 Hz, 2H), 2.25 (d, J = 2.0 Hz, 3H), 1.27 (s, 9H).

Example 49: 1-(tert-butyl)-3-(1-(2-fluoro-5-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea



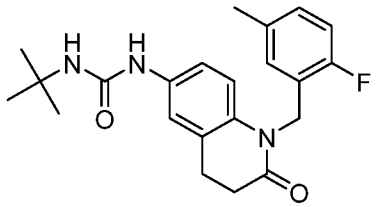
1-(2-fluoro-5-methylbenzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one

To a stirred solution of 6-nitro-3,4-dihydro-1H-quinolin-2-one (300 mg, 1.561 mmol, 1 equiv) in DMF (5 mL) was added 2-(bromomethyl)-1-fluoro-4-methylbenzene (412.08 mg, 2.029 mmol, 1.3 equiv) and Cs_2CO_3 (1.53 g, 4.683 mmol, 3 equiv) at rt and stirred for overnight. After completion of reaction, the resulting mixture was extracted with EA (3 x 20 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (3:1) to afford 1-(2-fluoro-5-methylbenzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (400 mg, 81.52%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{15}FN_2O$: 314.11 m/z, found 315.05 [M +H] +.



6-amino-1-(2-fluoro-5-methylbenzyl)-3,4-dihydroquinolin-2(1H)-one

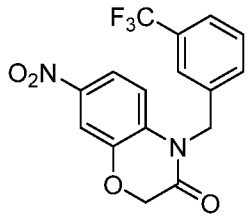
To a solution of 1-(2-fluoro-5-methylbenzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (200 mg, 0.636 mmol, 1 equiv) in 20 mL MeOH was added Pd/C (30 mg) under nitrogen atmosphere. The mixture was hydrogenated at room temperature for 30 min under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure to afford 6-amino-1-(2-fluoro-5-methylbenzyl)-3,4-dihydroquinolin-2(1H)-one (160 mg, 88.40%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{17}FN_2O$: 284.13 m/z, found 285.10 [M +H] +.



1-(tert-butyl)-3-(1-(2-fluoro-5-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

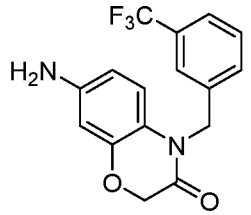
To a stirred solution of 6-amino-1-[(2-fluoro-5-methylphenyl)methyl]-3,4-dihydroquinolin-2-one (80 mg, 0.281 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (139.46 mg, 1.405 mmol, 5 equiv) and Et_3N (85.41 mg, 0.843 mmol, 3 equiv) at rt and stirred for overnight. The reaction progress was monitored by LCMS. After completion of reaction, the reaction mixture was concentrated under reduced pressure to give crude product which was further purified by HPLC with the following conditions Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9; Number Of Runs: 0 to afford 1-(tert-butyl)-3-(1-(2-fluoro-5-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea (8.1 mg, 7.49%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{26}FN_3O_2$: 383.20 m/z, found 384.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.16 – 7.04 (m, 2H), 7.00 (dd, J = 8.7, 2.5 Hz, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.93 (s, 1H), 5.06 (s, 2H), 2.89 (t, J = 7.2 Hz, 2H), 2.66 (dd, J = 8.8, 5.8 Hz, 2H), 2.19 (s, 3H), 1.27 (s, 9H).

Example 50: 1-(tert-butyl)-3-(3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea



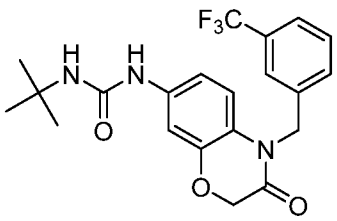
7-nitro-4-(3-(trifluoromethyl)benzyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of 7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (500 mg, 2.575 mmol, 1 equiv) in DMF (10 mL) was added Cs_2CO_3 (1.678 g, 5.150 mmol, 2 equiv) and 1-(bromomethyl)-3-(trifluoromethyl)benzene (676.8 mg, 2.832 mmol, 1.1 equiv). The resulting mixture was stirred for 16 h at rt. The mixture was diuted with EtOAc (100 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 7-nitro-4-(3-(trifluoromethyl)benzyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (473.8 mg, 52.23%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{11}F_3N_2O_4$: 352.07 m/z, found 353.05 $[M+H]^+$.



7-amino-4-(3-(trifluoromethyl)benzyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of 7-nitro-4-(3-(trifluoromethyl)benzyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (300 mg, 0.852 mmol, 1 equiv) in MeOH (10 mL) was added Pd/C (100 mg). The reaction mixture was then stirred for 1 h under hydrogen atmosphere (balloon). The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to afford 7-amino-4-(3-(trifluoromethyl)benzyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (263.6 mg, 96.0%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{13}F_3N_2O_2$, 322.09 m/z, found 323.05 $[M+H]^+$.

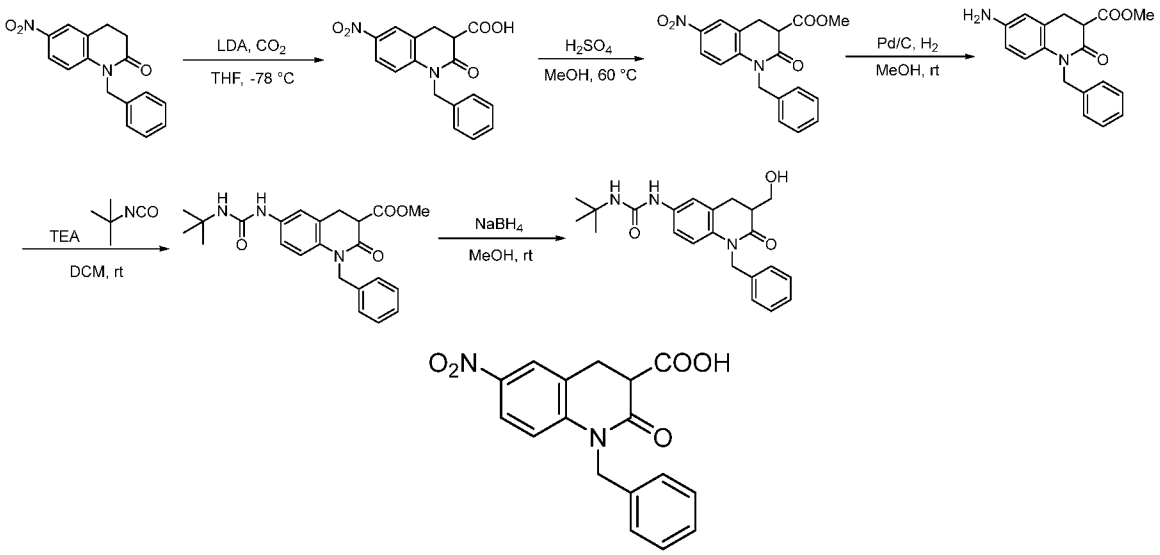


1-(tert-butyl)-3-(3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a stirred solution of 7-amino-4-(3-(trifluoromethyl)benzyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (90 mg, 0.279 mmol, 1 equiv) in DCM (6 mL) & toluene (2mL) was added 2-isocyanato-2-methylpropane (82.97 mg, 0.837 mmol, 3 equiv) stirred 16 h at 90 °C. The reaction mixture was concentrated under vacuum to yield a crude product which was directly purified Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 9; Number Of Runs: 0) to afford 1-(tert-butyl)-3-(3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea (2.1 mg, 1.7%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{22}F_3N_3O_3$, 421.16 m/z, found 422.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.49 – 7.70 (m, 4H), 7.21 (d, J = 2.3 Hz, 1H), 6.87 – 6.90 (m, 1H), 6.75 – 6.79 (m, 1H), 5.94 (s, 1H), 5.19 – 5.23 (m, 2H), 4.75 – 4.78 (m, 2H), 1.23 – 1.29 (m, 9H).

Example 51: 1-(1-benzyl-3-(hydroxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

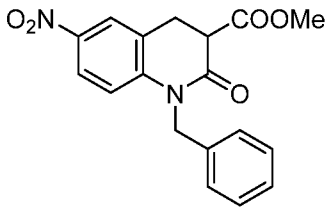
Synthetic Scheme



1-benzyl-6-nitro-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylic acid

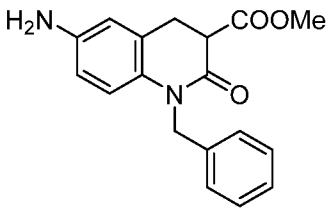
In a 50-mL round bottom flask, to a solution of 1-benzyl-6-nitro-3,4-dihydroquinolin-2-one (500 mg, 1.771 mmol, 1 equiv) in tetrahydrofuran (5 mL, 0.069 mmol, 0.04 equiv) was added dropwise 2M LDA (in THF) (1 mL, 1.948 mmol, 1.1 equiv) at -78 °C under N_2. The

reaction mixture was stirred at -78 °C for 30 min. The reaction was quenched with dry ice. The mixture was stirred for 10 min at rt. NH_4Cl (aq.) was added into the mixture. The mixture was acidified pH = 5 with HCl (1N). The solution was extracted with EA (3 x 50 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel column, eluted with DCM /MeOH (8:1) to afford 1-benzyl-6-nitro-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (150 mg, 25.95%) as an off-white solid. MS (ESI): mass calcd. for $C_{17}H_{14}N_2O_5$, 326.09 m/z, found 327.05 $[M+H]^+$.



methyl 1-benzyl-6-nitro-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate

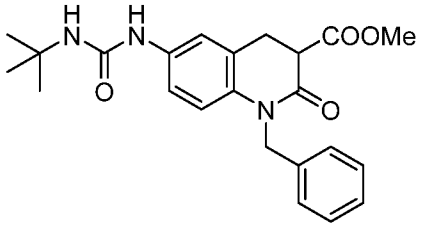
A solution of 1-benzyl-6-nitro-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (500 mg, 1.532 mmol, 1 equiv) in methanol (10 mL) was added sulfuric acid (0.1 mL) at rt. The resulting mixture was stirred for 2 h at 70 °C. Quench with water (10 mL) and extract with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column, eluted with PE /EA (3:1) to afford methyl 1-benzyl-6-nitro-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (150 mg, 28.76%) as white solid. MS (ESI): mass calcd. for $C_{18}H_{16}N_2O_5$, 340.11 m/z, found 341.05 $[M+H]^+$.



methyl 6-amino-1-benzyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate

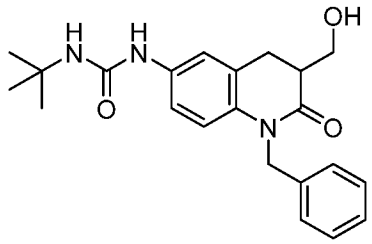
To a solution of methyl 1-benzyl-6-nitro-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (200 mg, 0.588 mmol, 1 equiv) in MeOH (10 mL) was added Pd/C (30 mg). The reaction mixture was then stirred for 1 h under hydrogen atmosphere (balloon). The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to afford methyl 6-

amino-1-benzyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (150 mg, 79.36%) as a yellow solid. MS (ESI): mass calcd. for $C_{18}H_{18}N_2O_3$, 310.13 m/z, found 311.15 $[M+H]^+$.



methyl 1-benzyl-6-(3-(tert-butyl)ureido)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate

To a stirred solution of methyl 6-amino-1-benzyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (150 mg, 0.483 mmol, 1 equiv) in DCM (8 mL) was added 2-isocyanato-2-methylpropane (239.5 mg, 2.417 mmol, 5 equiv) and TEA (146.7 mg, 1.450 mmol, 3 equiv) stirred overnight at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column eluted with PE / EA (2:1) to afford methyl 1-benzyl-6-[(tert-butylcarbamoyl)amino]-2-oxo-3,4-dihydroquinoline-3-carboxylate (70 mg, 31.95%) as a yellow solid. MS (ESI): mass calcd. for $C_{23}H_{27}N_3O_4$, 409.20 m/z, found 410.25 $[M+H]^+$.

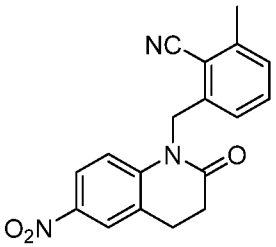


1-(1-benzyl-3-(hydroxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

To a stirred solution of methyl 1-benzyl-6-[(tert-butylcarbamoyl)amino]-2-oxo-3,4-dihydroquinoline-3-carboxylate (70 mg, 0.171 mmol, 1 equiv) in MeOH (5 mL) was added $NaBH_4$ (64.6 mg, 1.709 mmol, 10 equiv) stirred 3 h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9; Number Of Runs: 0) to afford 1-[1-

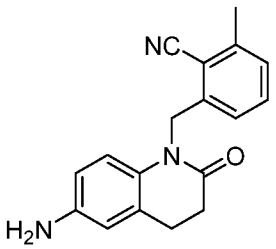
benzyl-3-(hydroxymethyl)-2-oxo-3,4-dihydroquinolin-6-yl]-3-tert-butylurea (9.9 mg, 15.13%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_3$, 381.21 m/z, found 382.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.11 (s, 1H), 7.25 – 7.36 (m, 3H), 7.12 – 7.24 (m, 3H), 6.96 (dd, J = 8.6, 2.4 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 5.93 (s, 1H), 5.08 (s, 2H), 4.78 (s, 1H), 3.68 – 3.83 (m, 1H), 3.59 (d, J = 10.8 Hz, 1H), 2.98 (dd, J = 15.4, 5.6 Hz, 1H), 2.75 – 2.90 (m, 1H), 2.65 – 2.75 (m, 1H), 1.26 (s, 9H).

Example 53: 3-tert-butyl-1-{1-[(2-cyano-3-methylphenyl)methyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea



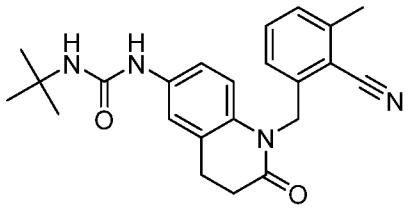
2-methyl-6-[(6-nitro-2-oxo-3,4-dihydroquinolin-1-yl)methyl]benzonitrile

To a stirred solution of 2-(bromomethyl)-6-methylbenzonitrile (400 mg, 1.904 mmol, 1 equiv) and 6-nitro-3,4-dihydro-1H-quinolin-2-one (548.88 mg, 2.856 mmol, 1.5 equiv) in DMF (15 mL) was added K_2CO_3 (662.69 mg, 4.760 mmol, 2.5 equiv) in portions at room temperature under nitrogen atmosphere. The final reaction mixture was stirred for 2 h at room temperature. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford 2-methyl-6-[(6-nitro-2-oxo-3,4-dihydroquinolin-1-yl)methyl]benzonitrile (400 mg, 65.38%) as a white solid. MS: mass calcd. for $C_{18}H_{15}N_3O_3$: 321.11 m/z, found 322.05 $[M+H]^+$.



2-[(6-amino-2-oxo-3,4-dihydroquinolin-1-yl)methyl]-6-methylbenzonitrile

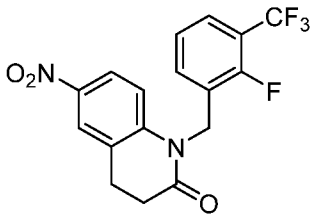
To a stirred solution of 2-methyl-6-[(6-nitro-2-oxo-3,4-dihydroquinolin-1-yl)methyl]benzonitrile (400 mg, 1.245 mmol, 1 equiv) in EtOH/H_2O (11 mL, 10/1) was added Fe (695.16 mg, 12.450 mmol, 10 equiv) and NH_4Cl (665.85 mg, 12.450 mmol, 10 equiv) in portions at room temperature under nitrogen atmosphere. The final reaction mixture was stirred for 2 h at 60°C. The reaction was quenched with water at rt. After filtration, the filter cake was washed with EA (3 x 20 mL). The filtrate was added water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The resulting mixture was concentrated under vacuum. The crude product was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford 2-[(6-amino-2-oxo-3,4-dihydroquinolin-1-yl)methyl]-6-methylbenzonitrile (300 mg, 82.72%) as a light yellow solid.MS: mass calcd. for $C_{18}H_{17}N_3O$: 291.14 m/z, found 292.10 $[M+H]^+$.



3-tert-butyl-1-{1-[(2-cyano-3-methylphenyl)methyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea

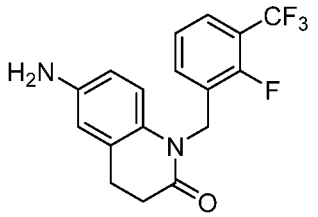
To a stirred solution of 2-[(6-amino-2-oxo-3,4-dihydroquinolin-1-yl)methyl]-6-methylbenzonitrile (150 mg, 0.515 mmol, 1 equiv) in toluene/DCM (10 mL, 1/2) was added 2-isocyanato-2-methylpropane (153.11 mg, 1.545 mmol, 3 equiv) in portions at room temperature under nitrogen atmosphere. The final reaction mixture was stirred for 3 h at 90°C. The reaction was monitored by LCMS. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford 3-tert-butyl-1-{1-[(2-cyano-3-methylphenyl)methyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea (10.3 mg, 5.10%) as a white solid. MS: mass calcd. For $C_{23}H_{26}N_4O_2$: 390.21 m/z, found 391.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.35 – 7.33 (m, 2H),6.99 – 6.97 (m, 2H), 6.66 (d, J = 8.7 Hz, 1H), 5.92 (s, 1H), 5.21 (s, 2H), 2.91 (t, J = 7.8 Hz, 2H), 2.67 (m, 2H), 2.51 (s, 3H), 1.26 (s, 9H).

Example 54: 1-(tert-butyl)-3-(1-(2-fluoro-3-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea



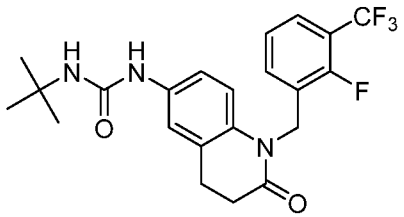
1-(2-fluoro-3-(trifluoromethyl)benzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one

To a solution of To a solution of 6-nitro-3,4-dihydro-1H-quinolin-2-one (500 mg, 2.602 mmol, 1 equiv) in DMF (10 mL) was added K_2CO_3 (431.50 mg, 3.122 mmol, 2 equiv) and 1-(bromomethyl)-2-fluoro-3-(trifluoromethyl)benzene (601.86 mg, 2.341 mmol, 1.5 equiv). The resulting mixture was stirred for 16 h at rt. The mixture was diuted with EtOAc (50 mL), washed with water (3 x 20 mL), brine (2 x 20 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 1-(2-fluoro-3-(trifluoromethyl)benzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (450 mg, 78.27%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{12}F_4N_2O_3$: 368.08 m/z, found 369.05 $[M+H]^+$.



6-amino-1-(2-fluoro-3-(trifluoromethyl)benzyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of 1-(2-fluoro-3-(trifluoromethyl)benzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (430 mg, 1.168 mmol, 1 equiv) in MeOH (10 mL) was added Pd/C (100 mg). The reaction mixture was then stirred for 1 h under hydrogen atmosphere (balloon). The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to afford 6-amino-1-(2-fluoro-3-(trifluoromethyl)benzyl)-3,4-dihydroquinolin-2(1H)-one (370 mg, 93.67%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{14}F_4N_2O$: 338.10 m/z, found 339.15 $[M+H]^+$.

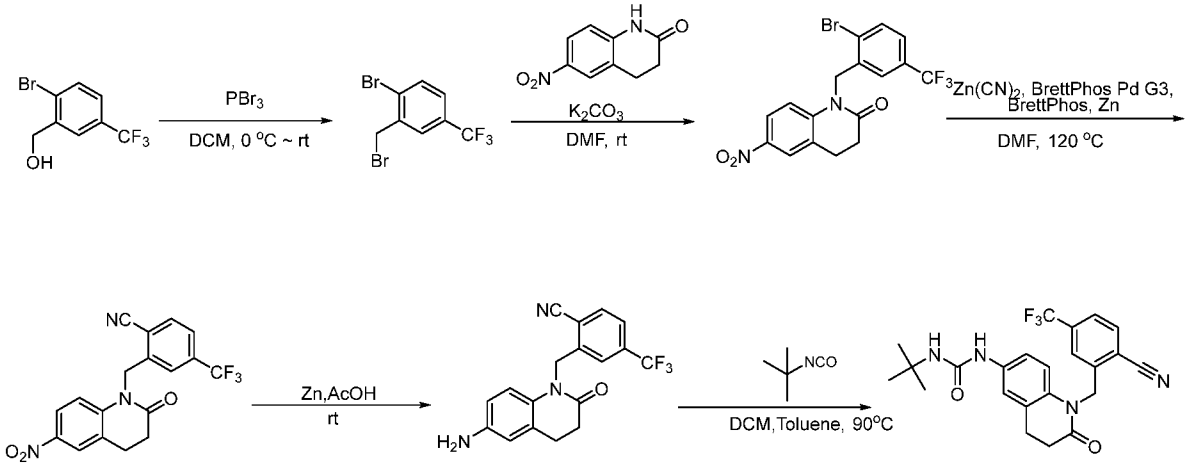


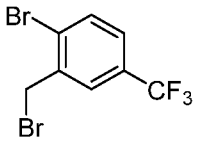
1-(tert-butyl)-3-(1-(2-fluoro-3-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a solution of 6-amino-1-(2-fluoro-3-(trifluoromethyl)benzyl)-3,4-dihydroquinolin-2(1H)-one (150 mg, 0.443 mmol, 1 equiv) in DCM (10 mL) was added TEA (179.47 mg, 1.772 mmol, 4 equiv) and 2-isocyanato-2-methylpropane (219.77 mg, 2.215 mmol, 5 equiv). The resulting mixture was stirred for 16 h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column eluted with PE / EA (2:1) & Prep-HPLC (XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9; Number Of Runs: 0) to afford 1-(tert-butyl)-3-(1-(2-fluoro-3-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea (45.3 mg, 23.26%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{23}F_4N_3O_2$: 437.17, found: 437.95 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.61 – 7.72 (m, 1H), 7.25 – 7.40 (m, 3H), 6.96 – 7.05 (m, 1H), 6.77 (d, J = 8.8 Hz, 1H), 5.93 (s, 1H), 5.18 (s, 2H), 2.85 – 2.95 (m, 2H), 2.61 – 2.71 (m, 2H), 1.26 (s, 9H).

Example 55: 3-tert-butyl-1-(1-{[2-cyano-5-(trifluoromethyl) phenyl] methyl}-2-oxo-3,4-dihydroquinolin-6-yl) urea

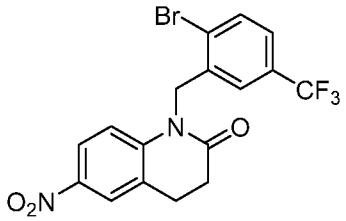
Synthetic Scheme





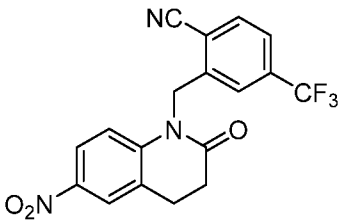
1-bromo-2-(bromomethyl)-4-(trifluoromethyl)benzene

To a stirred solution of [2-bromo-5-(trifluoromethyl) phenyl] methanol (2 g, 7.842 mmol, 1 equiv) in DCM (20 mL) was added phosphorus tribromide (2.12 g, 7.842 mmol, 1 equiv) in portions at 0°C under air atmosphere. The resulting mixture was stirred for 3 h at room temperature under air atmosphere. The reaction was quenched with water (30 mL). The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. This resulted in 1-bromo-2-(bromomethyl)-4-(trifluoromethyl) benzene (1.3 g, 52.14%) as a yellow oil. The crude product was used in the next step directly without further purification.



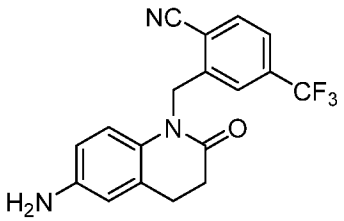
1-{[2-bromo-5-(trifluoromethyl) phenyl] methyl}-6-nitro-3,4-dihydroquinolin-2-one

To a stirred solution of 1-bromo-2-(bromomethyl)-4-(trifluoromethyl) benzene (1.39 g, 4.372 mmol, 1.2 equiv) and 6-nitro-3,4-dihydro-1H-quinolin-2-one (700.16 mg, 3.643 mmol, 1.0 equiv) in DMF (15 mL) was added K_2CO_3 (1014.40 mg, 7.287 mmol, 2 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 3 h at room temperature under air atmosphere. Desired product could be detected by LCMS. The reaction was quenched with water (30 mL). The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 1-{[2-bromo-5-(trifluoromethyl) phenyl] methyl}-6-nitro-3,4-dihydroquinolin-2-one (1.4 g, 89.76%) as a yellow oil. LC/MS: mass calcd. for $C_{17}H_{12}BrF_3N_2O_3$: 428.00, found: 428.95 $[M+H]^+$.



2-[(6-nitro-2-oxo-3,4-dihydroquinolin-1-yl) methyl]-4-(trifluoromethyl)benzonitrile

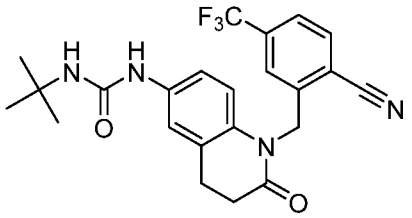
To a stirred solution of 1-{[2-bromo-5-(trifluoromethyl) phenyl] methyl}-6-nitro-3,4-dihydroquinolin-2-one (600 mg, 1.398 mmol, 1 equiv) and $Zn(CN)_2$ (196.98 mg, 1.678 mmol, 1.2 equiv) in DMF (10 mL) was added BrettPhos Pd G3 (253.45 mg, 0.280 mmol, 0.2 equiv) and BrettPhos (150.08 mg, 0.280 mmol, 0.2 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 3 h at 120°C under nitrogen atmosphere. After cooling down to rt, the reaction was quenched with water (30 mL). The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 2-[(6-nitro-2-oxo-3,4-dihydroquinolin-1-yl) methyl]-4-(trifluoromethyl) benzonitrile (100 mg, 19.06%) as a yellow oil. Desired product could be detected by TLC.



2-[(6-amino-2-oxo-3,4-dihydroquinolin-1-yl) methyl]-4-(trifluoromethyl)benzonitrile

To a stirred solution of 2-[(6-nitro-2-oxo-3,4-dihydroquinolin-1-yl) methyl]-4-(trifluoromethyl) benzonitrile (100 mg, 0.266 mmol, 1 equiv) in AcOH was added Zn (209.04 mg, 3.192 mmol, 12 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 3 h at room temperature under air atmosphere. Desired product could be detected by LCMS. The reaction was quenched with water (30 mL). The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 2-[(6-amino-2-oxo-3,4-

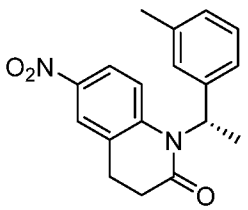
dihydroquinolin-1-yl) methyl]-4-(trifluoromethyl) benzonitrile (85 mg, 92.54%) as an off-white solid. LC/MS: mass calcd. for $C_{18}H_{14}F_3N_3O$: 345.11, found: 346.05 $[M+H]^+$.



3-tert-butyl-1-(1-{[2-cyano-5-(trifluoromethyl) phenyl] methyl}-2-oxo-3,4-dihydroquinolin-6-yl) urea

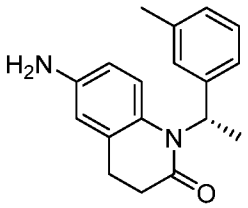
To a stirred solution of 2-[(6-amino-2-oxo-3,4-dihydroquinolin-1-yl) methyl]-4-(trifluoromethyl) benzonitrile (100 mg, 0.290 mmol, 1 equiv) in DCM/Toluene (10 mL, 2/1) was added 2-isocyanato-2-methylpropane (114.83 mg, 1.160 mmol, 4 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 3 h at 90 °C under air atmosphere. Desired product could be detected by LCMS. The reaction was quenched with water (30 mL). The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by Prep-HPLC with the following conditions to afford 3-tert-butyl-1-(1-{[2-cyano-5-(trifluoromethyl) phenyl] methyl}-2-oxo-3,4-dihydroquinolin-6-yl) urea (20.3 mg, 15.49%) as a white solid. MS (ESI): mass calcd. for $C_{23}H_{23}F_3N_4O_2$: 444.2m/z, found 445.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.09 – 8.19 (m, 2H), 7.86 (d, J = 8.1 Hz, 1H), 7.55 (s, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.03 (dd, J = 8.8, 2.4 Hz, 1H), 6.77 (d, J = 8.7 Hz, 1H), 5.94 (s, 1H), 5.33 (s, 2H), 2.92 (t, J = 7.3 Hz, 2H), 2.67 (t, J = 7.2 Hz, 2H), 1.27 (s, 9H). ^{19}F NMR (282 MHz, DMSO) δ -62.00.

Example 56: (S)-1-(tert-butyl)-3-(2-oxo-1-(1-(m-tolyl)ethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea



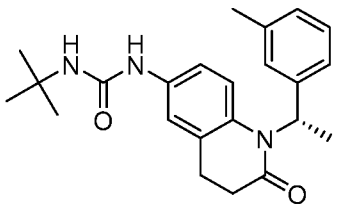
(S)-6-nitro-1-(1-(m-tolyl)ethyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of (1R)-1-(3-methylphenyl)ethanol (300 mg, 2.203 mmol, 1 equiv) in DCM (5 mL) was added 6-nitro-3,4-dihydro-1H-quinolin-2-one (465.64 mg, 2.423 mmol, 1.1 equiv) and PPh_3 (577.76 mg, 2.203 mmol, 1 equiv). DEAD (383.62 mg, 2.203 mmol, 1 equiv) was added the mixture at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 16 h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford (S)-6-nitro-1-(1-(m-tolyl)ethyl)-3,4-dihydroquinolin-2(1H)-one (310 mg, 45.35%) as a yellow solid. MS (ESI): mass calcd. for $C_{18}H_{18}N_2O_3$: 310.353, found: 311.10 $[M+H]^+$.



(S)-6-amino-1-(1-(m-tolyl)ethyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of (S)-6-nitro-1-(1-(m-tolyl)ethyl)-3,4-dihydroquinolin-2(1H)-one (200 mg, 0.644 mmol, 1 equiv) in MeOH (10 mL) was added Pd/C (30 mg). The reaction mixture was then stirred for 1 h under hydrogen atmosphere (balloon). The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to afford (S)-6-amino-1-(1-(m-tolyl)ethyl)-3,4-dihydroquinolin-2(1H)-one (170 mg, 94.44%) as a yellow solid. MS (ESI): mass calcd. For $C_{18}H_{20}N_2O$, 280.16 m/z, found 281.15 $[M+H]^+$.

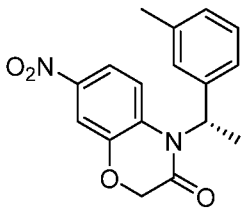


(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(m-tolyl)ethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a stirred solution of (S)-6-amino-1-(1-(m-tolyl)ethyl)-3,4-dihydroquinolin-2(1H)-one (100 mg, 0.357 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (176.79 mg, 1.785 mmol, 5 equiv) and TEA (144.37 mg, 1.428 mmol, 4 equiv) stirred overnight

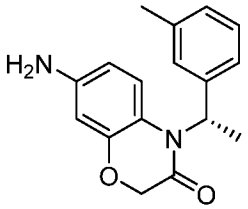
at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column eluted with PE / EA (2:1) & Prep-HPLC (XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 42% B in 10 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.6; Number Of Runs: 0) to afford (S)-1-(tert-butyl)-3-(2-oxo-1-(1-(m-tolyl)ethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea (20.4 mg, 15.03%) as a white solid. MS (ESI): mass calcd. for $C_{23}H_{29}N_3O_2$: 379.23 m/z, found 380.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.32 (d, J = 2.5 Hz, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.01 – 7.11 (m, 3H), 6.78 – 6.87 (m, 1H), 6.44 – 6.53 (m, 1H), 6.06 – 6.20 (m, 1H), 5.93 (s, 1H), 2.73 – 2.88 (m, 2H), 2.52 – 2.73 (m, 2H), 2.29 (s, 3H), 1.66 (d, J = 7.2 Hz, 3H), 1.26 (s, 9H).

Example 57: (S)-1-(tert-butyl)-3-(3-oxo-4-(1-(m-tolyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea



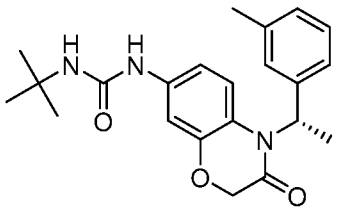
(S)-7-nitro-4-(1-(m-tolyl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (R)-1-(m-tolyl)ethan-1-ol (500 mg, 3.671 mmol, 1 equiv), 7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (784.03 mg, 4.038 mmol, 1.1 equiv) and PPh_3 (1.44 g, 5.506 mmol, 1.5 equiv) in DCM (20 mL) was added DEAD (958.87 mg, 5.506 mmol, 1.5 equiv) under N_2 at 0 °C. The reaction was stirred for 16 h at rt. The mixture was diuted with EtOAc (50 mL), washed with water (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE /EA (3:1) to afford (S)-7-nitro-4-(1-(m-tolyl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (620 mg, 54.07%) as a yellow oil. LC/MS: $C_{17}H_{16}N_2O_4$: 312.325, found: 313.10 $[M+H]^+$.



(S)-7-amino-4-(1-(m-tolyl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (S)-7-nitro-4-(1-(m-tolyl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (300 mg, 0.961 mmol, 1 equiv) in MeOH (10 mL) was added Pd/C (50 mg). The reaction mixture was then stirred for 1 h under hydrogen atmosphere (balloon). The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to afford (S)-7-amino-4-(1-(m-tolyl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (200 mg, 73.75%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{18}N_2O_2$, 282.14 m/z, found 283.20 $[M+H]^+$.

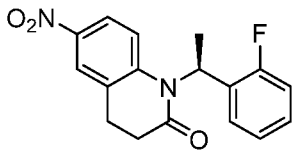


(S)-1-(tert-butyl)-3-(3-oxo-4-(1-(m-tolyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a stirred solution of (S)-7-amino-4-(1-(m-tolyl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (200 mg, 0.708 mmol, 1 equiv) in DCM (10 mL) was added 2-isocyanato-2-methylpropane (351.1 mg, 3.542 mmol, 5 equiv) and TEA (215.0 mg, 2.125 mmol, 3 equiv) stirred 16 h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 37% B to 57% B in 10 min; Wave Length: 220 nm; RT1(min): 9.5; Number Of Runs: 2) to afford (S)-1-(tert-butyl)-3-(3-oxo-4-(1-(m-tolyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea (44.8 mg, 16.56%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_3$, 381.21 m/z, found 382.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.20 – 7.28 (m, 2H), 7.10 (dd, J = 14.1, 6.8 Hz, 3H), 6.62 (dd, J = 8.9, 2.4 Hz, 1H), 6.55 (d, J =

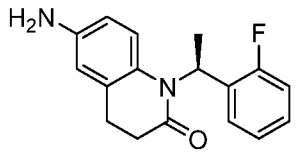
8.8 Hz, 1H), 6.09 (q, J = 7.2 Hz, 1H), 5.94 (s, 1H), 4.57 – 4.75 (m, 2H), 2.30 (s, 3H), 1.70 (d, J = 7.2 Hz, 3H), 1.25 (s, 9H).

Example 58: 3-tert-butyl-1-{1-[(1S)-1-(2-fluorophenyl)ethyl]-2-oxo-3,4-dihydroquinolin-6-yl}ure



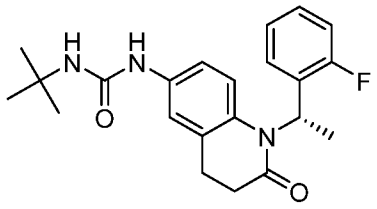
1-[(1S)-1-(2-fluorophenyl)ethyl]-6-nitro-3,4-dihydroquinolin-2-one

To a solution of (1R)-1-(2-fluorophenyl)ethanol (500 mg, 3.567 mmol, 1 equiv) and 6-nitro-3,4-dihydro-1H-quinolin-2-one (685.57 mg, 3.567 mmol, 1 equiv) in DCM (20 mL) was added triphenylphosphine (935.71 mg, 3.567 mmol, 1 equiv). The reaction was stirred at rt under N_2 for 0.5 hour. To the above mixture was added DEAD (621.29 mg, 3.567 mmol, 1 equiv) dropwise at 0 °C. The reaction was stirred at rt under N_2 for 3h. Quenched with water (20 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-[(1S)-1-(2-fluorophenyl)ethyl]-6-nitro-3,4-dihydroquinolin-2-one (723 mg, 64.48%) as a white solid. MS (ESI): mass calcd for $C_{17}H_{15}FN_2O_3$: 314.11 m/z, found 315.00$[M+H]^+$.



6-amino-1-[(1S)-1-(2-fluorophenyl)ethyl]-3,4-dihydroquinolin-2-one

To a solution of 1-[(1S)-1-(2-fluorophenyl)ethyl]-6-nitro-3,4-dihydroquinolin-2-one (710 mg, 2.259 mmol, 1 equiv) in methanol (20 mL) was added Pd/C (710 mg). The resulting mixture was stirred for 1 h at room temperature under hydrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-1-[(1S)-1-(2-fluorophenyl)ethyl]-3,4-dihydroquinolin-2-one (420 mg, 65.39%) as a black liquid. MS (ESI): mass calcd for $C_{17}H_{17}FN_2O$: 284.13m/z, found 285.10 $[M+H]^+$.

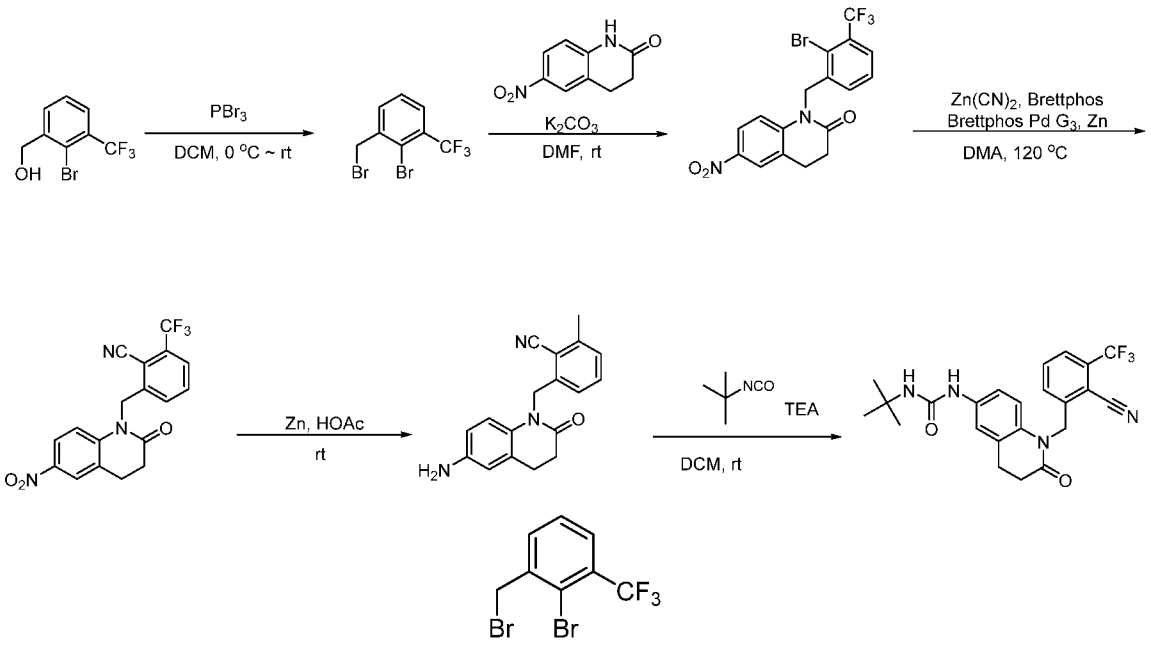


3-tert-butyl-1-{1-[(1S)-1-(2-fluorophenyl)ethyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea

To a solution of 6-amino-1-[(1S)-1-(2-fluorophenyl)ethyl]-3,4-dihydroquinolin-2-one (200 mg, 0.703 mmol, 1 equiv) and 2-isocyanato-2-methylpropane (139.46 mg, 1.406 mmol, 2 equiv) in DCM (20 mL,) was added TEA (213.54 mg, 2.109 mmol, 3.00 equiv). The reaction was stirred at rt for 16h. Quenched with water (20 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column150 mm x 30 mm x 5 μm (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-{1-[(1S)-1-(2-fluorophenyl)ethyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea (21.2 mg, 7.85%) as a white solid. LC/MS (ESI): mass calcd. for $C_{22}H_{26}FN_3O_2$:383.20 m/z, found:384.00 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.46 – 7.55 (m, 1H), 7.21 – 7.33 (m, 2H), 7.17 (m, 1H), 7.06 (m, 1H), 6.93 (m, 1H), 6.81 (m, 1H), 6.00 (m, 1H), 5.89 (s, 1H), 2.69 – 2.79 (m, 2H), 2.40 – 2.50 (m, 2H), 1.76 (s, 3H), 1.26 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ -116.16.

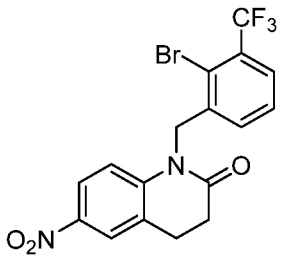
Example 59: 1-(tert-butyl)-3-(1-(2-cyano-3-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

Synthetic Scheme



2-bromo-1-(bromomethyl)-3-(trifluoromethyl)benzene

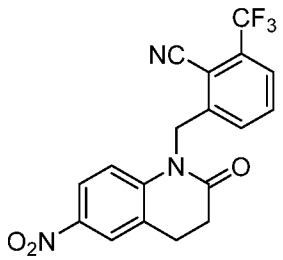
To a solution of [2-bromo-3-(trifluoromethyl)phenyl]methanol (1.5 g, 5.882 mmol, 1 equiv) in DCM (10 mL) was added phosphorus tribromide (3.18 g, 11.764 mmol, 2 equiv) at 0 °C. The reaction was stirred at rt for 2 hours. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. This resulted in 2-bromo-1-(bromomethyl)-3-(trifluoromethyl)benzene (1.83 g, 97.86%) as a yellow oil. MS (ESI): mass calcd. for $C_8H_5Br_2F_3$: 317.93m/z, found 318.90 $[M+H]^+$.



1-(2-bromo-3-(trifluoromethyl)benzyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one

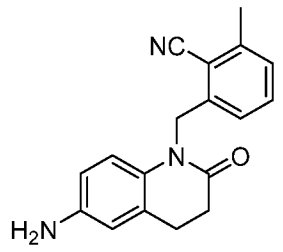
To a solution of 6-nitro-3,4-dihydro-1H-quinolin-2-one (426.14 mg, 2.217 mmol, 1 equiv) in DMF (10 mL) was added K_2CO_3 (617.40 mg, 4.434 mmol, 2 equiv) and 2-bromo-1-(bromomethyl)-3-(trifluoromethyl)benzene (705 mg, 2.217 mmol, 1 equiv). The reaction was stirred at rt for 1 hour. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated.

The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-{[2-bromo-3-(trifluoromethyl)phenyl]methyl}-6-nitro-3,4-dihydroquinolin-2-one (500 mg, 52.54%) as a white solid. MS(ESI): mass calcd. for $C_{17}H_{12}BrF_3N_2O_3$: 429.19 m/z, found 428.95 $[M+H]^+$.



2-((6-nitro-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)-6-(trifluoromethyl)benzonitrile

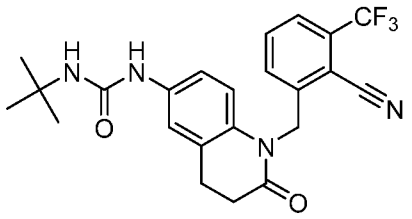
To a solution of 1-{[2-bromo-3-(trifluoromethyl)phenyl]methyl}-6-nitro-3,4-dihydroquinolin-2-one (250 mg, 0.582 mmol, 1 equiv) in DMF (10 mL) was added $Zn(CN)_2$ (82.07 mg, 0.698 mmol, 1.2 equiv), Zn (19.04 mg, 0.291 mmol, 0.5 equiv), BrettPhos (62.53 mg, 0.116 mmol, 0.2 equiv) and BrettPhos Pd G3 (158.41 mg, 0.175 mmol, 0.3 equiv). The reaction was stirred at 120 °C under N_2 for 1h. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 2-[(6-nitro-2-oxo-3,4-dihydroquinolin-1-yl)methyl]-6-(trifluoromethyl)benzonitrile (90 mg, 41.17%) as a white solid. MS (ESI): mass calcd. for $C_{18}H_{12}F_3N_3O_3$: 375.31 m/z, found:370.15 $[M+H]^+$.



2-((6-amino-2-oxo-3,4-dihydroquinolin-1(2H)-yl)methyl)-6-(trifluoromethyl)benzonitrile

To a solution of 2-[(6-nitro-2-oxo-3,4-dihydroquinolin-1-yl)methyl]-6-(trifluoromethyl)benzonitrile (140 mg, 0.373 mmol, 1 equiv) in HOAc (10 mL) was added zinc (243.89 mg, 3.730 mmol, 10 equiv). The reaction was stirred at rt for 1 hour. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with

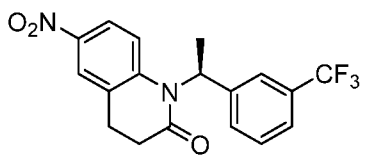
water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 2-[(6-amino-2-oxo-3,4-dihydroquinolin-1-yl)methyl]-6-(trifluoromethyl)benzonitrile (90 mg, 69.87%) as a white solid. MS (ESI): mass calcd. for $C_{18}H_{14}F_3N_3O$: 345.33m/z, found:368.10 $[M+Na]^+$.



1-(tert-butyl)-3-(1-(2-cyano-3-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

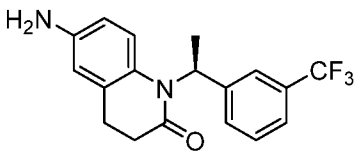
To a solution of 2-[(6-amino-2-oxo-3,4-dihydroquinolin-1-yl)methyl]-6-(trifluoromethyl)benzonitrile (90 mg, 0.261 mmol, 1 equiv) in DCM (10 mL) was added 2-isocyanato-2-methylpropane (103.35 mg, 1.044 mmol, 4 equiv) and TEA (79.12 mg, 0.783 mmol, 3 equiv). The reaction was stirred at rt for 1 day. Quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm column (eluent: 30% to 50% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-(1-{[2-cyano-3-(trifluoromethyl)phenyl]methyl}-2-oxo-3,4-dihydroquinolin-6-yl)urea (51 mg, 44.03%) as a white solid. MS (ESI): mass calcd. for $C_{23}H_{23}F_3N_4O_2$: 444.46m/z, found:445.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 8.04 - 8.29 (m, 1H), 7.89 - 8.00 (m, 1H), 7.73 - 8.00 (m, 1H), 7.45 – 7.55 (m, 1H), 7.35 – 7.45 (m, 1H), 6.88 – 7.09 (m, 1H), 6.67 – 6.80 (m, 1H), 5.82 – 6.07 (m, 1H), 5.20 – 5.50 (m, 2H), 2.86 – 3.07 (m, 2H), 2.60 – 2.78 (m, 2H), 1.15 – 1.38 (m, 9H). ^{19}F NMR (376 MHz, DMSO) δ (ppm): -60.5758.

Example 60: (S)-3-tert-butyl-1-(2-oxo-1-{1-[3-(trifluoromethyl)phenyl]ethyl}-3,4-dihydroquinolin-6-yl)urea



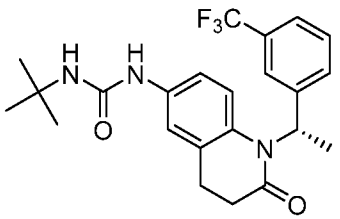
6-nitro-1-[(1S)-1-[3-(trifluoromethyl)phenyl]ethyl]-3,4-dihydroquinolin-2-one

To a solution of (1R)-1-[3-(trifluoromethyl)phenyl]ethanol (500 mg, 2.629 mmol, 1 equiv) and 6-nitro-3,4-dihydro-1H-quinolin-2-one (505.28 mg, 2.629 mmol, 1 equiv) in DCM (20 mL) was added triphenylphosphine (689.64 mg, 2.629 mmol, 1 equiv). The reaction was stirred at rt under N_2 for 0.5 hour. To the above mixture was addedDEAD (457.91 mg, 2.629 mmol, 1 equiv) dropwise at 0 °C. The reaction was stirred at rt under N_2 for 3h. Quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-nitro-1-[(1S)-1-[3-(trifluoromethyl)phenyl]ethyl]-3,4-dihydroquinolin-2-one (285 mg, 29.75%) as a white solid.MS (ESI): mass calcd. for $C_{18}H_{15}F_3N_2O_3$: 364.10 m/z, found 365.11$[M+H]^+$.



6-amino-1-[(1S)-1-[3-(trifluoromethyl)phenyl]ethyl]-3,4-dihydroquinolin-2-one

To a solution of 6-nitro-1-[(1S)-1-[3-(trifluoromethyl)phenyl]ethyl]-3,4-dihydroquinolin-2-one (285 mg, 0.782 mmol, 1 equiv) in methanol (3 mL) was added Pd/C (150 mg). The reaction was stirred at rt under H_2 for 1h. The resulting mixture was stirred for 1 h at room temperature under hydrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 10 mL). The filtrate was concentrated under reduced pressure.The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-1-[(1S)-1-[3-(trifluoromethyl)phenyl]ethyl]-3,4-dihydroquinolin-2-one (225 mg, 86.03%) as a white solid. MS (ESI): mass calcd for $C_{18}H_{17}F_3N_2O$: 334.13 m/z, found 335.15 $[M+H]^+$.

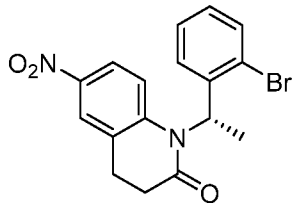


(S)-3-tert-butyl-1-(2-oxo-1-{1-[3-(trifluoromethyl)phenyl]ethyl}-3,4-dihydroquinolin-6-yl)urea

To a solution of 6-amino-1-[(1S)-1-[3-(trifluoromethyl)phenyl]ethyl]-3,4-dihydroquinolin-2-one (200 mg, 0.598 mmol, 1 equiv) and 2-isocyanato-2-methylpropane (177.90 mg, 1.794 mmol, 3

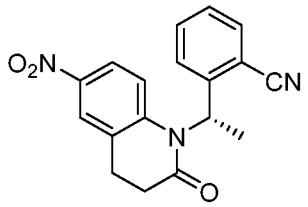
equiv) in DCM (3 mL) was added TEA (181.60 mg, 1.794 mmol, 3 equiv). The reaction was stirred at rt for 16h. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 150 mm x 30 mm x 5 μm column (eluent: 26% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound (S)-3-tert-butyl-1-(2-oxo-1-{1-[3-(trifluoromethyl)phenyl]ethyl}-3,4-dihydroquinolin-6-yl)urea (20.1 mg, 7.73%) as a white solid. LC/MS (ESI): mass calcd. for $C_{23}H_{26}F_3N_3O_2$:433.20 m/z, found:432.05 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.52 – 7.65 (m, 4H), 7.33 (s, 1H), 6.90 (m, 1H), 6.52 (m, 1H), 6.08 (m, 1H), 5.92 (s, 1H), 2.79-2.89 (m, 2H), 2.52 – 2.66 (m, 2H), 1.74 (m, 3H), 1.26 (s, 9H). ^{19}F NMR (282 MHz, DMSO) δ -60.93.

Example 61: (S)-1-(tert-butyl)-3-(1-(1-(2-cyanophenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea



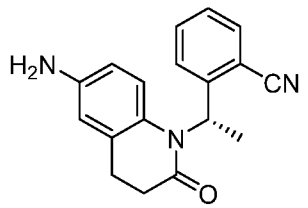
(S)-1-(1-(2-bromophenyl)ethyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one

To a solution of (1R)-1-(2-bromophenyl)ethanol (1 g, 4.974 mmol, 1 equiv) in THF (10 mL) was added 6-nitro-3,4-dihydro-1H-quinolin-2-one (1.05 g, 5.471 mmol, 1.1 equiv), PPh_3 (1.30 g, 4.974 mmol, 1 equiv) at rt. The resulting mixture was stirred at 0 °C under a nitrogen atmosphere, which was added DEAD (0.87 g, 4.974 mmol, 1 equiv). The resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (PE/EA=3:1) to afford (S)-1-(1-(2-bromophenyl)ethyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (1.2 g, 64.30%) as a yellow oil. MS (ESI): mass calcd. for $C_{17}H_{15}BrN_2O_3$: 374.03, found: 375.05$[M+H]^+$.



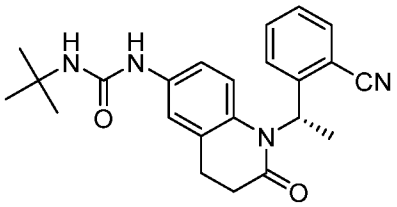
(S)-2-(1-(6-nitro-2-oxo-3,4-dihydroquinolin-1(2H)-yl)ethyl)benzonitrile

A solution of 1-[(1S)-1-(2-bromophenyl)ethyl]-6-nitro-3,4-dihydroquinolin-2-one (400 mg, 1.066 mmol, 1 equiv) in dimethylformamide (10 mL) was added $Zn(CN)_2$ (250.35 mg, 2.132 mmol, 2.0 equiv) and $Pd(PPh_3)_4$ (123.19 mg, 0.107 mmol, 0.1 equiv) at rt. The resulting mixture was stirred for overnight at 110 °C. The resulting mixture was extracted with EA (3 x 10 mL). The combined organic layers were washed with NaCl (3x5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (3/1) to afford (S)-2-(1-(6-nitro-2-oxo-3,4-dihydroquinolin-1(2H)-yl)ethyl)benzonitrile (78 mg, 22.77%) as an off-white solid. MS (ESI): mass calcd. for $C_{18}H_{15}N_3O_3$, 321.11 m/z, found 322.20 $[M+H]^+$.



(S)-2-(1-(6-amino-2-oxo-3,4-dihydroquinolin-1(2H)-yl)ethyl)benzonitrile

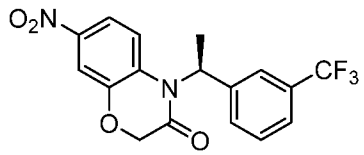
solution of (S)-2-(1-(6-nitro-2-oxo-3,4-dihydroquinolin-1(2H)-yl)ethyl)benzonitrile (70 mg, 0.218 mmol, 1 equiv) in MeOH (5 mL)/H_2O (0.5 mL) was added Fe (121.65 mg, 2.180 mmol, 10 equiv) and NH_4Cl (116.52 mg, 2.180 mmol, 10 equiv) at rt. The resulting mixture was stirred for 1 h at 60 °C. The precipitated solids were collected by filtration and washed with MeOH (3 x 5 mL). The aqueous layer was extracted with DCM (3 x 5 mL). The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (2:1) to afford (S)-2-(1-(6-amino-2-oxo-3,4-dihydroquinolin-1(2H)-yl)ethyl)benzonitrile (60 mg, 94.53%) as a yellow solid. MS (ESI): mass calcd. for $C_{18}H_{17}N_3O$, 291.14 m/z, found 292.20 $[M+H]^+$.



(S)-1-(tert-butyl)-3-(1-(1-(2-cyanophenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

A solution of (S)-2-(1-(6-amino-2-oxo-3,4-dihydroquinolin-1(2H)-yl)ethyl)benzonitrile (70 mg, 0.240 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (119.09 mg, 1.200 mmol, 5.0 equiv) and TEA (97.25 mg, 0.960 mmol, 4.0 equiv) at rt. The resulting mixture was stirred for overnight at TR. The resulting mixture was extracted with EA (5 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product 50 mg was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 54% B in 7 min; Wave Length: 220 nm; RT1(min): 6.5; Number Of Runs: 0) to afford (S)-1-(tert-butyl)-3-(1-(1-(2-cyanophenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea (22.5 mg, 23.93%) as white solid. MS (ESI):mass calcd.$C_{23}H_{26}N_4O_2$ for :390.21 m/z, found 391.20 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 7.9 Hz, 1H), 7.56 – 7.66 (m, 2H), 7.21 – 7.32 (m, 1H), 7.18 – 7.20 (m, 1H),7.09 – 7.12(m,1H), 6.79 – 6.92 (m, 1H), 6.61 – 6.74 (m, 1H), 5.87 – 6.02 (m, 2H), 2.92 – 3.01 (m, 1H), 2.71 – 2.83 (m, 1H), 2.53 – 2.69 (m, 1H), 2.42 – 2.53 (m, 1H), 1.96 (d, *J* = 7.1 Hz, 3H), 1.35 – 1.40 (m, 9H).

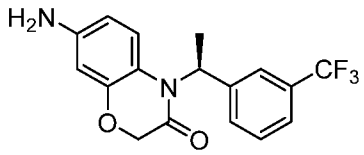
Example 62: (S)-1-(tert-butyl)-3-(3-oxo-4-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea



(S)-7-nitro-4-(1-(3-(trifluoromethyl)phenyl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

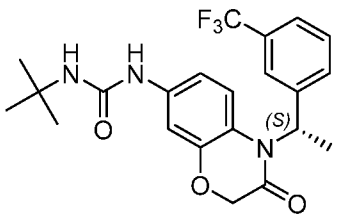
To a solution of (1R)-1-[3-(trifluoromethyl)phenyl]ethanol (500 mg, 2.629 mmol, 1 equiv), 7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (510.47 mg, 2.629 mmol, 1 equiv) and PPh_3 (1034.46 mg, 3.944 mmol, 1.5 equiv) in DCM (10 mL). The reaction was stirred at rt under N_2

for 0.5 hour. To the above mixture was added DEAD (686.86 mg, 3.944 mmol, 1.5 equiv) dropwise at 0 °C. The resulting mixture was stirred for additional 1h at rt. Quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-nitro-4-[(1S)-1-[3-(trifluoromethyl)phenyl]ethyl]-2H-1,4-benzoxazin-3-one (550 mg, 57.11%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{13}F_3N_2O_4$: 366.30m/z, found 367.00 $[M+H]^+$.



(S)-7-amino-4-(1-(3-(trifluoromethyl)phenyl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of 7-nitro-4-[(1S)-1-[3-(trifluoromethyl)phenyl]ethyl]-2H-1,4-benzoxazin-3-one (500 mg, 1.365 mmol, 1 equiv) in MeOH/H_2O (16.5 mL, 10:1) was added Fe (762.29 mg, 13.650 mmol, 10 equiv) and NH_4Cl (730.15 mg, 13.650 mmol, 10 equiv). The reaction was stirred at 80 °C for 1 hour. The reaction was quenched with water at rt. After filtration, the filter cake was washed with EA (3 x 20 mL). The filtrate was added water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. This resulted in 7-amino-4-[(1S)-1-[3-(trifluoromethyl)phenyl]ethyl]-2H-1,4-benzoxazin-3-one (450 mg, 98.02%) as a yellow soild. MS (ESI): mass calcd. for $C_{17}H_{15}F_3N_2O_2$: 336.31m/z, found 337.15 $[M+H]^+$.



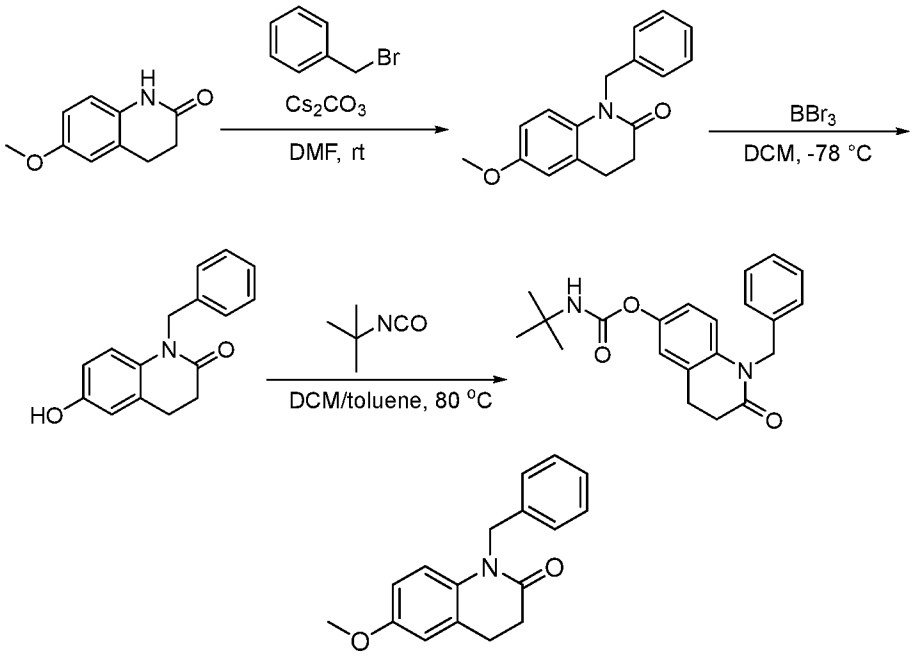
(S)-1-(tert-butyl)-3-(3-oxo-4-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a solution of 7-amino-4-[(1S)-1-[3-(trifluoromethyl)phenyl]ethyl]-2H-1,4-benzoxazin-3-one (150 mg, 0.446 mmol, 1 equiv) in DCM (10 mL) was added 2-isocyanato-2-methylpropane (176.86 mg, 1.784 mmol, 4 equiv) and TEA (135.40 mg, 1.338 mmol, 3 equiv). The reaction was stirred at rt for 1 day. Quenched with water (20 mL) and extracted with EA (3 x

20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm column (eluent: 35% to 60% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-{3-oxo-4-[(1S)-1-[3-(trifluoromethyl)phenyl]ethyl]-2H-1,4-benzoxazin-7-yl}urea (50.1 mg, 25.80%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{24}F_3N_3O_3$: 435.45 m/z, found:436.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 8.10 – 8.31 (m, 1H), 7.45 – 7.80 (m, 4H), 7.07 – 7.38 (m, 1H), 6.44 – 6.85 (m, 2H), 6.01 – 6.19 (m, 1H), 5.79 – 6.01 (m, 1H), 4.50 – 4.90 (m, 2H), 1.70 – 1.90 (m, 3H), 1.21 – 1.32 (m, 9H). ^{19}F NMR (376 MHz, DMSO) δ (ppm): -60.8904.

Example 63: 5-benzyl-6-oxo-7,8-dihydro-5H-naphthalen-2-yl N-tert-butylcarbamate

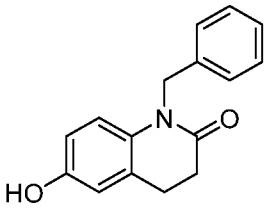
Synthetic Scheme



1-benzyl-6-methoxy-3,4-dihydroquinolin-2-one

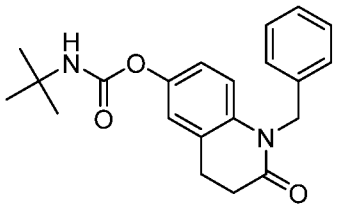
To a solution of 6-methoxy-3,4-dihydro-1H-quinolin-2-one (473.5 mg, 2.672 mmol, 1 equiv) and benzyl bromide (1142.56 mg, 6.680 mmol, 2.5 equiv) in dimethylformamide (25 mL) was added Cs_2CO_3 (2619.92 mg, 8.016 mmol, 3 equiv). The reaction was stirred at rt for 3h. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give tert-butyl 1-

benzyl-6-methoxy-3,4-dihydroquinolin-2-one (640 mg, 89.60%) as a white solid.MS (ESI): mass calcd. for $C_{17}H_{17}NO_2$: 267.13 m/z, found 268.10$[M+H]^+$.



1-benzyl-6-hydroxy-3,4-dihydroquinolin-2-one

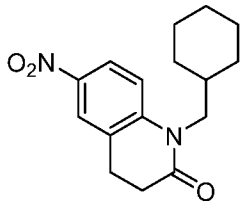
To a solution of 1-benzyl-6-methoxy-3,4-dihydroquinolin-2-one (620 mg, 2.319 mmol, 1 equiv) in DCM (8 mL) was added boron tribromide (7 mL) at -78 °C under nitrogen atmosphere. The reaction was stirred at -78 °C for 3h. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-benzyl-6-hydroxy-3,4-dihydroquinolin-2-one (312 mg, 53.11%) as a black solid. MS (ESI): mass calcd for $C_{16}H_{15}NO_2$: 253.11 m/z, found 253.95$[M+H]^+$.



5-benzyl-6-oxo-7,8-dihydro-5H-naphthalen-2-yl N-tert-butylcarbamate

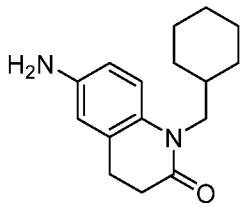
To a solution of 1-benzyl-6-hydroxy-3,4-dihydro-1H-naphthalen-2-one (132 mg, 0.523 mmol, 1 equiv) and 2-isocyanato-2-methylpropane (103.32 mg, 1.042 mmol, 2 equiv) in DCM (2 mL) was added TEA (158.20 mg, 1.563 mmol, 3 equiv). The reaction was stirred at rt for 16h. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 150 mm x 30 mm x 5 μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 5-benzyl-6-oxo-7,8-dihydro-5H-naphthalen-2-yl N-tert-butylcarbamate (50.2 mg, 27.27%) as a white solid. LC/MS (ESI): mass calcd. for $C_{21}H_{24}N_2O_3$:352.18 m/z, found:353.05 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 7.50 (s, 1H), 7.22 – 7.37 (m, 5H), 6.97 (m, 1H), 6.76 – 6.91 (m, 2H), 5.13 (s, 2H), 2.89-3.01 (m, 2H), 2.69-2.73 (m, 2H), 1.25 (s, 9H).

Example 64: 1-(tert-butyl)-3-(1-(cyclohexylmethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea



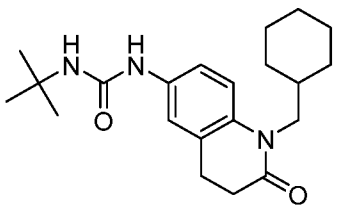
1-(cyclohexylmethyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one

To a stirred solution of 6-nitro-3,4-dihydro-1H-quinolin-2-one (300 mg, 1.561 mmol, 1.0 equiv) in DMF (15 mL) was added Cs_2CO_3 (1.53 g, 4.683 mmol, 3.0 equiv) and (bromomethyl)cyclohexane (276.44 mg, 1.561 mmol, 1 equiv) at rt and stirred for overnight. The reaction progress was monitored by LCMS. After completion of reaction, the resulting mixture was extracted with EA (3 x 30 mL). The combined organic layers were washed with water (3 x2 0 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EA =3:1) to afford 1-(cyclohexylmethyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (310 mg, 68.87%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{20}N_2O_3$: 288.15 m/z, found 289.15 $[M+H]^+$.



6-amino-1-(cyclohexylmethyl)-3,4-dihydroquinolin-2(1H)-one

To a solution of 1-(cyclohexylmethyl)-6-nitro-3,4-dihydroquinolin-2-one (100 mg, 0.347 mmol, 1 equiv) in methanol (5 mL) was added Pd/C (30 mg) under nitrogen atmosphere. The mixture was hydrogenated at room temperature for 50 min under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 6-amino-1-(cyclohexylmethyl)-3,4-dihydroquinolin-2(1H)-one as a white solid. MS (ESI): mass calcd. for $C_{16}H_{22}N_2O$: 258.17 m/z, found 259.30 $[M+H]^+$.

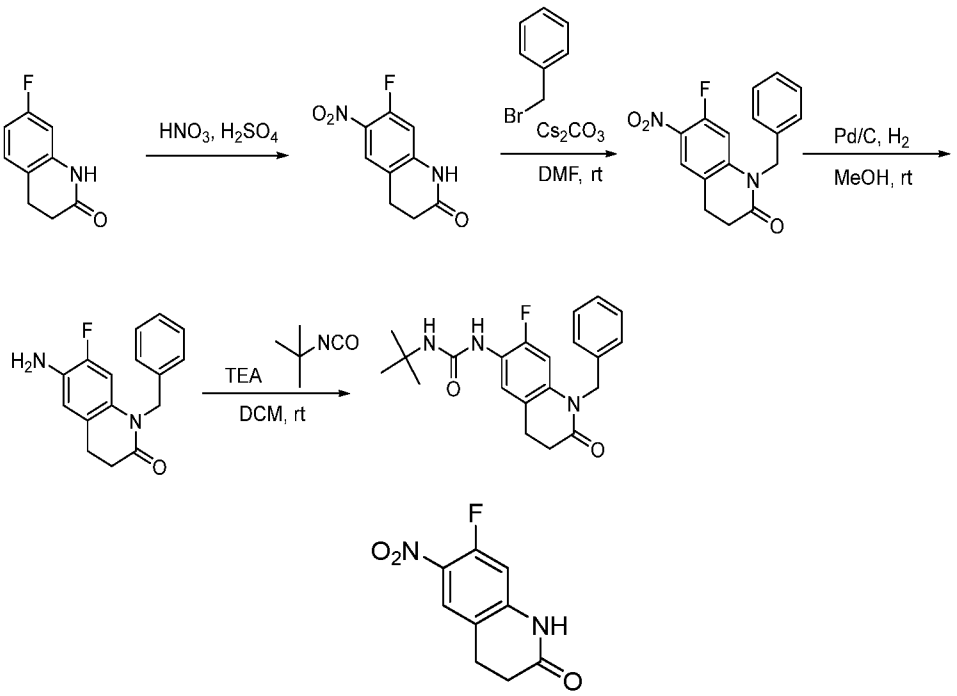


1-(tert-butyl)-3-(1-(cyclohexylmethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

A solution of 6-amino-1-(cyclohexylmethyl)-3,4-dihydroquinolin-2(1H)-one (50 mg, 0.194 mmol, 1 equiv), triethylamine (58.75 mg, 0.582 mmol, 3 equiv) and 2-isocyanato-2-methylpropane (57.55 mg, 0.582 mmol, 3 equiv) in DCM (5 mL) was stirred for overnight at rt. The residue was purified by silica gel column chromatography (PE/EA = 2:1) to afford crude products. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 50% B in 9 min, 50% B; Wave Length: 254/220 nm; RT1(min): 8.9;) to afford 1-(tert-butyl)-3-(1-(cyclohexylmethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea (26.5 mg, 38.18%) as a white solid. MS (ESI):mass calcd. for $C_{21}H_{31}N_3O_2$: 357.24 m/z, found 358.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.28 (d, J = 2.4 Hz, 1H), 7.12 (dd, J = 8.8, 2.5 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 5.94 (s, 1H), 3.76 (d, J = 6.9 Hz, 2H), 2.77 (dd, J = 8.8, 5.8 Hz, 2H), 2.47 (d, J = 6.3 Hz, 2H), 1.55 - 1.64 (m, 6H), 1.28 (s, 9H), 1.09 (t, J = 9.5 Hz, 3H), 0.95 (t, J = 11.2 Hz, 2H).

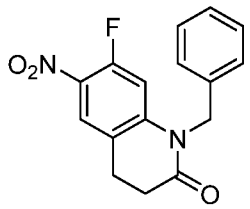
Example 65:1-(1-benzyl-7-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

Synthetic Scheme



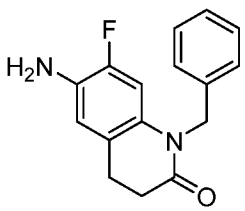
7-fluoro-6-nitro-3,4-dihydroquinolin-2(1H)-one

To a solution of 7-fluoro-3,4-dihydro-1H-quinolin-2-one (526 mg, 3.185 mmol, 1 equiv) in H_2SO_4 (3.2 mL) was added HNO_3 (200.6 mg,3.185 mmol, 1.0 equiv)at 0 °C.The resulting mixture was stirred at 0 °C until the starting material was totally consumed by LCMS, the reaction mixture was quenched by water and extracted with EA (3 x 20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (PE/EA = 3:1) to afford 7-fluoro-6-nitro-3,4-dihydro-1H-quinolin-2-one (300 mg, 35.30%) as a yellow solid. MS (ESI): mass calcd. for $C_9H_7FN_2O_3$, 210.04 m/z, found 211.10 $[M+H]^+$.



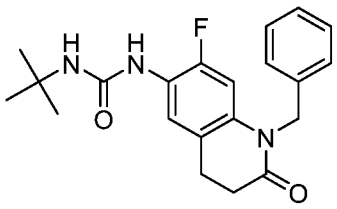
1-benzyl-7-fluoro-6-nitro-3,4-dihydroquinolin-2(1H)-one

To a solution of 7-fluoro-6-nitro-3,4-dihydro-1H-quinolin-2-one (300 mg, 1.427 mmol, 1 equiv) in DMF (8 mL) was added K_2CO_3 (591.8 mg, 4.282 mmol, 3 equiv) and benzyl bromide(488.3 mg, 2.855 mmol, 2 equiv). The resulting mixture was placed at rt and stirred overnight until the starting material was totally consumed by LCMS. The reaction mixture was quenched by water and extracted with EA (3*20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 1-benzyl-7-fluoro-6-nitro-3,4-dihydroquinolin-2-one (250 mg, 57.56%) as a white solid.MS (ESI): mass calcd. for $C_{16}H_{13}FN_2O_3$, 300.09 m/z, found 301.10 $[M+H]^+$.



6-amino-1-benzyl-7-fluoro-3,4-dihydroquinolin-2(1H)-one

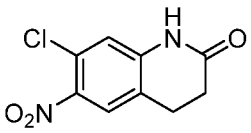
To a solution of 1-benzyl-7-fluoro-6-nitro-3,4-dihydroquinolin-2-one (250 mg, 0.833 mmol, 1 equiv) in MeOH (10 mL) was added Pd/C (30 mg). The mixture was hydrogenated at room temperature for 50 min under hydrogen atmosphere using a hydrogen balloon, then filtered through a Celite pad and concentrated under reduced pressure to afford 6-amino-1-benzyl-7-fluoro-3,4-dihydroquinolin-2-one (220 mg, 86.79%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{15}FN_2O$, 270.12 m/z, found 271.10 $[M+H]^+$



1-(1-benzyl-7-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

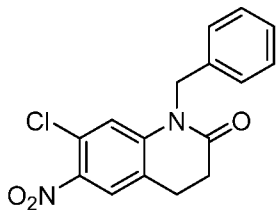
To a stirred solution of 6-amino-1-benzyl-7-fluoro-3,4-dihydroquinolin-2-one (200 mg, 0.740 mmol, 1 equiv) in DCM (10.00 mL) was added 2-isocyanato-2-methylpropane (366.7 mg, 3.699 mmol, 5 equiv) and TEA (224.6 mg, 2.220 mmol, 3 equiv) stirred overnight at rt. The reaction progress was monitored by LCMS. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 100 mg crude product as a white solid. The compound was separated by preparative HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 52% B in 10 min; Wave Length: 254 nm; RT1(min): 10.2; Number Of Runs: 3) to afford 1-(1-benzyl-7-fluoro-2-oxo-3,4-dihydroquinolin-6-yl)-3-tert-butylurea (34.5 mg, 12.51%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{24}FN_3O_2$, 369.19 m/z, found 370.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 7.94 (dd, J = 5.7, 3.2 Hz, 2H), 7.27 – 7.37 (m, 2H), 7.18 – 7.27 (m, 3H), 6.79 (d, J = 13.3 Hz, 1H), 6.43 (s, 1H), 5.10 (s, 2H), 2.87 (t, J = 7.2 Hz, 2H), 2.66 (dd, J = 8.7, 5.8 Hz, 2H), 1.26 (s, 9H).

Example 66: 1-(1-benzyl-7-chloro-2-oxo-3,4-dihydroquinolin-6-yl)-3-tert-butylurea



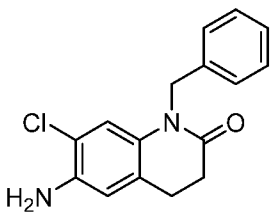
Synthesis of 7-chloro-6-nitro-3,4-dihydro-1H-quinolin-2-one

To a stirred solution of 7-chloro-3,4-dihydro-1H-quinolin-2-one (2 g, 11.012 mmol, 1 equiv) in H_2SO_4 was added KNO_3 (1.11 g, 11.012 mmol, 1 equiv) at 0°C. The final reaction mixture was stirred overnight at room temperature. The reaction was monitored by LCMS. The reaction was poured into the Water/Ice (100 mL). The resulting mixture was extracted with EA (3 x 50 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. MS: mass calcd. for $C_9H_7ClN_2O_3$: 226.01 m/z, found 227.00 $[M+H]^+$.



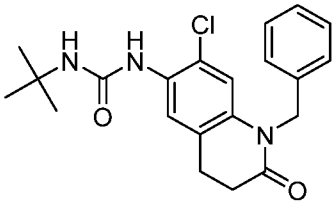
1-benzyl-7-chloro-6-nitro-3,4-dihydroquinolin-2-one

To a stirred solution of 7-chloro-6-nitro-3,4-dihydro-1H-quinolin-2-one (1.8 g, 7.943 mmol, 1 equiv) in DMF (20 mL) was added benzyl bromide (2.72 g, 15.886 mmol, 2 equiv) and Cs_2CO_3 (5.19 g, 15.886 mmol, 2 equiv) at room temperature. The final reaction mixture was stirred for 3 h at room temperature. The reaction was monitored by LCMS. The resulting mixture was quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford 1-benzyl-7-chloro-6-nitro-3,4-dihydroquinolin-2-one (1.3 g, 51.67%) as an orange solid. MS: mass calcd. for $C_{16}H_{13}ClN_2O_3$: 316.06 m/z, found 317.15 $[M+H]^+$.



6-amino-1-benzyl-7-chloro-3,4-dihydroquinolin-2-one

To a stirred solution of 1-benzyl-7-chloro-6-nitro-3,4-dihydroquinolin-2-one (500 mg, 1.579 mmol, 1 equiv) in EtOH/H_2O (10 mL, 10/1) were added Fe (881.56 mg, 15.790 mmol, 10 equiv) and NH_4Cl (844.38 mg, 15.790 mmol, 10 equiv) at room temperature. The final reaction mixture was stirred for 3 h at 60°C. The reaction was monitored by LCMS. The reaction was quenched with water at rt. After filtration, the filter cake was washed with EA (3 x 20 mL). The filtrate was added water (20 mL) and extracted with EA (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 6-amino-1-benzyl-7-chloro-3,4-dihydroquinolin-2-one (300 mg, 66.27%) as a yellow solid. The crude product was used in the next step directly without further purification. MS (ESI): mass calcd. for $C_{16}H_{15}ClN_2O$: 286.09 m/z, found 287.05 $[M+H]^+$.

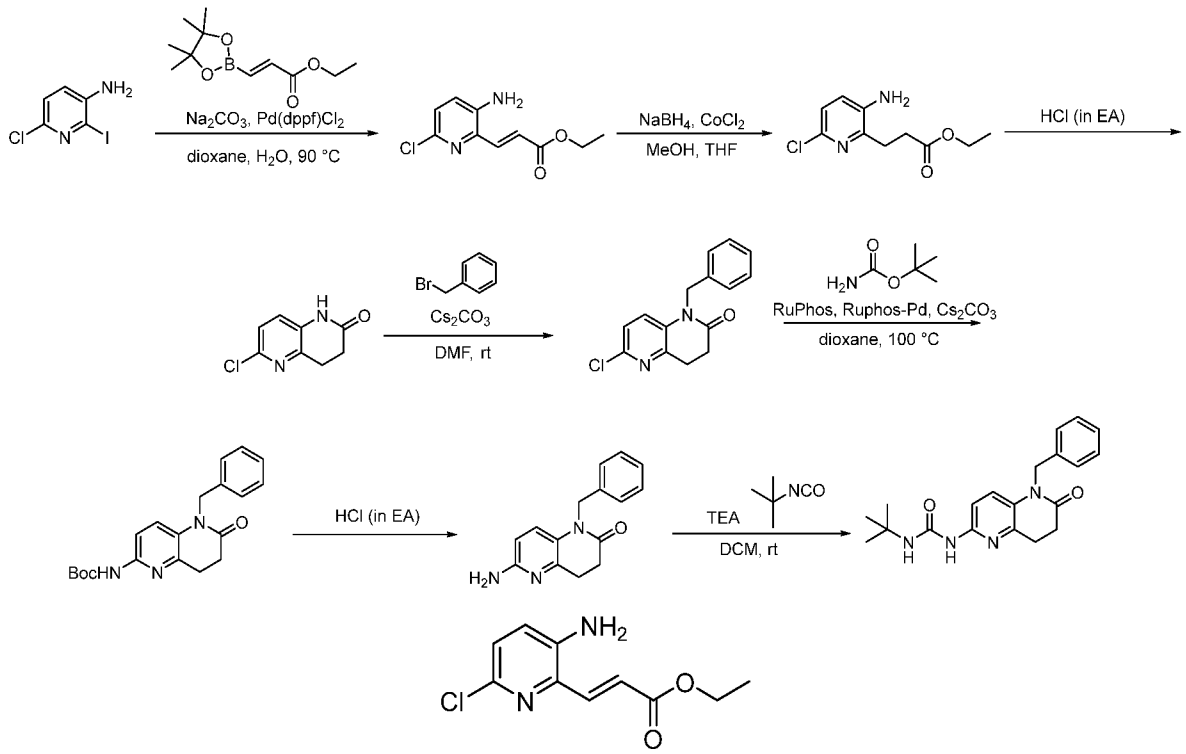


1-(1-benzyl-7-chloro-2-oxo-3,4-dihydroquinolin-6-yl)-3-tert-butylurea

To a stirred solution of 6-amino-1-benzyl-7-chloro-3,4-dihydroquinolin-2-one (140 mg, 0.488 mmol, 1 equiv) in toluene/DCM (10 mL, 1/2) was added 2-isocyanato-2-methylpropane (145.19 mg, 1.464 mmol, 3 equiv) dropwise at room temperature under nitrogen atmosphere. The final reaction mixture was stirred for 3 h at 90°C. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by Prep-HPLC to afford 1-(1-benzyl-7-chloro-2-oxo-3,4-dihydroquinolin-6-yl)-3-tert-butylurea (5.0 mg, 2.65%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{24}ClN_3O_2$: 385.16 m/z, found 386.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.98 (s, 1H), 7.74 (s, 1H), 7.32 – 7.22 (m, 5H), 6.92 (s, 1H), 6.80 (s, 1H), 5.12 (s, 2H), 2.91 (t, J = 7.2 Hz, 2H), 2.67 (t, J = 7.2 Hz, 2H), 1.28 (s, 9H).

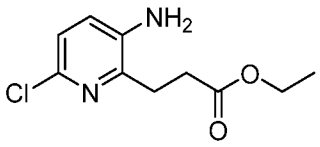
Example 67: 1-(5-benzyl-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)-3-(tert-butyl)urea

Synthetic Scheme



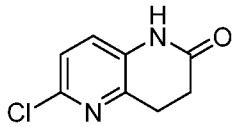
ethyl (E)-3-(3-amino-6-chloropyridin-2-yl)acrylate

A solution of 6-chloro-2-iodopyridin-3-amine (2 g, 7.860 mmol, 1 equiv), ethyl (2E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-enoate (1.77 g, 7.860 mmol, 1 equiv), sodium methaneperoxoate sodium (2.5 g, 23.580 mmol, 3 equiv) and $Pd(dppf)Cl_2$ (575.11 mg, 0.786 mmol, 0.1 equiv) in water (3 mL) and 1,4-dioxane (30 mL) was stirred for overnight at 90 °C under N_2 atmosphere. The mixture was allowed to cool down to rt.The reaction progress was monitored by LCMS. The resulting mixture was extracted with EA (3 x 60 mL). The combined organic layers were washed with brine (1x100 mL). After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EA = 3:1) to afford ethyl (E)-3-(3-amino-6-chloropyridin-2-yl)acrylate (1.5 g, 84.20%) as a yellow solid. MS (ESI): mass calcd. for $C_{10}H_{11}ClN_2O_2$: 226.05 m/z, found 227.20 [M +H] +.



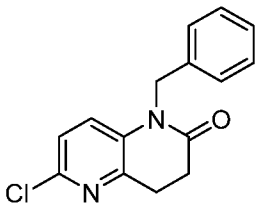
ethyl 3-(3-amino-6-chloropyridin-2-yl)propanoate

A solution of ethyl (2E)-3-(3-amino-6-chloropyridin-2-yl)prop-2-enoate (1 g, 4.412 mmol, 1 equiv) in methanol (10 mL) and tetrahydrofuran (20 mL) was treated with cobalt (II) chloride (286.40 mg, 2.206 mmol, 0.5 equiv) for 30 min at 0 °C under nitrogen atmosphere followed by the addition of $NaBH_4$ (834.51 mg, 22.060 mmol, 5 equiv) in portions at 0 °C. The resulting mixture was stirred for additional 1 h at rt. The reaction was quenched with H_2O at 0 °C. The resulting mixture was filtered. The filter cake was washed with EA (50 mL). The filtrate was concentrated under reduced pressure. This resulted in ethyl 3-(3-amino-6-chloropyridin-2-yl)propanoate (950 mg, 94.16%) as a yellow solid. MS (ESI): mass calcd. for $C_{10}H_{13}ClN_2O_2$: 228.07 m/z, found 229.15 [M +H] +.



6-chloro-3,4-dihydro-1,5-naphthyridin-2(1H)-one

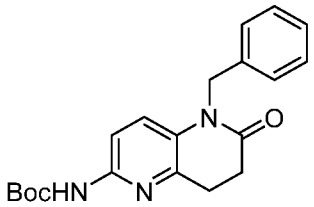
To a stirred solution of ethyl 3-(3-amino-6-chloropyridin-2-yl)propanoate (900 mg, 3.936 mmol, 1 equiv) in HCl (2M, in EA) (30 mL) at rt and stirred for 2 h. The precipitated solids were collected by filtration and washed with diethyl ether (3 x 50 mL). This resulted in 6-chloro-3,4-dihydro-1H-1,5-naphthyridin-2-one (600 mg, 83.49%) as a white solid. MS (ESI): mass calcd. for $C_8H_7ClN_2O$: 182.02 m/z, found 183.05 [M +H] +.



1-benzyl-6-chloro-3,4-dihydro-1,5-naphthyridin-2(1H)-one

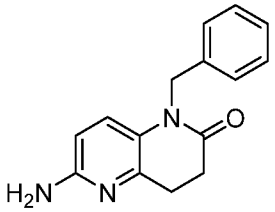
To a stirred solution of 6-chloro-3,4-dihydro-1H-1,5-naphthyridin-2-one (600 mg, 3.286 mmol, 1 equiv) in anhydrous dimethylformamide (15 mL, 0.027 mmol, 0.17 equiv) was added benzyl bromide (730.57 mg, 4.272 mmol, 1.3 equiv) and Cs_2CO_3 (3.22 g, 9.858 mmol, 3 equiv) at rt and stirred for 2 h. After completion of reaction, the resulting mixture was extracted with EA (3 x 20 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA = (3:1) to

afford 1-benzyl-6-chloro-3,4-dihydro-1,5-naphthyridin-2(1H)-one (680 mg, 75.88%) as a yellow solid. MS (ESI): mass calcd. for $C_{15}H_{13}ClN_2O$: 272.07 m/z, found 273.05 [M +H] +.



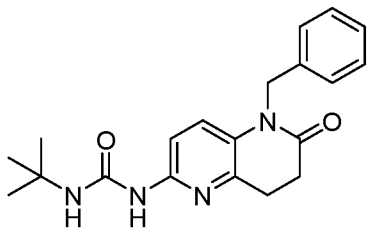
tert-butyl (1-benzyl-2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridin-6-yl)carbamate

A solution of 1-benzyl-6-chloro-3,4-dihydro-1,5-naphthyridin-2-one (200 mg, 0.733 mmol, 1 equiv) in 1,4-dioxane (15 mL, 0.023 mmol, 0.31 equiv) was treated with tert-butyl carbamate (171.82 mg, 1.466 mmol, 2 equiv), Cs_2CO_3 (477.86 mg, 1.466 mmol, 2 equiv), EPHOS (39.22 mg, 0.073 mmol, 0.1 equiv) and EPhos Pd G4 (67.36 mg, 0.073 mmol, 0.1 equiv) for overnight at 90 °C under nitrogen atmosphere. The residue was purified by silica gel column chromatography, eluted with PE/EA (3:1) to afford tert-butyl (1-benzyl-2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridin-6-yl)carbamate (180 mg, 69.45%) as a white solid. MS (ESI): mass calcd. for $C_{20}H_{23}N_3O_3$: 353.17 m/z, found 354.25 [M +H] +.



6-amino-1-benzyl-3,4-dihydro-1,5-naphthyridin-2(1H)-one

Into a 20 mL bar were added tert-butyl N-(5-benzyl-6-oxo-7,8-dihydro-1,5-naphthyridin-2-yl)carbamate (80 mg, 0.226 mmol, 1 equiv) and HCl (10 mL, 10.000 mmol, 44.18 equiv) at rt and strried for 3 h. The crude product/ resulting mixture was used in the next step directly without further purification. This resulted in 6-amino-1-benzyl-3,4-dihydro-1,5-naphthyridin-2(1H)-one (60 mg, 75%) as a white solid. MS (ESI): mass calcd. for $C_{15}H_{15}N_3O$: 253.12 m/z, found 254.20 [M +H] +.

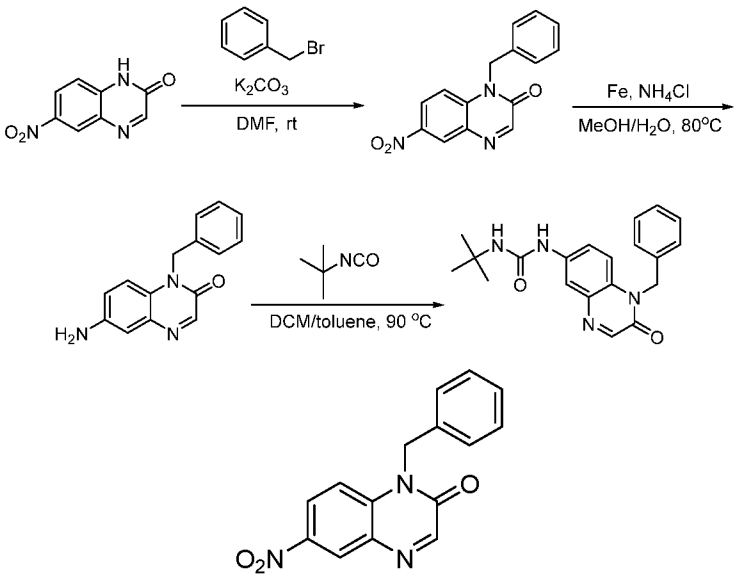


1-(5-benzyl-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)-3-(tert-butyl)urea

A solution of 6-amino-1-benzyl-3,4-dihydro-1,5-naphthyridin-2-one (60 mg, 0.237 mmol, 1 eq uiv), TEA (71.91 mg, 0.711 mmol, 3 equiv) and 2-isocyanato-2-methylpropane (117.41 mg, 1.185 mmol, 5 equiv) in DCM (10 mL, 157.306 mmol, 664.11 equiv) was stirred for overnight at rt. The residue was purified by silica gel column chromatography, eluted with EA (2:1) to afford 1-(5-benzyl-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)-3-(tert-butyl)urea (43.1 mg, 51.44%) as a white solid. MS (ESI): mass calcd. for $C_{20}H_{24}N_4O_2$: 352.19 m/z, found 353.15 [M+H]+.^{1}H NMR (300 MHz, DMSO-d_6) δ 8.87 (s, 1H), 7.95 (s, 1H), 7.37 – 7.16 (m, 6H), 7.11 (d, J = 8.9 Hz, 1H), 5.10 (s, 2H), 2.99 (dd, J = 8.7, 6.2 Hz, 2H), 2.80 (dd, J = 8.8, 6.2 Hz, 2H), 1.31 (s, 9H).

Example 68: 1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea

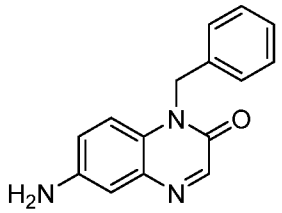
Synthetic Scheme



1-benzyl-6-nitroquinoxalin-2(1H)-one

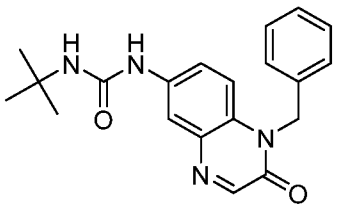
To a solution of 6-nitro-1H-quinoxalin-2-one (500 mg, 2.616 mmol, 1 equiv) in DMF (20 mL) was added benzyl bromide (671.10 mg, 3.924 mmol, 1.5 equiv) and K_2CO_3 (728.31 mg, 5.232 mmol, 2 equiv). The reaction was stirred at rt for 1 hour. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on

silica gel with EA/PE (0-100%) to give 1-benzyl-6-nitroquinoxalin-2-one (450 mg, 61.16%) as a yellow solid. MS (ESI): mass calcd. for $C_{15}H_{11}N_3O_3$: 281.27m/z, found 282.00 $[M+H]^+$.



6-amino-1-benzylquinoxalin-2(1H)-one

To a solution of 1-benzyl-6-nitroquinoxalin-2-one (250 mg, 0.889 mmol, 1 equiv) in MeOH/H_2O (11 mL, 10:1) was added Fe (496.36 mg, 8.890 mmol, 10 equiv) and NH_4Cl (475.43 mg, 8.890 mmol, 10 equiv). The reaction was stirred at 80 °C for 1 hour. The reaction was quenched with water at rt. After filtration, the filter cake was washed with EA (3 x 20 mL). The filtrate was added water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. This resulted in 6-amino-1-benzylquinoxalin-2-one (220 mg, 98.50%) as a yellow soild. MS (ESI): mass calcd. for $C_{15}H_{13}N_3O$: 251.29 m/z, found 252.05 $[M+H]^+$.

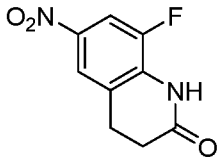


1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea

To a solution of 6-amino-1-benzylquinoxalin-2-one (220 mg, 0.875 mmol, 1 equiv) in DCM/Toluene (15 mL, 2:1) was added 2-isocyanato-2-methylpropane (520.74 mg, 5.250 mmol, 6 equiv). The reaction was stirred at 90 °C for 2 hours. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm column (eluent: 26% to 45% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 1-(1-benzyl-2-oxoquinoxalin-6-yl)-3-tert-butylurea (55 mg, 17.93%) as a yellow solid. MS (ESI): mass calcd. for $C_{20}H_{22}N_4O_2$: 350.42 m/z, found:351.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 8.40 – 8.52 (m, 1H), 8.25

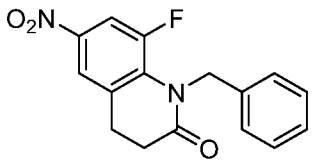
– 7.38 (m, 1H), 7.83 – 8.01 (m, 1H), 7.20 – 7.50(m, 7H), 5.90 – 6.10 (m, 1H), 5.35 – 5.61 (m, 2H), 1.19 – 1.39 (m, 9H).

Example 69: 1-(1-benzyl-8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea



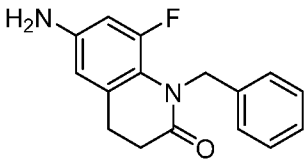
8-fluoro-6-nitro-3,4-dihydroquinolin-2(1H)-one

To a solution of 8-fluoro-3,4-dihydro-1H-quinolin-2-one (500 mg, 3.027 mmol, 1 equiv) in H_2SO_4 (3 mL) was added HNO_3 (190.7 mg, 3.027 mmol, 1.0 equiv)at -10 °C.The resulting mixture was stirred at -10 °C until the starting material was totally consumed by LCMS, The reaction mixture was quenched by water and adjusting PH with saturaed sodium bicarbonate aqueous solution and then extracted with EA (3 x 20 mL).The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (PE/EA=3:1) to afford 8-fluoro-6-nitro-3,4-dihydro-1H-quinolin-2-one (300 mg, 46.66%) as a yellow solid. MS (ESI): mass calcd. for $C_9H_7FN_2O_3$, 210.04 m/z, found 211.10 $[M+H]^+$



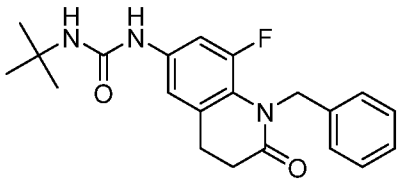
1-benzyl-8-fluoro-6-nitro-3,4-dihydroquinolin-2(1H)-one

To a solution of 8-fluoro-6-nitro-3,4-dihydro-1H-quinolin-2-one (250 mg, 1.190 mmol, 1 equiv) in DMF (10 mL) was added K_2CO_3 (493.2 mg, 3.569 mmol, 3 equiv) and benzyl bromide (305.1 mg, 1.784 mmol, 1.5 equiv). The resulting mixture was placed at rt and stirred overnight until the starting material was totally consumed by LCMS. The mixture was diuted with EtOAc (100 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 4-benzyl-7-nitro-2H-1,4-benzoxazin-3-one (250 mg, 65.39%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{13}FN_2O_3$: 300.09 m/z, found 301.15 [M+H]+.



6-amino-1-benzyl-8-fluoro-3,4-dihydroquinolin-2(1H)-one

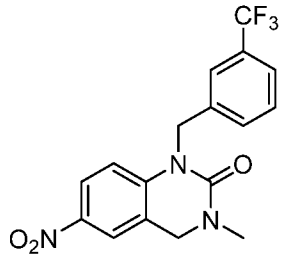
To a solution of 1-benzyl-8-fluoro-6-nitro-3,4-dihydroquinolin-2-one (250 mg, 0.833 mmol, 1 equiv) in MeOH (10 mL) was added Pd/C (30 mg). The reaction mixture was then stirred for 1 h under hydrogen atmosphere (balloon). The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to afford 6-amino-1-benzyl-8-fluoro-3,4-dihydroquinolin-2-one (180 mg, 77.83%) as a yellow solid.MS (ESI): mass calcd. for $C_{16}H_{15}FN_2O$, 270.12 m/z, found 271.10 $[M+H]^+$.



1-(1-benzyl-8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

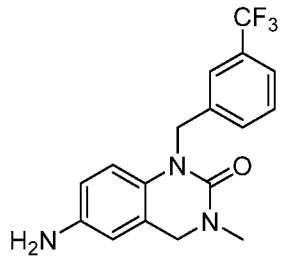
To a stirred solution of 6-amino-1-benzyl-8-fluoro-3,4-dihydroquinolin-2-one (140 mg, 0.518 mmol, 1 equiv) in DCM (10.00 mL) was added 2-isocyanato-2-methylpropane (256.7 mg, 2.590 mmol, 5 equiv) and TEA (157.2 mg, 1.554 mmol, 3 equiv) stirred overnight at rt. The reaction progress was monitored by LCMS. The reaction mixture was quenched by water and extracted with EA (3*20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 100 mg crude product as a white solid.The compound was separated by preparative HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 39% B to 58% B in 7 min; Wave Length: 254 nm; RT1(min): 6.4; Number Of Runs: 3) to afford 1-(1-benzyl-8-fluoro-2-oxo-3,4-dihydroquinolin-6-yl)-3-tert-butylurea (23.4 mg, 12.13%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{24}FN_3O_2$, 369.19 m/z, found 370.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.31 (s, 1H), 7.26 (t, J = 7.3 Hz, 2H), 7.08 – 7.21 (m, 4H), 6.87 (s, 1H), 6.01 (s, 1H), 5.11 (s, 2H), 2.86 (t, J = 6.7 Hz, 2H), 2.54 – 2.70 (m, 2H), 1.25 (s, 9H).

Example 70: 1-(tert-butyl)-3-(3-methyl-2-oxo-1-(3-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea



3-methyl-6-nitro-1-(3-(trifluoromethyl)benzyl)-3,4-dihydroquinazolin-2(1H)-one

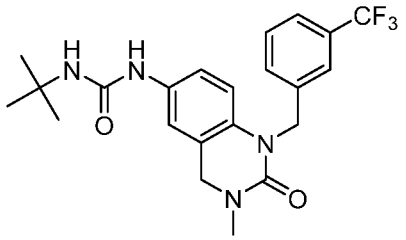
To a solution of 3-methyl-6-nitro-1,4-dihydroquinazolin-2-one (120 mg, 0.579 mmol, 1 equiv) in DMF (10 mL) was added 1-(bromomethyl)-3-(trifluoromethyl)benzene (152.29 mg, 0.637 mmol, 1.1 equiv) and Cs_2CO_3 (378.58 mg, 1.158 mmol, 2 equiv). The reaction was stirred at rt for 1 hour. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 3-methyl-6-nitro-1-{[3-(trifluoromethyl)phenyl]methyl}-4H-quinazolin-2-one (170 mg, 80.35%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{14}F_3N_3O_3$: 365.31m/z, found 366.05 $[M+H]^+$.



6-amino-3-methyl-1-(3-(trifluoromethyl)benzyl)-3,4-dihydroquinazolin-2(1H)-one

To a solution of 3-methyl-6-nitro-1-{[3-(trifluoromethyl)phenyl]methyl}-4H-quinazolin-2-one (170 mg, 0.465 mmol, 1 equiv) in MeOH/H_2O (11 mL, 10:1) was added Fe (259.88 mg, 4.650 mmol, 10 equiv) and NH_4Cl (248.92 mg, 4.650 mmol, 10 equiv). The reaction was stirred for 1 hour at 80 °C. The reaction was quenched with water at rt. After filtration, the filter cake was washed with EA (3 x 20 mL). The filtrate was added water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. This resulted in 6-amino-3-methyl-1-{[3-(trifluoromethyl)phenyl]methyl}-4H-

quinazolin-2-one (150 mg, 96.15%) as a yellow oil. MS (ESI): mass calcd. for $C_{17}H_{16}F_3N_3O$: 335.33m/z, found 336.05 $[M+H]^+$.



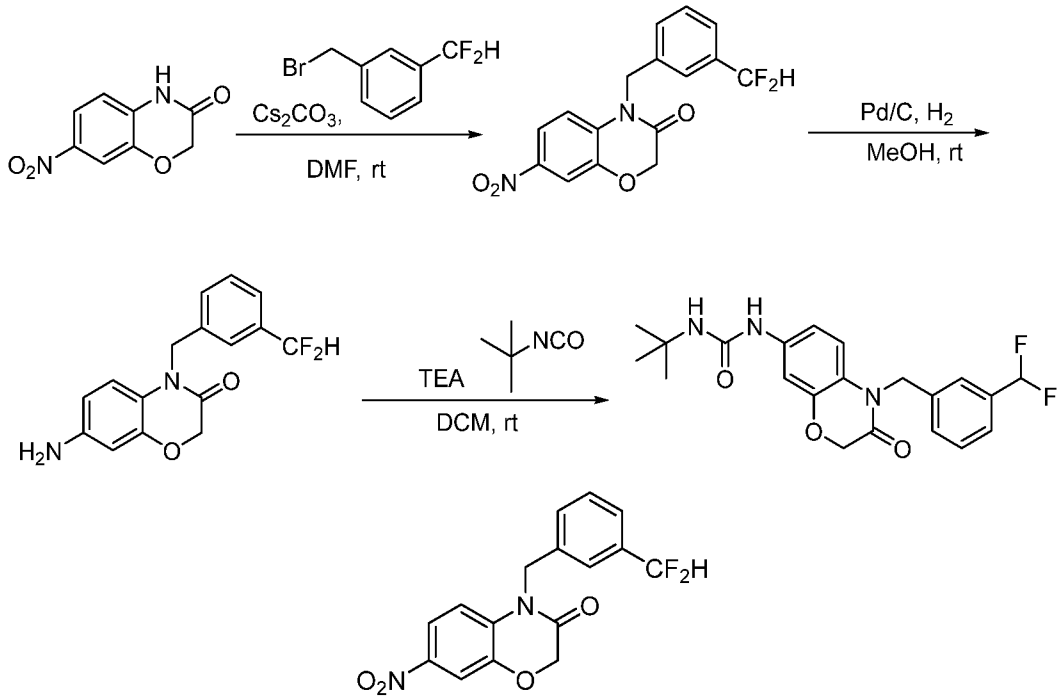
1-(tert-butyl)-3-(3-methyl-2-oxo-1-(3-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea

To a solution of 6-amino-3-methyl-1-{[3-(trifluoromethyl)phenyl]methyl}-4H-quinazolin-2-one (160 mg, 0.477 mmol, 1 equiv) in DCM/Toluene (15 mL, 2:1) was added 2-isocyanato-2-methylpropane (283.80 mg, 2.862 mmol, 6 equiv). The reaction was stirred at 90 °C for 2 hours. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-(3-methyl-2-oxo-1-{[3-(trifluoromethyl)phenyl]methyl}-4H-quinazolin-6-yl)urea (21.3 mg, 10.27%) as a white solid.MS (ESI): mass calcd. for $C_{22}H_{25}F_3N_4O_2$: 434.46 m/z, found:435.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 7.91 – 8.20 (m, 1H), 7.43 – 7.66 (m, 4H), 7.17 – 7.36 (m, 1H), 6.84 – 7.02 (m, 1H), 6.45 – 6.62 (m, 1H), 5.76 – 6.00 (m, 1H), 4.94 – 5.20 (m, 2H), 4.30 – 4.48 (m, 2H), 2.85 – 3.01 (m, 3H), 1.17 – 1.33 (m, 9H).^{19}F NMR (376 MHz, DMSO) δ (ppm): -60.9887.

Experimental Procedures

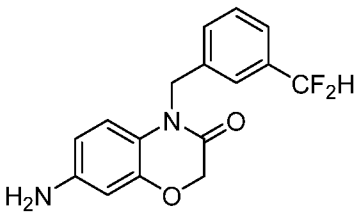
Example 71: 1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

Synthetic Scheme



4-(3-(difluoromethyl)benzyl)-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

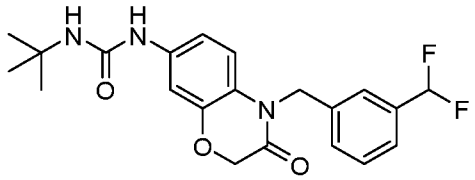
To a stirred solution of 7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (300 mg, 1.545 mmol, 1 equiv) in DMF (15 mL) was added 1-(bromomethyl)-3-(difluoromethyl)benzene (376 mg, 1.700 mmol, 1.1 equiv) and Cs_2CO_3 (1.5 g, 4.635 mmol, 3 equiv) at rt and stirred for overnight. The reaction was quenched with water (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The residue was purified by silica gel column chromatography, eluted with PE/EA (3:1) to afford 4-(3-(difluoromethyl)benzyl)-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (220 mg, 42.59%).



7-amino-4-(3-(difluoromethyl)benzyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of 4-(3-(difluoromethyl)benzyl)-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (100 mg, 0.299 mmol, 1 equiv) in MeOH (15 mL) was added Pd/C (50 mg) under nitrogen atmosphere. The resulting mixture was placed at rt under a hydrogen atmosphere until the starting material was totally consumed by LCMS. The mixture was filtered and concentrated under vacuum to afford The catalyst was removed by filtration through a pad of Celite and rinsed with MeOH. The filtrate

was concentrated to afford 7-amino-4-(3-(difluoromethyl)benzyl)-2H-benzo[b][1,4]oxazin-3(4H)-on (57 mg, 62.62%) as a white solid.

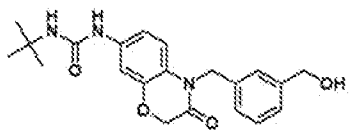


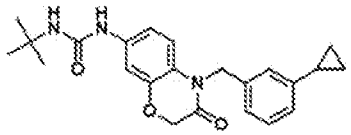
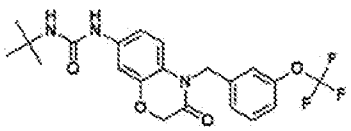
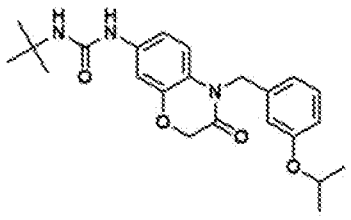
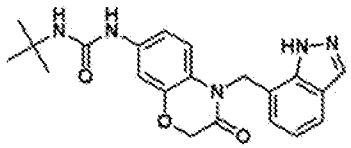
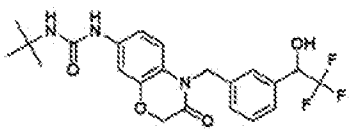
1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

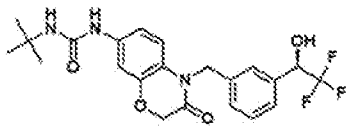
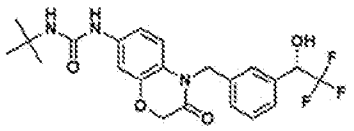
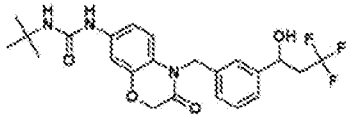
A solution of 7-amino-4-(3-(difluoromethyl)benzyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (50 mg, 0.164 mmol, 1 equiv), TEA (49.88 mg) and 2-isocyanato-2-methylpropane (48.87 mg, 0.492 mmol, 3 equiv) in DCM (5 mL) was stirred for overnight at rt. The residue was purified by silica gel column chromatography, eluted with EA (35%-46%) to afford crude product. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 61% B in 9 min, 61% B; Wave Length: 220/254 nm) to afford1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea (4 mg, 6.03%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{23}F_2N_3O_3$: 403.17 m/z, found 404.15 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.44 – 7.51 (m, 4H), 7.21 (s, 1H), 7.01 (s, 1H), 6.82 – 6.88 (m, 1H), 6.76 (d, J = 9.0 Hz, 1H), 5.93 (s, 1H), 5.16 (s, 2H), 4.75 (s, 2H), 1.25 (s, 9H).

The following examples in Table 3 were made according to the procedure for Example 71.

Table 3

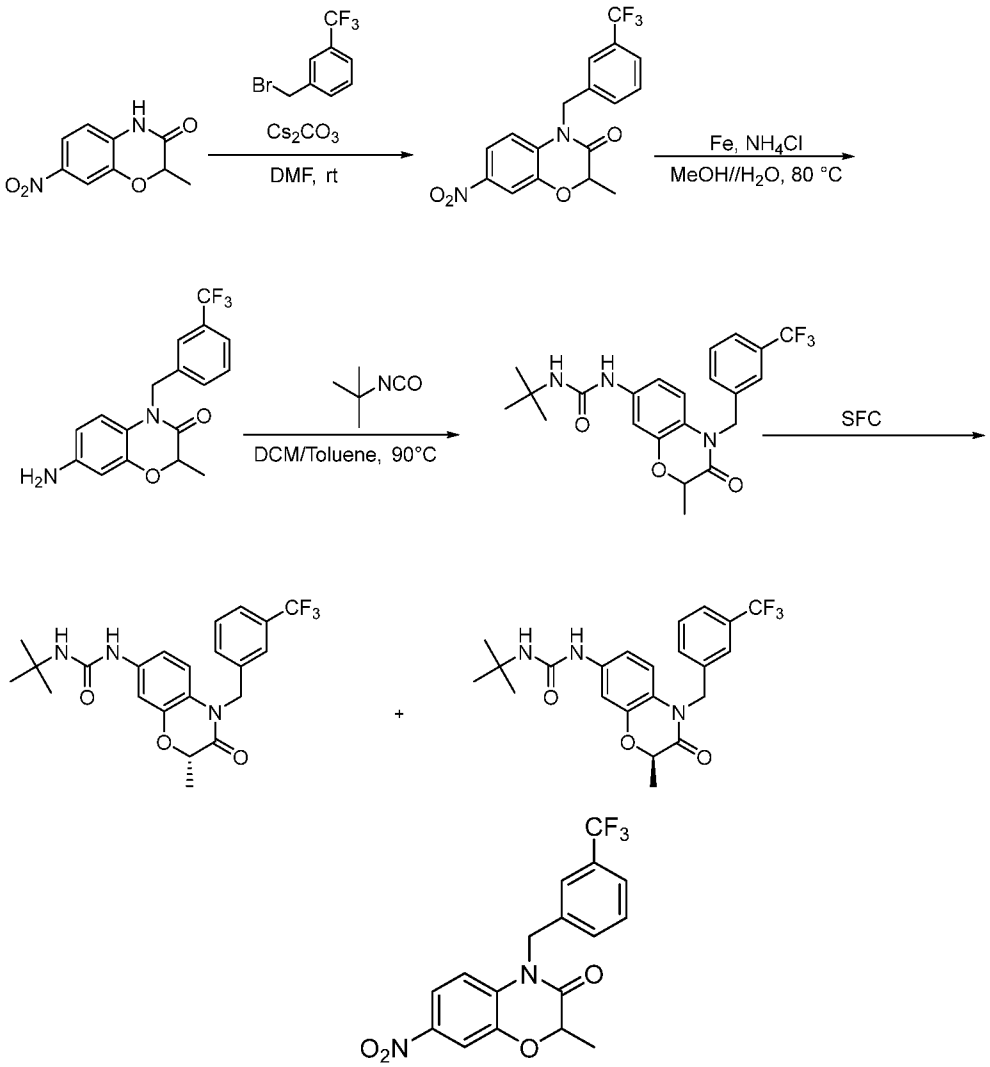
Structure	Ex.	IUPAC Name	1H NMR	LCMS
	72	1-(tert-butyl)-3-(4-(3-(hydroxymethyl)benzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.08 – 7.31 (m, 5H), 6.85 (d, J = 8.8 Hz, 1H), 6.71 – 6.78 (m, 1H), 5.94 (s, 1H), 5.18 (t, J = 5.7 Hz, 1H), 5.09 (s, 2H), 4.73 (s, 2H), 4.45 (d, J = 5.6 Hz, 2H), 1.25 (s, 9H).	calcd. for $C_{21}H_{25}N_3O_4$, 383.18 m/z, found 384.05 $[M+H]^+$

	73	1-(tert-butyl)-3-(4-(3-cyclopropylbenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.14 – 7.24(m, 2H), 6.81–7.07(m, 4H), 6.72–6.79(m, 1H), 5.93 (s, 1H), 5.05 (s, 2H), 4.74 (s, 2H), 1.87 (tt, J = 8.4, 5.1 Hz, 1H), 1.26 (s, 9H), 0.91 – 0.97 (m, 2H), 0.59 – 0.68 (m, 2H).	calcd. for $C_{23}H_{27}N_3O_3$: 393.21 m/z, found 394.20 $[M+H]^+$
	74	1-(tert-butyl)-3-(3-oxo-4-(3-(trifluoromethoxy)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.47 (t, J = 8.1 Hz, 1H), 7.33 – 7.23 (m, 3H), 7.21 (d, J = 2.3 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 6.78 (dd, J = 8.8, 2.3 Hz, 1H), 5.93 (s, 1H), 5.16 (s, 2H), 4.76 (s, 2H), 1.27 (s, 9H).	calcd. for $C_{21}H_{22}F_3N_3O_4$, 437.16 m/z, found 438.15 $[M+H]^+$
	75	1-(tert-butyl)-3-(4-(3-isopropoxybenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.21 (d, J = 2.5 Hz, 2H), 6.88 (d, J = 8.8 Hz, 1H), 6.82 – 6.71 (m, 4H), 5.93 (s, 1H), 5.06 (s, 2H), 4.74 (s, 2H), 4.56 (p, J = 6.0 Hz, 1H), 1.26 (s, 9H), 1.24 (d, J = 6.0 Hz, 6H).	calcd. for $C_{23}H_{29}N_3O_4$: 411.22 m/z, found 412.25 $[M+H]^+$
	76	1-(4-((1H-indazol-7-yl)methyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.30 (s, 1H), 8.22 (s, 1H), 8.16 (s, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 2.2 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 7.1 Hz, 1H), 6.68 – 6.78 (m, 2H), 5.93 (s, 1H), 5.37 (s, 2H), 4.81 (s, 2H), 1.26 (s, 9H).	calcd. for $C_{21}H_{23}N_5O_3$, 393.18 m/z, found 394.15 $[M+H]^+$
	77	1-(tert-butyl)-3-(3-oxo-4-(3-(2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.42 (s, 1H), 7.36 (d, J = 4.7 Hz, 2H), 7.23 – 7.27 (m, 1H), 7.19 (d, J = 2.2 Hz, 1H), 6.80 – 6.90 (m, 2H), 6.75 (dd, J = 8.7, 2.3 Hz, 1H), 5.92 (s, 1H), 5.12 (s, 2H), 5.11 (s, 1H), 4.73 (s, 2H), 1.25 (s, 9H).	calcd. for $C_{22}H_{24}F_3N_3O_4$, 451.17 m/z, found 452.10 $[M+H]^+$

	78	(R)-1-(tert-butyl)-3-(3-oxo-4-(3-(2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.42 (s, 1H), 7.31 – 7.39 (m, 2H), 7.22 – 7.29 (m, 1H), 7.18 (d, J = 2.3 Hz, 1H), 6.80 – 6.88 (m, 2H), 6.75 (dd, J = 8.8, 2.4 Hz, 1H), 5.92 (s, 1H), 5.10 – 5.14 (m, 3H), 4.73 (s, 2H), 1.25 (s, 9H).	calcd. for $C_{22}H_{24}F_3N_3O_4$, 451.17 m/z, found 452.10 $[M+H]^+$
	79	(S)-1-(tert-butyl)-3-(3-oxo-4-(3-(2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.42 (s, 1H), 7.31 – 7.39 (m, 2H), 7.22 – 7.29 (m, 1H), 7.18 (d, J = 2.3 Hz, 1H), 6.80 – 6.88 (m, 2H), 6.75 (dd, J = 8.8, 2.4 Hz, 1H), 5.92 (s, 1H), 5.10 – 5.14 (m, 3H), 4.73 (s, 2H), 1.25 (s, 9H).	calcd. for $C_{22}H_{24}F_3N_3O_4$, 451.17 m/z, found 452.10 $[M+H]^+$
	80	1-(tert-butyl)-3-(3-oxo-4-(3-(3,3,3-trifluoro-1-hydroxypropyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.20 (s, 1H), 7.35 (s, 1H), 7.32 – 7.28 (m, 2H), 7.18 – 7.12 (m, 2H), 6.85 (d, J = 8.7 Hz, 1H), 6.77 – 6.73 (m, 1H), 5.92 (s, 1H), 5.67 (d, J = 5.1 Hz, 1H), 5.09 (s, 2H), 4.86 (q, J = 5.1 Hz, 1H), 4.74 (s, 2H), 2.50 (q, J = 1.8 Hz, 2H), 1.26 (s, 9H). ^{19}F NMR (282 MHz, DMSO-d$_6$) δ -61.56.	calcd. for $C_{23}H_{26}F_3N_3O_4$: 465.2 m/z, found 466.10 $[M+H]^+$

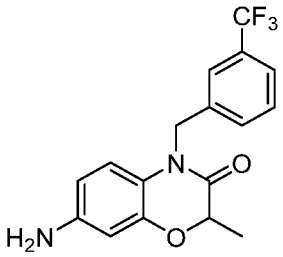
Examples 81 and 82: (S)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea and (R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

Synthetic Scheme



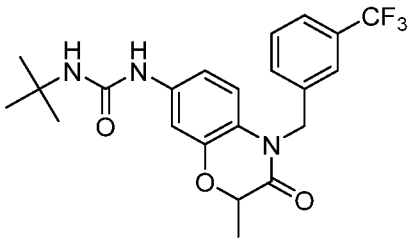
2-methyl-7-nitro-4-(3-(trifluoromethyl)benzyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of 2-methyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (250 mg, 1.201 mmol, 1 equiv) in DMF (10 mL) was added 1-(bromomethyl)-3-(trifluoromethyl)benzene (315.77 mg, 1.321 mmol, 1.1 equiv) and Cs_2CO_3 (784.99 mg, 2.402 mmol, 2 equiv). The reaction was stirred at rt for 1 hours. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 2-methyl-7-nitro-4-{[3-(trifluoromethyl)phenyl]methyl}-2H-1,4-benzoxazin-3-one (390 mg, 88.66%) as a yellow solid.MS (ESI): mass calcd. for $C_{17}H_{13}F_3N_2O_4$: 366.08 m/z, found 367.00 $[M+H]^+$.



7-amino-2-methyl-4-(3-(trifluoromethyl)benzyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

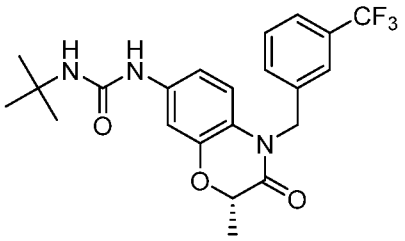
To a solution of 2-methyl-7-nitro-4-{[3-(trifluoromethyl)phenyl]methyl}-2H-1,4-benzoxazin-3-one (390 mg, 1.065 mmol, 1 equiv) in MeOH/H_2O (10:1 ,11 mL) was added Fe (594.59 mg, 10.650 mmol, 10 equiv) and NH_4Cl (569.51 mg, 10.650 mmol, 10 equiv). The resulting mixture was filtered, and the filter cake was washed with EA (3 x 30 mL). The filtrate was concentrated under reduced pressure. The mixture was diluted with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. This resulted in 7-amino-2-methyl-4-{[3-(trifluoromethyl)phenyl]methyl}-2H-1,4-benzoxazin-3-one (350 mg, 97.74%) as a yellow oil. MS (ESI): mass calcd. for$C_{17}H_{15}F_3N_2O_2$: 336.11m/z, found 337.05 $[M+H]^+$.

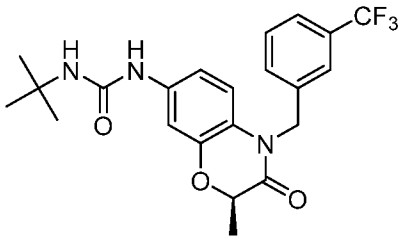


1-(tert-butyl)-3-(2-methyl-3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a solution of 7-amino-2-methyl-4-{[3-(trifluoromethyl)phenyl]methyl}-2H-1,4-benzoxazin-3-one (190 mg, 0.565 mmol, 1 equiv) in DCM/Toluene (2:1, 15 mL) was added 2-isocyanato-2-methylpropane (336.03 mg, 3.390 mmol, 6 equiv). The reaction was stirred at 90℃ for 2 hours. After cooling down to rt, the reaction was quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm column (eluent: 26% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-(2-methyl-3-oxo-4-{[3-

(trifluoromethyl)phenyl]methyl}-2H-1,4-benzoxazin-7-yl)urea (40 mg, 16.25%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{24}F_3N_3O_3$: 435.18 m/z, found:436.20 $[M+H]^+$.





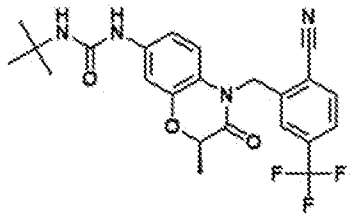
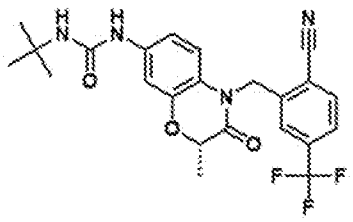
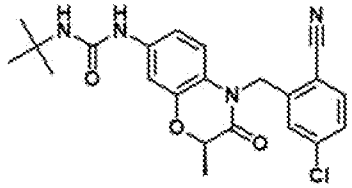
(S)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea and (R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

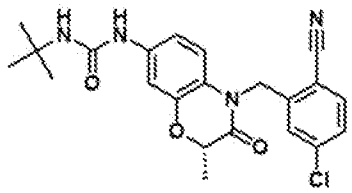
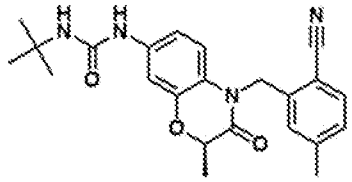
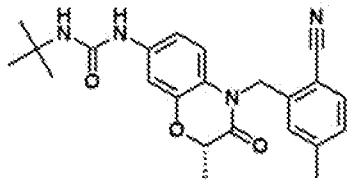
A sample of 3-tert-butyl-1-(2-methyl-3-oxo-4-{[3-(trifluoromethyl)phenyl]methyl}-2H-1,4-benzoxazin-7-yl)urea (40 mg) was separated by chiral-HPLC using a CHIRALPAK ID, 2*25 cm, 5 μm column (eluent: 10% to 10% (v/v) Hex(0.5% 2M NH_3-MeOH) and EtOH) to yield first enantiomer example example 3-tert-butyl-1-[(2R)-2-methyl-3-oxo-4-{[3-(trifluoromethyl)phenyl]methyl}-2H-1,4-benzoxazin-7-yl]urea (16.4 mg, 41.00%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{24}F_3N_3O_3$: 435.18 m/z, found:436.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.10 – 8.40 (m, 1H), 7.45 – 7.72 (m, 4H), 7.13 – 7.30 (m, 1H), 6.81 – 6.96 (m, 1H), 6.61 – 6.81 (m, 1H), 5.87 – 6.10 (m, 1H), 5.10 – 5.30 (m, 1H), 4.75 – 4.92 (m, 1H), 1.40 – 1.53 (m, 3H), 1.24 – 1.30 (m, 9H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -61.0904.and to yield second enantiomer example 3-tert-butyl-1-[(2S)-2-methyl-3-oxo-4-{[3-(trifluoromethyl)phenyl]methyl}-2H-1,4-benzoxazin-7-yl]urea (14.4 mg, 36.00%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{24}F_3N_3O_3$: 435.18 m/z, found:436.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.10 – 8.35 (m, 1H), 7.50 – 7.71 (m, 4H), 7.13 – 7.30 (m, 1H), 6.82 – 6.99 (m, 1H), 6.70 – 6.81 (m, 1H), 5.85 – 6.02 (m, 1H), 5.09 – 5.27 (m, 2H), 4.72 – 4.92 (m, 1H), 1.40 – 1.56 (m, 3H), 1.24 – 1.30 (m, 9H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -61.0913.

The following examples in Table 4 were made according to the procedure for examples 81 and 82.

Table 4

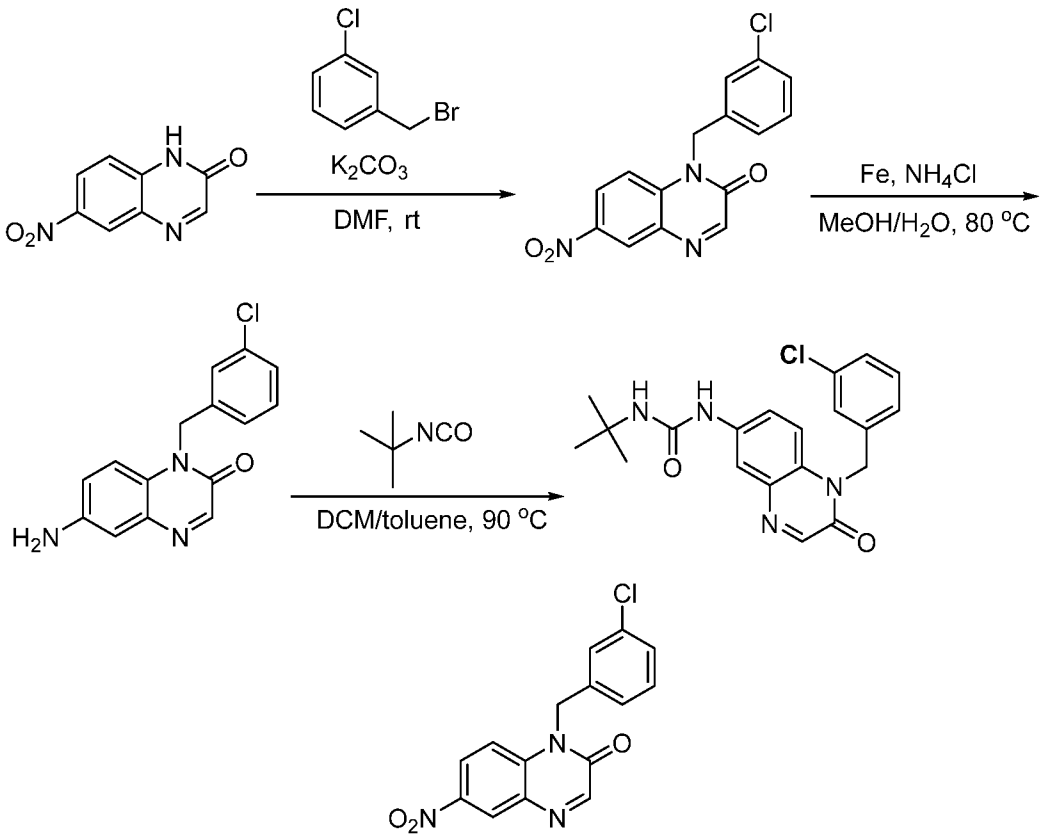
Structure	Ex.	IUPAC Name	1H NMR	LCMS

	83	(R)-1-(tert-butyl)-3-(4-(2-cyano-5-(trifluoromethyl)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 – 8.46 (m, 1H), 8.09 – 8.25 (m, 1H), 7.76 – 8.00 (m, 1H), 7.40 – 7.62 (m, 1H), 7.11 – 7.38 (m, 1H), 6.68 – 6.96 (m, 2H), 5.80 – 6.14 (m, 1H), 5.20 – 5.50 (m, 2H), 4.72 – 4.93 (m, 1H), 1.40 – 1.56 (m, 3H), 1.24 – 1.30 (m, 9H). ^{19}F NMR (376 MHz, DMSO) δ (ppm): -62.0673.	calcd. for $C_{23}H_{23}F_3N_4O_3$: 460.17 m/z, found 461.20 $[M+H]^+$
	84	(S)-1-(tert-butyl)-3-(4-(2-cyano-5-(trifluoromethyl)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 – 8.40 (m, 1H), 8.08 – 8.21 (m, 1H), 7.73 – 8.00 (m, 1H), 7.40 – 7.55 (m, 1H), 7.19 – 7.34 (m, 1H), 6.66 – 7.02 (m, 2H), 5.82 – 6.10 (m, 1H), 5.20 – 5.50 (m, 2H), 4.67 – 4.90 (m, 1H), 1.40 – 1.64 (m, 3H), 1.17 – 1.36 (m, 9H). ^{19}F NMR (376 MHz, DMSO) δ (ppm): -62.0706.	calcd. for $C_{23}H_{23}F_3N_4O_3$: 460.17 m/z, found 461.20 $[M+H]^+$
	85	(R)-1-(tert-butyl)-3-(4-(5-chloro-2-cyanobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 – 8.41 (m, 1H), 7.82 – 8.00 (m, 1H), 7.50 – 7.72 (m, 1H), 7.10 – 7.40 (m, 2H), 6.56 – 6.96 (m, 2H), 5.62 – 6.10 (m, 1H), 5.26 – 5.41 (m, 1H), 5.00 – 5.26 (m, 1H), 4.67 – 5.00 (m, 1H), 1.40 – 1.60 (m, 3H), 1.17 – 1.38 (m, 9H).	calcd. for $C_{22}H_{23}ClN_4O_3$: 426.15 m/z, found 427.15 $[M+H]^+$

	86	(S)-1-(tert-butyl)-3-(4-(5-chloro-2-cyanobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 – 8.45 (m, 1H), 7.78 – 8.10 (m, 1H), 7.50 – 7.78 (m, 1H), 7.08 – 7.40 (m, 2H), 6.52 – 6.90 (m, 2H), 5.66 – 6.16 (m, 1H), 5.24 – 5.40 (m, 1H), 5.07 – 5.24 (m, 1H), 4.69 – 5.00 (m, 1H), 1.45 – 1.55 (m, 3H), 1.25 – 1.30 (m, 9H).	calcd. for $C_{22}H_{23}ClN_4O_3$: 426.15 m/z, found 427.20 $[M+H]^+$
	87	(R)-1-(tert-butyl)-3-(4-(2-cyano-5-methylbenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 1H), 7.76 - 7.78 (m, 1H), 7.23 - 7.33 (m, 2H), 7.02 (s, 1H), 6.72 – 6.83 (m, 2H), 5.96 (s, 1H), 5.14-5.27 (m, 2H), 4.83 - 4.88 (m, 1H), 2.31 (s, 3H), 1.50 (d, J = 6.7 Hz, 3H), 1.27 (s, 9H)	calcd. for $C_{23}H_{26}N_4O_3$:406.20 m/z, found: 407.05 $[M+H]^+$.
	88	(S)-1-(tert-butyl)-3-(4-(2-cyano-5-methylbenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 7.76 - 7.78 (m, 1H), 7.23 - 7.33 (m, 2H), 7.02 (s, 1H), 6.72 - 6.83 (m, 2H), 5.96 (s, 1H), 5.11 - 5.27 (m, 2H), 4.84 - 4.88 (m, 1H), 2.31 (s, 3H), 1.50 (d, J = 6.7 Hz, 3H), 1.27 (s, 9H)	calcd. for $C_{23}H_{26}N_4O_3$:406.20 m/z, found: 407.05 $[M+H]^+$.

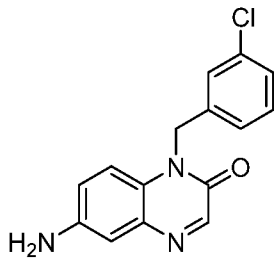
Example 89: 1-(tert-butyl)-3-(1-(3-chlorobenzyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

Synthetic Scheme



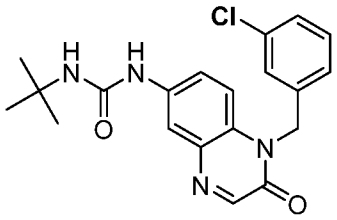
1-(3-chlorobenzyl)-6-nitroquinoxalin-2(1H)-one

To a solution of 6-nitro-1H-quinoxalin-2-one (400 mg, 2.093 mmol, 1 equiv) in DMF (10 mL) was added 1-(bromomethyl)-3-chlorobenzene (644.99 mg, 3.139 mmol, 1.5 equiv) and K_2CO_3 (582.65 mg, 4.186 mmol, 2 equiv). The reaction was stirred at rt for 1hour. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-[(3-chlorophenyl)methyl]-6-nitroquinoxalin-2-one (510 mg, 77.19%) as a yellow solid. MS (ESI): mass calcd. for $C_{15}H_{10}ClN_3O_3$: 315.04m/z, found 316.05 $[M+H]^+$.



6-amino-1-(3-chlorobenzyl)quinoxalin-2(1H)-one

To a solution of 1-[(3-chlorophenyl)methyl]-6-nitroquinoxalin-2-one (400 mg, 1.267 mmol, 1 equiv) in MeOH/H_2O (10:1, 11 mL) was added Fe (707.55 mg, 12.670 mmol, 10 equiv) and NH_4Cl (677.71 mg, 12.670 mmol, 10 equiv). The reaction was stirred at 80 °C for 1 hour. The mixture was allowed to cool down to rt. The resulting mixture was filtered, and the filter cake was washed with MeOH (3 x 20 mL). The filtrate was concentrated under reduced pressure. The mixture was diluted with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-1-[(3-chlorophenyl)methyl]quinoxalin-2-one (266 mg, 73.48%) as a yellow solid. MS (ESI): mass calcd. for $C_{15}H_{12}ClN_3O$: 285.07m/z, found 286.00 $[M+H]^+$.



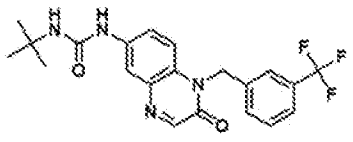
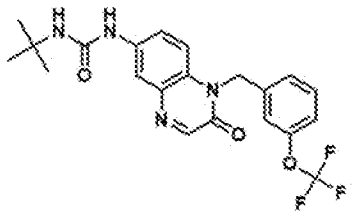
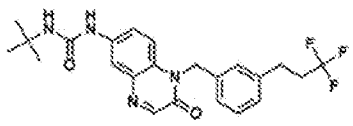
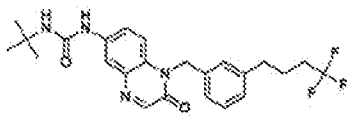
1-(tert-butyl)-3-(1-(3-chlorobenzyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

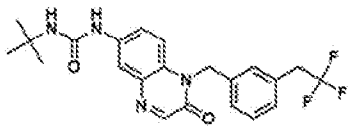
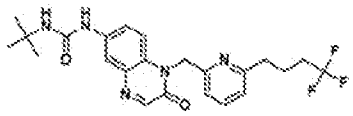
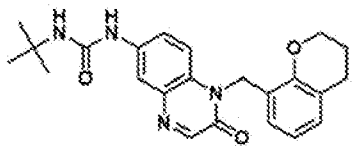
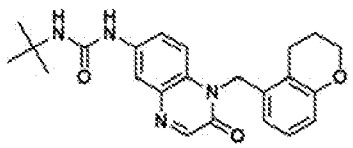
To a solution of 6-amino-1-[(3-chlorophenyl)methyl]quinoxalin-2-one (130 mg, 0.455 mmol, 1 equiv) in DCM: Toluene (2:1 , 15 mL) was added 2-isocyanato-2-methylpropane (270.62 mg, 2.730 mmol, 6 equiv). The reaction was stirred at 90 °C under N_2 for 3h. After cooling down to rt, the reaction was quenched with water (30 mL) and extracted with DCM (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-{1-[(3-chlorophenyl)methyl]-2-oxoquinoxalin-6-yl}urea (22.2 mg, 12.68%) as a yellow solid. MS (ESI): mass calcd. for $C_{20}H_{21}ClN_4O_2$: 384.14m/z, found:383.10 $[M-H]^-$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.53 (m, 1H), 8.20 – 8.40 (m, 1H), 7.91 – 8.10 (m, 1H), 7.30 – 7.50 (m, 5H), 7.10– 7.27 (m, 1H), 5.80 – 6.20 (m, 1H), 5.30 – 5.60 (m, 2H), 1.21 – 1.40 (m, 9H).

The following examples in Table 5 were made according to the procedure for example 89.

Table 5

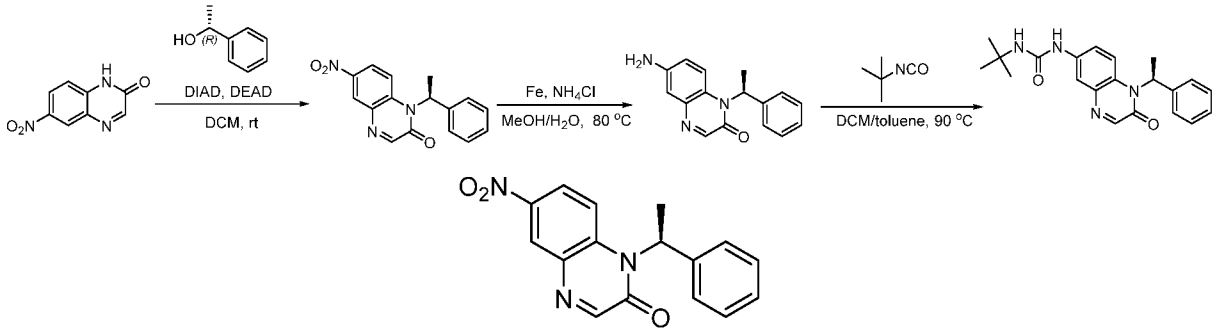
Structure	Ex.	IUPAC Name	1H NMR	LCMS

	90	1-(tert-butyl)-3-(2-oxo-1-(3-(trifluoromethyl)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, Methanol-d$_4$) δ 8.32 (s, 1H), 7.92 (d, *J* = 2.4 Hz, 1H), 7.64 (s, 1H), 7.56 – 7.50 (m, 4H), 7.36 (d, *J* = 9.3 Hz, 1H), 5.61 (s, 2H), 1.36 (s, 9H).^{19}F NMR (282 MHz, Methanol-d4) δ -64.21.	calcd. for $C_{21}H_{21}F_3N_4O_2$: 418.16 m/z, found 419.15 $[M+H]^+$
	91	1-(tert-butyl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d6) δ 8.49 (s, 1H), 8.33 (s, 1H), 7.98 (d, *J* = 2.4 Hz, 1H), 7.51 – 7.26 (m, 5H), 7.25 (d, *J* = 7.5 Hz, 2H), 6.06 (s, 1H), 5.49 (s, 2H), 1.29 (s, 9H). ^{19}F NMR (376 MHz, DMSO-d$_6$) δ -56.69.	calcd. for $C_{21}H_{21}F_3N_4O_3$:434.16 m/z, found:435.05 $[M+H]^+$
	92	1-(tert-butyl)-3-(2-oxo-1-(3-(3,3,3-trifluoropropyl)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.44 (s, 1H), 8.32 (s, 1H), 7.96 (d, *J* = 2.4 Hz, 1H), 7.43 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.07 – 7.29 (m, 4H), 7.05 (d, *J* = 7.3 Hz, 1H), 6.02 (s, 1H), 5.41 (s, 2H), 2.78 (dd, *J* = 10.1, 6.1 Hz, 2H), 2.58 (d, *J* = 10.8 Hz, 2H), 1.29 (s, 9H).	calcd. for $C_{23}H_{25}F_3N_4O_2$, 446.19 m/z, found 447.10 $[M+H]^+$
	93	1-(tert-butyl)-3-(2-oxo-1-(3-(4,4,4-trifluorobutyl)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.44 (s, 1H), 8.32 (s, 1H), 7.98 (d, *J* = 2.4 Hz, 1H), 7.41 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.34 (d, *J* = 9.1 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.09 – 7.18 (m, 2H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.02 (s, 1H), 5.42 (s, 2H), 2.63 (t, *J* = 7.7 Hz, 2H), 2.15 – 2.24 (m, 2H), 1.69 – 1.75 (m, 2H), 1.29 (s, 9H).	calcd. for $C_{24}H_{27}F_3N_4O_2$, 460.21 m/z, found 461.15 $[M+H]^+$

	94	1-(tert-butyl)-3-(2-oxo-1-(3-(2,2,2-trifluoroethyl)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.33 (s, 1H), 7.97 (d, J = 2.5 Hz, 1H), 7.42 (dd, J = 9.1, 2.5 Hz, 1H), 7.29 – 7.38 (m, 2H), 7.26 (s, 2H), 7.21 – 7.25 (m, 1H), 6.03 (s, 1H), 5.45 (s, 2H), 3.60 (q, J = 11.6 Hz, 2H), 1.29 (s, 9H).	calcd. for $C_{22}H_{23}F_3N_4O_2$, 432.18 m/z, found 431.00 $[M-H]^-$
	95	1-(tert-butyl)-3-(2-oxo-1-((6-(4,4,4-trifluorobutyl)pyridin-2-yl)methyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.30 (s, 1H), 7.97 (d, J = 2.4 Hz, 1H), 7.67 (t, J = 7.7 Hz, 1H), 7.39 (dd, J = 9.1, 2.5 Hz, 1H), 7.32 (d, J = 9.1 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 7.08 (d, J = 7.8 Hz, 1H), 6.03 (s, 1H), 5.50 (s, 2H), 2.75 (t, J = 7.4 Hz, 2H), 2.06 – 2.23 (m, 2H), 1.73 – 1.80 (m, 2H), 1.29 (s, 9H).	calcd. for $C_{23}H_{26}F_3N_5O_2$, 461.20 m/z, found 462.15 $[M+H]^+$
	96	1-(tert-butyl)-3-(1-(chroman-8-ylmethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.31 (s, 1H),7.89-8.04 (m, 1H),7.38-7.52 (m, 1H),7.10-7.20 (m, 1H), 6.90-7.02 (m, 1H), 6.60-6.72 (m, 1H), 6.35-6.48 (m, 1H), 6.00 (s, 1H), 5.11-5.32 (m, 2H), 4.20-4.38 (m, 2H), 2.78-2.85 (m, 2H), 1.98-2.09 (m, 2H), 1.25-1.48 (m, 9H)	calcd. for $C_{23}H_{26}N_4O_3$: 406.20, found: 407.05 $[M+H]^+$
	97	1-(tert-butyl)-3-(1-(chroman-5-ylmethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, Chloroform-d) δ 8.40 (s, 1H), 7.70 (d, J = 2.5 Hz, 1H), 7.62 (dd, J = 8.9, 2.6 Hz, 1H), 7.28 (s, 2H), 6.87 – 7.05 (m, 1H), 6.74 (d, J = 8.2 Hz, 1H), 6.26 (s, 1H), 6.19 (d, J = 7.6 Hz, 2H), 5.35 (s, 1H), 4.18 – 4.27 (m, 2H), 2.85 (t, J = 6.6 Hz, 2H), 2.10 – 2.20 (m, 2H), 1.40 (s, 9H).	calcd. for $C_{23}H_{26}N_4O_3$: 406.20 m/z found: 407.05 $[M+H]^+$

Example 98: (S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea

Synthetic Scheme



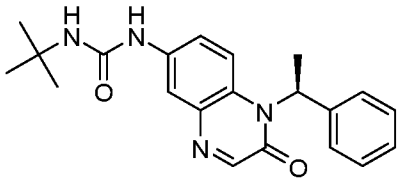
(S)-6-nitro-1-(1-phenylethyl)quinoxalin-2(1H)-one

To a solution of 6-nitro-1H-quinoxalin-2-one (400 mg, 2.093 mmol, 1 equiv) in DCM (10 mL) was added (R)-1-phenylethan-1-ol (255.65 mg, 2.093 mmol, 1 equiv) and PPh_3 (823.32 mg, 3.139 mmol, 1.5 equiv). The reaction was stirred at rt under N_2 for 0.5h. To the above mixture was added DEAD (546.67 mg, 3.139 mmol, 1.5 equiv) in portions at 0℃. The resulting mixture was stirred for additional 1 hour at rt. Quenched with water (30 mL) and extracted with DCM (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to 6-nitro-1-[(1S)-1-phenylethyl]quinoxalin-2-one (108 mg, 17.48%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{13}N_3O_3$: 295.10m/z, found 296.00 $[M+H]^+$.

(S)-6-amino-1-(1-phenylethyl)quinoxalin-2(1H)-one

To a solution of 6-nitro-1-[(1S)-1-phenylethyl]quinoxalin-2-one (100 mg, 0.339 mmol, 1 equiv) in MeOH/H_2O (10:1 , 11 mL) was added Fe (189.11 mg, 3.390 mmol, 10 equiv) and NH_4Cl (181.14 mg, 3.390 mmol, 10 equiv).The reaction was stirred at 80 °C for 1 hour. The mixture was allowed to cool down to rt. The resulting mixture was filtered, and the filter cake was washed with MeOH (3 x 20 mL). The filtrate was concentrated under reduced pressure. The mixture was diluted with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-1-[(1S)-1-

phenylethyl]quinoxalin-2-one (85 mg, 94.61%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{15}N_3O$: 265.12m/z, found 266.15 $[M+H]^+$.

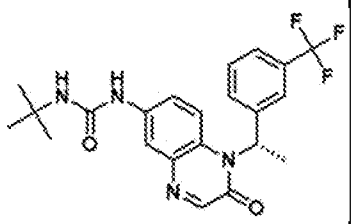


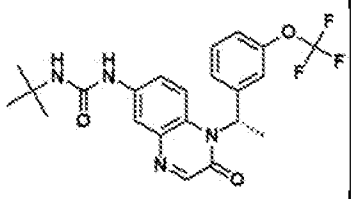
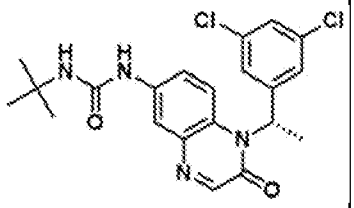
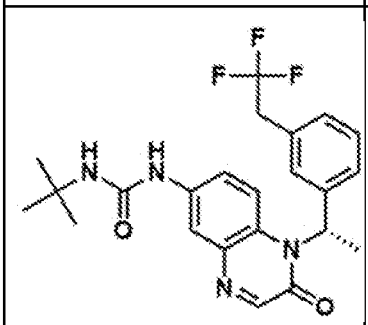
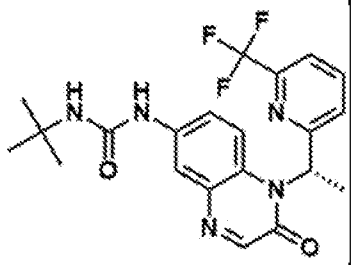
(S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea

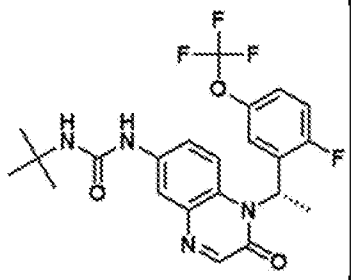
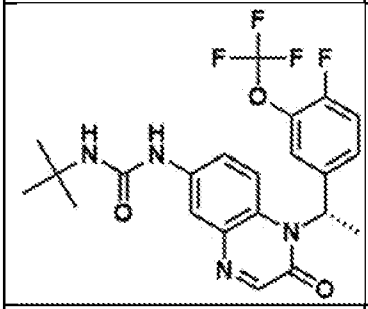
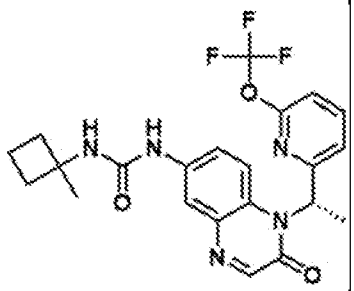
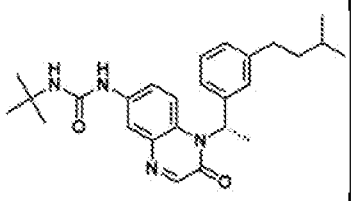
To a solution of 6-amino-1-[(1S)-1-phenylethyl]quinoxalin-2-one (85 mg, 0.320 mmol, 1 equiv) in DCM: Toluene (2:1, 15 mL) was added 2-isocyanato-2-methylpropane (190.56 mg, 1.920 mmol, 6 equiv). The reaction was stirred at 90 °C under N_2 for 3 hours. After cooling down to rt, the reaction was quenched with water (30 mL) and extracted with DCM (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Shield RP18 OBD Column, 30*150 mm, 5μm column (eluent: 34% to 56% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-{2-oxo-1-[(1S)-1-phenylethyl]quinoxalin-6-yl}urea (22.1 mg, 18.93%) as a yellow solid. MS (ESI): mass calcd. for $C_{21}H_{24}N_4O_2$: 364.19m/z, found:365.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.31 – 8.50 (m, 1H), 8.17 – 8.31 (m, 1H), 7.77 – 8.02 (m, 1H), 7.20 – 7.40 (m, 6H), 6.86 – 7.20 (m, 1H), 6.50 – 6.80 (m, 1H), 5.67 – 6.20 (m, 1H), 1.76 – 1.95 (m, 1H), 1.17 – 1.32 (m, 9H).

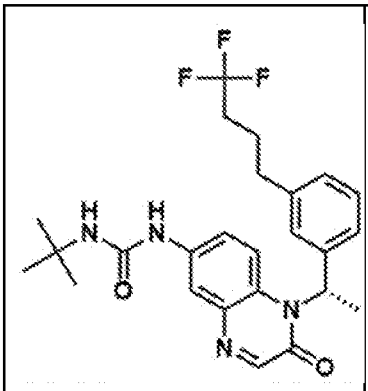
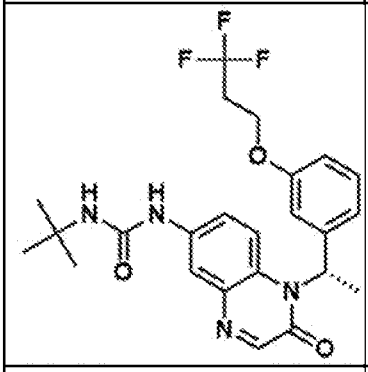
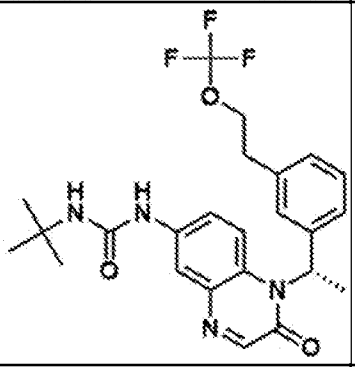
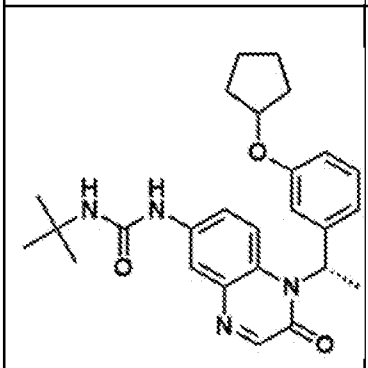
The following examples in Table 6 were made according to the procedure for example 98.

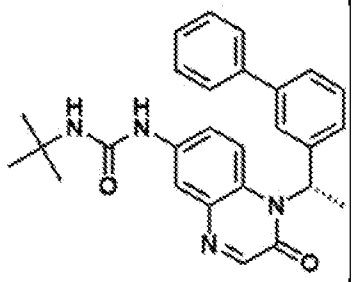
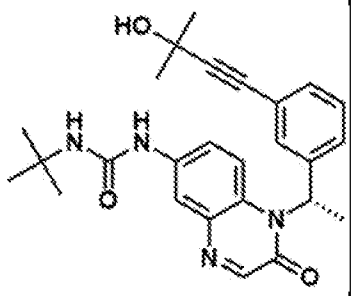
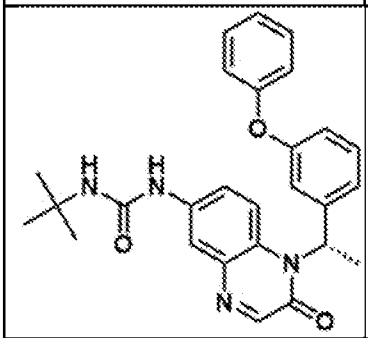
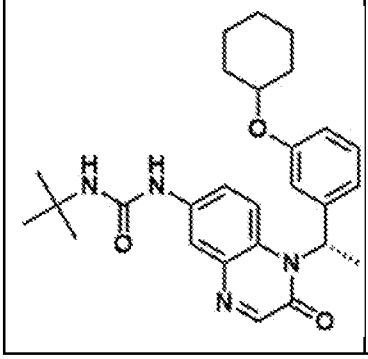
Table 6

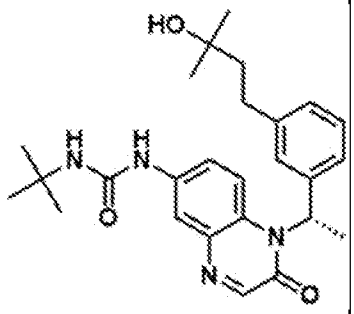
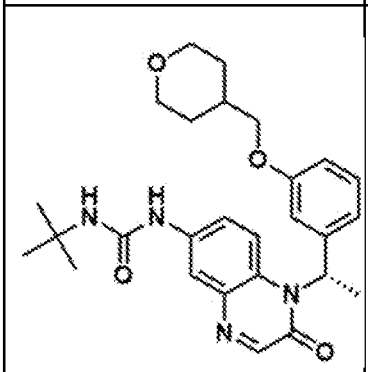
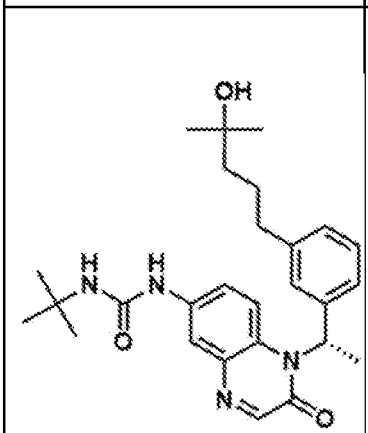
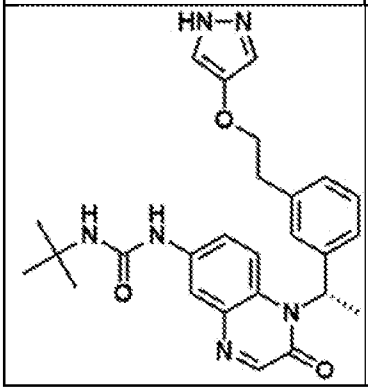
Structure	Ex.	IUPAC Name	1H NMR	LCMS
	99	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^1H NMR (300 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.24 (s, 1H), 7.94 (s, 1H), 7.60 - 7.70 (m, 4H), 7.31 - 7.38 (m, 1H), 7.14 (s, 1H), 6.59 (s, 1H), 6.04 (s, 1H), 1.91 - 1.93 (d, J = 6 Hz, 3H), 1.29 (s, 9H). ^{19}F NMR (282 MHz, DMSO) δ -60.88.	calcd. for $C_{22}H_{23}F_3N_4O_2$:432.18 m/z, found:433.00 $[M+H]^+$

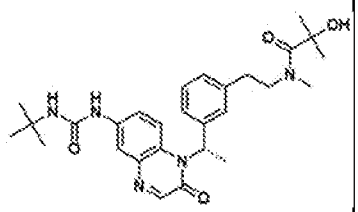
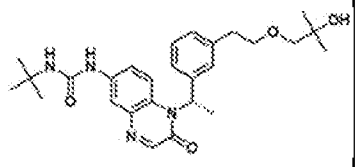
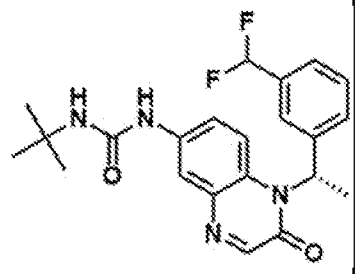
	100	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.42 (s, 1H), 8.24 (s, 1H), 7.94 (d, J = 2.4 Hz, 1H), 7.48 (t, J = 8.1 Hz, 1H), 7.31 – 7.27 (m, 4H), 7.09 (s, 1H), 6.03 (s, 1H), 1.88 (d, J = 7.2 Hz, 3H), 1.29 (s, 9H). ^{19}F NMR (282 MHz, DMSO-d6) δ -56.68.	calcd. for $C_{22}H_{23}F_3N_4O_3$:448.1 m/z, found:449.15 $[M+H]^+$
	101	(S)-1-(tert-butyl)-3-(1-(1-(3,5-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.23 (s, 1H), 7.95 (d, J = 2.4 Hz, 1H), 7.54 (d, J = 2.4 Hz, 1H), 7.34 – 7.26 (m, 3H), 7.06 (s, 1H), 6.49 (s, 1H), 6.05 (s, 1H), 1.86 (d, J = 7.2 Hz, 3H), 1.29 (s, 9H).	calcd. for $C_{21}H_{22}Cl_2N_4O_2$:432.1 m/z, found:433.10 $[M+H]^+$.
	102	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2,2,2-trifluoroethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (s, 1H), 8.26 (s, 1H), 7.92 (d, J = 2.6 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.23 – 7.31 (m, 4H), 7.07 (s, 1H), 6.60 (s, 1H), 3.61 (q, J = 11.6 Hz, 2H), 1.88 (d, J = 7.1 Hz, 3H), 1.28 (s, 9H).	calcd. for $C_{23}H_{25}F_3N_4O_2$, 446.19 m/z, found 447.10 $[M+H]^+$
	103	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 – 8.50 (m, 1H), 8.14 – 8.27 (m, 1H), 7.98 – 8.10 (m, 1H), 7.89 – 7.98 (m, 1H), 7.70 – 7.89 (m, 1H), 7.52 – 7.66 (m, 1H), 7.32 – 7.45 (m, 1H), 6.95 – 7.32 (m, 1H), 6.34 – 6.78 (m, 1H), 5.90 – 6.15 (m, 1H), 1.80 – 1.99 (m, 3H), 1.24 – 1.35 (m, 9H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -66.5322.	calcd. for $C_{21}H_{22}F_3N_5O_2$: 433.17 m/z, found 434.20 $[M+H]^+$

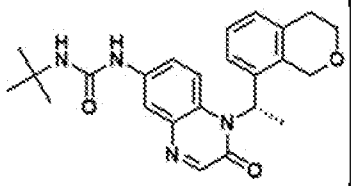
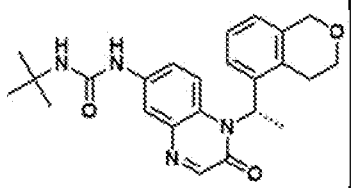
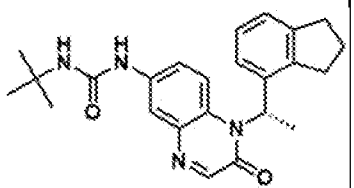
	104	(S)-1-(tert-butyl)-3-(1-(1-(2-fluoro-5-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.13 (s, 1H), 7.90 (d, J = 2.5 Hz, 1H), 7.69 (s, 1H), 7.56 (s, 1H), 7.47 (s, 1H), 7.39 (d, J = 8.9 Hz, 1H), 7.23 (t, J = 9.5 Hz, 1H), 6.48 (s, 1H), 6.04 (s, 1H), 1.87 (d, J = 6.9 Hz, 3H), 1.30 (s, 9H).	calcd. for $C_{22}H_{22}F_4N_4O_3$, 466.16 m/z, found 467.10 $[M+H]^+$
	105	(S)-1-(tert-butyl)-3-(1-(1-(4-fluoro-3-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.23 (s, 1H), 7.93 (d, J = 2.5 Hz, 1H), 7.42 – 7.53 (m, 2H), 7.31 – 7.42 (m, 2H), 7.14 (br, 1H), 6.52 (br, 1H), 6.03 (s, 1H), 1.88 (d, J = 7.0 Hz, 3H), 1.29 (s, 9H).	calcd. For $C_{22}H_{22}F_4N_4O_3$: 466.16 m/z, found: 467.10 $[M+H]^+$.
	106	(S)-1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(6-(trifluoromethoxy)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.22 (s, 1H), 7.95 – 8.05 (m, 1H), 7.93 (d, J = 2.5 Hz, 1H), 7.39 (d, J = 7.7 Hz, 2H), 7.02 – 7.29 (m, 2H), 6.50 (s, 1H), 6.33 (s, 1H), 2.21 – 2.34 (m, 2H), 1.82 – 1.93 (m, 5H), 1.70 – 1.82 (m, 2H), 1.40 (s, 3H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -55.2989.	calcd. for $C_{22}H_{22}F_3N_5O_3$: 461.17 m/z, found 462.15 $[M+H]^+$
	107	(S)-1-(tert-butyl)-3-(1-(1-(3-isopentylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 8.27 (s, 1H), 7.92 (d, J = 2.6 Hz, 1H), 7.25 (t, J = 7.7 Hz, 2H), 7.00 – 7.12 (m, 4H), 6.59 (s, 1H), 6.01 (s, 1H), 2.55 (s, 2H), 1.87 (d, J = 7.1 Hz, 3H), 1.33 – 1.44 (m,3H), 1.28 (s, 9H), 0.76 – 0.88 (m,6H).	calcd. for $C_{26}H_{34}N_4O_2$: 434.27 m/z, found: 435.20 $[M+H]^+$

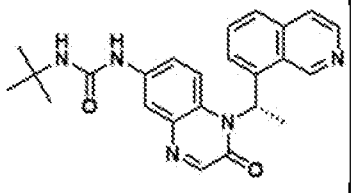
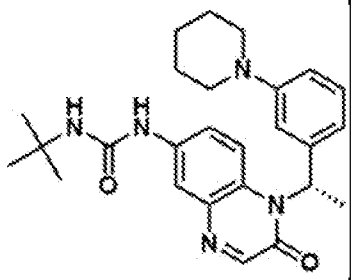
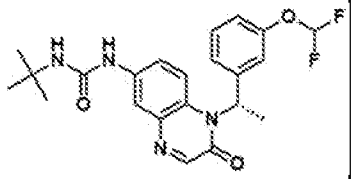
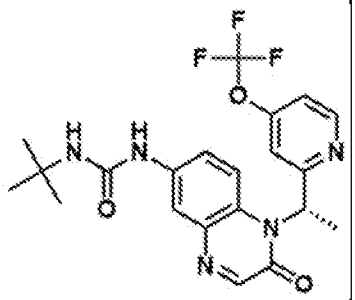
	108	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(4,4,4-trifluorobutyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 8.27 (s, 1H), 7.93 (d, J = 2.6 Hz, 1H), 7.20 – 7.32 (m,2H),7.08 – 7.16 (m, 3H), 7.04 (s, 1H), 6.59 (s, 1H), 6.02 (s, 1H), 2.62 (t, J = 7.6 Hz, 2H), 2.05 – 2.19 (m, 2H),1.88 (d, J = 7.2 Hz, 3H), 1.65 – 1.78 (m, 2H), 1.28 (s, 9H).	calcd. for $C_{25}H_{29}F_3N_4O_2$: 474.22 m/z, found: 475.20 $[M+H]^+$
	109	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(3,3,3-trifluoropropoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 8.26 (s, 1H), 7.93 (d, J = 2.5 Hz, 1H), 7.27 (t, J = 7.8 Hz, 2H), 7.06 (s, 1H), 6.80 – 6.93(m, 3H), 6.57 (s, 1H), 6.02 (s, 1H), 4.11 – 4.24 (m, 2H), 2.66 – 2.83 (m,2H), 1.87 (d, J = 7.1 Hz, 3H), 1.28 (s, 9H).	calcd. for $C_{24}H_{27}F_3N_4O_3$: 476.20 m/z, found: 477.20 $[M+H]^+$
	110	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2-(trifluoromethoxy)ethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.38 (s, 1H), 8.27 (s, 1H), 7.93 (d, J = 2.5 Hz, 1H), 7.17 – 7.35 (m, 4H),7.09 – 7.17(m,1H),7.05 (s, 1H), 6.60 (s, 1H), 6.00 (s, 1H), 4.25 (t, J = 6.5 Hz, 2H), 2.96 (t, J = 6.5 Hz, 2H), 1.88 (d, J = 7.2 Hz, 3H), 1.28 (s, 9H).	calcd. for $C_{24}H_{27}F_3N_4O3$: 476.20 M/Z, found: 477.15 $[M+H]^+$
	111	(S)-1-(tert-butyl)-3-(1-(1-(3-(cyclopentyloxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (s, 1H), 8.26 (s, 1H), 7.20-7.80 (m, 1H), 7.18-7.38 (m, 2H), 6.91-7.18 (m, 1H), 6.78-6.90 (m, 2H), 6.70-6.79 (m, 1H), 6.55 (s, 1H), 6.02 (s, 1H), 4.51-4.91 (m, 1H), 1.78-1.98 (m, 5H), 1.51-1.71 (m, 6H), 1.22-1.33 (m, 9H)	calcd. for $C_{26}H_{32}N_4O_3$: 448.25, found: 449.10 $[M+H]^+$.

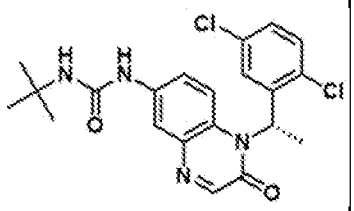
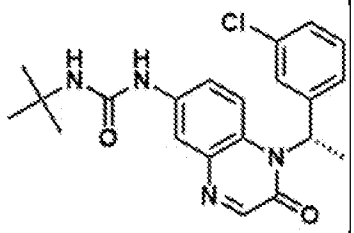
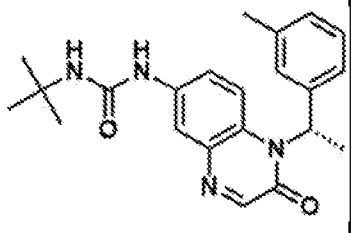
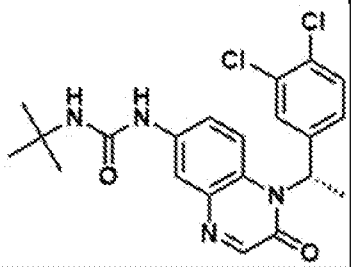
	112	(S)-1-(1-(1-([1,1'-biphenyl]-3-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (d, *J* = 45.8 Hz, 2H), 7.94 (d, *J* = 2.5 Hz, 1H), 7.60 – 7.67 (m, 2H), 7.54 – 7.60 (m, 2H), 7.33 – 7.50 (m, 4H), 7.10 – 7.32 (m, 3H), 6.66 (s, 1H), 6.02 (s, 1H), 1.95 (d, *J* = 7.1 Hz, 3H), 1.28 (s, 9H).	calcd. for $C_{27}H_{28}N_4O_2$: 440.20 m/z, found 441.20 $[M+H]^+$
	113	(S)-1-(tert-butyl)-3-(1-(1-(3-(3-hydroxy-3-methylbut-1-yn-1-yl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.38 (s, 1H), 7.60 (s, 1H), 7.47-7.50 (d, *J* = 12 Hz, 1H), 7.23-7.35(m, 2H), 7.17-7.19 (m, 1H), 6.97-6.99 (d, *J* = 8.0 Hz, 1H), 6.80 (s, 1H), 6.15 (s, 1H), 4.51 (s, 1H), 2.07 (s, 1H), 1.92-1.94 (d, *J* = 8.0 Hz, 3H), 1.57-1.63(m, 6H), 1.39 (s, 9H).	$C_{26}H_{30}N_4O_3$: 446.23 m/z, found: 469.15 $[M+Na]^+$
	114	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-phenoxyphenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.24 (s, 1H), 7.93 (d, *J* = 2.5 Hz, 1H), 7.40 – 7.29 (m, 4H), 7.15 – 7.02 (m, 3H), 6.97 – 6.83 (m, 4H), 6.59 (s, 1H), 6.05 (s, 1H), 1.86 (d, *J* = 7.1 Hz, 3H), 1.29 (s, 9H).	calcd. for $C_{27}H_{28}N_4O_3$: 456.22 m/z, found 457.20 $[M+H]^+$
	115	(S)-1-(tert-butyl)-3-(1-(1-(3-(cyclohexyloxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (s, 1H), 8.26 (s, 1H), 7.80-8.04 (m, 1H), 7.19-7.35 (m, 2H), 6.90-7.13 (m, 1H), 6.68-6.90 (m, 3H), 6.41-6.68 (m, 1H), 6.03 (s, 1H), 4.16-4.35 (m, 1H), 1.83-1.92 (m, 4H), 1.47-1.75 (m, 3H), 1.16-1.42 (m, 15H).	calcd. for $C_{27}H_{34}N_4O_3$:462.2 m/z, found 463.10 $[M+H]^+$.

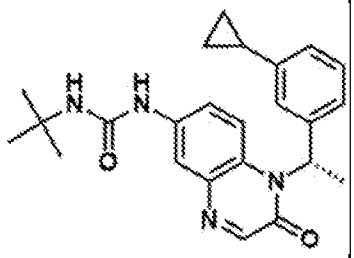
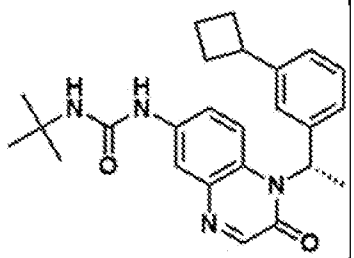
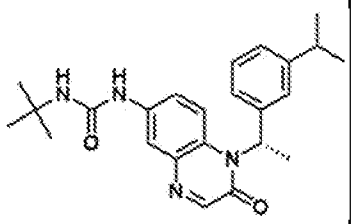
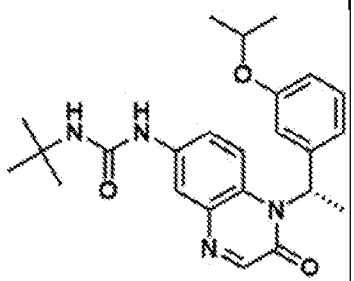
	116	(S)-1-(tert-butyl)-3-(1-(1-(3-(3-hydroxy-3-methylbutyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.36 (s, 1H), 8.26 (s, 1H), 7.92 (d, *J* = 2.4 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 2H), 7.14 – 7.01 (m, 3H), 6.57 (s, 1H), 6.02 (s, 1H), 5.44 (s, 1H), 4.22 (s, 1H), 2.51 (d, *J* = 1.8 Hz, 2H), 1.87 (d, *J* = 7.2 Hz, 2H), 1.27 – 1.10 (m, 18H).	calcd. for $C_{26}H_{34}N_4O_3$: 450.3 m/z, found 451.2 $[M+H]^+$
	117	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.48 (s, 1H), 8.27 (s,1H),7.85-8.02 (m,1H),7.20-7.38 (m, 2H), 6.94-7.12 (m, 1H), 6.72-6.90 (m, 3H),6.49-6.68 (m, 1H), 6.10 (s, 1H), 3.71-3.91 (m, 4H), 3.20-3.30 (m, 2H), 1.82-1.90 (m, 3H), 1.58-1.69 (m, 2H), 1.19-1.39 (m,12H).	calcd. for $C_{27}H_{34}N_4O_4$: 478.26, found: 479.25 $[M+H]^+$
	118	(S)-1-(tert-butyl)-3-(1-(1-(3-(4-hydroxy-4-methylpentyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, Chloroform-d) δ 8.37 (s, 1H), 7.54 (d, *J* = 2.6 Hz, 1H), 7.50 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 7.9 Hz, 2H), 7.02 (d, *J* = 9.2 Hz, 2H), 6.85 (d, *J* = 7.7 Hz, 1H), 6.28 (s, 1H), 4.59 (s, 1H), 2.57 (t, *J* = 7.5 Hz, 2H), 1.93 (d, *J* = 7.2 Hz, 3H), 1.55 – 1.68 (m, 4H), 1.38 (s, 9H), 1.17 (d, *J* = 5.3 Hz, 6H).	calcd. for $C_{27}H_{36}N_4O_3$: 464.28 m/z found: 465.30 $[M+H]^+$
	119	(S)-1-(1-(1-(3-(2-((1H-pyrazol-4-yl)oxy)ethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea	^{1}H NMR (300 MHz, DMSO-d$_6$) δ 12.3 (s, 1H), 8.39 (s, 1H), 8.26 (s, 1H), 7.93 (d, *J* = 2.1 Hz, 1H), 7.29 – 7.18 (m, 6H), 7.09 (d, *J* = 7.2 Hz, 2H), 6.59 (s, 1H), 6.02 (s, 1H), 4.00 (t, *J* = 6.6 Hz, 2H), 2.94 (t, *J* = 6.8 Hz, 2H), 1.87 (d, *J* = 7.2 Hz, 3H), 1.26 (s, 9H).	calcd. for $C_{26}H_{30}N_6O_3$: 474.2 m/z, found 475.2 $[M+H]^+$

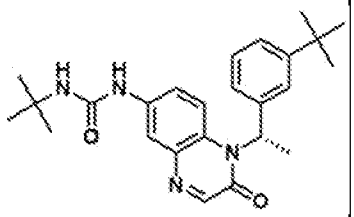
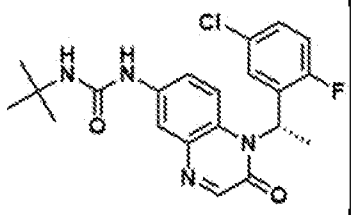
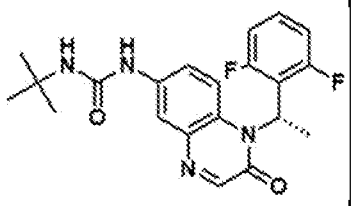
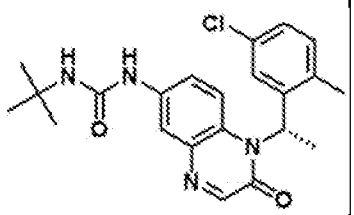
	120	(S)-N-(3-(1-(6-(3-(tert-butyl)ureido)-2-oxoquinoxalin-1(2H)-yl)ethyl)phenethyl)-2-hydroxy-N,2-dimethylpropanamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.39 (s, 1H), 8.27 (s, 1H), 7.90 – 8.04 (m, 1H), 7.23 – 7.29 (m, 2H), 7.04 – 7.19 (m, 4H), 6.50 – 6.57 (m, 1H), 6.02 (s, 1H), 5.24 – 5.34 (m, 1H), 3.78 – 3.84 (m, 1H), 3.39 – 3.44 (m, 1H), 3.09 – 3.15 (m, 2H), 2.79 – 2.85 (s, 3H), 1.88 (d, J = 7.1 Hz, 3H), 1.28 (s, 9H), 1.26 (s, 6H).	calcd. for $C_{28}H_{37}N_5O_4$: 507.28 m/z, found 508.35 $[M+H]^+$
	121	(S)-1-(tert-butyl)-3-(1-(1-(3-(2-(2-hydroxy-2-methylpropoxy)ethyl) phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, Chloroform-d) δ 8.34 (s, 1H), 7.47 – 7.58 (m, 2H), 7.27 (d, J = 7.8 Hz, 1H), 7.06 – 7.17 (m, 3H), 7.01 (d, J = 9.1 Hz, 1H), 6.80 (d, J = 7.2 Hz, 1H), 6.64 (s, 1H), 3.65 (t, J = 6.7 Hz, 2H), 3.23 (s, 2H), 2.85 (t, J = 6.7 Hz, 2H), 1.91 (d, J = 7.2 Hz, 3H), 1.45 (d, J = 3.6 Hz, 9H).1.17 (d, J = 3.6 Hz, 6H).	calcd. for $C_{27}H_{36}N_4O_4$: 480.27 m/z found: 479.20 $[M-H]^-$
	122	(S)-1-(tert-butyl)-3-(1-(1-(3-(difluoromethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.26 (s, 1H), 7.94 (d, J = 2.5 Hz, 1H), 7.42 – 7.55 (m, 4H), 7.30 (s, 1H), 6.80 – 7.21 (m, 2H), 6.60 (s, 1H), 6.03 (s, 1H), 1.91 (d, J = 7.1 Hz, 3H), 1.28 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -109.2872.	calcd. for $C_{22}H_{24}F_2N_4O_2$: 414.19 m/z, found 415.05 $[M+H]^+$

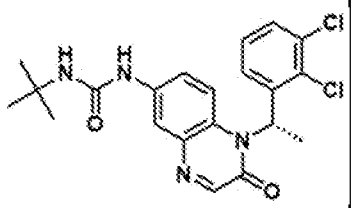
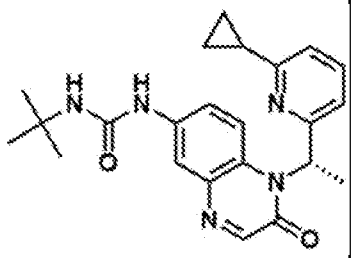
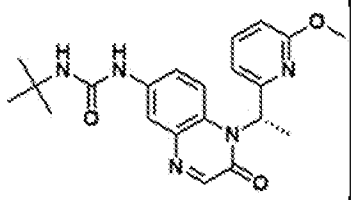
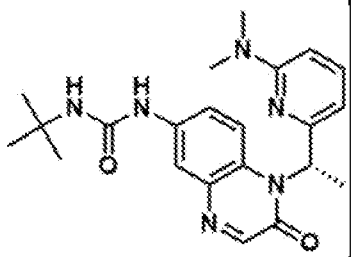
	123	(S)-1-(tert-butyl)-3-(1-(1-(isochroman-8-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.20 (s, 1H), 7.88 (s, 1H), 7.57-7.60 (m, 1H), 7.41-7.43 (m, 1H), 7.28-7.33 (m, 2H), 7.08-7.10 (m, 1H), 6.29 (s, 1H), 6.04 (s, 1H), 4.45-4.50 (d, J = 15.0 Hz, 1H), 3.80 – 3.92 (m, 1H), 3.62-3.67 (d, J = 15.0 Hz, 1H), 3.43-3.44 (m, 1H), 2.65-2.72 (m, 1H), 2.64-2.67 (m, 1H), 1.82-1.84 (d, J = 6.0 Hz, 3H), 1.28 (s, 9H)	calcd. for $C_{24}H_{28}N_4O_3$:420.22 m/z, found:421.10 $[M+H]^+$.
	124	(S)-1-(tert-butyl)-3-(1-(1-(isochroman-5-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, Chloroform-d) δ 8.33 (s, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.47 – 7.56 (m, 2H), 7.25 – 7.37 (m, 2H), 6.97 (d, J = 7.6 Hz, 1H), 6.67 (d, J = 7.3 Hz, 1H), 6.11 (s, 1H), 4.72 (s, 2H), 4.50 (s, 1H), 3.98 (d, J = 11.9 Hz, 1H), 3.57 – 3.66 (m, 1H), 2.50 (d, J = 16.4 Hz, 1H), 2.04 (s, 1H), 1.96 (d, J = 7.1 Hz, 3H), 1.39 (s, 9H)	calcd. for $C_{24}H_{28}N_4O_3$: 420.22 m/z found: 443.10 $[M+Na]^+$
	125	(S)-1-(tert-butyl)-3-(1-(1-(2,3-dihydro-1H-inden-4-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 8.23 (s, 1H),7.88-7.98 (m, 1H), 7.40-7.52(m, 1H), 7.21-7.38(m, 3H), 7.10-7.20 (m, 1H), 6.48 (s, 1H), 6.00 (s, 1H), 2.59-2.85 (m, 3H), 1.72-1.98 (m, 6H), 1.22-1.38 (m, 9H).	calcd. for $C_{24}H_{28}N_4O_2$:404.22, found: 405.10 $[M+H]^+$

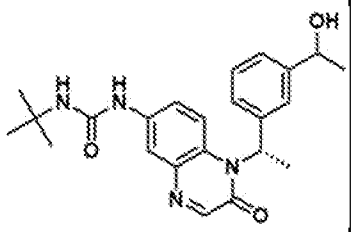
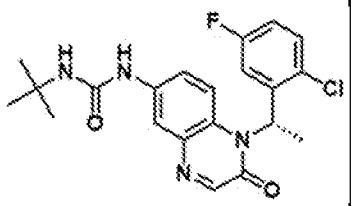
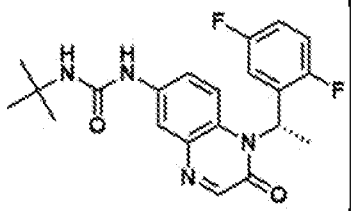
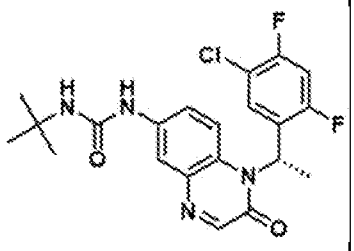
	126	(S)-1-(tert-butyl)-3-(1-(1-(isoquinolin-8-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 8.38-8.58 (m, 2H), 8.02-8.05 (m, 2H), 7.93-8.02 (m, 1H), 7.76-7.93 (m, 3H), 7.50-7.76 (m, 1H), 7.21-7.76 (m, 1H), 6.85-7.20 (m, 1H), 5.78-6.25 (m, 1H), 1.95-2.13 (m, 3H), 1.25-1.35 (m, 9H).	calcd. for $C_{24}H_{25}N_5O_2$:415.2 m/z, found: 416.15 $[M+H]^+$
	127	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(piperidin-1-yl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 8.27 (s, 1H), 7.92 (d, J = 2.6 Hz, 1H), 7.26 (dd, J = 9.5, 2.5 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H), 7.10 (s, 1H), 6.81 – 6.83 (m, 2H), 6.65 – 6.59 (m, 1H), 6.58 – 6.53 (m, 1H), 6.03 (s, 1H), 3.05 – 3.09 (m, 4H), 1.85 (d, J = 7.2 Hz, 3H), 1.48 – 1.59 (m, 6H), 1.28 (s, 9H).	calcd. for $C_{26}H_{33}N_5O_2$: 447.28 m/z, found 448.25 $[M+H]^+$
	128	(S)-1-(tert-butyl)-3-(1-(1-(3-(difluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.41 (s, 1H), 8.26 (s, 1H),7.88-8.00 (m, 1H), 7.21-7.50 (m, 3H), 7.00-7.17 (m, 4H), 6.49-6.67 (m, 1H), 6.03 (s, 1H), 1.88 (d, J = 7.1 Hz, 3H), 1.25-1.34 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ -82.14.	LC/MS (ESI): calcd. for $C_{22}H_{24}F_2N_4O_3$:430.2 m/z, found:431.20 $[M+H]^+$
	129	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(4-(trifluoromethoxy)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (d, J = 5.6 Hz, 1H), 8.43 (s, 1H), 8.21 (s, 1H), 7.94 (d, J = 2.5 Hz, 1H), 7.30 – 7.48 (m, 3H), 7.15 (s, 1H), 6.51 (s, 1H), 6.04 (s, 1H), 1.89 (d, J = 7.0 Hz, 3H), 1.29 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -56.5140.	calcd. for $C_{21}H_{22}F_3N_5O_3$: 449.17 m/z, found 450.05 $[M+H]^+$

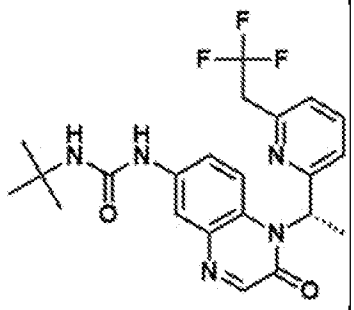
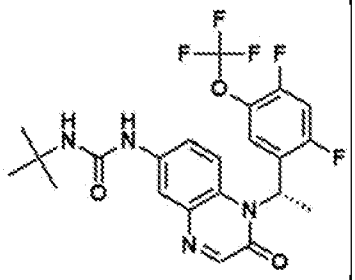
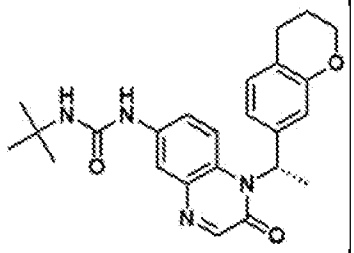
	130	(S)-1-(tert-butyl)-3-(1-(1-(2,5-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.08 (s, 1H), 7.83 – 7.91 (m, 2H), 7.61 (s, 1H), 7.47 – 7.54 (m, 1H), 7.35 – 7.46 (m, 2H), 6.15 (s, 1H), 6.06 (s, 1H), 1.86 (d, J = 6.9 Hz, 3H), 1.30 (s, 9H).	calcd. for $C_{21}H_{22}Cl_2N_4O_2$:432.11 m/z, found:432.95 $[M+H]^+$
	131	(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 8.25 (s, 1H), 7.90-8.01 (m, 1H), 7.28-7.44 (m, 4H), 7.18-7.28 (m, 1H), 6.90-7.28 (m, 1H), 6.41-6.65 (m, 1H), 6.03 (s, 1H), 1.88 (d, J = 7.1 Hz, 3H), 1.29 (s, 9H).	calcd. for $C_{21}H_{23}ClN_4O_2$:398.1m/z, found:399.15 $[M+H]^+$
	132	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(m-tolyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 8.27 (s, 1H), 7.93 (s, 1H), 7.23 – 7.25 (m, 2H), 7.07 – 7.10 (m, 4H), 6.57 (s, 1H), 6.03 (s, 1H), 2.27 (s, 3H), 1.85 (d, J = 7.1 Hz, 3H), 1.282 (s, 9H).	calcd. for $C_{22}H_{26}N_4O_2$: 378.21 m/z, found 379.25 $[M+H]^+$
	133	(S)-1-(tert-butyl)-3-(1-(1-(3,4-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.09 – 8.29 (m, 1H), 7.93 – 7.98 (m, 1H), 7.55 – 7.62 (m, 2H), 6.82 – 7.47 (m, 3H), 6.52 (m, 1H), 6.04 (s, 1H), 1.87 (d, J = 7.0 Hz, 3H), 1.29 (s, 9H).	calcd. for $C_{21}H_{22}Cl_2N_4O_2$:432.11 m/z, found:433.10 $[M+H]^+$

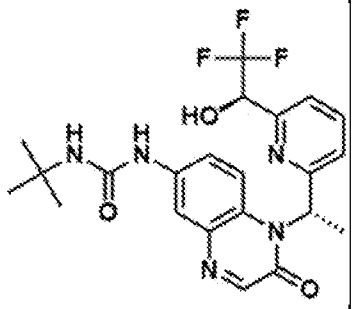
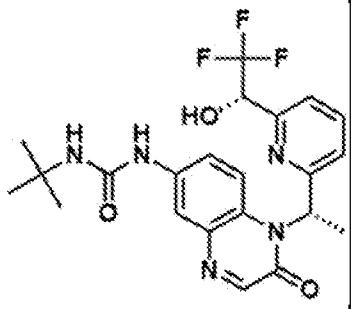
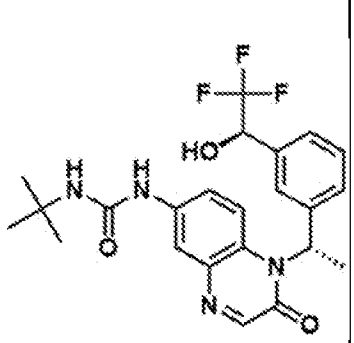
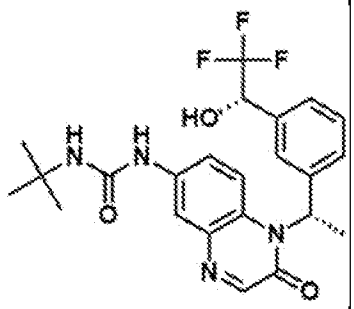
	134	(S)-1-(tert-butyl)-3-(1-(1-(3-cyclopropylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, Chloroform-d) δ 8.35 (s, 1H), 7.57 (d, *J* = 2.6 Hz, 1H), 7.50 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.19 (td, *J* = 7.3, 1.3 Hz, 1H), 7.04 (d, *J* = 9.2 Hz, 1H), 7.00 (dt, *J* = 8.4, 1.1 Hz, 2H), 6.88 (d, *J* = 7.7 Hz, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 3.08 (s, 2H), 1.90 (d, *J* = 7.2 Hz, 3H), 1.82 (d, *J* = 8.5, 5.1 Hz, 1H), 1.36 (s, 9H), 0.93 (dq, *J* = 8.4, 1.8 Hz, 2H), 0.56 – 0.71 (m, 2H)	calcd. for $C_{24}H_{28}N_4O_2$: 404.22 m/z found: 403.05 $[M-H]^-$
	135	(S)-1-(tert-butyl)-3-(1-(1-(3-cyclobutylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (s, 1H), 8.27 (s, 1H), 7.92 (d, *J* = 2.5 Hz, 1H), 7.27 (t, *J* = 7.7 Hz, 2H), 7.00 – 7.20 (m, 4H), 6.57 (s, 1H), 6.04 (s, 1H), 3.48 – 3.75 (m, 1H), 2.18 – 2.38 (m, 2H), 1.88 – 2.12 (m, 6H), 1.70 – 1.88 (m, 1H), 1.28 (s, 9H).	calcd. For $C_{25}H_{30}N_4O_2$:418.24 m/z, found:419.05 $[M+H]^+$.
	136	(S)-1-(tert-butyl)-3-(1-(1-(3-isopropylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.39 (s, 1H), 8.26 (s, 1H), 7.92 (d, *J* = 3.0 Hz, 1H), 7.20 - 7.33 (m, 2H), 7.00 - 7.19 (m, 4H), 6.55 - 6.62 (m, 1H), 6.02 (s, 1H), 2.77 - 2.95 (m, 1H), 1.88 (d, *J* = 6.0 Hz, 3H), 1.28 (s, 9H), 1.10 - 1.19 (m, 6H).	calcd. For $C_{24}H_{30}N_4O_2$:406.24 m/z, found:407.20 $[M+H]^+$.
	137	(S)-1-(tert-butyl)-3-(1-(1-(3-isopropoxyphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.26 (s, 1H), 7.85-8.08 (m, 1H), 7.19-7.40 (m, 2H), 7.07 (s, 1H), 6.67-6.90 (m, 3H), 6.55 (s, 1H), 6.04 (s, 1H), 4.47-4.68 (m, 1H), 1.86 (d, *J* = 7.1 Hz, 3H), 1.11-1.38 (m, 15H).	calcd. for $C_{24}H_{30}N_4O_3$:422.24 m/z, found:423.20 $[M+H]^+$

	138	(S)-1-(tert-butyl)-3-(1-(1-(3-(tert-butyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.27 (s, 1H), 7.81-8.02 (m, 1H), 7.20-7.40 (m, 4H), 6.95-7.20 (s, 1H), 6.59 (s, 1H), 6.03 (s, 1H), 1.90 (d, J = 7.2 Hz, 3H), 1.21-1.31 (m, 18H).	calcd. for $C_{25}H_{32}N_4O_2$:420.2 m/z, found:421.25 $[M+H]^+$.
	139	(S)-1-(tert-butyl)-3-(1-(1-(5-chloro-2-fluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.14 (s, 1H), 7.90 (m, 1H), 7.73 (m, 1H), 7.37 –7.56 (m, 3H), 7.09 – 7.19 (m, 1H), 6.47 (m, 1H), 6.04 (s, 1H), 1.87 (d, J = 7.0 Hz, 3H), 1.30 (s, 9H). 19F NMR (376 MHz, DMSO) δ -118.23.	calcd. for $C_{21}H_{22}ClFN_4O_2$:416.14 m/z, found:417.10 $[M+H]^+$
	140	(S)-1-(tert-butyl)-3-(1-(1-(2,6-difluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.11 (s, 1H), 7.91 (d, J = 2.5 Hz, 1H), 7.61-7.79 (m, 1H), 7.49-7.61 (m, 1H), 7.29-7.49 (m, 1H), 6.96-7.10 (m, 2H), 6.39-6.59 (m, 1H), 6.05 (s, 1H),1.77-1.99 (m, 3H),1.31 (s, 9H).^{19}F NMR (282 MHz, DMSO) δ -110.22.	calcd. for $C_{21}H_{22}F_2N_4O_2$:400.17 m/z, found:401.20 $[M+H]^+$
	141	(S)-1-(tert-butyl)-3-(1-(1-(5-chloro-2-methylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.14 (s, 1H), 7.88 (d, J = 2.3 Hz, 1H), 7.66 – 7.72 (m, 1H), 7.36 – 7.54 (m, 2H), 7.22 – 7.30 (m, 1H), 7.11 (d, J = 8.2 Hz, 1H), 6.18 – 6.34 (m, 1H), 6.05 (s, 1H), 1.86 (d, J = 6.9 Hz, 3H), 1.80 (s, 3H), 1.29 (s, 9H).	calcd. for $C_{22}H_{25}ClN_4O_2$:412.17 m/z, found:413.20 $[M+H]^+$

	142	(S)-1-(tert-butyl)-3-(1-(1-(2,3-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.10 (s, 1H), 7.89 (d, J = 2.5 Hz, 1H), 7.81 – 7.87 (m, 1H), 7.62 (dd, J = 8.0, 1.4 Hz, 1H), 7.53 – 7.58 (m, 1H), 7.47 (t, J = 8.0 Hz, 2H), 6.22 (s, 1H), 6.05 (s, 1H), 1.88 (d, J = 6.9 Hz, 3H), 1.30 (s, 9H).	calcd. for $C_{21}H_{22}Cl_2N_4O_2$: 432.11 m/z, found 433.10 $[M+H]^+$
	143	(S)-1-(tert-butyl)-3-(1-(1-(6-cyclopropylpyridin-2-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.40 (s, 1H), 8.24 (s, 1H), 7.90 (d, J = 2.5 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.31 (dd, J = 9.3, 2.5 Hz, 1H), 7.16 (d, J = 7.7 Hz, 1H), 7.05 (dd, J = 7.8, 0.9 Hz, 2H), 6.50 (s, 1H), 6.03 (s, 1H), 2.03 (tt, J = 7.6, 5.0 Hz, 1H), 1.78 – 1.95 (m, 3H), 1.20 – 1.40 (m, 9H), 0.75 – 0.95 (m, 3H), 0.53 – 0.70 (m, 1H).	calcd. for $C_{23}H_{27}N_5O_2$: 405.22 m/z, found 406.20 $[M+H]^+$
	144	(S)-1-(tert-butyl)-3-(1-(1-(6-methoxypyridin-2-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.40 (s, 1H), 8.25 (s, 1H), 7.93 (d, J = 3.0 Hz, 1H), 7.60 - 7.72 (m, 1H), 7.34 - 7.39 (m, 1H), 7.12 (s, 1H), 6.91 (d, J = 9.0 Hz, 1H), 6.70 (d, J = 9.0 Hz, 1H), 6.52 (s, 1H), 6.03 (s, 1H), 3.68 (s, 3H), 1.90 (d, J = 9.0 Hz, 3H), 1.29 (s, 9H).	calcd. For $C_{21}H_{25}N_5O_3$:395.2 m/z, found:396.15 $[M+H]^+$.
	145	(S)-1-(tert-butyl)-3-(1-(1-(6-(dimethylamino)pyridin-2-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 8.25 (s, 1H), 7.90 (d, J = 2.5 Hz, 1H), 7.43 – 7.54 (m, 1H), 7.26 – 7.33 (m, 1H), 7.13 (s, 1H), 6.43 – 6.52 (m, 3H), 6.03 (s, 1H), 2.92 (s, 6H), 1.86 (d, J = 7.2 Hz, 3H), 1.29 (s, 9H).	calcd. for $C_{20}H_{21}FN_4O_2$, 408.23 m/z, found 409.20 $[M+H]^+$

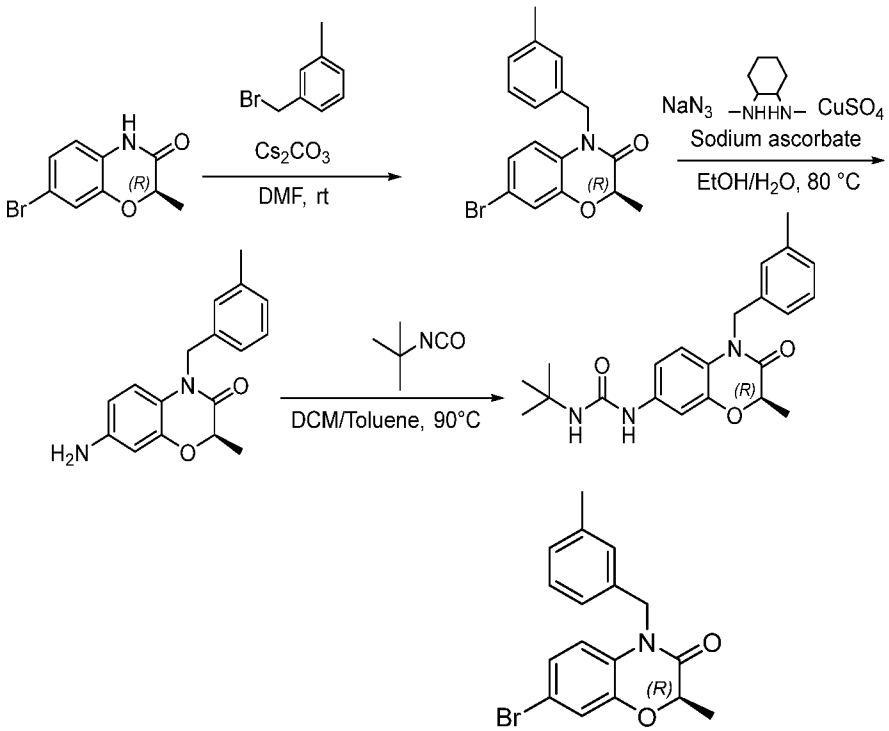
	146	1-(tert-butyl)-3-(1-((1S)-1-(3-(1-hydroxyethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.38 (s, 1H), 8.27 (s, 1H), 7.91 (d, J = 2.5 Hz, 1H), 7.18 – 7.36 (m, 4H), 6.98 – 7.18 (m, 2H), 6.59 (s, 1H), 6.01 (s, 1H), 5.13 (dd, J = 4.3, 3.4 Hz, 1H), 4.67 (q, J = 5.6 Hz, 1H), 1.88 (d, J = 7.1 Hz, 3H), 1.21 – 1.31 (m, 12H).	calcd. for $C_{23}H_{28}N_4O_3$: 408.22 m/z, found 409.25 $[M+H]^+$
	147	(S)-1-(tert-butyl)-3-(1-(1-(2-chloro-5-fluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.09 (s, 1H), 7.89(d, J =2.5 Hz, 1H), 7.67-7.80(m, 1H),7.58 (s, 1H),7.47(d, J=8.0 z, 1H), 7.30-7.45 (m, 1H), 6.17 (s, 1H), 6.05 (s, 1H),1.86(d, J =6.90 Hz, 3H), 1.30(s, 9H); ^{19}F NMR (376 MHz, DMSO) δ -115.01	calcd. for $C_{21}H_{22}ClFN_4O_2$: 416.14, found: 417.20 $[M+H]^+$
	148	(S)-1-(tert-butyl)-3-(1-(1-(2,5-difluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.15 (s, 1H), 7.90 (d, J = 2.4 Hz, 1H), 7.31-7.67(m, 3H), 7.00-7.28(m, 2H), 8.15 (s, 1H), 6.04 (s, 1H), 1.86(d, J = 7.1 Hz, 3H), 1.30(s, 9H); ^{19}F NMR (376 MHz, DMSO) δ -118.38,-121.67	calcd. for $C_{21}H_{22}F_2N_4O_2$: 400.17, found: 401.20 $[M+H]^+$
	149	(S)-1-(tert-butyl)-3-(1-(1-(5-chloro-2,4-difluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.12 (s, 1H), 7.85 – 8.05 (m, 2H), 7.30 – 7.79 (m, 3H), 6.43 (s, 1H), 6.05 (s, 1H), 1.86 (d, J = 7.0 Hz, 3H), 1.25 – 1.40 (m, 9H).^{19}F NMR (282 MHz, DMSO) δ -112.655, -112.996.	calcd. for $C_{21}H_{21}ClF_2N_4O_2$: 434.13 m/z, found 435.13 $[M+H]^+$

	150	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(6-(2,2,2-trifluoroethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.24 (s, 1H), 7.84-7.97 (m, 1H), 7.66-7.84 (m, 1H), 7.33 (dd, J = 20.3, 7.8 Hz, 3H), 7.15 (s, 1H), 6.59 (s, 1H), 6.00 (s, 1H), 3.70-3.90 (m, 2H), 1.89 (d, J = 7.1 Hz, 3H), 1.28 (s, 9H).^{19}F NMR (282 MHz, DMSO) δ -63.10.	calcd. for $C_{22}H_{24}F_3N_5O_2$:447.1 m/z, found:448.20 $[M+H]^+$
	151	(S)-1-(tert-butyl)-3-(1-(1-(2,4-difluoro-5-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.12 (s, 1H), 7.88 – 7.95 (m, 2H), 7.61 (s, 1H), 7.52 (q, J = 10.3 Hz, 2H), 6.44 (s, 1H), 6.04 (s, 1H), 1.86 (d, J = 7.0 Hz, 3H), 1.30 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -58.2434, -111.0659, -126.3474.	calcd. for $C_{22}H_{21}F_5N_4O_3$: 484.15 m/z, found 485.15 $[M+H]^+$
	152	(S)-1-(tert-butyl)-3-(1-(1-(chroman-7-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 8.25 (s, 1H), 7.91 (d, J = 2.6 Hz, 1H), 7.25 – 7.32 (m, 1H), 7.08 (s, 1H), 7.00 (d, J = 7.9 Hz, 1H), 6.67 (dd, J = 8.1, 2.1 Hz, 1H), 6.62 (t, J = 1.4 Hz, 1H), 6.51 (s, 1H), 6.03 (s, 1H), 4.10 (td, J = 6.6, 5.9, 3.5 Hz, 2H), 2.70 (d, J = 6.5 Hz, 2H), 1.89 (td, J = 6.5, 6.1, 3.7 Hz, 2H), 1.83 (d, J = 7.2 Hz, 3H), 1.28 (s, 9H).	calcd. for $C_{24}H_{28}N_4O_3$: 420.22 m/z, found 421.15 $[M+H]^+$

	153	1-(tert-butyl)-3-(2-oxo-1-((S)-1-(6-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.22 (s, 1H), 7.80 – 8.00 (m, 2H), 7.46 (d, J = 7.7 Hz, 1H), 7.38 (d, J = 7.5 Hz, 2H), 7.09 (d, J = 13.0 Hz, 2H), 6.72 (s, 1H), 5.10 – 5.20 (s, 1H), 5.00 (s, 1H), 1.2 – 1.40 (m, 12H). ^{19}F NMR (376 MHz, CD_3CN) δ -78.28.	calcd. For $C_{22}H_{24}F_3N_5O_3$:463.18 m/z, found:464.20 $[M+H]^+$.
	154	1-(tert-butyl)-3-(2-oxo-1-((S)-1-(6-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.21 (s, 1H), 7.85 – 7.76 (m, 2H), 7.47 (d, J = 7.7 Hz, 1H), 7.32 – 7.40 (m, 2H), 7.17 (s, 1H), 7.06 (d, J = 9.2 Hz, 1H), 6.70 (s, 1H), 5.13 – 5.25 (m, 2H), 5.05 (s, 1H), 1.97 – 1.99 (m, 3H), 1.34 (s, 9H). ^{19}F NMR (376 MHz, CD_3CN) δ -78.24.	calcd. For $C_{22}H_{24}F_3N_5O_3$:463.18 m/z, found:464.15 $[M+H]^+$.
	155	1-(tert-butyl)-3-(2-oxo-1-((S)-1-(3-((S)-2,2,2-trifluoro-1-hydroxyethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.23 (s, 1H), 7.80 (d, J = 2.6 Hz, 1H), 7.35 – 7.46 (m, 4H), 7.30 – 7.38 (m, 1H), 7.12 (s, 1H), 7.01 (d, J = 9.2 Hz, 1H), 6.70 (s, 1H), 5.17 (s, 1H), 4.99 – 5.27 (m, 1H), 4.61 (d, J = 5.4 Hz, 1H), 1.95 – 1.98 (m, 3H),1.34 (s, 9H). ^{19}F NMR (376 MHz, CD_3CN) δ -78.78.	calcd. For $C_{23}H_{25}F_3N_4O_3$: 462.19 m/z, found:463.15 $[M+H]^+$.
	156	1-(tert-butyl)-3-(2-oxo-1-((S)-1-(3-((R)-2,2,2-trifluoro-1-hydroxyethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.23 (s, 1H), 7.83 (d, J = 2.6 Hz, 1H), 7.30 – 7.50 (m, 5H), 7.12 (s, 1H), 7.04 (d, J = 9.0 Hz, 1H), 6.70 (s, 1H), 5.15 (s, 1H), 5.02 – 5.13 (m, 1H), 4.56 (d, J = 5.7 Hz, 1H), 1.95 – 1.98 (m, 3H), 1.34 (s, 9H). ^{19}F NMR (376 MHz, CD_3CN) δ -78.78.	calcd. For $C_{23}H_{25}F_3N_4O_3$: 462.19 m/z, found:463.15 $[M+H]^+$.

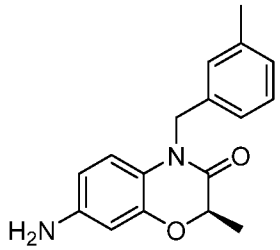
Example 157: 3-tert-butyl-1-[(2R)-2-methyl-4-[(3-methylphenyl)methyl]-3-oxo-2H-1,4-benzoxazin-7-yl]urea.

Synthetic Scheme



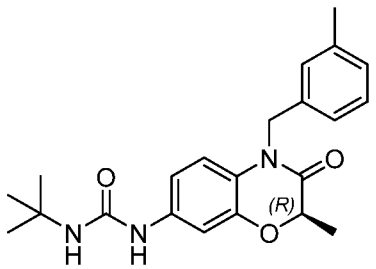
(2R)-7-bromo-2-methyl-4-[(3-methylphenyl)methyl]-2H-1,4-benzoxazin-3-one

To a stirred solution of (2R)-7-bromo-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (400 mg, 1.652 mmol, 1 equiv) in DMF (4 mL) was added 1-(bromomethyl)-3-methylbenzene (458.70 mg, 2.478 mmol, 1.5 equiv) and Cs_2CO_3 (1080.10 mg, 3.304 mmol, 2 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford (2R)-7-bromo-2-methyl-4-[(3-methylphenyl)methyl]-2H-1,4-benzoxazin-3-one (500 mg, 87.40%) as a white solid. LC/MS(ESI): mass calcd. for $C_{17}H_{16}BrNO_2$: 345.04 m/z, found 346.00 $[M+H, M+H+2]^+$.



(2R)-7-amino-2-methyl-4-[(3-methylphenyl)methyl]-2H-1,4-benzoxazin-3-one

To a stirred solution of (2R)-7-bromo-2-methyl-4-[(3-methylphenyl)methyl]-2H-1,4-benzoxazin-3-one (490 mg, 1.192 mmol, 1 equiv) in EtOH/H_2O(4:1, 5 mL) was added N_1,N_2-dimethylcyclohexane-1,2-diamine (101.69 mg, 0.715 mmol, 0.6 equiv), $CuSO_4$ (190.17 mg, 1.192 mmol, 1 equiv), sodium ascorbate (474.50 mg, 2.384 mmol, 2 equiv) and NaN_3 (232.39 mg, 3.576 mmol, 3 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 80 °C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. Quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford (2R)-7-amino-2-methyl-4-[(3-methylphenyl)methyl]-2H-1,4-benzoxazin-3-one (150 mg, 44.59%) as a white solid. LC/MS(ESI): mass calcd. for $C_9H_{18}N_2O_3$: 282.14 m/z, found 283.10 $[M+H]^+$.



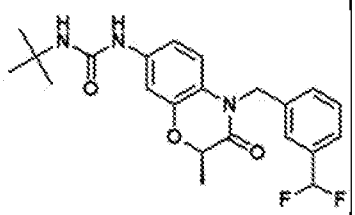
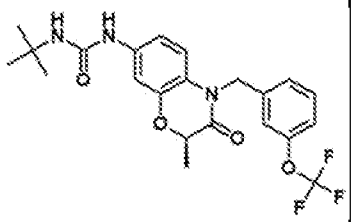
3-tert-butyl-1-[(2R)-2-methyl-4-[(3-methylphenyl)methyl]-3-oxo-2H-1,4-benzoxazin-7-yl]urea

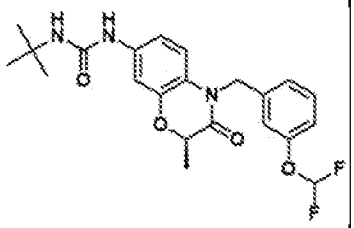
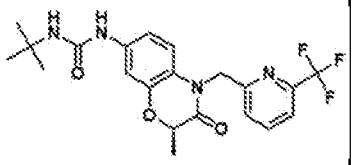
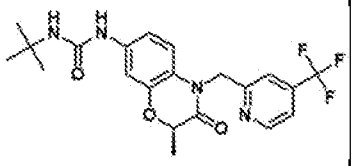
To a stirred solution of (2R)-7-amino-2-methyl-4-[(3-methylphenyl)methyl]-2H-1,4-benzoxazin-3-one (140 mg, 0.496 mmol, 1 equiv) in DCM / Toluene(2:1, 2mL) was added 2-isocyanato-2-methylpropane (147.47 mg, 1.488 mmol, 3 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 90 °C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined

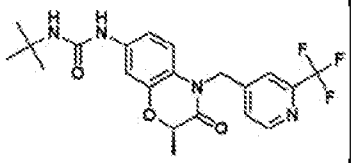
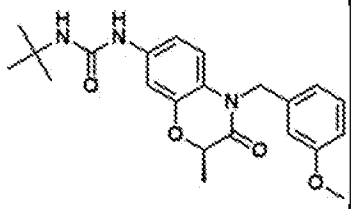
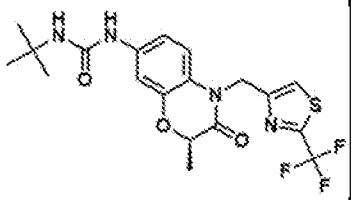
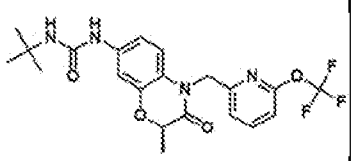
extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by Prep-HPLC using a X Bridge Prep OBD C18 150 mm x 30 mm x 5 μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford 3-tert-butyl-1-[(2R)-2-methyl-4-[(3-methylphenyl)methyl]-3-oxo-2H-1,4-benzoxazin-7-yl]urea (41.1 mg, 21.37%) as a white solid. LC/MS(ESI): mass calcd. for $C_{22}H_{27}N_3O_3$: 381.21 m/z, found 382.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.23 – 7.18 (m, 2H), 7.06 – 6.99 (m, 3H), 6.84 (d, J = 8.7 Hz, 1H), 6.76 – 6.72 (m, 1H), 5.93 (s, 1H), 5.05 (m, 2H), 4.84 – 4.78 (m, 1H), 2.26 (s, 3H), 1.48 (d, J = 6.6 Hz, 3H), 1.26 (s, 9H).

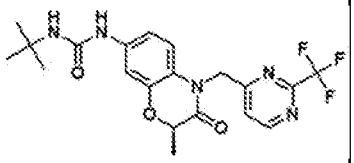
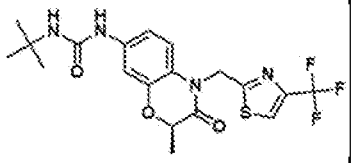
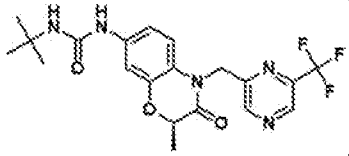
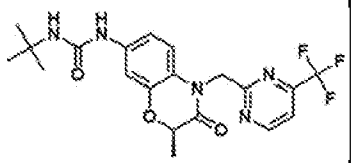
The following examples in Table 7 were made according to the procedure for example 157.

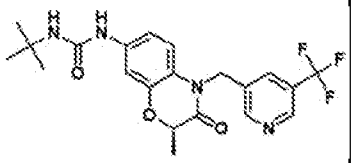
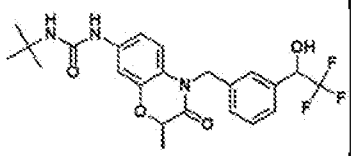
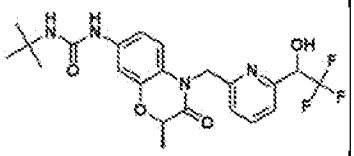
Table 7

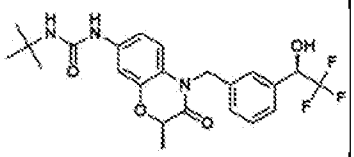
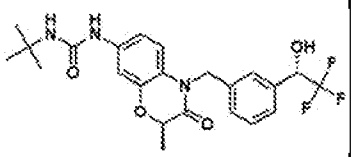
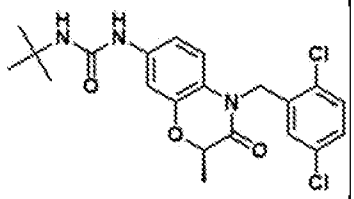
Structure	Ex.	IUPAC Name	1H NMR	LCMS
	158	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^1H NMR (300 MHz, DMSO-d_6) δ 8.17 – 8.30 (m, 1H), 7.34– 7.55 (m, 4H), 6.97 – 7.30 (m, 2H), 6.80 – 6.91 (m, 1H), 6.68 – 6.91 (m, 1H), 5.86 – 6.01 (m, 1H), 5.08 – 5.27 (m, 2H), 4.73 – 4.99 (m, 1H), 1.44 – 1.59 (m, 3H), 1.20 – 1.37 (m, 9H). ^{19}F NMR (282 MHz, DMSO) δ(ppm): -109.702, -109.742.	calcd. for $C_{22}H_{25}F_2N_3O_3$: 417.19 m/z, found 418.15 $[M+H]^+$
	159	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-(3-(trifluoromethoxy)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^1H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 7.48 (m, 1H), 7.22 – 7.29 (m, 4H), 6.77 – 6.88 (m, 2H), 5.95 (s, 1H), 5.14 (m, 2H), 4.84 (m, 1H), 1.48 (m, 3H), 1.26 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ -56.70.	calcd. for $C_{22}H_{24}N_3O_4$: 451.17 m/z, found 452.05 $[M+H]^+$

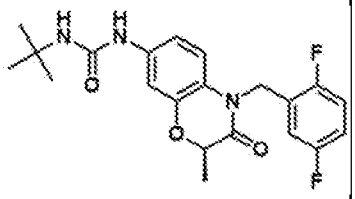
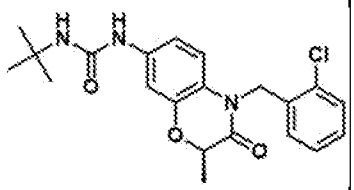
	160	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethoxy) benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.23 (s, 1H), 7.41 (m, 1H), 7.23 – 7.06 (m, 5H), 6.86 (d, *J* = 8.8 Hz, 1H), 6.78 (m, 1H), 5.95 (s, 1H), 5.11 – 5.10 (m, 2H), 4.83 (q, *J* = 6.8 Hz, 1H), 1.48 (d, *J* = 6.8 Hz, 3H), 1.26 (s, 9H).	calcd. for $C_{22}H_{25}F_2N_3O_4$: 433.2 m/z, found:434.15 $[M+H]^+$
	161	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.16 – 8.30 (m, 1H), 7.96 – 8.16 (m, 1H), 7.76 – 6.90 (m, 1H), 7.43 – 7.60 (m, 1H), 7.15 – 6.29 (m, 1H), 6.70 – 6.86 (m, 2H), 5.90 – 6.04 (m, 1H), 5.12 – 5.30 (m, 2H), 4.75 – 4.90 (m, 1H), 1.35 – 1.50 (m, 3H), 1.15 – 1.35 (m, 9H). ^{19}F NMR (282 MHz, DMSO) δ(ppm): -66.548.	calcd. for $C_{21}H_{23}F_3N_4O_3$: 436.17 m/z, found 437.15 $[M+H]^+$
	162	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((4-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.55 – 8.98 (m, 1H), 8.09 – 8.35 (m, 1H), 7.53 – 7.84 (m, 2H), 7.14 – 7.40 (m, 1H), 6.82 – 6.98 (m, 1H), 6.62 – 6.80 (m, 1H), 5.76 – 6.10 (m, 1H), 5.13 – 5.45 (m, 2H), 4.60 – 4.92 (m, 1H), 1.40 – 1.55 (m, 3H), 1.20 – 1.37 (m, 9H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -63.3996.	calcd. for $C_{21}H_{23}F_3N_4O_3$: 436.17 m/z, found 437.15 $[M+H]^+$

	163	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((2-(trifluoromethyl)pyridin-4-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.70 (d, J = 5.0 Hz, 1H), 8.24 (s, 1H), 7.81 (d, J = 1.6 Hz, 1H), 7.43 – 7.51 (m, 1H), 7.27 (d, J = 2.0 Hz, 1H), 6.72 – 6.86 (m, 2H), 5.95 (s, 1H), 5.13 – 5.36 (m, 1H), 4.83 – 4.95 (m, 1H), 1.50 (d, J = 6.8 Hz, 3H), 1.27 (s, 9H).^{19}F-NMR (282 MHz, DMSO) δ -66.54.	calcd. for $C_{21}H_{23}F_3N_4O_3$: 436.17 m/z, found:437.00 $[M+H]^+$.
	164	(R)-1-(tert-butyl)-3-(4-(3-methoxybenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.18 - 7.29 (m, 2H), 6.70 - 6.89 (m, 5H), 5.93 (s, 1H), 5.05 (s, 2H), 4.79 -4.82 (m, 1H), 3.71 (s, 3H), 1.47 (s, 3H), 1.26 (s, 9H).	calcd. for $C_{22}H_{27}N_3O_4$: 397.20 m/z, found:398.10 $[M+H]^+$.
	165	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((2-(trifluoromethyl)thiazol-4-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.23 (s, 1H), 7.89 (s, 1H), 7.22 (d, J = 2.1 Hz, 1H), 6.99 (d, J = 8.7 Hz, 1H), 6.82 (d, J = 8.7 Hz, 1H), 5.95 (s, 1H), 5.25 – 5.16 (m, 2H), 4.79 – 4.77 (m, 1H), 1.45 (d, J = 6.6 Hz, 3H), 1.27 (s, 9H). ^{19}F NMR (282 MHz, DMSO-d$_6$) δ -59.59.	calcd. for $C_{19}H_{21}F_3N_4O_3S$:442.1 m/z, found:443.10 $[M+H]^+$.
	166	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethoxy)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.96-8.01 (m, 1H), 7.29-7.31 (m, 1H), 7.13 - 7.26 (m, 2H), 6.82 - 6.84 (m, 1H), 6.77 - 6.82 (m, 1H), 5.94 (s, 1H), 5.14 (s, 2H), 4.75 - 4.77 (m, 1H), 1.43-1.46 (d, J = 6 Hz, 3H), 1.27 (s, 9H)	calcd. for $C_{21}H_{23}F_3N_4O_4$: 452.17 m/z, found:451.00[M-H]$^-$

	167	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((2-(trifluoromethyl)pyrimidin-4-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (d, J = 5.2 Hz, 1H), 8.25 (s, 1H), 7.68 (d, J = 5.2 Hz, 1H), 7.27 (d, J = 2.2 Hz, 1H), 6.67 – 6.85 (m, 2H), 5.95 (s, 1H), 5.21 – 5.36 (m, 2H), 4.75 – 4.90 (m, 1H), 1.47 (d, J = 6.8 Hz, 3H), 1.27 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -69.1848.	calcd. for $C_{20}H_{22}F_3N_5O_3$: 437.17 m/z, found 438.15 $[M+H]^+$
	168	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((4-(trifluoromethyl)thiazol-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.27 (s, 1H), 7.25 - 7.26 (d, J = 3 Hz, 1H), 7.06 - 7.09 (m, 1H), 6.79 - 6.86 (m, 1H), 5.98 (s, 1H), 5.38 - 5.51 (m, 2H), 4.78 - 4.80 (m, 1H), 1.43 - 1.45 (d, J = 6 Hz, 3H), 1.23 - 1.26 (m, 9H)	calcd. for $C_{19}H_{21}F_3N_4O_3S$: 442.13 m/z, found 443.00 $[M+H]^+$
	169	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyrazin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.98 (s, 1H), 8.23 (s, 1H), 7.22-7.23 (m, 1H), 6.88-6.90 (m, 1H), 6.76-6.79 (m, 1H), 5.95 (s, 1H), 5.34 (s, 2H), 4.78-4.83 (m, 1H), 1.43-1.45 (d, J = 6 Hz, 3H), 1.27 (s, 9H), 1.19 (s, 2H)	calcd. for $C_{20}H_{22}F_3N_5O_3$: 437.17 m/z, found:438.00 $[M+H]^+$
	170	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((4-(trifluoromethyl)pyrimidin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.13-9.15 (d, J = 6 Hz, 1H), 8.22 (s, 1H), 7.93-7.95 (d, J = 6 Hz, 1H), 7.24 (s, 1H), 6.71-6.86 (m, 2H), 5.94 (s, 1H), 5.28-5.41 (m, J = 4.1 Hz, 2H), 4.72-4.79 (m, 1H), 1.42-1.44 (d, J = 6 Hz, 3H), 1.27 (s, 9H). ^{19}F NMR (282 MHz, DMSO) δ-68.72	$C_{20}H_{22}F_3N_5O_3$: 437.17 m/z, found:438.00 $[M+H]^+$

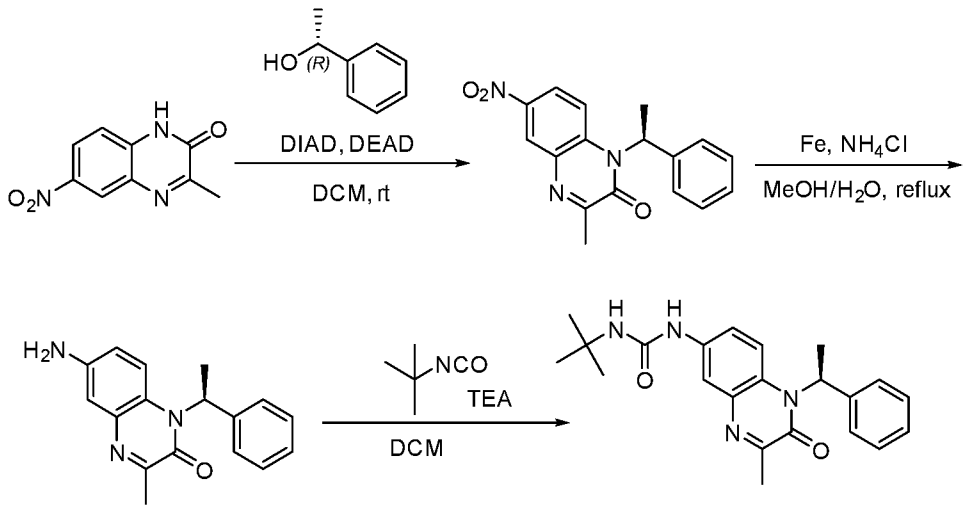
	171	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((5-(trifluoromethyl)pyridin-3-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.85-8.92 (m, 1H), 8.72-8.79 (m, 1H), 8.22 (s, 1H), 8.05 (s, 1H), 7.22 (s, 1H), 6.93-6.96 (m, 1H), 6.78-6.82 (m, 1H), 5.93 (s, 1H), 5.29-5.32 (m, 1H), 5.15-5.26 (m, 1H), 4.83-4.98 (m, 1H), 1.46-1.49 (d, J = 9 Hz, 3H), 1.26 (s, 9H). ^{19}F NMR (282 MHz, DMSO) δ-60.93.	$C_{21}H_{23}F_3N_4O_3$: 436.17 m/z, found:437.05 $[M+H]^+$
	172	1-(tert-butyl)-3-((2R)-2-methyl-3-oxo-4-(3-(2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.20 (s, 1H), 7.39 – 7.35 (m, 3H), 7.21 – 7.20 (m, 2H), 6.83 – 6.81 (m, 2H), 6.79 – 6.77 (m, 1H), 5.93 (s, 1H), 5.15 – 5.11 (m, 3H), 4.81 (q, J = 6.6 Hz, 1H), 1.47 (d, J = 6.6 Hz, 3H), 1.26 (s, 9H). ^{19}F NMR (282 MHz, DMSO-d$_6$) δ -76.69.	calcd. for $C_{23}H_{26}F_3N_3O_4$: 465.2 m/z, found:466.2 $[M+H]^+$
	173	1-(tert-butyl)-3-((2R)-2-methyl-3-oxo-4-((6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.75 – 7.98 (m, 1H), 7.40 – 7.60 (m, 1H), 7.15 – 7.30 (m, 2H), 7.01 (d, J = 6.0 Hz, 1H), 6.88 – 6.78 (m, 1H), 6.65 – 6.78 (m, 1H), 5.93 (s, 1H), 4.96 – 5.30 (m, 3H), 4.70 – 4.90 (m, 1H), 4.86 – 4.76 (m, 1H), 1.47 (d, J = 6.7, 2.3 Hz, 3H), 1.26 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -75.7620, -75.7743.	calcd. for $C_{22}H_{25}F_3N_4O_4$: 466.18 m/z, found 467.20 $[M+H]^+$

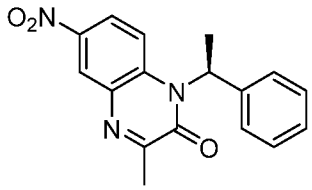
	174	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-(3-((R)-2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.39 – 7.35 (m, 3H), 7.23 – 7.21 (m, 2H), 6.86 – 6.74 (m, 3H), 5.94 (s, 1H), 5.12 – 5.11 (m, 3H), 4.81 (q, *J* = 6.6 Hz, 1H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.26 (s, 9H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -76.69.	calcd. for $C_{23}H_{26}F_3N_3O_4$: 465.3 m/z, found:488.15 $[M+Na]^+$
	175	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-(3-((S)-2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.39 – 7.35 (m, 3H), 7.22 – 7.21 (m, 2H), 6.83 – 6.77 (m, 3H), 5.93 (s, 1H), 5.12 – 5.11 (m, 3H), 4.81 (q, *J* = 6.6 Hz, 1H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.26 (s, 9H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -76.69.	calcd. for $C_{23}H_{26}F_3N_3O_4$: 465.3 m/z, found:488.15 $[M+Na]^+$
	176	(R)-1-(tert-butyl)-3-(4-(2,5-dichlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.53 - 7.62 (m, 1H), 7.36 - 7.46 (m, 1H), 7.29 (d, *J* = 3.0 Hz, 1H), 6.99 (d, *J* = 3.0 Hz, 1H), 6.76 - 6.84 (m, 1H), 6.65 - 6.74 (m, 1H), 5.96 (s, 1H), 5.14 - 5.23 (m, 2H), 4.86 - 5.05 (m, 1H), 1.49 (d, *J* = 9.0 Hz, 3H), 1.27 (s, 9H).	calcd. For $C_{21}H_{23}Cl_2N_3O_3$:435.1 m/z, found:436.10 $[M+H]^+$.

	177	(R)-1-(tert-butyl)-3-(4-(2,5-difluorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.24 (s, 1H), 7.11 – 7.38 (m, 3H), 6.88 – 6.97 (m, 1H), 6.75 – 6.88 (m, 2H), 5.95 (s, 1H), 5.11 – 5.23 (m, 1H), 4.98 – 5.10 (m, 1H), 4.79 – 4.92 (m, 1H), 1.48 (d, J = 6.7 Hz, 3H), 1.27 (s, 9H). ^{19}F NMR (282 MHz, DMSO) δ -118.31 - 123.38.	calcd. for $C_{21}H_{23}F_2N_3O_3$: 403.17 m/z, found:404.15 [M+H]+.
	178	(R)-1-(tert-butyl)-3-(4-(2-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.23 (s, 1H), 7.53 – 7.50 (m, 1H), 7.32 – 7.27 (m, 3H), 6.99 – 6.96 (m, 1H), 6.77 – 6.73 (m, 1H), 6.66 (d, J = 9.0 Hz, 1H), 5.94 (s, 1H), 5.17 – 5.00 (m, 2H), 4.86 (q, J = 6.9 Hz, 1H), 1.49 (d, J = 6.9 Hz, 3H), 1.26 (s, 9H).	calcd. for $C_{21}H_{24}ClN_3O_3$: 401.2 m/z, found:402.10 $[M+H]^+$

Example 179: 3-tert-butyl-1-{3-methyl-2-oxo-1-[(1S)-1-phenylethyl]quinoxalin-6-yl}urea

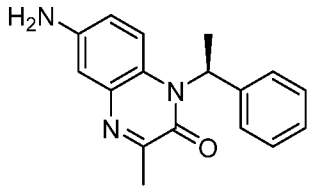
Synthetic Scheme





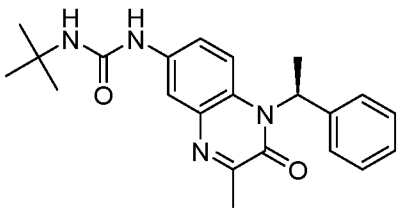
(S)-3-methyl-6-nitro-1-(1-phenylethyl)quinoxalin-2(1H)-one

To a solution of 3-methyl-6-nitro-1H-quinoxalin-2-one (600 mg, 2.924 mmol, 1 equiv) and 1-phenyl-ethanol (357.26 mg, 2.924 mmol, 1 equiv) in DCM (10 mL) was added PPh_3 (1150.55 mg, 4.386 mmol, 1.5 equiv). After the reaction was stirred at rt for 30 min under N_2, DEAD (509.30 mg, 2.924 mmol, 1 equiv) was added at 0 °C. The reaction was stirred at rt under N_2 for 3 h. Quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 3-methyl-6-nitro-1-[(1S)-1-phenylethyl]quinoxalin-2-one (217 mg, 23.99%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{15}N_3O_3$: 309.11m/z, found 310.05 $[M+H]^+$



6-amino-3-methyl-1-[(1S)-1-phenylethyl]quinoxalin-2-one

To a solution of 3-methyl-6-nitro-1-[(1S)-1-phenylethyl]quinoxalin-2-one (200 mg, 0.647 mmol, 1 equiv) in methanol (8 mL) and water (0.8 mL) was added iron (361.08 mg, 6.470 mmol, 10 equiv) and NH_4Cl (345.85 mg, 6.470 mmol, 10 equiv). The reaction was stirred at 60 °C for 3 h. After cooling down to rt, the reaction was quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-3-methyl-1-[(1S)-1-phenylethyl]quinoxalin-2-one (95 mg, 52.60%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{17}N_3O$: 279.14 m/z, found 280.10 $[M+H]^+$

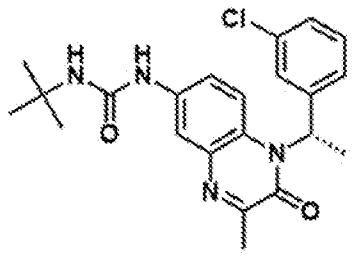
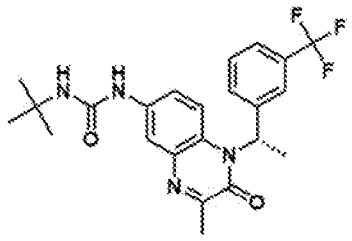


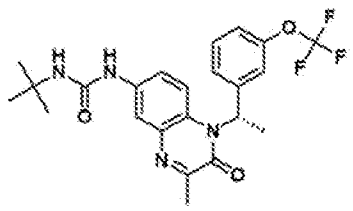
3-tert-butyl-1-{3-methyl-2-oxo-1-[(1S)-1-phenylethyl]quinoxalin-6-yl}urea

To a solution of 6-amino-3-methyl-1-[(1S)-1-phenylethyl]quinoxalin-2-one (85 mg, 0.304 mmol, 1 equiv) and 2-isocyanato-2-methylpropane (60.33 mg, 0.608 mmol, 2 equiv) in DCM (2 mL) was added TEA (92.37 mg, 0.912 mmol, 3 equiv). The reaction was stirred at rt for 6h. Quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 150 mm x 30 mm x 5 μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-{3-methyl-2-oxo-1-[(1S)-1-phenylethyl]quinoxalin-6-yl}urea (20.1 mg, 17.37%) as a white solid. LC/MS (ESI): mass calcd. for $C_{22}H_{26}N_4O_2$:378.21 m/z, found:379.05 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.33 (s, 1H), 7.79 (s, 1H), 7.16-7.40 (m, 6H), 7.00 (s, 1H), 6.64 (s, 1H), 6.00 (s, 1H), 2.47-2.51 (m, 3H), 1.86-1.88 (d, J = 6 Hz, 3H), 1.27 (s, 9H).

The following examples in Table 8 were made according to the procedure for example 179.

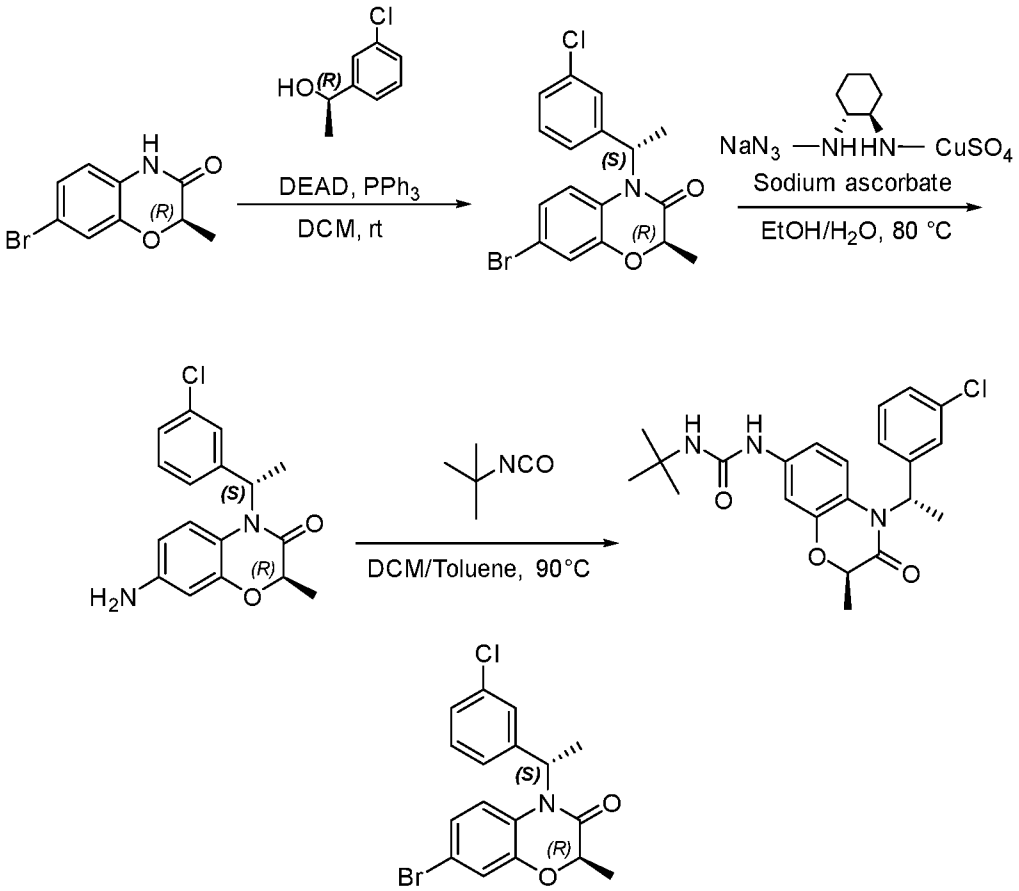
Table 8

Structure	Ex.	IUPAC Name	1H NMR	LCMS
	180	(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^1H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 7.81 (s, 1H), 7.30-7.41 (m, 3H), 7.20-7.34 (m, 2H), 7.01 (s, 1H), 6.59 (s, 1H), 6.01 (s, 1H), 2.46-2.51 (m, 3H), 1.85-1.87 (d, J= 8 Hz, 3H), 1.29 (s, 9H)	calcd. for $C_{22}H_{25}ClN_4O_2$: 412.17 m/z, found:413.00 $[M+H]^+$
	181	(S)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^1H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.81 (s, 1H), 7.49-7.68 (m, 4H), 7.29 (s, 1H), 7.08 (s, 1H), 6.62 (s, 1H), 6.02 (s, 1H), 2.45 (s, 3H), 1.90-1.92 (d, J = 8 Hz, 3H), 1.28 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ -60.85.	calcd. for $C_{23}H_{25}F_3N_4O_2$: 446.19 m/z, found:447.05 $[M+H]^+$.

	182	(S)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.80 (d, J = 2.4 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.28 – 7.26 (m, 4H), 6.55 (s, 1H), 6.01 (s, 1H), 2.45 (s, 3H), 1.88 (d, J = 7.2 Hz, 3H), 1.28 (s, 9H).	calcd. for $C_{23}H_{25}F_3N_4O_3$: 462.2 m/z, found:463.15 $[M+H]^+$

Example 183: 1-(tert-butyl)-3-((R)-4-((S)-1-(3-chlorophenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

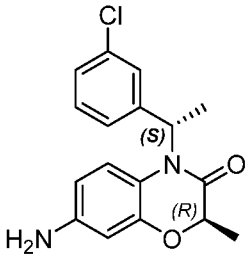
Synthetic Scheme



(R)-7-bromo-4-((S)-1-(3-chlorophenyl)ethyl)-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

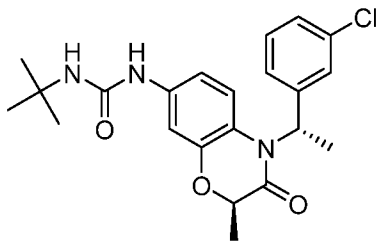
To a solution of(2R)-7-bromo-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (270 mg, 1.115 mmol, 1 equiv) in DCM (10 mL) was added 1-[(1R)-1-bromoethyl]-3-chlorobenzene (9.07 mg, 0.041 mmol, 1 equiv) and PPh_3 (438.83 mg, 1.672 mmol, 1.5 equiv). The reaction was stirred at rt under

N_2 for 0.5 hour. To the above mixture was added DEAD (291.37 mg, 1.672 mmol, 1.5 equiv) in portions at 0°C. The resulting mixture was stirred for additional 1 hour at rt. Quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-bromo-4-[(1S)-1-(3-chlorophenyl)ethyl]-2-methyl-2H-1,4-benzoxazin-3-one (194 mg, 45.69%) as a white oil. MS (ESI): mass calcd. for $C_{17}H_{15}BrClNO_2$: 379.00m/z, found 380.95,382.95 $[M+H, M+H+2]^+$.



(R)-7-amino-4-((S)-1-(3-chlorophenyl)ethyl)-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-7-bromo-4-[(1S)-1-(3-chlorophenyl)ethyl]-2-methyl-2H-1,4-benzoxazin-3-one (180 mg, 0.473 mmol, 1 equiv) in EtOH/H_2O (4:1, 10 mL) was added (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (40.36 mg, 0.284 mmol, 0.6 equiv), $CuSO_4$ (75.47 mg, 0.473 mmol, 1 equiv), azidosodium (92.22 mg, 1.419 mmol, 3 equiv) and sodium ascorbate (188.30 mg, 0.946 mmol, 2 equiv). The reaction was stirred at 80 °C under N_2 for 1 day. After cooling down to rt, the reaction was quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-4-[(1S)-1-(3-chlorophenyl)ethyl]-2-methyl-2H-1,4-benzoxazin-3-one (110 mg, 73.43%) as a yellow oil. MS (ESI): mass calcd. for $C_{17}H_{17}ClN_2O_2$: 316.10m/z, found 317.15 $[M+H]^+$.

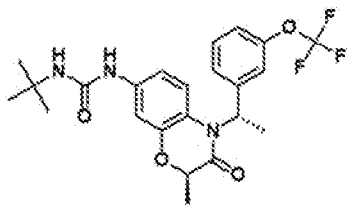


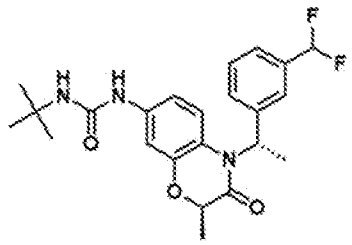
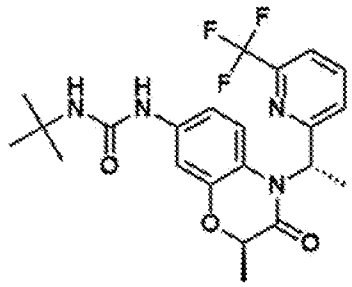
1-(tert-butyl)-3-((R)-4-((S)-1-(3-chlorophenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

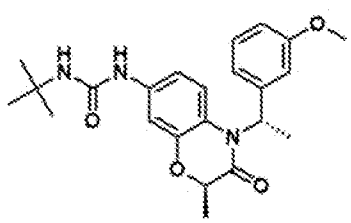
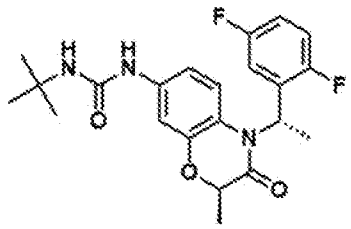
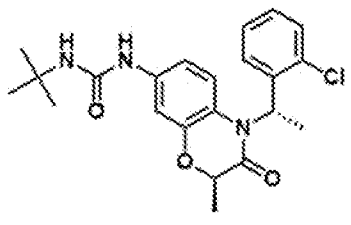
To a solution of (2R)-7-amino-4-[(1S)-1-(3-chlorophenyl)ethyl]-2-methyl-2H-1,4-benzoxazin-3-one (100 mg, 0.316 mmol, 1 equiv) in DCM/Toluene (2:1, 12 mL) was added 2-isocyanato-2-methylpropane (312.93 mg, 3.160 mmol, 10 equiv). The reaction was stirred at 90 °C under N_2 for 3h. After cooling down to rt, the reaction was quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm column (eluent: 53% to 66% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-[(2R)-4-[(1S)-1-(3-chlorophenyl)ethyl]-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]urea (27.5 mg, 20.95%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{26}ClN_3O_3$: 415.17 m/z, found:416.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-*d*$_6$) δ 8.07 – 8.37 (m, 1H), 7.30 – 7.60 (m, 3H), 7.00 – 7.30 (m, 2H), 6.52 – 6.74 (m, 2H), 5.83 – 6.10 (m, 2H), 4.55 – 4.88 (m, 1H), 1.66 – 1.85 (m, 3H), 1.40 – 1.53 (m, 3H), 1.22 – 1.30 (m, 9H).

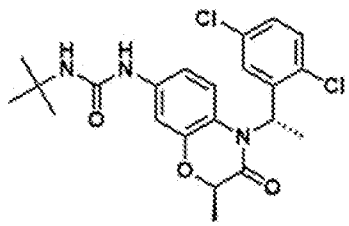
The following examples in Table 9 were made according to the procedure for example 183.

Table 9

Structure	Ex.	IUPAC Name	1H NMR	LCMS
	184	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^1H NMR (300 MHz, DMSO-d$_6$) δ 8.20 (s, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.31 – 7.20 (m, 4H), 6.66 – 6.64 (m, 2H), 6.04 (q, *J* = 7.2 Hz, 1H), 5.94 (s, 1H), 4.74 (q, *J* = 6.9 Hz, 1H), 1.76 (d, *J* = 7.2 Hz, 3H), 1.44 (d, *J* = 6.0 Hz, 3H), 1.26 (s, 9H).	calcd. for $C_{23}H_{26}F_3N_3O_4$:465.2 m/z, found:466.15 $[M+H]^+$.

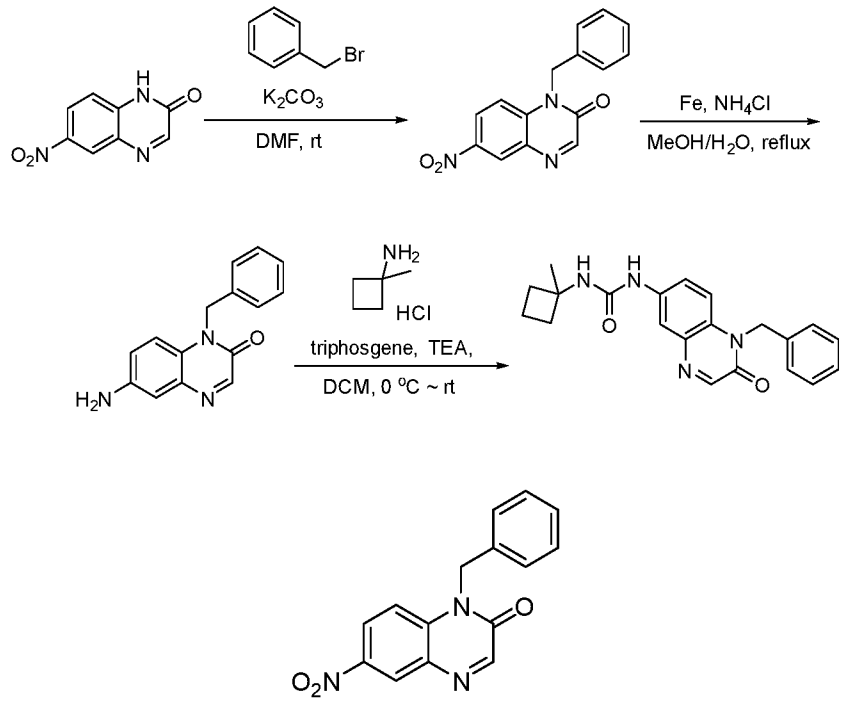
	185	1-(tert-butyl)-3-((R)-4-((S)-1-(3-(difluoromethyl)phenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 – 8.30 (m, 1H), 7.33 – 7.65 (m, 4H), 7.23 – 7.33 (m, 1H), 6.80 – 7.20 (m, 1H), 6.52 – 6.76 (m, 2H), 6.00 – 6.20 (m, 1H), 5.72 – 6.00 (m, 1H), 4.66 – 4.83 (m, 1H), 1.68 – 1.88 (m, 3H), 1.40 – 1.60 (m, 3H), 1.18 – 1.34 (m, 9H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -109.432, -109.5495.	calcd. for $C_{23}H_{27}F_2N_3O_3$: 431.20 m/z, found 432.20 $[M+H]^+$
	186	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 – 8.39 (m, 1H), 8.00 – 8.14 (m, 1H), 7.68 – 7.86 (m, 1H), 7.53 – 7.67 (m, 1H), 7.03 – 7.30 (m, 1H), 6.53 – 6.80 (m, 2H), 6.00 – 6.25 (m, 1H), 5.72 – 6.00 (m, 1H), 4.38 – 4.83 (m, 1H), 1.70 – 1.87 (m, 3H), 1.36 – 1.54 (m, 3H), 1.20 – 36 (m, 9H). ^{19}F NMR (376 MHz, DMSO) δ (ppm): -66.5649.	calcd. for $C_{24}H_{29}N_3O_4$: 450.19 m/z, found 451.20 $[M+H]^+$

	187	1-(tert-butyl)-3-((R)-4-((S)-1-(3-methoxyphenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.21-7.34 (m, 2H), 6.78-6.89 (m, 3H), 6.54-6.67 (m, 2H), 6.05-6.07 (m, 1H), 5.94 (s, 1H), 4.74-4.76 (m, 1H), 3.72 (s, 3H), 1.71-1.73 (d, J = 6 Hz, 3H), 1.41-1.43 (d, J = 6 Hz, 3H), 1.26 (s, 9H).	calcd. for $C_{23}H_{29}N_3O_4$: 411.22m/z, found:412.05 $[M+H]^+$
	188	1-(tert-butyl)-3-((R)-4-((S)-1-(2,5-difluorophenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.32-7.50 (m, 1H), 7.03-7.28 (m, 3H), 6.85-7.02 (m, 1H), 6.66-6.84 (m, 1H), 5.96-6.09 (m, 1H), 5.93 (s, 1H), 4.59 (q, J = 6.6 Hz, 1H), 1.77 (d, J = 7.1 Hz, 3H), 1.41 (d, J = 6.7 Hz, 3H),1.26 (s, 9H). ^{19}F NMR (282 MHz, DMSO) δ -118.57, -121.56.	calcd. for $C_{22}H_{25}F_2N_3O_3$:417.19 m/z, found:418.20 $[M+H]^+$
	189	1-(tert-butyl)-3-((R)-4-((S)-1-(2-chlorophenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.77 (dd, J = 7.8, 1.6 Hz, 1H), 7.22 – 7.44 (m, 3H), 7.10 (d, J = 2.4 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.69 (dd, J = 8.8, 2.4 Hz, 1H), 5.80 – 5.97 (m, 2H), 4.55 (q, J = 6.6 Hz, 1H), 1.82 (d, J = 7.1 Hz, 3H), 1.44 (d, J = 6.7 Hz, 3H), 1.25 (s, 9H).	calcd. For $C_{22}H_{26}ClN_3O_3$:415.17 m/z, found:416.20 $[M+H]^+$.

	190	1-(tert-butyl)-3-((R)-4-((S)-1-(2,5-dichlorophenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.20 (d, J = 13.3 Hz, 1H), 7.78 (d, J = 1.7 Hz, 1H), 7.37 (d, J = 1.5 Hz, 2H), 7.11 (d, J = 2.4 Hz, 1H), 6.98 (d, J = 8.9 Hz, 1H), 6.76 (dd, J = 8.8, 2.4 Hz, 1H), 5.94 (d, J = 6.9 Hz, 1H), 5.70 – 5.85 (m, 1H), 4.55 (q, J = 6.7 Hz, 1H), 1.81 (d, J = 6.9 Hz, 3H), 1.41 (d, J = 6.7 Hz, 3H), 1.20 – 1.28 (m, 9H).	calcd. for $C_{22}H_{25}Cl_2N_3O_3$: 449.13 m/z, found 450.15 $[M+H]^+$

Example 191: 1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1-methylcyclobutyl)urea

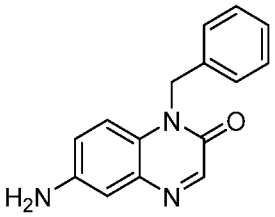
Synthetic Scheme



benzyl-6-nitroquinoxalin-2(1H)-one

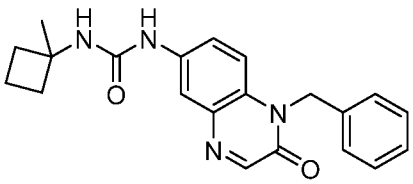
To a solution of 6-nitro-1H-quinoxalin-2-one (3 g, 15.695 mmol, 1 equiv) and benzyl bromide (5368.79 mg, 31.390 mmol, 2 equiv) in dimethylformamide (100 mL) was added Cs_2CO_3 (15388.46 mg, 47.085 mmol, 3 equiv). The reaction was stirred at rt for 3 h. Quenched with

water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-benzyl-6-nitroquinoxalin-2-one (3.1 g, 70.22%) as a yellow solid. MS (ESI): mass calcd. for $C_{15}H_{11}N_3O_3$: 281.08 m/z, found 282.10 $[M+H]^+$



6-amino-1-benzylquinoxalin-2(1H)-one

To a solution of 1-benzyl-6-nitroquinoxalin-2-one (3.1 g, 11.021 mmol, 1 equiv) in methanol (80 mL) and water (8 mL) was added iron (6.15 g, 110.210 mmol, 10 equiv) and NH_4Cl (5.90 g, 110.210 mmol, 10 equiv). The reaction was stirred at 60 °C for 6 h. After cooling down to rt, the reaction was quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-1-benzylquinoxalin-2-one (1 g, 36.11%) as a red solid. MS (ESI): mass calcd. for $C_{15}H_{13}N_3O$: 251.11 m/z, found 252.10 $[M+H]^+$



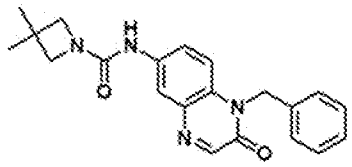
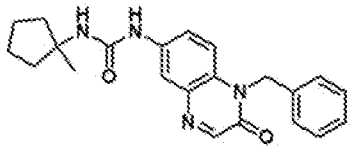
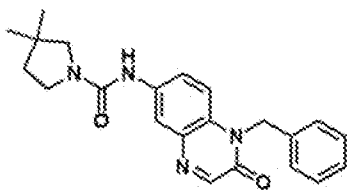
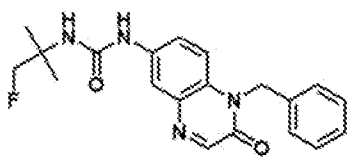
1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1-methylcyclobutyl)urea

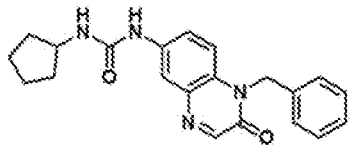
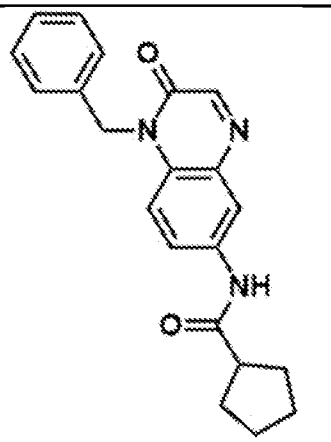
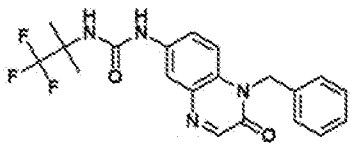
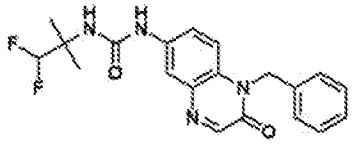
To a solution of 6-amino-1-benzylquinoxalin-2-one (100 mg, 0.398 mmol, 1 equiv) in DCM (3 mL) was added triphosgene (47.23 mg, 0.159 mmol, 0.4 equiv). The reaction was stirred at 0 °C under N_2 for 1h. The reaction was added TEA (201.35 mg, 1.990 mmol, 5 equiv) and stirred at rt under N_2 for 1h. The reaction was added 1-methylcyclobutan-1-amine (67.77 mg, 0.796 mmol, 2 equiv) and stirred at rt under N_2 for 1h. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column 21.2 mm X 250 mm, 5 μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O

with 10 mmol/L NH_4HCO_3) to afford the title compound 1-(1-benzyl-2-oxoquinoxalin-6-yl)-3-(1-methylcyclobutyl)urea (32.5 mg, 22.48%) as a white solid. LC/MS (ESI): mass calcd. for $C_{21}H_{22}N_4O_2$:362.17 m/z, found:363.00 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.33 (s, 1H), 7.99 (s, 1H), 7.42-7.43 (m, 1H), 7.20-7.39 (m, 6H), 6.32 (s, 1H), 5.45 (s, 2H), 2.24-2.28 (m, 2H), 1.68-1.96 (m, 4H), 1.40 (s, 3H).

The following examples in Table 10 were made according to the procedure for example 191.

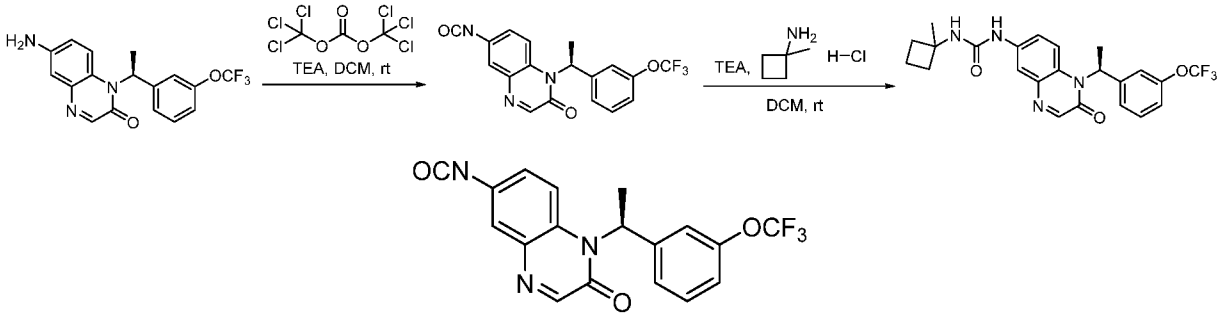
Table 10

Structure	Ex.	IUPAC Name	1H NMR	LCMS
	192	N-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3,3-dimethylazetidine-1-carboxamide	^1H NMR (300 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.32 (s, 1H), 8.06 (s, 1H), 7.65-7.69 (m, 1H), 7.20-7.38 (m, 6H), 5.45 (s, 2H), 3.65 (s, 4H), 1.24 (s, 6H).	calcd. for $C_{21}H_{22}N_4O_2$: 362.17 m/z, found:363.00 $[M+H]^+$.
	193	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1-methylcyclopentyl) urea	^1H NMR (300 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.34 (s, 1H), 7.99 (s, 1H), 7.39-7.44 (m, 1H), 7.32-7.43 (m, 3H), 7.24-7.37 (m, 3H), 6.11 (s, 1H), 5.46 (s, 2H), 1.88-1.93 (m, 2H), 1.50-1.65 (m, 6H), 1.36 (s, 3H).	calcd. for $C_{22}H_{24}N_4O_2$: 376.19 m/z, found:377.05 $[M+H]^+$.
	194	N-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3,3-dimethylpyrrolidine-1-carboxamide	^1H NMR (300 MHz, DMSO-d_6) δ 8.21-8.39 (m, 2H), 8.04-8.11 (m, 1H), 7.62-7.78 (m, 1H), 7.20-7.41 (m, 6H), 5.46 (s, 2H), 3.47 (t, J = 7.0 Hz, 2H), 3.16 (s, 2H), 1.62-1.73 (m, 2H), 1.07 (s, 6H).	calcd. for $C_{22}H_{24}N_4O_2$:376.2 m/z, found:377.20 $[M+H]^+$
	195	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1-fluoro-2-methylpropan-2-yl)urea	^1H NMR (300 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.32 (s, 1H), 7.97 (d, J = 2.4 Hz, 1H), 7.24 – 7.41 (m, 7H), 6.16 (s, 1H), 5.45 (s, 2H), 4.54 (s, 1H), 4.38 (s, 1H), 1.27 (d, J = 2.0 Hz, 6H).	calcd. for $C_{20}H_{21}FN_4O_2$, 368.16 m/z, found 369.10 $[M+H]^+$

	196	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-cyclopentylurea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.32 (s, 1H), 8.00 (d, J = 2.5 Hz, 1H), 7.42-7.52 (m, 1H), 7.29 – 7.39 (m, 2H), 7.20-7.33 (m, 4H), 6.24 (d, J = 7.2 Hz, 1H), 5.45 (s, 2H), 3.86-4.01 (m, 1H), 1.76 – 1.92 (m, 2H), 1.48 – 1.69 (m, 4H), 1.29-1.45 (m, 2H).	calcd. for $C_{21}H_{22}N_4O_2$:362.2 m/z, found:363. 10 $[M+H]^+$
	197	N-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)cyclopentanecarboxamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.35 (s, 1H), 8.22 (d, J = 2.4 Hz, 1H), 7.70 (dd, J = 9.1, 2.5 Hz, 1H), 7.43 (d, J = 9.1 Hz, 1H), 7.20–7.38 (m, 5H), 5.47 (s, 2H), 2.77 (p, J = 7.7 Hz, 1H), 1.80 – 1.94 (m, 2H), 1.55-1.80 (m, 6H).	calcd. for $C_{21}H_{21}N_3O_2$:347.2 m/z, found:348. 05 $[M+H]^+$
	198	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1,1,1-trifluoro-2-methylpropan-2-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.34 (s, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.23 – 7.45 (m, 7H), 6.57 (s, 1H), 5.46 (s, 2H), 1.52 (s, 6H).	calcd. for $C_{20}H_{19}F_3N_4O_2$, 404.15 m/z, found 405.05 $[M+H]^+$
	199	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1,1-difluoro-2-methylpropan-2-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.33 (s, 1H), 7.98 (s, 1H), 7.24-7.44 (m, 7H), 6.15-6.53 (m, 2H), 5.45 (s, 2H), 1.32 (s, 6H). ^{19}F NMR (282 MHz, DMSO) δ-131.24.	calcd. for $C_{20}H_{20}F_2N_4O_2$:386.16 m/z, found:387. 00 $[M+H]^+$.

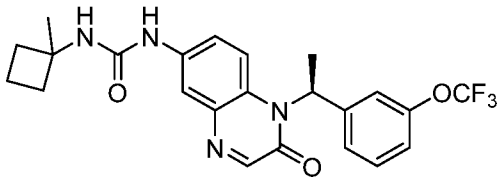
Example 200: (S)-1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

Synthetic Scheme



(S)-6-isocyanato-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)quinoxalin-2(1H)-one

To a stirred solution of (S)-6-amino-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)quinoxalin-2(1H)-one (70 mg, 0.200 mmol, 1 equiv) in DCM (5 mL) was added TEA (81 mg, 0.802 mmol, 4 equiv) and triphosgene (24 mg, 0.080 mmol, 0.4 equiv) at 0 °C under a nitrogen atmosphere, the reaction was stirred 1 h at rt. The reaction progress was monitored by LCMS. The reaction mixture was quenched by water (5 mL) and extracted with DCM (3 x 10 mL). The combined organic extracts were concentrated under vacuum to yield a 70 mg crude (S)-6-isocyanato-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)quinoxalin-2(1H)-one as a yellow solid.

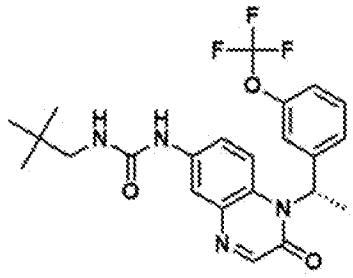
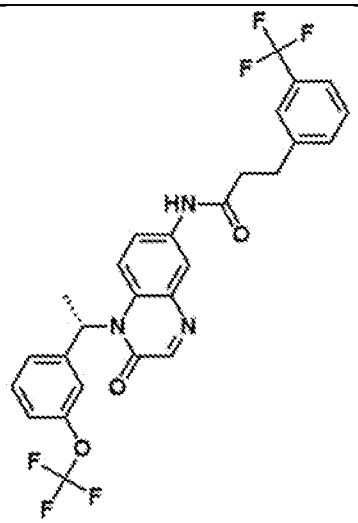
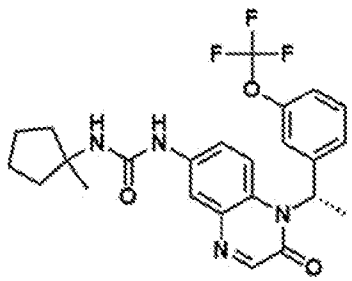


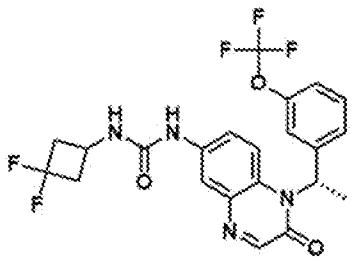
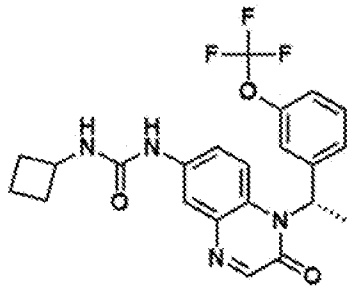
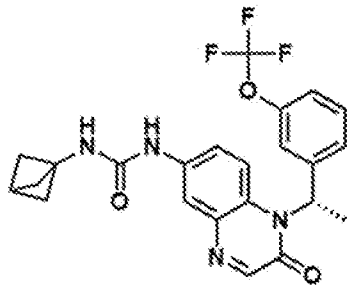
(S)-1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

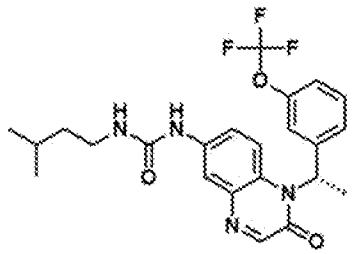
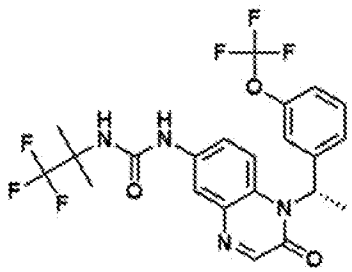
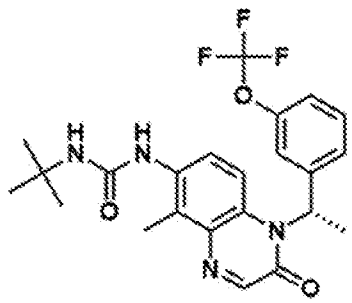
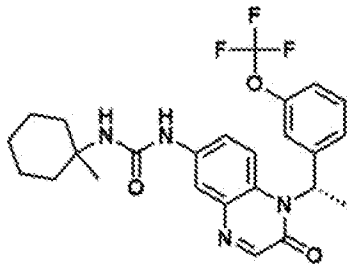
To a stirred solution of (S)-6-isocyanato-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)quinoxalin-2(1H)-one (70 mg, 0.187 mmol, 1 equiv) in DCM (5 mL) was added TEA (57 mg, 0.560 mmol, 3 equiv) and 1-methylcyclobutanamine hydrochloride (27 mg, 0.224 mmol, 1.2 equiv) at 0 °C under a nitrogen atmosphere, the reaction was stirred 1 h at rt. The reaction progress was monitored by LCMS. The reaction mixture was quenched by water (10 mL) and extracted with DCM (3 x 10 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford (S)-1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea (9.2 mg, 10.67%) as a yellow solid. MS (ESI): mass calcd. for $C_{23}H_{23}F_3N_4O_3$, 460.17 m/z, found 461.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.24 (s, 1H), 7.95 (d, J = 2.5 Hz, 1H), 7.47 (t, J = 8.3 Hz, 1H), 7.29 (d, J = 8.2 Hz, 4H), 7.11 (s, 1H), 6.57 (s, 1H), 6.31 (s, 1H), 2.28 (q, J = 9.5 Hz, 2H), 1.89 (d, J = 7.0 Hz, 4H), 1.76 (dd, J = 9.2, 6.0 Hz, 3H), 1.39 (s, 3H).

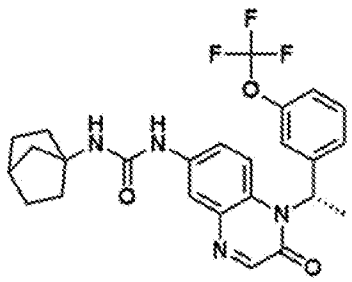
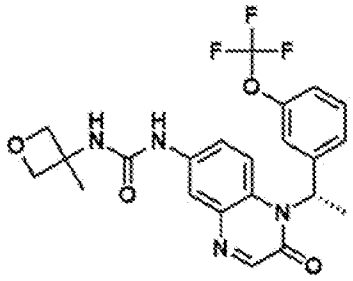
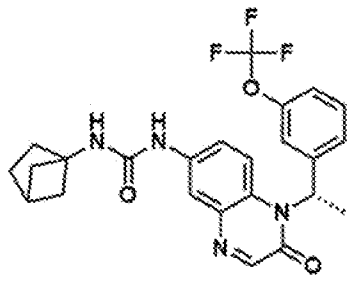
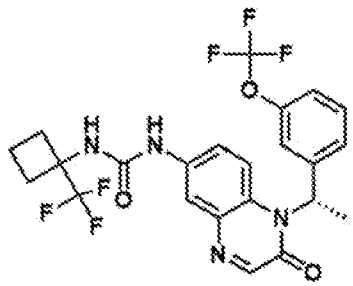
The following examples in Table 11 were made according to the procedure for example 200.

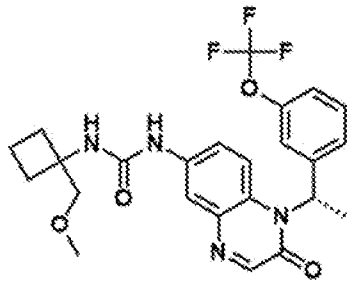
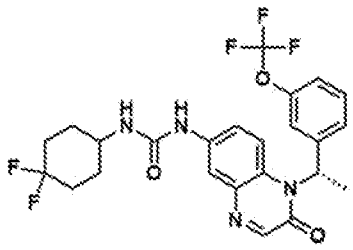
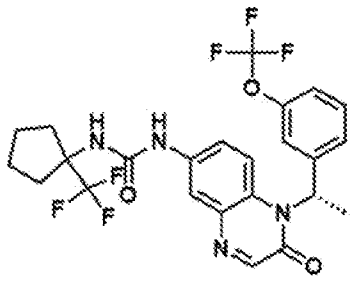
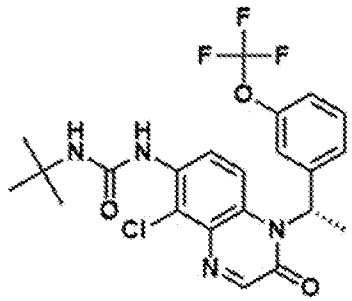
Table 11

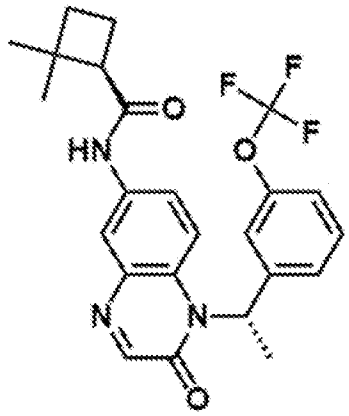
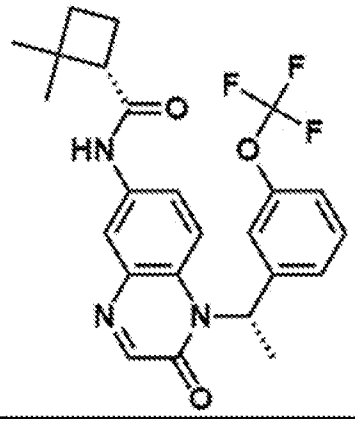
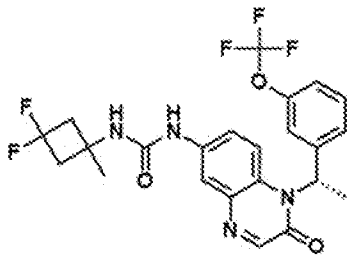
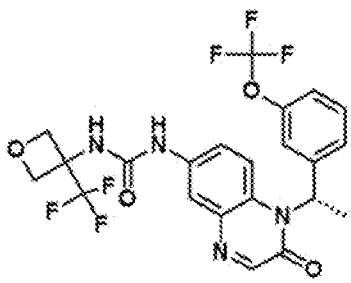
Structure	Ex.	IUPAC Name	1H NMR	LCMS
	201	(S)-1-neopentyl-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.25 (s, 1H), 7.99 (d, J = 2.5 Hz, 1H), 7.48 (dd, J = 10.6, 6.0 Hz, 1H), 7.36 (d, J = 8.9 Hz, 1H), 7.29 (d, J = 7.2 Hz, 3H), 7.11 (s, 1H), 6.58 (s, 1H), 6.24 (t, J = 6.1 Hz, 1H), 2.92 (d, J = 6.0 Hz, 2H), 1.90 (d, J = 7.0 Hz, 3H), 0.86 (s, 9H)	calcd. for $C_{23}H_{25}F_3N_4O_3$, 462.19 m/z, found 463.10 $[M+H]^+$
	202	(S)-N-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)phenyl)propanamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 10.14 (s, 1H), 8.27 (s, 1H), 8.14 (d, J = 2.4 Hz, 1H), 7.42 – 7.66 (m, 6H), 7.00 – 7.40 (m, 4H), 6.57 (s, 1H), 3.02 (t, J = 7.5 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 1.90 (d, J = 7.0 Hz, 3H). ^{19}F NMR (282 MHz, DMSO) δ -56.70, -61.00.	calcd. for $C_{27}H_{21}F_6N_3O_3$:549.15, found: 571.95 [M+Na]+
	203	(S)-1-(1-methylcyclopentyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.40 (s, 1H), 8.25 (s, 1H), 7.95 (d, J = 3 Hz, 1H), 7.42 – 7.54 (m, 1H), 7.26 – 7.29 (m, 4H), 7.12 (s, 1H), 6.58 (s, 1H), 6.11 (s, 1H), 1.87 – 1.89 (m, 5H), 1.41 – 1.69 (m, 6H), 1.35 (s, 2H).^{19}F NMR (282 MHz, DMSO-d$_6$) δ -56.67.	calcd. for $C_{24}H_{25}F_3N_4O_3$:474.2 m/z, found:475.15 $[M+H]^+$.

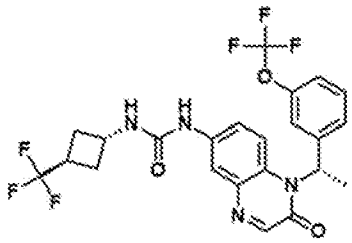
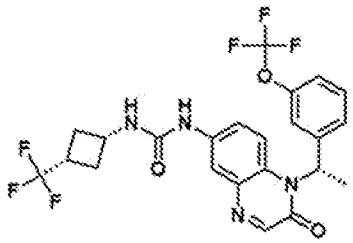
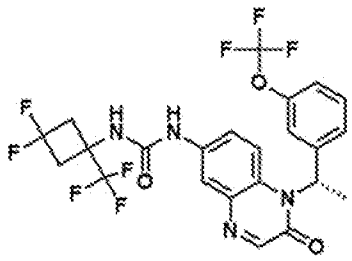
	204	(S)-1-(3,3-difluorocyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.74 (s, 1H), 8.25 (s, 1H), 7.96-7.98 (m, 1H), 7.46-7.48 (m, 1H), 7.37-7.39 (m, 1H), 7.27-7.29 (m, 3H), 7.12 (s, 1H), 6.75-6.77 (d, J = 6 Hz, 1H), 6.57 (s, 1H), 4.00-4.03 (m, 1H), 2.82-2.93 (m, 2H), 2.72-2.73 (m, 2H), 1.87-1.89 (d, J = 6 Hz, 3H). ^{19}F NMR (282 MHz, DMSO) δ-56.68, -82.40, -96.16.	calcd. for $C_{22}H_{19}F_5N_4O_3$:482.14 m/z, found:481.00 $[M-H]^-$.
	205	(S)-1-cyclobutyl-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.53 (s, 1H), 8.24 (s, 1H), 7.96 (d, J = 2.5 Hz, 1H), 7.42 – 7.51 (m, 1H), 7.32 – 7.40 (m, 1H), 7.22 – 7.31 (m, 3H), 7.10 (s, 1H), 6.40 – 6.70 (m, 2H), 4.02 - 4.22 (m, 1H), 2.19 (q, J = 7.7 Hz, 2H), 1.79-1.98 (m, 5H), 1.50 – 1.70 (m, 2H).^{19}F NMR (282 MHz, DMSO-d$_6$) δ -56.67.	calcd. for $C_{22}H_{21}F_3N_4O_3$:446.4 m/z, found:447.10 $[M+H]^+$.
	206	(S)-1-(bicyclo[1.1.1]pentan-1-yl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.44-7.49 (m, 1H), 7.25-7.39 (m, 4H), 7.11 (s, 1H), 6.86 (s, 1H), 6.57 (s, 1H), 2.40 (s, 1H), 1.98 (s, 6H), 1.87-1.89 (d, J = 6 Hz, 3H). ^{19}F NMR (282 MHz, DMSO) δ-56.68.	calcd. for $C_{23}H_{21}F_3N_4O_3$:458.16 m/z, found:457.00 $[M-H]^-$.

	207	(S)-1-isopentyl-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.24 (s, 1H), 7.97 (d, *J* = 2.5 Hz, 1H), 7.40 – 7.53 (m, 1H), 7.33 – 7.53 (m, 1H), 7.20 – 7.32 (m, 3H), 6.90 – 7.20 (m, 1H), 6.46 – 6.69 (m, 1H), 6.08 – 6.21 (m, 1H), 3.02 – 3.18 (m, 2H), 1.89 (d, *J* = 7.0 Hz, 3H), 1.47 – 1.73 (m, 1H), 1.25 – 1.44 (m, 2H), 0.89 (d, *J* = 6.7 Hz, 6H).^{19}F NMR (282 MHz, DMSO-d_6) δ -56.67.	calcd. for $C_{23}H_{25}F_3N_4O_3$:462.2 m/z, found:463.15 $[M+H]^+$.
	208	(S)-1-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(1,1,1-trifluoro-2-methylpropan-2-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.26 (s, 1H), 7.95 (s, 1H), 7.42-7.54 (m, 1H), 7.21-7.30 (m, 4H), 7.01 (s, 1H), 6.58 (s, 2H), 1.87-1.90 (d, *J* = 9 Hz, 3H), 1.52 (s, 6H). ^{19}F NMR (282 MHz, DMSO) δ-56.69.	calcd. for $C_{22}H_{20}F_6N_4O_3$:502.14 m/z, found:501.00 $[M-H]^-$.
	209	(S)-1-(tert-butyl)-3-(5-methyl-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (s, 1H), 7.88-7.90 (d, *J* = 6 Hz, 1H), 7.67 (s, 1H), 7.40-7.52 (m, 1H), 7.25-7.27 (m, 3H), 7.00 (s, 1H), 6.60 (s, 1H), 6.42 (s, 1H), 2.48 (s, 3H), 1.87-1.90 (m, 3H), 1.28 (s, 9H). ^{19}F NMR (282 MHz, DMSO) δ -56.65.	calcd. for $C_{23}H_{25}F_3N_4O_3$:462.19 m/z, found:461.00 $[M-H]^-$.
	210	(S)-1-(1-methylcyclohexyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.24 (s, 1H), 7.94 (d, *J* = 2.7 Hz, 1H), 7.54 – 7.42 (m, 1H), 7.29 – 7.27 (m, 4H), 7.11 (s, 1H), 6.58 (s, 1H), 5.86 (s, 1H), 1.90 – 1.88 (m, 5H), 1.45 – 1.43 (m, 5H), 1.30 – 1.28 (m, 6H).^{19}F NMR (282 MHz, DMSO-d_6) δ -56.67.	calcd. for $C_{25}H_{27}F_3N_4O_3$:488.2 m/z, found:489.2 $[M+H]^+$.

	211	(S)-1-(bicyclo[2.2.1]heptan-1-yl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.24 (s, 1H), 7.95 (d, *J* = 2.4 Hz, 1H), 7.47 (t, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 11.1 Hz, 4H), 7.08 (s, 1H), 6.56 (s, 1H), 6.45 (s, 1H), 2.09 (s, 1H), 1.89 (d, *J* = 7.2 Hz, 3H), 1.76 – 1.62 (m, 4H), 1.57 – 1.52 (m, 4H), 1.36 – 1.30 (m, 2H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -56.67.	calcd. for $C_{25}H_{25}F_3N_4O_3$:486.2 m/z, found:487.15 $[M+H]^+$.
	212	(S)-1-(3-methyloxetan-3-yl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.71 (s, 1H), 8.25 (s, 1H), 7.96 (d, *J* = 2.5 Hz, 1H), 7.44 - 7.53 (m, 1H), 7.34 – 7.43 (m, 1H), 7.20 – 7.32 (m, 3H), 7.11 (s, 1H), 6.71 (s, 1H), 6.57 (s, 1H), 4.52 – 4.70 (m, 2H), 4.20 – 4.34(m, 2H), 1.89 (d, *J* = 7.1 Hz, 3H), 1.55 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ(ppm): -56.678.	calcd. for $C_{22}H_{21}F_3N_4O_4$: 462.15 m/z, found 463.15 $[M+H]^+$
	213	(S)-1-(bicyclo[2.1.1]hexan-1-yl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.48 (s, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.44-7.50 (m, 1H), 7.27-7.34 (m, 4H), 7.07 (s, 1H), 6.73 (s, 1H), 6.57 (s, 1H), 2.27 (s, 1H), 1.87-1.89 (m, 5H), 1.58-1.69 (m, 4H), 1.21 – 1.34 (m, 2H). ^{19}F NMR (282 MHz, DMSO) δ-56.68.	calcd. for $C_{24}H_{23}F_3N_4O_3$:472.17 m/z, found:473.05 $[M+H]^+$.
	214	(S)-1-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(1-(trifluoromethyl)cyclobutyl)urea	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.60 (s, 1H), 8.26 (s, 1H), 7.86-8.07(m,1H), 7.43-7.61 (m, 1H), 7.28-7.38 (m, 4H), 6.96-7.21(m, 1H), 6.82-6.96 (m, 1H), 6.34-6.65 (m, 1H), 2.38-2.49 (m, 4H), 1.96-2.09 (m, 1H), 1.84-1.96 (m, 4H). ^{19}F NMR (376 MHz, DMSO) δ -56.68, -79.81.	calcd. for $C_{23}H_{20}F_6N_4O_3$:514.1 m/z, found:515.15 $[M+H]^+$.

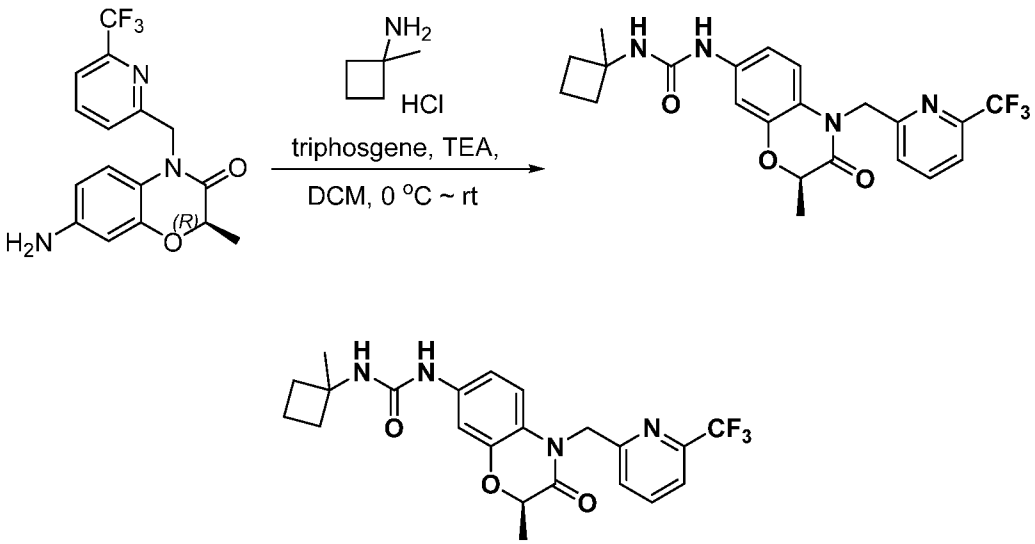
	215	(S)-1-(1-(methoxymethyl)cyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67(s, 1H),8.22(s, 1H),7.99(s, 1H), 7.38-7.58(m, 1H),7.23-7.37(m, 4H),7.02 (s, 1H), 6.60(s, 1H), 6.22 (s, 1H),3.50 (s, 2H),3.29-3.38 (m, 3H),2.22-2.34 (m,2H),1.95-2.05 (m, 2H),1.88-1.93 (m, 3H),1.78-1.87 (m, 1H),1.69-1.77 (m, 1H).^{19}F NMR (376 MHz, DMSO) δ -56.68.	calcd. $C_{24}H_{25}F_3N_4O_4$:490.1 m/z, found:491 .15 $[M+H]^+$
	216	(S)-1-(4,4-difluorocyclohexyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.25 (s, 1H), 7.91-8.05 (m, 1H), 7.44-7.58 (m, 1H), 7.26-7.41(m, 4H), 6.98-7.22 (m, 1H), 6.43-6.69 (m, 1H), 6.30-6.38 (m, 1H), 3.57-3.79 (m, 1H), 1.84-2.05 (m, 9H), 1.42-1.61(m, 2H), 1.21-1.30 (m, 1H).^{19}F NMR (376 MHz, DMSO) δ -56.82	$C_{24}H_{23}F_5N_4O_3$:510.4 m/z, found:511 .20 $[M+H]^+$.
	217	(S)-1-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(1-(trifluoromethyl)cyclopentyl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H),7.41-7.59 (m, 1H),7.28-7.39(m,4H),7.08(s,1H),6.52 (s,2H),2.20-2.31(m, 2H),1.84-2.04(m, 5H),1.58-1.78(m, 4H).^{19}F NMR (376 MHz, DMSO) δ -56.67, -75.81.	calcd. for $C_{24}H_{22}F_6N_4O_3$:528.1 m/z, found:529 .20 $[M+H]^+$.
	218	(S)-1-(tert-butyl)-3-(5-chloro-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.22-8.23 (m, 1H), 8.10 (s, 1H), 7.44-7.49 (m, 1H), 7.27-7.30 (m, 4H), 6.95 (s, 1H), 6.59 (s, 1H), 1.87-1.90 (d, J = 9 Hz, 3H), 1.29 (s, 9H). ^{19}F NMR (282 MHz, DMSO) δ -56.66.	calcd. for $C_{22}H_{22}ClF_3N_4O_3$:482 .13 m/z,found : 483.00 $[M+H]^+$

	219	(S)-2,2-dimethyl-N-(2-oxo-1-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)cyclobutane-1-carboxamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.27 (s, 1H), 8.20 (s, 1H), 7.58-7.60 (m, 1H), 7.44-7.49 (m, 1H), 7.27-7.30 (m, 3H), 7.18 (s, 1H), 6.58 (s, 1H), 2.85-2.90 (m, 1H), 2.19-2.28 (m, 1H), 1.78-1.94 (m, 4H), 1.57-1.78 (m, 2H), 1.24 (s, 3H), 0.97 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ -56.68.	calcd. for $C_{24}H_{24}F_3N_3O_3$:459.18 m/z, found:460.05 $[M+H]^+$
	220	(S)-2,2-dimethyl-N-(2-oxo-1-((R)-1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)cyclobutane-1-carboxamide	^{1}H NMR (300 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.27 (s, 1H), 8.19 (s, 1H), 7.58-7.61 (m, 1H), 7.44-7.49 (m, 1H), 7.29 (s, 3H), 7.19 (s, 1H), 6.57 (s, 1H), 2.84-2.90 (m, 1H), 2.22-2.28 (m, 1H), 1.88-1.90 (d, J = 6.0 Hz, 4H), 1.59-1.79 (m, 2H), 1.25 (s, 3H), 0.97 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ-56.68.	calcd. for $C_{24}H_{24}F_3N_3O_3$:459.18 m/z, found:460.05 $[M+H]^+$.
	221	(S)-1-(3,3-difluoro-1-methylcyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.25 (s, 1H), 7.91-8.01 (m, 1H), 7.42-7.53 (m, 1H),7.31-7.42 (m, 1H), 7.23-7.31 (m, 3H), 6.92-7.19 (m, 1H), 6.65-6.79(m, 1H), 6.46-6.65 (m, 1H), 2.83-3.01 (m, 2H), 2.55-2.70 (m, 2H), 1.82-1.94(m, 3H), 1.42-1.51 (m, 3H).^{19}F NMR (376 MHz, DMSO) δ -56.68, -85.00, -89.66.	calcd. For $C_{23}H_{21}F_5N_4O_3$:496.15 m/z, found:497.15 $[M+H]^+$
	222	(S)-1-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)oxetan-3-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.26 (s, 1H), 7.90-8.07 (m, 1H), 7.38-7.63 (m, 3H), 7.24-7.38 (m, 3H), 6.95-7.25 (m, 1H), 6.34-6.72 (m, 1H), 4.74-4.93 (m, 2H), 4.63-4.74 (m, 2H), 1.85-1.95(m, 3H).^{19}F NMR (376 MHz, DMSO) δ-56.68, -79.66.	calcd. for $C_{22}H_{18}F_6N_4O_4$:516.13 m/z, found:517.15 $[M+H]^+$.

	223	1-(2-oxo-1-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-((1r,3R)-3-(trifluoromethyl)cyclobutyl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.24 (s, 1H), 7.96 (s, 1H), 7.47-7.49 (m, 1H), 7.36-7.44 (m, 1H), 7.25-7.33 (m, 3H), 7.11 (s, 1H), 6.65-6.69 (m, 1H), 6.57 (s, 1H), 4.28 (m, 1H), 2.98-3.08 (m, 1H), 2.28-2.47 (m, 4H), 1.87-1.89 (d, J = 6.0 Hz, 3H). ^{19}F NMR (282 MHz, DMSO) δ -56.69, -71.44.	calcd. for $C_{23}H_{20}F_6N_4O_3$:514.14 m/z, found:515.05 $[M+H]^+$.
	224	1-(2-oxo-1-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-((1s,3S)-3-(trifluoromethyl)cyclobutyl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.24 (s, 1H), 7.96 (s, 1H), 7.46-7.49 (m, 1H), 7.35-7.38 (m, 1H), 7.27-7.29 (m, 3H), 7.12 (s, 1H), 6.69-6.72 (m, 1H), 6.57 (s, 1H), 4.12-4.20 (m, 1H), 2.83-2.92 (m, 1H), 2.36-2.48 (m, 2H), 1.98-2.02 (m, 2H), 1.87-1.92 (m, 3H). ^{19}F NMR (282 MHz, DMSO) δ -56.69, -71.04.	calcd. for $C_{23}H_{20}F_6N_4O_3$:514.14 m/z, found:515.05 $[M+H]^+$.
	225	(S)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.26 (s, 1H), 7.96 (s, 1H), 7.43-7.52 (m, 1H), 7.37-7.41 (m, 2H), 7.28-7.30 (m, 3H), 7.12 (s, 1H), 6.58 (s, 1H), 3.15-3.18 (t, J = 12 Hz, 4H), 1.88-1.90 (d, J = 8 Hz, 3H). ^{19}F NMR (376 MHz, DMSO) δ -56.69, -78.33, -86.27.	calcd. for $C_{23}H_{18}F_8N_4O_3$:550.13 m/z, found:551.00 $[M+H]^+$.

Example 226: 1-[(2R)-2-methyl-3-oxo-4-{[6-(trifluoromethyl)pyridin-2-yl]methyl}-2H-1,4-benzoxazin-7-yl]-3-(1-methylcyclobutyl)urea

Synthetic Scheme

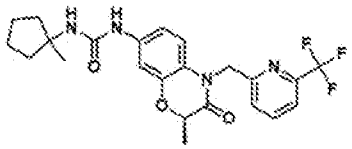
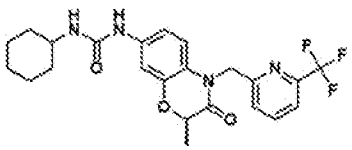


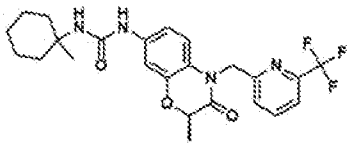
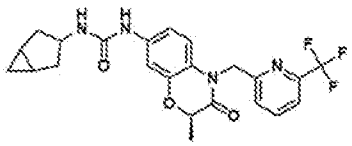
1-[(2R)-2-methyl-3-oxo-4-{[6-(trifluoromethyl)pyridin-2-yl]methyl}-2H-1,4-benzoxazin-7-yl]-3-(1-methylcyclobutyl)urea

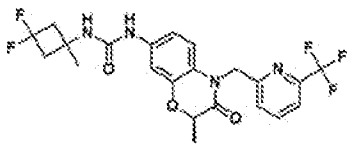
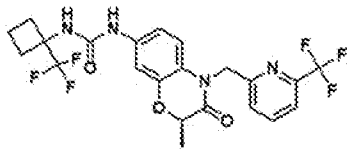
To a solution of (2R)-7-amino-2-methyl-4-{[6-(trifluoromethyl)pyridin-2-yl]methyl}-2H-1,4-benzoxazin-3-one (100 mg, 0.296 mmol, 1 equiv) in DCM (5 mL) was added triphosgene (35.19 mg, 0.118 mmol, 0.4 equiv) at 0°C under N_2 atmosphere. The resulting mixture was stirred for 1 h at 25 °C. Then TEA (90.00 mg, 0.888 mmol, 3 equiv) was added into above system at 0 °C. The resulting mixture was stirred for 1 h at 25 °C. To the above mixture was added 1-methylcyclobutan-1-amine (50.49 mg, 0.592 mmol, 2 equiv) dropwise at 0 °C. The reaction was stirred at 25 °C for 2 h. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Shield RP18 OBD 30*150 mm, 5μm column (eluent: 42% to 60% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 1-[(2R)-2-methyl-3-oxo-4-{[6-(trifluoromethyl)pyridin-2-yl]methyl}-2H-1,4-benzoxazin-7-yl]-3-(1-methylcyclobutyl)urea (32.5 mg, 24.40%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{23}F_3N_4O_3$:448.17 m/z, found:449.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 8.03 – 8.12 (m, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 2.0 Hz, 1H), 6.76 – 6.86 (m, 2H), 6.23 (s, 1H), 5.24 (s, 2H), 4.78 – 4.88 (m, 1H), 2.22 – 2.30 (m, 2H), 1.82 – 1.93 (m, 2H), 1.69 – 1.82 (m, 2H), 1.47 (d, J = 6.7 Hz, 3H), 1.38 (s, 3H). ^{19}F NMR (376 MHz, DMSO) δ -66.54.

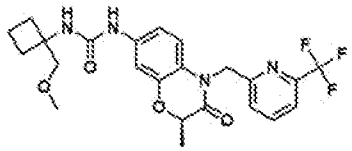
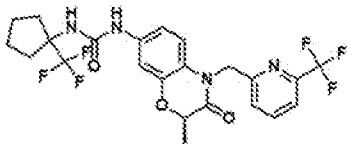
The following examples in Table 12 were made according to the procedure for example 226.

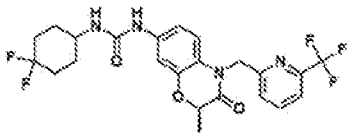
Table 12

Structure	Ex.	IUPAC Name	1H NMR	LCMS
	227	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.21 (s, 1H), 8.00-8.15 (m, 1H), 7.72-7.88 (m, 1H), 7.39-7.55 (m, 1H), 7.11-7.32 (m, 1H), 6.61-6.91 (m, 2H), 6.00 (s, 1H), 5.24 (s, 2H), 4.81 (q, J = 6.7 Hz, 1H), 1.80-2.00 (m, 2H), 1.58-1.71 (m, 4H), 1.49-1.58 (m, 2H), 1.41-1.49 (m, 3H), 1.33 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ -66.55.	calcd. for $C_{23}H_{25}F_3N_4O_3$: 462.19 m/z, found:463.20 $[M+H]^+$
	228	(R)-1-cyclohexyl-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H),8.07 (t, J = 7.9 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 1.9 Hz, 1H), 6.74 – 6.92 (m, 2H), 6.03 (d, J = 7.8 Hz, 1H),5.24 (d, J = 3.4 Hz, 2H), 4.80 (q, J = 6.7 Hz, 1H),3.45 (m,1H), 1.80 (d, J = 11.6 Hz, 2H), 1.61 – 1.69 (m, 2H), 1.53 (s, 4H), 1.28– 1.40 (m, 2H), 0.83– 1.07 (m, 3H). ^{19}F NMR (376 MHz, DMSO) δ -66.54	calcd. for $C_{23}H_{25}F_3N_4O_3$: 462.19, 463.05 $[M+H]^+$

	229	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclohexyl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.07 (t, J = 7.9 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 2.3 Hz, 1H), 6.76 (d, J = 8.7 Hz, 2H), 5.79 (s, 1H), 5.24 (s, 2H), 4.80 (q, J = 6.7 Hz, 1H), 1.92 (d, J = 12.7 Hz, 2H), 1.48-1.68 (m, 8H), 1.44 – 1.90 (m, 6H). ^{19}F NMR (376 MHz, DMSO) δ -66.54	calcd. for $C_{24}H_{27}F_3N_4O_3$: 476.20, found: 477.05 $[M+H]^+$
	230	1-(bicyclo[3.1.0]hexan-3-yl)-3-((R)-2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.99 – 8.12 (m, 1H), 7.70–7.92 (m, 1H), 7.40–7.69(m, 1H), 7.14– 7.31(m, 1H), 6.59 – 7.00(m, 2H), 5.78– 6.15 (m, 1H), 5.05 – 5.35 (m, 2H), 4.62 – 4.96 (m, 1H), 3.92 – 4.25 (m, 1H), 2.06 – 2.26 (m, 2H), 1.38 – 1.59 (m, 5H), 1.22–1.31 (m, 2H), 0.45 – 0.65 (m, 1H), 0.17 – 0.28 (m, 1H).^{19}F NMR (376 MHz, DMSO) δ -66.55.	calcd. for $C_{23}H_{23}F_3N_4O_3$: 460.1 m/z, found:461.10 $[M+H]^+$.

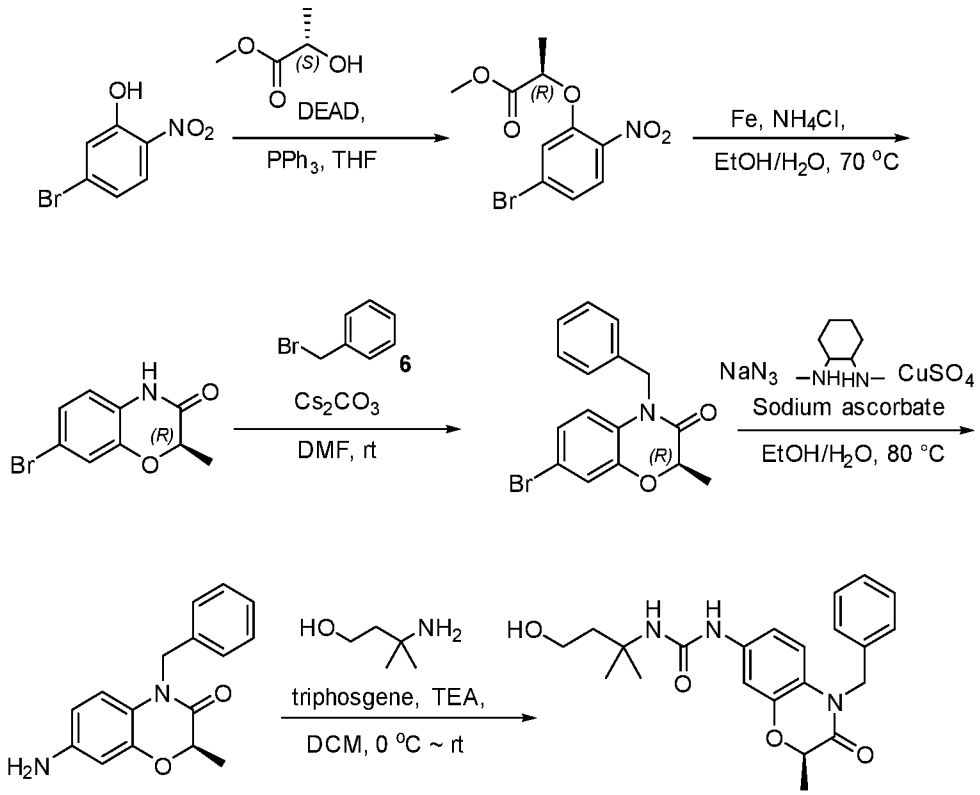
	231	(R)-1-(3,3-difluoro-1-methylcyclobutyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.95-8.21 (m, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.42-7.68 (m, 1H), 7.20 (d, J = 1.3 Hz, 1H), 6.84 (d, J = 1.4 Hz, 2H), 6.51 (s, 1H), 5.24 (s, 2H), 4.59-4.99 (m, 1H), 2.78-3.02 (m, 2H), 2.55-2.68 (m, 2H), 1.39-1.59 (m, 6H). ^{19}F NMR (376 MHz, DMSO) δ -66.55, -85.05, -89.67	calcd. for $C_{22}H_{21}F_5N_4O_3$: 484.15, found: 484.95 $[M+H]^+$
	232	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-(trifluoromethyl)cyclobutyl)urea	^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.38 (s, 1H), 8.07 (t, J = 7.8 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.24 (s, 1H), 6.81 (d, J = 15.3 Hz, 3H), 5.24 (s, 2H), 4.84 (q, J = 6.6 Hz, 1H), 2.40 (t, J = 7.4 Hz, 4H), 1.97 – 1.90 (m, 2H), 1.47 (d, J = 6.6 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d$_6$) δ -66.55, -79.85.	calcd. for $C_{22}H_{20}F_6N_4O_3$: 502.1 m/z, found:503.30 $[M+H]^+$.

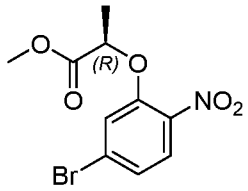
	233	(R)-1-(1-(methoxymethyl)cyclobutyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.07 (t, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.25 (d, *J* = 2.1 Hz, 1H), 6.84 – 6.79 (m, 2H), 6.19 (s, 1H), 5.24 (s, 2H), 4.83 (q, *J* = 6.6 Hz, 1H), 3.47 (s, 2H), 3.30 (s, 3H), 2.24 (q, *J* = 9.9 Hz, 2H), 1.99 – 1.92 (m, 2H), 1.79 – 1.72 (m, 2H), 1.47 (d, *J* = 6.6 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -66.18.	calcd. for $C_{23}H_{25}F_3N_4O_4$: 478.2 m/z, found:479.15 $[M+H]^+$.
	234	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-(trifluoromethyl)cyclopentyl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35 (s, 1H), 8.07 (t, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.23 (d, *J* = 1.8 Hz, 1H), 6.85 – 6.77 (m, 2H), 6.49 (s, 1H), 5.24 (s, 2H), 4.84 (q, *J* = 6.6 Hz, 1H), 2.26 – 2.22 (m, 2H), 1.93 – 1.86 (m, 2H), 1.80 – 1.60 (m, 4H), 1.47 (d, *J* = 6.6 Hz, 3H).^{19}F NMR (282 MHz, DMSO-d_6) δ -66.56, -75.84.	calcd. for $C_{23}H_{22}F_6N_4O_3$: 516.2 m/z, found:517.15 $[M+H]^+$.

	235	(R)-1-(4,4-difluorocyclohexyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.02-8.22 (m, 1H), 7.75-7.91 (m, 1H),7.42-7.58 (m, 1H), 7.18-7.32 (m, 1H), 6.85 (s, 2H), 6.12-6.38 (m, 1H), 5.18-5.37(m, 2H), 4.68-4.91(m, 1H), 3.69(s, 1H), 1.81-2.10 (m, 6H), 1.41-1.58 (m, 5H) .^{19}F NMR (376 MHz, DMSO) δ -66.59	calcd. for $C_{23}H_{23}F_5N_4O_3$: 498.17, found: 499.05 $[M+H]^+$

Example 236:
(R)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(4-hydroxy-2-methylbutan-2-yl)urea

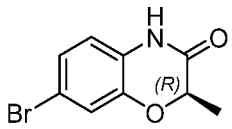
Synthetic Scheme





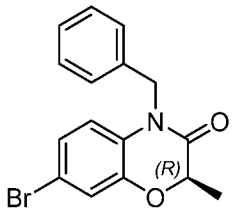
methyl (R)-2-(5-bromo-2-nitrophenoxy)propanoate

To a solution of 2-amino-5-nitrophenol (900 mg, 0.065 mmol, 1 equiv) in THF (15 mL) was added methyl (2S)-2-hydroxypropanoate (649.68 mg, 6.240 mmol, 1.5 equiv) and PPh_3 (1636.87 mg, 6.240 mmol, 1.5 equiv). The resulting mixture was maintained under nitrogen and stirred at rt for 1 h. Then DEAD (1086.85 mg, 6.240 mmol, 1.5 equiv) was added at 0 °C. The resulting mixture was maintained under nitrogen and stirred at 80°C for 3 h. After cooling down to rt, the reaction was quenched with water (100 mL). The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% ethyl acetate/petroleum ether) to afford the methyl (2R)-2-(5-bromo-2-nitrophenoxy)propanoate (1.12 g, 88.53%) as a yellow oil. LC/MS: mass calcd. for $C_{10}H_{10}BrNO_5$: 302.97, found: 304.09, 306.09 $[M+H, M+H+2]^+$.



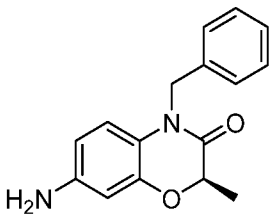
(R)-7-bromo-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of methyl (2R)-2-(5-bromo-2-nitrophenoxy)propanoate (1.1 g, 3.63 mmol, 1 equiv) in MeOH (15 mL) and H_2O (1.5 mL) was added Fe (2.03 g, 36.3mmol, 10 equiv) and NH_4Cl (1.96 g, 36.3 mmol, 10 equiv). The resulting mixture was maintained under nitrogen and stirred at 70 °C for 3 h. After cooling down to rt, the reaction was quenched with water (50 mL). The resulting mixture was extracted with EA (3 x 50 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% ethyl acetate/petroleum ether) to afford the methyl (2R)-2-(5-bromo-2-nitrophenoxy)propanoate (800 mg, 91.53%) as a yellow oil. LC/MS: mass calcd. for $C_9H_8BrNO_2$: 240.97, found: 241.07, 243.97 $[M+H, M+H+2]^+$.



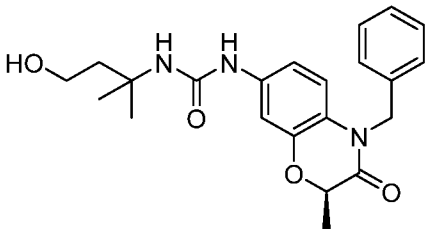
(R)-4-benzyl-7-bromo-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-7-bromo-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (2 g, 8.262 mmol, 1 equiv) and benzyl bromide (2826.22 mg, 16.524 mmol, 2 equiv) in dimethylformamide (50 mL) was added Cs_2CO_3 (8100.74 mg, 24.786 mmol, 3 equiv). The reaction was stirred at 100 °C under N_2 for 3 h. After cooling down to rt, the reaction was quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-4-benzyl-7-bromo-2-methyl-2H-1,4-benzoxazin-3-one (2.35 g, 85.62%) as a white solid. LC/MS (ESI): mass calcd. for $C_{16}H_{14}BrNO_2$: 331.02 m/z, found:332.00, 334.00 $[M+H, M+H+2]^+$.



(R)-7-amino-4-benzyl-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-4-benzyl-7-bromo-2-methyl-2H-1,4-benzoxazin-3-one (2.35 g, 5.916 mmol, 1 equiv) in ethyl alcohol (60 mL) and water (15 mL) was added N1,N2-dimethylcyclohexane-1,2-diamine (0.50 g, 3.550 mmol, 0.6 equiv), $CuSO_4$ (0.94 g, 5.916 mmol, 1 equiv) and NaN_3 (1.15 g, 17.75 mmol, 3 equiv). The reaction was stirred at 80 °C under N_2 for 3 h. After cooling down to rt, the reaction was quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-4-benzyl-2-methyl-2H-1,4-benzoxazin-3-one (1.3 g, 81.89%) as a white solid. LC/MS (ESI): mass calcd. for $C_{16}H_{16}N_2O_2$: 268.12 m/z, found:269.15 $[M+H]^+$.



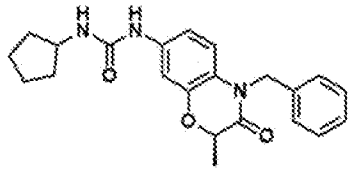
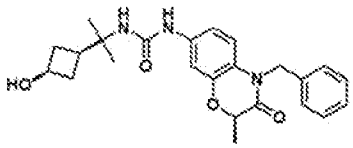
(R)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(4-hydroxy-2-methylbutan-2-yl)urea

To a solution of (2R)-7-amino-4-benzyl-2-methyl-2H-1,4-benzoxazin-3-one (100 mg, 0.373 mmol, 1 equiv) in DCM (5 mL) was added triphosgene (44.24 mg, 0.149 mmol, 0.4 equiv). The reaction was stirred at 0 °C under N_2 for 1 h. The reaction was added TEA (188.57 mg, 1.865 mmol, 5 equiv) and stirred at rt under N_2 for 1 h. The reaction was added 3-amino-3-methylbutan-1-ol (153.80 mg, 1.492 mmol, 4 equiv) and stirred at rt under N_2 for 1 h. Quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep Phenyl OBD Column 19*150 mm, 5μm (eluent: 27% to 49% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford 1-[(2R)-4-benzyl-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]-3-(4-hydroxy-2-methylbutan-2-yl)urea (36.2 mg, 24.36%) as a white solid. LC/MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_4$:397.20 m/z, found:398.00 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.26-7.38 (m, 2H), 7.20-7.25 (m, 4H), 6.75-6.86 (m, 2H), 5.95 (s, 1H), 5.09 (s, 2H), 4.79-4.81 (m, 1H), 4.37-4.41 (m, 1H), 3.44-3.50 (m, 2H), 1.78-1.80 (t, J = 6 Hz, 2H), 1.46-1.48 (m, 3H), 1.25 (s, 6H).

The following examples in Table 13 were made according to the procedure for example 236.

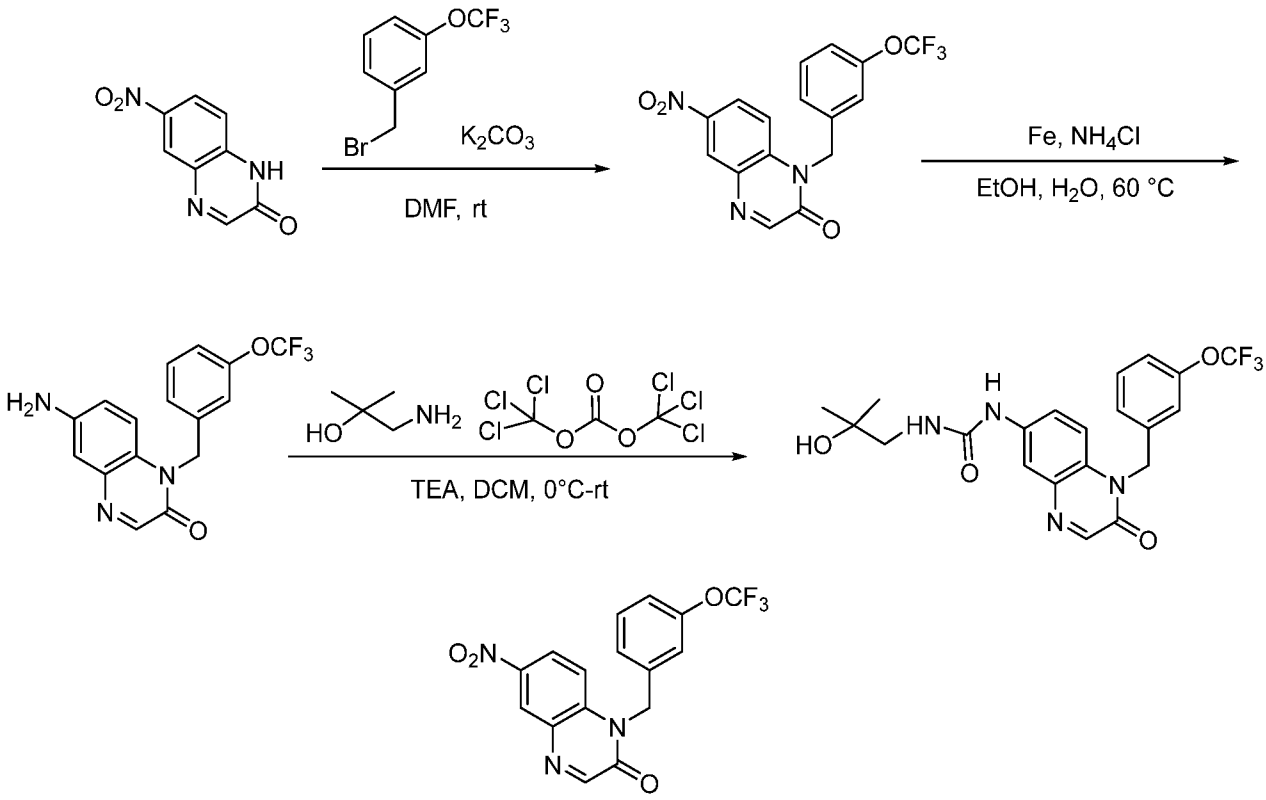
Table 13

Structure	Ex.	IUPAC Name	1H NMR	LCMS

	237	(R)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-cyclopentylurea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.35 – 7.30 (m, 2H), 7.25 – 7.22 (m, 4H), 6.86 (d, J = 8.7 Hz, 1H), 6.80 – 6.77 (m, 1H), 6.12 (d, J = 7.2 Hz, 1H), 5.09 (d, J = 2.7 Hz, 2H), 4.82 (q, J = 6.6 Hz, 1H), 3.89 (q, J = 6.6 Hz, 1H), 1.83 – 1.77 (m, 2H), 1.61 – 1.35 (m, 7H), 1.33 – 1.29 (m, 2H).	calcd. for $C_{22}H_{25}N_3O_3$:379.2 m/z, found:380.15 $[M+H]^+$.
	238	1-((R)-4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(2-((1s,3S)-3-hydroxycyclobutyl)propan-2-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 – 8.52 (m, 1H), 7.10 – 7.44 (m, 6H), 6.80 – 6.97 (m, 1H), 6.60 – 6.80 (m, 1H), 5.56 – 5.91 (m, 1H), 5.03 – 5.22 (m, 2H), 4.90 – 5.03 (m, 1H), 4.63 – 4.90 (m, 1H), 3.69 – 3.93 (m, 1H), 1.83 – 2.15 (m, 4H), 1.53 – 1.69 (m, 2H), 1.35 – 1.53 (m, 3H), 1.00 – 1.30 (m, 6H).	calcd. for $C_{24}H_{29}N_3O_4$: 423.22 m/z, found 424.05 $[M+H]^+$

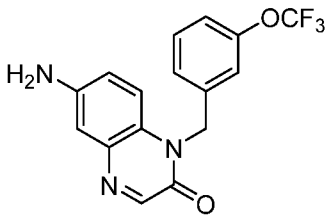
Example 239: 1-(2-hydroxy-2-methylpropyl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea

Synthetic Scheme



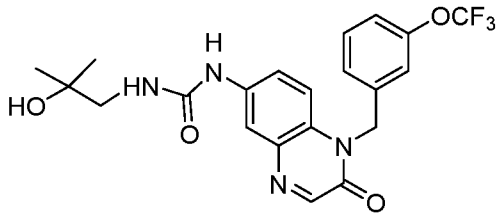
6-nitro-1-(3-(trifluoromethoxy)benzyl)quinoxalin-2(1H)-one

To a mixture of 6-nitroquinoxalin-2(1H)-one (1.8 g, 9.417 mmol, 1.2 equiv) and 1-(bromomethyl)-3-(trifluoromethoxy)benzene (2.00 g, 7.848 mmol, 1 equiv) in DMF (30 mL) was stirred and added K_2CO_3 (2.18 g, 15.695 mmol, 2 equiv). The reaction was stirred at rt for 1 h. The reaction mixture was quenched by ice water (30 mL) and extracted with EA (3 x 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column, eluted with PE/EA (3:1) to afford 6-nitro-1-(3-(trifluoromethoxy)benzyl)quinoxalin-2(1H)-one (1.7 g, 59.31%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{10}F_3N_3O_4$, 365.06 m/z, found 366.00 $[M+H]^+$.



6-amino-1-(3-(trifluoromethoxy)benzyl)quinoxalin-2(1H)-one

To a mixture of 6-nitro-1-(3-(trifluoromethoxy)benzyl)quinoxalin-2(1H)-one (1.0 g, 2.738 mmol, 1 equiv) in EtOH (25 mL) and water (5 mL). Fe (1.53 g, 27.380 mmol, 10 equiv) and NH_4Cl (1.46 g, 27.380 mmol, 10 equiv) was added into the mixture. The resulting solution was stirred at 60 °C for 1 h. The reaction was quenched with water (30 mL) at rt. After filtration, the filter cake was washed with EA (3 x 20 mL). The filtrate was added water (20 mL) and extracted with EA (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford 6-amino-1-(3-(trifluoromethoxy)benzyl)quinoxalin-2(1H)-one (700 mg, 75.51%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{12}F_3N_3O_2$, 335.09 m/z, found 336.05 $[M+H]^+$.

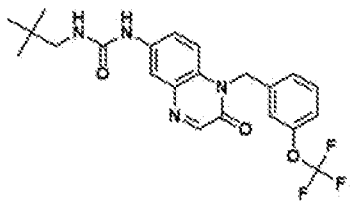
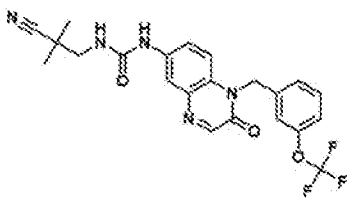
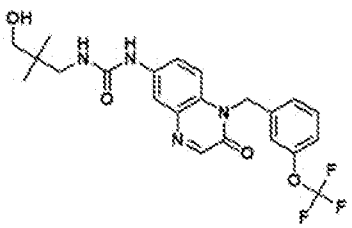
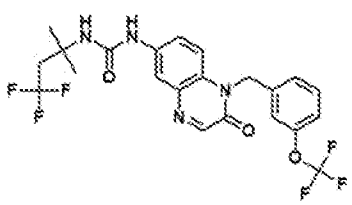


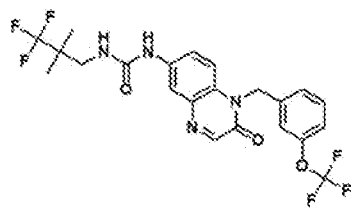
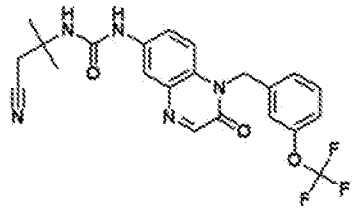
1-(2-hydroxy-2-methylpropyl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea

To a mixture of 6-amino-1-(3-(trifluoromethoxy)benzyl)quinoxalin-2(1H)-one (70 mg, 0.209 mmol, 1 equiv) in DCM (6 mL) was stirred under nitrogen atmosphere and added triphosgene (19 mg, 0.063 mmol, 0.3 equiv) at 0 °C. The reaction was stirred at rt for 1 h. TEA (53 mg, 0.522 mmol, 2.5 equiv) was added into the mixture at 0°C. The reaction was stirred at rt for 1 h. 1-amino-2-methylpropan-2-ol (23 mg, 0.251 mmol, 1.2 equiv) was added into the mixture at 0 °C. The reaction was stirred at rt for 1 h. The reaction mixture was quenched by 1N hydrochloric acid (5 mL) and extracted with DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford 1-(2-hydroxy-2-methylpropyl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea (26.1 mg, 27.71%) as a yellow solid. MS (ESI): mass calcd. for $C_{21}H_{21}F_3N_4O_4$, 450.15 m/z, found 451.00 [M+H]+. ^1H NMR (300 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.33 (s, 1H), 8.01 (d, J = 2.4 Hz, 1H), 7.41 – 7.53 (m, 2H), 7.32 – 7.41 (m, 2H), 7.21 – 7.32 (m, 2H), 6.18 (t, J = 5.7 Hz, 1H), 5.49 (s, 2H), 4.55 (s, 1H), 3.05 (d, J = 5.7 Hz, 2H), 1.09 (s, 6H).

The following examples in Table 14 were made according to the procedure for example 239.

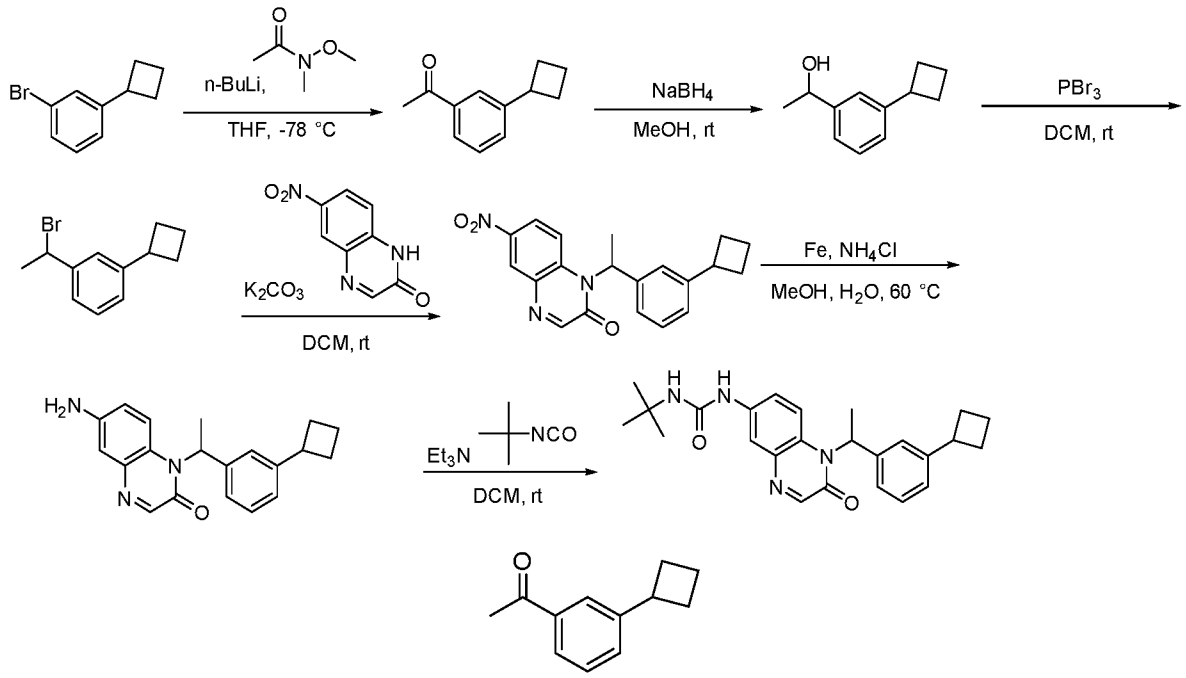
Table 14

Structure	Ex.	IUPAC Name	1H NMR	LCMS
	240	1-neopentyl-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.32 (s, 1H), 8.02 (d, J = 2.5 Hz, 1H), 7.43 – 7.50(m, 2H), 7.32 – 7.40 (m, 2H), 7.26 (dd, J = 8.8, 7.6 Hz, 2H), 6.24 (t, J = 6.2 Hz, 1H), 5.50 (s, 2H), 2.92 (d, J = 6.1 Hz, 2H), 0.87 (s, 9H).	calcd. for $C_{22}H_{23}F_3N_4O_3$, 448.17 m/z, found 448.95 $[M+H]^+$
	241	1-(2-cyano-2-methylpropyl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.33 (s, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.33 – 7.53 (m, 4H), 7.26 (t, J = 7.0 Hz, 2H), 6.64 (t, J = 6.5 Hz, 1H), 5.50 (s, 2H), 3.31 (d, J = 6.6 Hz, 2H), 1.29 (s, 6H).	calcd. for $C_{22}H_{20}F_3N_5O_3$, 459.15 m/z, found 460.05 $[M+H]^+$
	242	1-(3-hydroxy-2,2-dimethylpropyl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.32 (s, 1H), 8.00 (d, J = 2.4 Hz, 1H), 7.41 – 7.51 (m, 2H), 7.36 (d, J = 9.4 Hz, 2H), 7.26 (t, J = 7.2 Hz, 2H), 6.23 (t, J = 6.1 Hz, 1H), 5.49 (s, 2H), 4.63 (t, J = 5.5 Hz, 1H), 3.13 (d, J = 5.5 Hz, 2H), 2.98 (d, J = 6.0 Hz, 2H), 0.79 (s, 6H).	calcd. for $C_{22}H_{23}F_3N_4O_4$, 464.17 m/z, found 465.05 $[M+H]^+$
	243	1-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)-3-(4,4,4-trifluoro-2-methylbutan-2-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.33 (s, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.41 – 7.48 (m, 2H), 7.36 (d, J = 9.1 Hz, 2H), 7.26 (t, J = 7.8 Hz, 2H), 6.26 (s, 1H), 5.49 (s, 2H), 2.84 (q, J = 12.1 Hz, 2H), 1.37 (s, 6H).	calcd. for $C_{22}H_{20}F_6N_4O_3$, 502.14 m/z, found 503.05 $[M+H]^+$

	244	1-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)-3-(3,3,3-trifluoro-2,2-dimethylpropyl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.33 (s, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.41 – 7.55 (m, 2H), 7.32 – 7.41 (m, 2H), 7.21 – 7.31 (m, 2H), 6.41 (t, J = 6.5 Hz, 1H), 5.50 (s, 2H), 3.30 (d, J = 6.4 Hz, 2H), 1.08 (s, 6H).	calcd. For $C_{22}H_{20}F_6N_4O_3$: 502.14 m/z, found: 503.10 $[M+H]^+$
	245	1-(1-cyano-2-methylpropan-2-yl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.33 (s, 1H), 8.00 (d, J = 2.5 Hz, 1H), 7.42 – 7.50 (m, 2H), 7.33 – 7.42 (m, 2H), 7.26 (t, J = 8.1 Hz, 2H), 6.42 (s, 1H), 5.50 (s, 2H), 3.09 (s, 2H), 1.36 (s, 6H).	calcd. For $C_{22}H_{20}F_3N_5O_3$: 459.15 m/z, found: 460.10 $[M+H]^+$

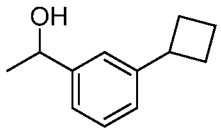
Example 246: 1-(tert-butyl)-3-(1-(1-(3-cyclobutylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

Synthetic Scheme



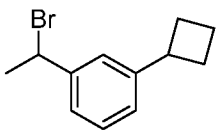
1-(3-cyclobutylphenyl)ethan-1-one

In a 100-mL round bottom flask, to a solution of 1-bromo-3-cyclobutylbenzene (500 mg, 2.369 mmol, 1 equiv) in tetrahydrofuran (5 mL) was added dropwise n-BuLi (2.5 M, 1.1 mL, 2.843 mmol, 1.2 equiv) at -78 °C under N_2 atmosphere. The reaction mixture was stirred at -78 °C for 30 mins. N-methoxy-N-methylacetamide (292 mg, 2.843 mmol, 1.2 equiv) was added into the solution and the mixture was stirred for another 1 h. The reaction was quenched with water/sat. NH_4Cl (5 mL), and then the mixture was extracted with ether/EtOAc (2 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EA (5/1) to afford 1-(3-cyclobutylphenyl)ethan-1-one (280 mg, 67.96%) as a white solid. MS (ESI): mass calcd. for $C_{12}H_{14}O$, 174.10 m/z, found 175.20 $[M+H]^+$.



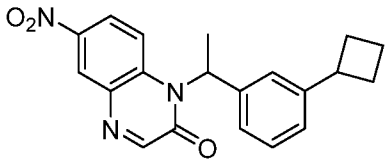
1-(3-cyclobutylphenyl)ethan-1-ol

A solution of 1-(3-cyclobutylphenyl)ethanone (280 mg, 1.607 mmol, 1 equiv) in MeOH (5 mL) was added $NaBH_4$ (152 mg, 4.018 mmol, 2.5 equiv) at rt. The resulting mixture was stirred for 1h at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography with PE/EA (3:1) to afford 1-(3-cyclobutylphenyl)ethan-1-ol (200 mg, 70.61%) as a white solid. MS: mass calcd. for $C_{12}H_{16}O$: 176.12, found: 159.15 $[M-OH]^+$.



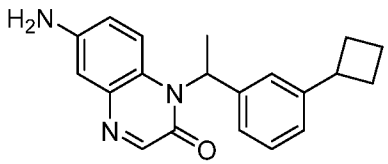
1-(1-bromoethyl)-3-cyclobutylbenzene

A solution of 1-(3-cyclobutylphenyl)ethan-1-ol (40 mg, 0.227 mmol, 1 equiv) in DCM (5 mL) was added phosphorus tribromide (154 mg, 0.568 mmol, 2.5 equiv) at rt. The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by ice-water (10 mL) and extracted with EA (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product 1-(1-bromoethyl)-3-cyclobutylbenzene (40 mg, 73.70%) was used in the next step directly without further purification.



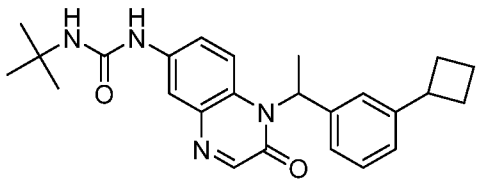
1-(1-(3-cyclobutylphenyl)ethyl)-6-nitroquinoxalin-2(1H)-one

A solution of 1-(1-bromoethyl)-3-cyclobutylbenzene (150 mg, 0.627 mmol, 1 equiv) in dimethylformamide (5 mL) was added 6-nitroquinoxalin-2(1H)-one (239 mg, 1.254 mmol, 2.0 equiv) and K_2CO_3 (260 mg, 1.881 mmol, 3.0 equiv) at rt. The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water (10 mL)The resulting mixture was extracted with EA (3 x 10 mL). The combined organic layers were washed with NaCl (aq., 3 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (1/3) to afford 1-(1-(3-cyclobutylphenyl)ethyl)-6-nitroquinoxalin-2(1H)-one (50 mg, 23.00%) as a light yellow solid. MS (ESI): mass calcd. $C_{20}H_{19}N_3O_3$ for: 349.14 m/z, found 350.20 $[M+H]^+$.



6-amino-1-(1-(3-cyclobutylphenyl)ethyl)quinoxalin-2(1H)-one

A solution of 1-(1-(3-cyclobutylphenyl)ethyl)-6-nitroquinoxalin-2(1H)-one (60 mg, 0.172 mmol, 1 equiv) in EtOH (5 mL)/H_2O (0.5 mL) was added Fe (96 mg, 1.720 mmol, 10 equiv) and NH_4Cl (92 mg, 1.720 mmol, 10 equiv) at rt. The resulting mixture was stirred for 1 h at 60 °C. The mixture was allowed to cool down to rt. The reaction mixture was quenched by water (10 mL) and extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography with PE/EA (3:1) to afford 6-amino-1-(1-(3-cyclobutylphenyl)ethyl)quinoxalin-2(1H)-one (45 mg, 82.04%) as a light yellow solid. MS: mass calcd. for $C_{20}H_{21}N_3O$: 319.17, found: 320.20 $[M+H]^+$.

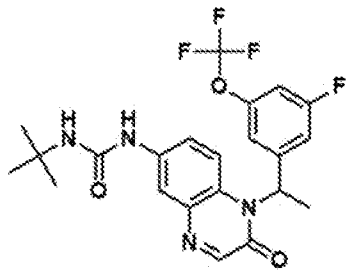


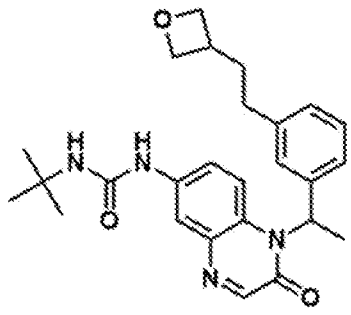
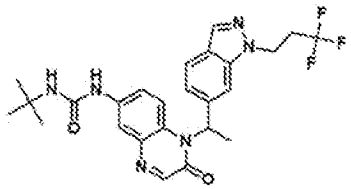
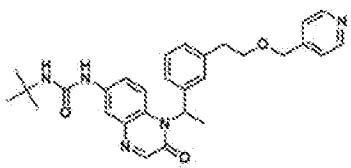
1-(tert-butyl)-3-(1-(1-(3-cyclobutylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

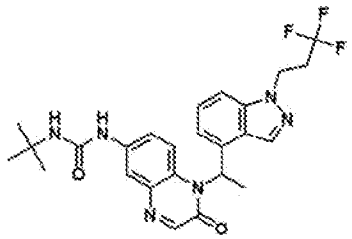
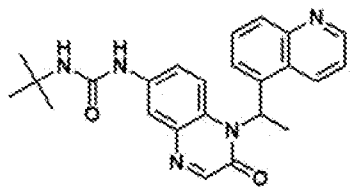
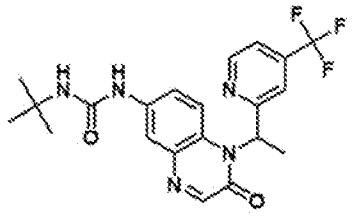
A solution of 6-amino-1-(1-(3-cyclobutylphenyl)ethyl)quinoxalin-2(1H)-one (40 mg, 0.125 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (37 mg, 0.375 mmol, 3.0 equiv) and triethylamine (51 mg, 0.500 mmol, 4.0 equiv) at rt. The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water (10 mL). The resulting mixture was extracted with EA (5 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product 30 mg was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9; Number Of Runs: 0) to affored 3-tert-butyl-1-{1-[1-(3-cyclobutylphenyl)ethyl]-2-oxoquinoxalin-6-yl}urea (7.8 mg, 14.70%) as a yellow solid. MS (ESI): mass calcd. $C_{25}H_{30}N_4O_2$ for: 418.24 m/z, found 419.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 8.27 (s, 1H), 7.92 (d, J = 2.6 Hz, 1H), 7.21 – 7.32 (m, 2H), 6.98 – 7.21 (m, 4H), 6.55 – 6.59 (m, 1H), 6.03 (s, 1H), 3.45 – 3.51 (m, 1H), 2.16 – 2.30 (m, 2H), 1.98 – 2.09 (m, 2H), 1.90 – 1.98 (m, 1H), 1.82 – 1.89 (m, 3H), 1.72 –1.81 (m, 1H), 1.30 (s, 9H).

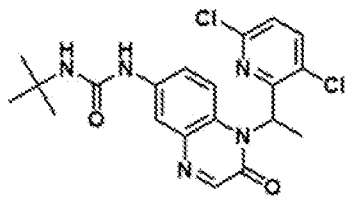
The following examples in Table 15 were made according to the procedure for example 246.

Table 15

Structure	Ex.	IUPAC Name	1H NMR	LCMS
	247	1-(tert-butyl)-3-(1-(1-(3-fluoro-5-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^1H NMR (300 MHz, Methanol-d_4) δ 8.25 (s, 1H), 7.92 (d, J = 2.6 Hz, 1H), 7.41 – 7.50 (m, 1H), 7.10 – 7.19 (m, 2H), 7.07 (s, 2H), 6.66 (br, 1H), 1.98 (d, J = 7.1 Hz, 3H), 1.38 (s, 9H).	calcd. For $C_{22}H_{22}F_4N_4O_3$: 466.16 m/z, found: 467.05 $[M+H]^+$

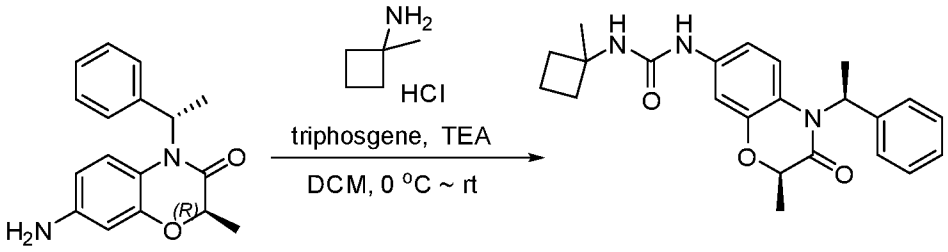
	248	1-(tert-butyl)-3-(1-(1-(3-(2-(oxetan-3-yl)ethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.24 (s, 1H), 7.84 (d, J = 2.5 Hz, 1H), 7.24 – 7.36 (m, 2H), 7.00 – 7.18 (m, 5H), 6.69 (s, 1H), 5.10 (s, 1H), 4.49 – 4.60 (m, 2H), 4.15 – 4.23 (m, 2H), 2.75 – 2.91 (m, 1H), 2.45 – 2.56 (m, 2H), 2.13 – 2.17 (m, 1H), 1.83 – 1.98 (m, 4H), 1.27 – 1.36 (m, 9H).	calcd. for $C_{27}H_{35}N_5O_3$: 448.2 m/z, found 449.20 $[M+H]^+$.
	249	1-(tert-butyl)-3-(2-oxo-1-(1-(1-(3,3,3-trifluoropropyl)-1H-indazol-6-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.29-8.35 (d, J = 18 Hz, 2H), 8.08 (s, 1H), 7.92 (s, 1H), 7.80 (s, 1H), 7.63-7.66 (d, J = 9 Hz, 1H), 7.15-7.16 (m, 2H), 6.88-6.91 (m, 1H), 6.76 (s, 1H), 5.99 (s, 1H), 4.69-4.74 (t, J = 15 Hz, 2H), 2.87-2.96 (m, 2H), 1.96-1.99 (m, 3H), 1.27 (s, 9H). ^{19}F NMR (282 MHz, DMSO) δ -63.77.	calcd. for $C_{25}H_{27}F_3N_6O_2$: 500.21 m/z, found:501.05[M+H]$^+$.
	250	1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2-(pyridin-4-ylmethoxy)ethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 – 8.46 (m, 2H), 8.39 (s, 1H), 8.26 (s, 1H), 7.03 – 7.38 (m, 8H), 6.63 – 6.68 (m, 1H), 6.03 (s, 1H), 4.47 (s, 2H), 3.64 (t, J = 6.6 Hz, 2H), 2.85 (t, J = 6.6 Hz, 2H), 1.87 (d, J = 7.1 Hz, 3H), 1.28 (s, 9H).	calcd. for $C_{29}H_{33}N_5O_3$, 449.28 m/z, found 500.25 $[M+H]^+$

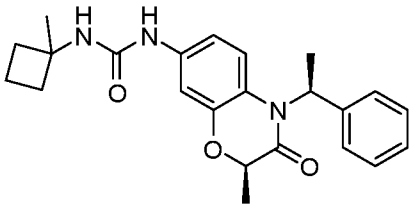
	251	1-(tert-butyl)-3-(2-oxo-1-(1-(1-(3,3,3-trifluoropropyl)-1H-indazol-4-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 8.32 (s, 1H),7.82-7.92 (m, 1H), 7.65-7.76 (m, 1H), 7.46-7.51(m, 2H), 7.21-7.41 (m, 3H), 6.90 (s, 1H), 6.00 (s, 1H), 4.52-4.70 (m, 2H), 2.80-2.94 (m, 2H), 1.98-2.08 (m, 3H), 1.25-1.30 (m, 9H). ^{19}F NMR (376 MHz, DMSO) δ -63.94	calcd. for $C_{25}H_{27}F_3N_6O_2$: 500.21, found: 501.05 $[M+H]^+$
	252	1-(tert-butyl)-3-(2-oxo-1-(1-(quinolin-5-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (dd, J = 4.0, 1.5 Hz, 1H), 8.39 (s, 1H), 8.23 (s, 1H), 8.04 (dd, J = 19.4, 7.9 Hz, 3H), 7.82 – 7.91 (m, 2H), 7.54 (s, 1H), 7.43 (dd, J = 8.7, 4.2 Hz, 1H), 7.34 (s, 1H), 6.97 (s, 1H), 6.02 (s, 1H), 2.04 (d, J = 7.0 Hz, 3H), 1.27 (s, 9H).	calcd. for $C_{24}H_{25}N_5O_2$: 415.20 m/z, found 416.05 $[M+H]^+$
	253	1-(tert-butyl)-3-(2-oxo-1-(1-(4-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (d, J = 5.1 Hz, 1H), 8.44 (s, 1H), 8.20 (s, 1H), 7.94 (d, J = 2.5 Hz, 1H), 7.74 (s, 1H), 7.69 (d, J = 5.2 Hz, 1H), 6.93 – 7.50 (m, 2H), 6.04 (s, 1H), 1.93 (d, J = 7.0 Hz, 3H), 1.30 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -63.0934.	calcd. for $C_{21}H_{22}F_3N_5O_2$: 433.17 m/z, found 434.00 $[M+H]^+$

	254	1-(tert-butyl)-3-(1-(1-(3,6-dichloropyridin-2-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.15 (s, 1H),7.85-8.04(m, 2H), 7.56(*d*, *J* = 8.3 Hz, 1H),7.26-7.50(m, 2H), 6.41(*d*, *J* =7.3 Hz, 1H),6.07(s, 1H), 1.80(*d*, *J* = 6.9 Hz, 3H), 1.30 (s, 9H)	calcd. for $C_{20}H_{21}Cl_2N_5O_2$: 433.11, found: 434.15 $[M+H]^+$

Example 255: 1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclobutyl)urea

Synthetic Scheme





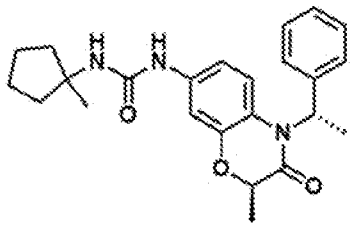
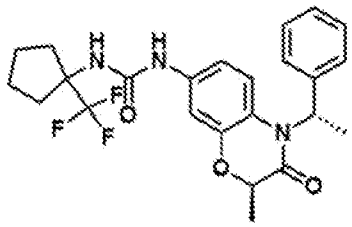
1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclobutyl)urea

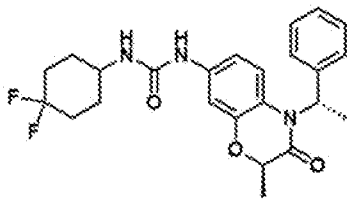
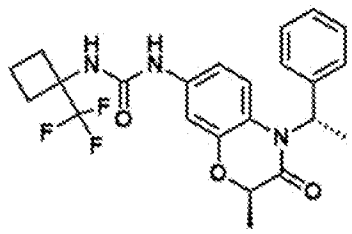
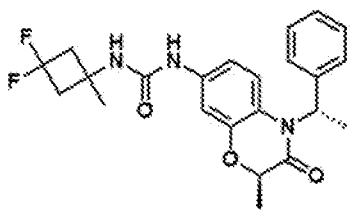
To a stirred mixture of (R)-7-amino-2-methyl-4-((S)-1-phenylethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (100 mg, 0.354 mmol, 1 equiv) in DCM (5 mL) was added triphosgene (42.04 mg, 0.142 mmol, 0.4 equiv) at 0 degrees C under nitrogen atmosphere. After 30 min, the TEA (107.52 mg, 1.062 mmol, 3 equiv) was added at 0 degrees C. After stirring for 30 min at 0 degrees C, the 1-methylcyclobutan-1-amine (60.32 mg, 0.708 mmol, 2 equiv) and TEA (107.52 mg, 1.062 mmol, 3 equiv) was added to the mixture at 0 degrees C. The resulting mixture was stirred for 2h at room temperature. Desired product could be detected by LCMS. The mixture was diluted with water (20 mL). The resulting mixture was extracted with EA (3 x 20 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by

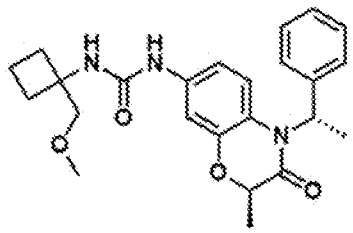
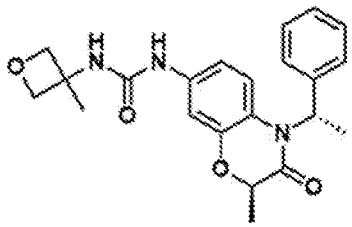
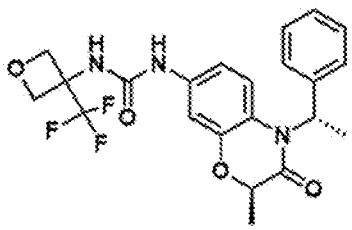
preparative HPLC using a X Bridge Prep OBD C18 150 mm x 30 mm x 5μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10 mmol /L NH_4HCO_3) to afford the 1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclobutyl)urea (63.0 mg, 45.21%) as a white solid. MS (ESI): mass calcd. for $C_{23}H_{27}N_3O_3$: 393.21 m/z, found 394.05[M +H] $^+$.^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.31 – 7.42 (m, 2H), 7.20 – 7.31 (m, 4H), 6.55 – 6.69 (m, 2H), 6.22 (s, 1H), 6.03 – 6.16 (m, 1H), 4.69 – 4.82 (m, 1H), 2.17 – 2.32 (m, 2H), 1.81 – 1.93 (m, 2H), 1.65 – 1.80 (m, 5H), 1.44 (d, J = 6.8 Hz, 3H), 1.36 (s, 3H).

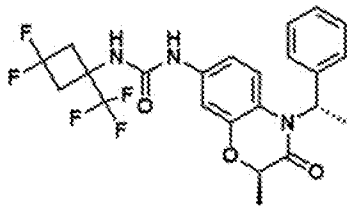
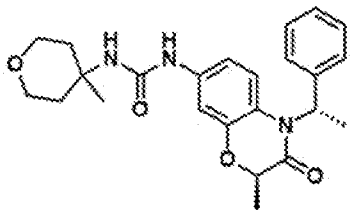
The following examples in Table 16 were made according to the procedure for example 255.

Table 16

Structure	Ex.	IUPAC Name	1H NMR	LCMS
	256	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea	^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.31 – 7.42 (m, 2H), 7.20 – 7.31 (m, 4H), 6.60 (d, J = 2.2 Hz, 2H), 6.06 – 6.16 (m, 1H), 6.01 (s, 1H), 4.68 – 4.82 (m, 1H), 1.81 – 1.92 (m, 2H), 1.75 (d, J = 7.1 Hz, 3H), 1.49 – 1.68 (m, 6H), 1.40 – 1.47 (m, 3H), 1.33 (s, 3H).	calcd. for $C_{24}H_{29}N_3O_3$:407.22 m/z, found:408.10 $[M+H]^+$
	257	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-(trifluoromethyl)cyclopentyl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.30 – 7.50 (m, 2H), 7.15 – 7.30 (m, 4H), 6.50 – 6.74 (m 2H), 6.47 (s, 1H), 5.98 – 6.20 (m, 1H), 4.60 – 4.87 (m, 1H), 2.13 – 2.25 (m, 2H), 1.82 – 1.97 (m, 2H), 1.63 – 1.80 (m, 7H), 1.44 (d, J = 6.8 Hz, 3H). ^{19}F NMR (282 MHz, DMSO) δ(ppm): -75.852.	calcd. for $C_{24}H_{26}F_3N_3O_3$: 461.19 m/z, found 462.15 $[M+H]^+$

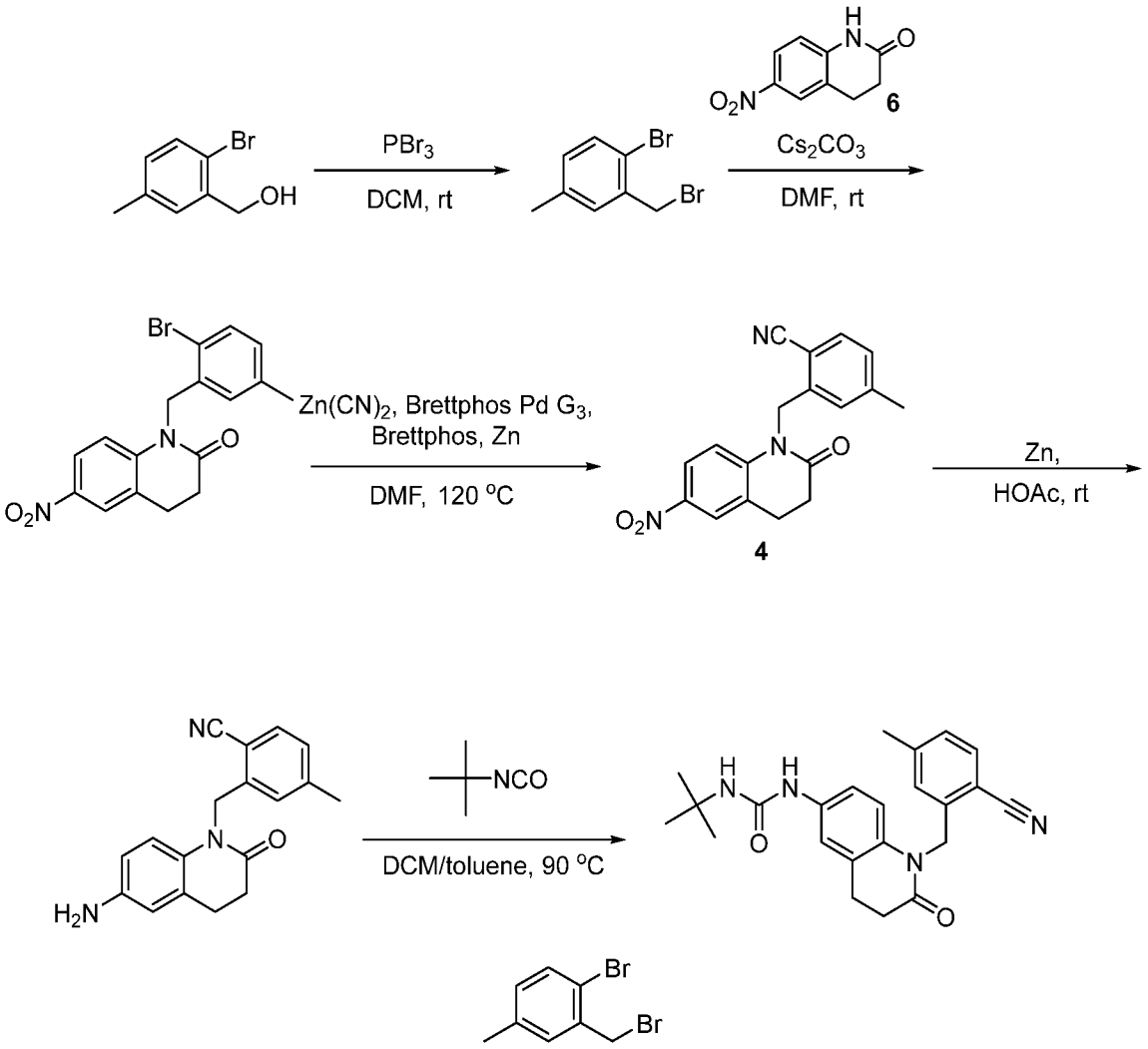
	258	1-(4,4-difluorocyclohexyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 1H), 7.31-7.44 (m,2H), 7.13-7.42 (m, 4H), 6.52-6.80 (m, 2H), 6.18-6.38 (m, 1H), 5.88-6.17(m, 1H), 4.55-4.94 (m, 1H), 3.65 (s, 1H), 1.90-2.05 (m, 4H), 1.80-1.89 (m, 2H), 1.70-1.79 (m, 3H), 1.41-1.51(m, 5H). ^{19}F NMR (376 MHz, DMSO) δ -93.2970, 96.8730.	calcd. for $C_{24}H_{27}F_2N_3O_3$: 443.20, found: 444.05 $[M+H]^+$
	259	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-(trifluoromethyl)cyclobutyl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.42 – 7.31 (m, 2H), 7.30 – 7.19 (m, 4H), 6.88 (s, 1H), 6.78 – 6.58 (m, 2H), 6.10 (q, J = 7.2 Hz, 1H), 4.76 (q, J = 6.6 Hz, 1H), 2.47 – 2.32 (m, 4H), 2.02 – 1.92 (m, 2H), 1.76 (d, J = 7.2 Hz, 3H), 1.44 (d, J = 6.6 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -79.87.	calcd. for $C_{23}H_{24}F_3N_3O_3$: 447.2 m/z, found:448.15 $[M+H]^+$.
	260	1-(3,3-difluoro-1-methylcyclobutyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35 (s, 1H), 6.98 – 7.50 (m, 6H), 6.40 – 6.84 (m, 3H), 6.10 (q, J = 7.1 Hz, 1H), 4.76 (q, J = 6.8 Hz, 1H), 2.88 (q, J = 13.9 Hz, 2H), 2.51 – 2.65 (m, 2H), 1.76 (d, J = 7.1 Hz, 3H), 1.37 – 1.50 (m, 6H). ^{19}F NMR (282 MHz, DMSO) δ(ppm): -85.659, -89.598.	calcd. for $C_{23}H_{25}F_2N_3O_3$: 429.19 m/z, found 430.20 $[M+H]^+$

	261	1-(1-(methoxymethyl)cyclobutyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.36 – 7.33 (m, 2H), 7.28 – 7.23 (m, 4H), 6.62 – 6.60 (m, 2H), 6.18 (s, 1H), 6.10 (q, J = 7.2 Hz, 1H), 4.75 (q, J = 6.9 Hz, 1H), 3.45 (s, 2H), 3.30 (s, 3H), 2.26 – 2.22 (m, 2H), 2.01 – 1.84 (m, 2H), 1.75 (d, J = 7.2 Hz, 3H), 1.43 (d, J = 6.6 Hz, 3H).	calcd. for $C_{24}H_{29}N_3O_4$:423.2 m/z, found:424.15 $[M+H]^+$.
	262	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(3-methyloxetan-3-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.19-7.42 (m, 6H),6.52-6.78 (m, 3H), 6.01-6.18 (m, 1H), 4.70-4.88 (m, 1H), 4.50-4.65(m, 2H), 4.21-4.35 (m, 2H), 1.71-1.80 (m, 3H), 1.50 (s, 3H), 1.38-1.49 (m, 3H)	calcd. for $C_{22}H_{25}N_3O_4$:395.18, found: 396.05 $[M+H]^+$
	263	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(3-(trifluoromethyl)oxetan-3-yl)urea	^{1}H NMR (300 MHz, DMSO-d_6) δ 8.71 (s, 1H), 7.31 – 7.47 (m, 3H), 7.05 – 7.31 (m, 4H), 6.70 – 6.82 (m, 1H), 6.58 – 6.70 (m, 1H), 5.99 – 6.21 (m, 1H), 4.71 – 4.88 (m, 3H), 4.55 – 4.71 (m, 2H), 1.68 – 1.83 (m 3H), 1.39 – 1.51 (m, 3H).	calcd. for $C_{22}H_{22}F_3N_3O_4$, 449.16 m/z, found 450.10 $[M+H]^+$

	264	1-(3,3-difluoro-1-(trifluoromethyl)cyclobutyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	^{1}H NMR (300 MHz, Methanol-d4) δ 7.24 – 7.43 (m, 5H), 7.18 (d, *J* = 2.0 Hz, 1H), 6.64 – 6.77 (m, 2H), 6.25 (q, *J* = 7.2 Hz, 1H), 4.74 (q, *J* = 6.9 Hz, 1H), 3.13 (t, *J* = 11.6 Hz, 4H), 1.83 (d, *J* = 7.1 Hz, 3H), 1.54 (d, *J* = 6.8 Hz, 3H). ^{19}F-NMR (282 MHz, MeOD) δ -80.80, -92.37, -93.07.	calcd. for $C_{23}H_{22}F_5N_3O_3$: 483.16 m/z found: 484.15 $[M+H]^+$.
	265	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(4-methyltetrahydro-2H-pyran-4-yl)urea	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 1H),7.32-7.49 (m, 2H), 7.18-7.31 (m, 4H), 6.50-6.68 (m, 2H), 6.08-6.18 (m, 1H), 5.90-6.07 (m, 1H), 4.64-4.88 (m, 1H), 3.48-3.71(m, 4H), 1.88-1.98 (m, 2H), 1.71-1.81 (m, 3H), 1.42-1.59 (m, 5H), 1.28-1.38 (m, 3H).	calcd. for $C_{24}H_{29}N_3O_4$: 423.22, found: 424.10 $[M+H]^+$

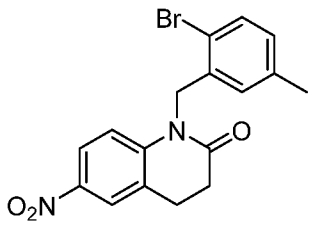
Example 266: 3-tert-butyl-1-{1-[(2-cyano-5-methylphenyl)methyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea.

Synthetic Scheme



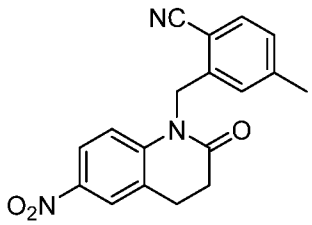
1-bromo-2-(bromomethyl)-4-methylbenzene

To a stirred solution of (2-bromo-5-methylphenyl) methanol (600 mg, 2.984 mmol, 1 equiv) in DCM (6 mL) was added mg, 8.952 mmol, 3 equiv) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS. Quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na2SO4, filtered and concentrated.The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 1-bromo-2-(bromomethyl)-4-methylbenzene (300 mg, 38.09%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_8H_8Br_2$: 263.90 m/z, found: 265.05, 267.05 $[M+H, M+H+2]^+$.



1-[(2-bromo-5-methylphenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one

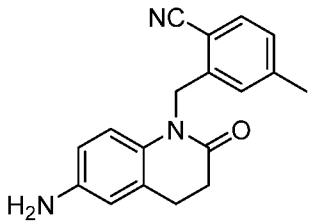
To a stirred solution of 1-bromo-2-(bromomethyl)-4-methylbenzene (280 mg, 1.061 mmol, 1 equiv) in DMF (3 mL) was added 6-nitro-3,4-dihydro-1H-quinolin-2-one (203.85 mg, 1.061 mmol, 1 equiv) and Cs_2CO_3 (691.24 mg, 2.122 mmol, 2 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. Quenched with water (20 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 1-[(2-bromo-5-methylphenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one (100 mg, 25.12%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{17}H_{15}BrN_2O_3$: 374.03 m/z, found 375.00, 377.00 $[M+H, M+H+2]^+$.



4-methyl-2-[(6-nitro-2-oxo-3,4-dihydroquinolin-1-yl)methyl]benzonitrile

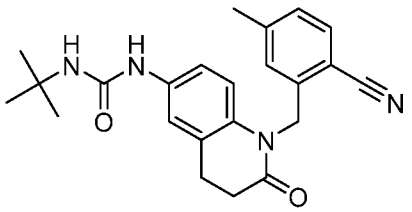
To a stirred solution of 1-[(2-bromo-5-methylphenyl)methyl]-6-nitro-3,4-dihydroquinolin-2-one (150 mg, 0.400 mmol, 1 equiv) and $Zn(CN)_2$ (31.36 mg, 0.480 mmol, 1.2 equiv) in DMF(2 mL) was added BrettPhos Pd G3 (72.48 mg, 0.080 mmol, 0.2 equiv), BrettPhos (42.92 mg, 0.080 mmol, 0.2 equiv) and Zn (3.92 mg, 0.060 mmol, 0.15 equiv) in portions at room temperature under nitrogen atmosphere.The resulting mixture was stirred for 3 h at 120 °C under nitrogen atmosphere.The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated.The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 4-methyl-2-[(6-nitro-2-oxo-3,4-dihydroquinolin-1-yl)methyl]benzonitrile (50

mg, 38.92%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{18}H_{15}N_3O_3$:321.11 m/z, found 322.10 $[M+H]^+$.



2-[(6-amino-2-oxo-3,4-dihydroquinolin-1-yl)methyl]-4-methylbenzonitrile

To a stirred solution of 4-methyl-2-[(6-nitro-2-oxo-3,4-dihydroquinolin-1-yl) methyl] benzonitrile (70 mg, 0.218 mmol, 1 equiv) in HOAc (1 mL) was added Zn (142.42 mg, 2.180 mmol, 10 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 3 h at room temperature under air atmosphere. The reaction was monitored by LCMS. Quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. This resulted in 2-[(6-amino-2-oxo-3,4-dihydroquinolin-1-yl)methyl]-4-methylbenzonitrile (60 mg, 94.53%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{18}H_{17}N_3O$:291.14 m/z, found 292.10 $[M+H]^+$



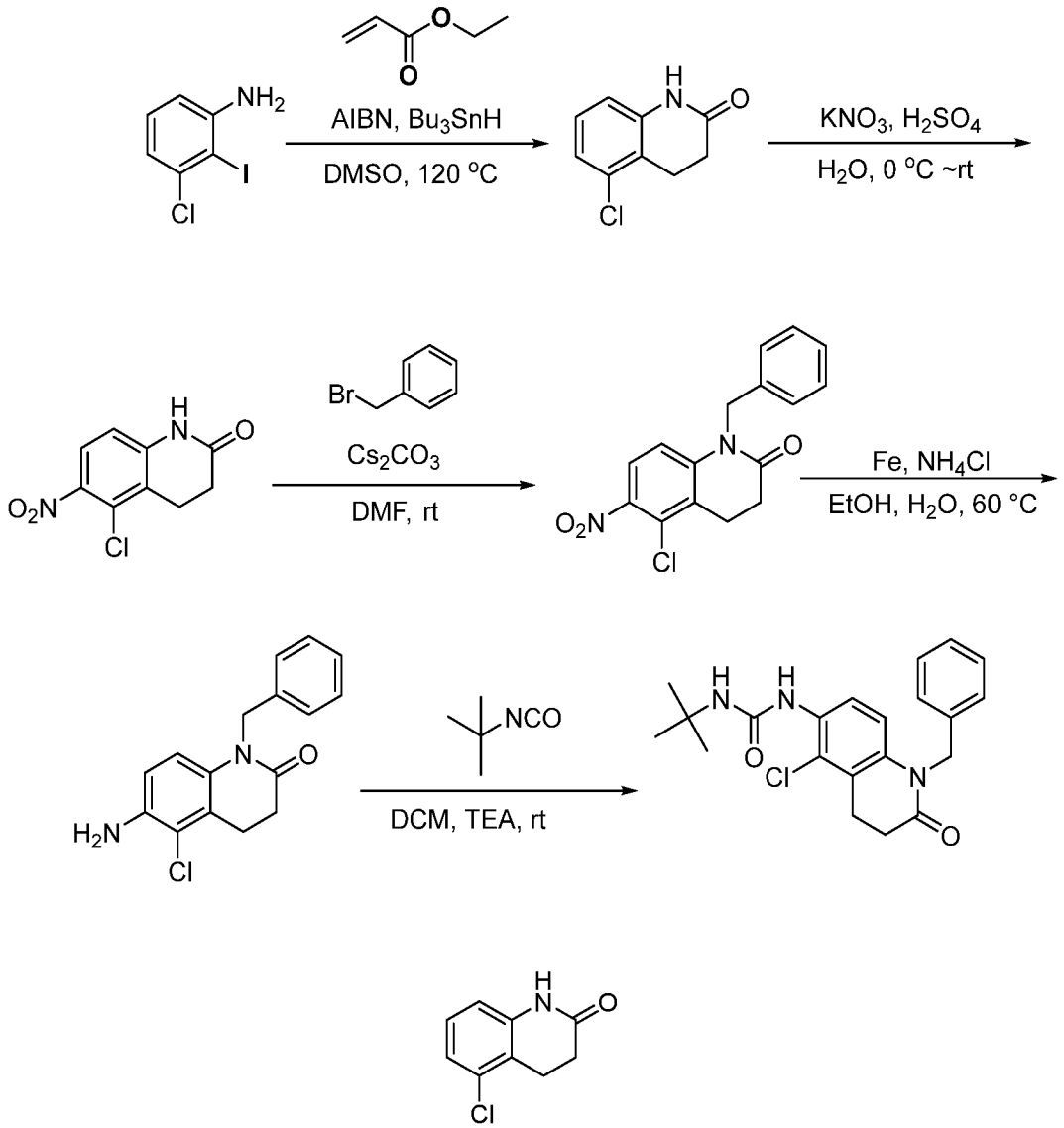
3-tert-butyl-1-{1-[(2-cyano-5-methylphenyl)methyl]-2-oxo-3,4-dihydroquinolin-6-yl}urea

To a stirred solution of 2-[(6-amino-2-oxo-3,4-dihydroquinolin-1-yl)methyl]-4-methylbenzonitrile (50 mg, 0.172 mmol, 1 equiv) in DCM/Toluene(2:1,1 mL) was added 2-isocyanato-2-methylpropane (51.04 mg, 0.516 mmol, 3 equiv) in portions at room temperature. The final reaction mixture was stirred overnight at 90 °C. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by Prep-HPLC using a X Bridge Prep OBD C18 150 mm x 30 mm x 5 μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford 3-tert-butyl-1-{1-[(2-cyano-5-methylphenyl)methyl]-

2-oxo-3,4-dihydroquinolin-6-yl}urea (6.7 mg, 9.68%) as a white solid. LC/MS (ESI): mass calcd. for $C_{23}H_{26}N_4O_2$:390.20 m/z, found 391.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.34 (s, 1H), 7.26 (d, J = 8.1 Hz, 1H), 7.00 (d, J = 11.4 Hz, 2H), 6.66 (d, J = 9.0 Hz, 1H), 5.93 (s, 1H), 5.19 (s, 2H), 2.95 – 2.90 (m, 2H), 2.73 – 2.65 (m, 2H), 2.31 (s, 3H), 1.26 (s, 9H).

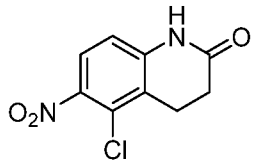
Example 267: 1-(1-benzyl-5-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

Synthetic Scheme



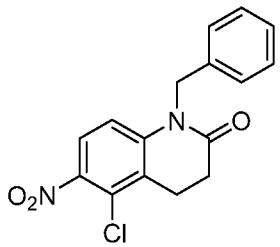
5-chloro-3,4-dihydroquinolin-2(1H)-one

To a solution of 3-chloro-2-iodoaniline (1.5 g, 5.918 mmol, 1 equiv), AIBN (388.71 mg, 2.367 mmol, 0.4 equiv) and tributyltin (2583.73 mg, 8.877 mmol, 1.5 equiv) in DMSO (10 mL) was added ethyl acrylate (2369.91 mg, 23.672 mmol, 4 equiv). The reaction was stirred at 120 °C under N_2 for 3 h. After cooling down to rt, the reaction was quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 5-chloro-3,4-dihydro-1H-quinolin-2-one (348 mg, 32.38%) as a white solid. LC/MS: mass calcd. for C_9H_8ClNO: 181.03, found: 182.05 $[M+H]^+$.



5-chloro-6-nitro-3,4-dihydroquinolin-2(1H)-one

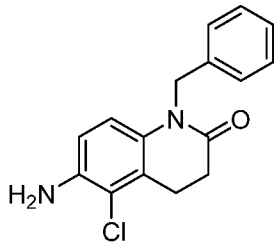
To a solution of 5-chloro-3,4-dihydro-1H-quinolin-2-one (376 mg, 2.070 mmol, 1 equiv) in sulfuric acid (4 mL) was added KNO_3 (167.84 mg, 1.660 mmol, 0.80 equiv). The reaction was stirred at rt for 1 h. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 5-chloro-6-nitro-3,4-dihydro-1H-quinolin-2-one (96 mg, 20.46%) as a white solid. LC/MS: mass calcd. for $C_9H_7ClN_2O_3$: 226.01, found: 226.85 $[M+H]^+$.



benzyl-5-chloro-6-nitro-3,4-dihydroquinolin-2(1H)-one

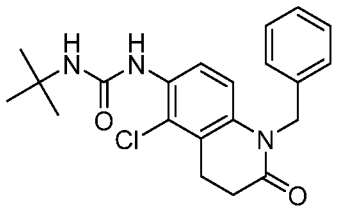
To a solution of 5-chloro-6-nitro-3,4-dihydro-1H-quinolin-2-one (151 mg, 0.666 mmol, 1 equiv) in dimethylformamide (3 mL) was added Cs_2CO_3 (653.31 mg, 1.998 mmol, 3 equiv) and (bromomethyl)benzene (653.31 mg, 1.998 mmol, 3 equiv). The reaction was stirred at rt for 1 h. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-benzyl-5-chloro-6-

nitro-3,4-dihydroquinolin-2-one (199 mg, 94.29%) as a white solid. LC/MS (ESI): mass calcd. for $C_{16}H_{13}ClN_2O_3$: 316.06 m/z, found:317.05 $[M+H]^+$.



6-amino-1-benzyl-5-chloro-3,4-dihydroquinolin-2(1H)-one

To a solution of 1-benzyl-5-chloro-6-nitro-3,4-dihydroquinolin-2-one (100 mg, 0.316 mmol, 1 equiv) in ethyl alcohol (3 mL) was added iron (177 mg, 3.169 mmol, 10.04 equiv), NH_4Cl (167 mg, 3.122 mmol, 9.89 equiv) and water (0.3 mL). The reaction was stirred at 60 °C for 3 h. After cooling down to rt, the reaction was quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-1-benzyl-5-chloro-3,4-dihydroquinolin-2-one (74.5 mg, 82.29%) as a white solid. LC/MS (ESI): mass calcd. for $C_{16}H_{15}ClN_2O$: 286.09 m/z, found:287.05 $[M+H]^+$.



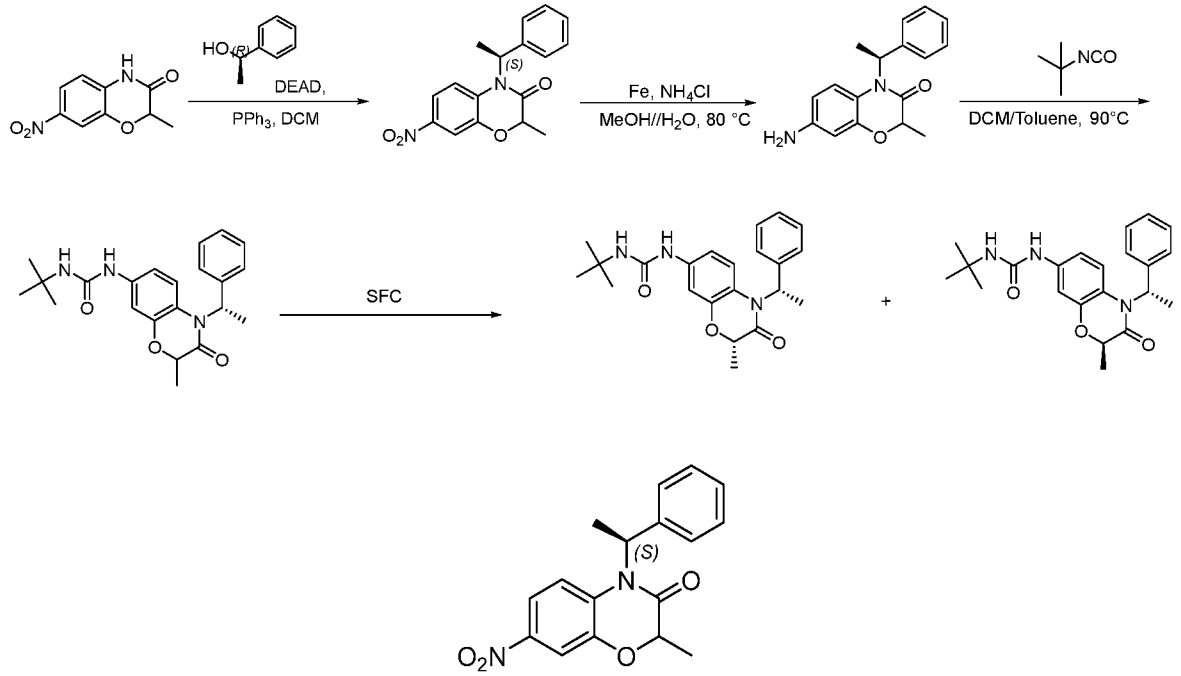
1-(1-benzyl-5-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

To a solution of 6-amino-1-benzyl-5-chloro-3,4-dihydroquinolin-2-one (70 mg, 0.244 mmol, 1 equiv) and 2-isocyanato-2-methylpropane (48.29 mg, 0.487 mmol, 2.00 equiv) in DCM (1 mL) was added TEA (73.93 mg, 0.731 mmol, 2.99 equiv). The reaction was stirred at rt for 3 h. Quenched with water (3 mL) and extracted with DCM (3 x 3 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column,50 mm x 30 mm x 5 μm (eluent: 36% to 56% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford the title compound 1-(1-benzyl-5-chloro-2-oxo-3,4-dihydroquinolin-6-yl)-3-tert-butylurea (23.4 mg, 24.79%) as a white solid. LC/MS (ESI): mass calcd. for $C_{21}H_{24}ClN_3O_2$:385.16 m/z, found:386.00 $[M+H]^+$. ^1H

NMR (400 MHz, DMSO-d_6) δ 7.78-7.85 (m, 2H), 7.26-7.34 (m, 2H), 7.18-7.26 (m, 3H), 6.87-6.91 (m, 2H), 5.13 (s, 2H), 3.04-3.05 (m, 2H), 2.68-2.71 (m, 2H), 1.26 (s, 9H).

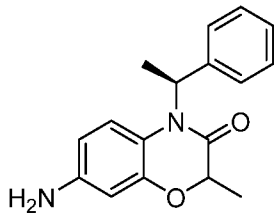
Example 268 and Example 269: 1-(tert-butyl)-3-((S)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea and 1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

Synthetic Scheme



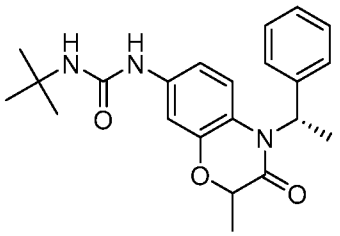
2-methyl-7-nitro-4-((S)-1-phenylethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of 2-methyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (350 mg, 1.681 mmol, 1 equiv) in DCM (10 mL) was added (R)-1-phenylethan-1-ol (205.40 mg, 1.681 mmol, 1 equiv) and PPh_3 (661.48 mg, 2.522 mmol, 1.5 equiv). The reaction was stirred at rt under N_2 for 0.5 h. To the above mixture was added DEAD (439.21 mg, 2.522 mmol, 1.5 equiv) dropwise at 0°C. The resulting mixture was stirred for additional 1 hour at rt. Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 2-methyl-7-nitro-4-[(1S)-1-phenylethyl]-2H-1,4-benzoxazin-3-one (270 mg, 51.42%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{16}N_2O_4$: 312.11 m/z, found 313.15 $[M+H]^+$.



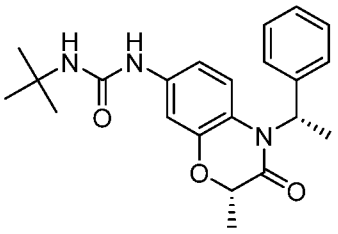
7-amino-2-methyl-4-((S)-1-phenylethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

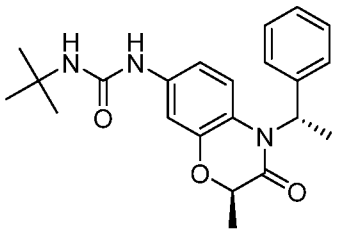
To a solution of 2-methyl-7-nitro-4-[(1S)-1-phenylethyl]-2H-1,4-benzoxazin-3-one (270 mg, 0.864 mmol, 1 equiv) in MeOH/H_2O (10:1 ,11 mL) was added Fe (482.77 mg, 8.640 mmol, 10 equiv) and NH_4Cl (462.41 mg, 8.640 mmol, 10 equiv). The reaction was stirred at 80℃ for 1 hour. The resulting mixture was filtered, and the filter cake was washed with EA (3 x 30 mL). The filtrate was concentrated under reduced pressure. The mixture was diluted with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. This resulted in 7-amino-2-methyl-4-[(1S)-1-phenylethyl]-2H-1,4-benzoxazin-3-one (200 mg, 81.96%) as a yellow oil. MS (ESI): mass calcd. for $C_{17}H_{18}N_2O_2$: 282.14 m/z, found 283.00 $[M+H]^+$.



1-(tert-butyl)-3-(2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a solution of 7-amino-2-methyl-4-[(1S)-1-phenylethyl]-2H-1,4-benzoxazin-3-one (130 mg, 0.460 mmol, 1 equiv) in DCM/Toluene (2:1, 15 mL) was added 2-isocyanato-2-methylpropane (273.86 mg, 2.760 mmol, 6 equiv). The reaction was stirred at 90℃ for 2 hours. After cooling to rt, the reaction was quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Shield RP18 OBD Column, 30*150 mm, 5μm column (eluent: 43% to 65% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-{2-methyl-3-oxo-4-[(1S)-1-phenylethyl]-2H-1,4-benzoxazin-7-yl}urea (40 mg, 22.77%) as a white solid.MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_3$: 381.21 m/z, found:382.20 $[M+H]^+$.



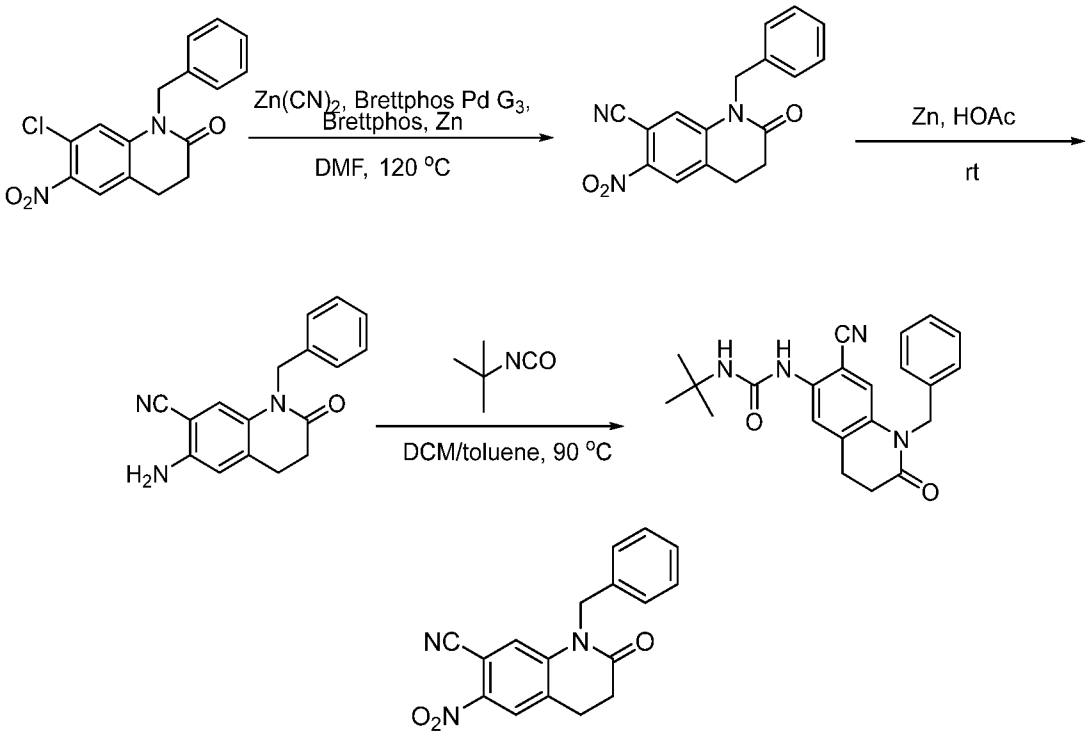


1-(tert-butyl)-3-((S)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea and 1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

A sample of 3-tert-butyl-1-{2-methyl-3-oxo-4-[(1S)-1-phenylethyl]-2H-1,4-benzoxazin-7-yl}urea (40 mg) was separated by chiral-HPLC using a CHIRALPAK IE, 2*25 cm, 5 μm column (eluent: 10% to 10% (v/v) Hex(0.5% 2M NH_3-MeOH) and EtOH) to yield first enantiomer example 3-tert-butyl-1-[(2S)-2-methyl-3-oxo-4-[(1S)-1-phenylethyl]-2H-1,4-benzoxazin-7-yl]urea (17.6 mg, 44.00%) as a white solid. MS(ESI): mass calcd. for $C_{22}H_{27}N_3O_3$: 381.21 m/z, found: 382.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.11 – 8.29 (m, 1H), 7.25 – 7.45 (m, 6H), 6.55 – 6.68 (m, 1H), 6.35 – 6.55 (m, 1H), 6.11 – 6.26 (m, 1H), 5.85 – 6.03 (m, 1H), 4.63 – 4.79 (m, 1H), 1.64 – 1.71 (m, 3H), 1.43 – 1.59 (m, 3H), 1.25 – 1.26 (m, 9H).and to yield second enantiomer example 3-tert-butyl-1-[(2R)-2-methyl-3-oxo-4-[(1S)-1-phenylethyl]-2H-1,4-benzoxazin-7-yl]urea (17 mg, 42.50%) as a white solid. MS(ESI): mass calcd. for $C_{22}H_{27}N_3O_3$: 381.21 m/z, found: 382.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.84 – 8.20 (m, 1H), 7.32 – 7.46 (m, 2H), 7.10 – 7.32 (m, 4H), 6.49 – 6.65 (m, 2H), 6.02 – 6.18 (m, 1H), 5.76 – 5.97 (m, 1H), 4.63 – 4.79 (m, 1H), 1.73 – 1.81 (m, 3H), 1.40 – 1.55 (m, 3H), 1.26 – 1.29 (m, 9H).

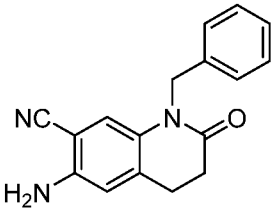
Example 270: 1-(1-benzyl-7-cyano-2-oxo-3,4-dihydroquinolin-6-yl)-3-tert-butylurea.

Synthetic Scheme



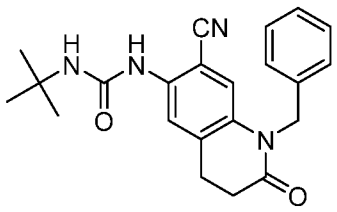
1-benzyl-6-nitro-2-oxo-3,4-dihydroquinoline-7-carbonitrile

To a stirred solution of 1-benzyl-7-chloro-6-nitro-3,4-dihydroquinolin-2-one (500 mg, 1.579 mmol, 1 equiv) in DMF (5 mL) was added $Zn(CN)_2$ (222.43 mg, 1.895 mmol, 1.2 equiv), BrettPhos Pd G_3 (286.20 mg, 0.316 mmol, 0.2 equiv), BrettPhos (169.47 mg, 0.316 mmol, 0.2 equiv) and Zn (15.48 mg, 0.237 mmol, 0.15 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 120 °C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. Quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 1-benzyl-6-nitro-2-oxo-3,4-dihydroquinoline-7-carbonitrile (200 mg, 41.23%) as a white solid. LC/MS (ESI): mass calcd. for $C_{17}H_{13}N_3O_3$: 307.10 m/z, found 308.05 $[M+H]^+$.



6-amino-1-benzyl-2-oxo-3,4-dihydroquinoline-7-carbonitrile

To a stirred solution of 1-benzyl-6-nitro-2-oxo-3,4-dihydroquinoline-7-carbonitrile (200 mg, 0.651 mmol, 1 equiv) in AcOH (2 mL) was added Zn (425.50 mg, 6.510 mmol, 10 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 3 h at room temperature under air atmosphere. The reaction was monitored by LCMS. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 6-amino-1-benzyl-2-oxo-3,4-dihydroquinoline-7-carbonitrile (80 mg, 44.44%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{17}H_{15}N_3O$: 277.12 m/z, found 278.05 $[M+H]^+$.

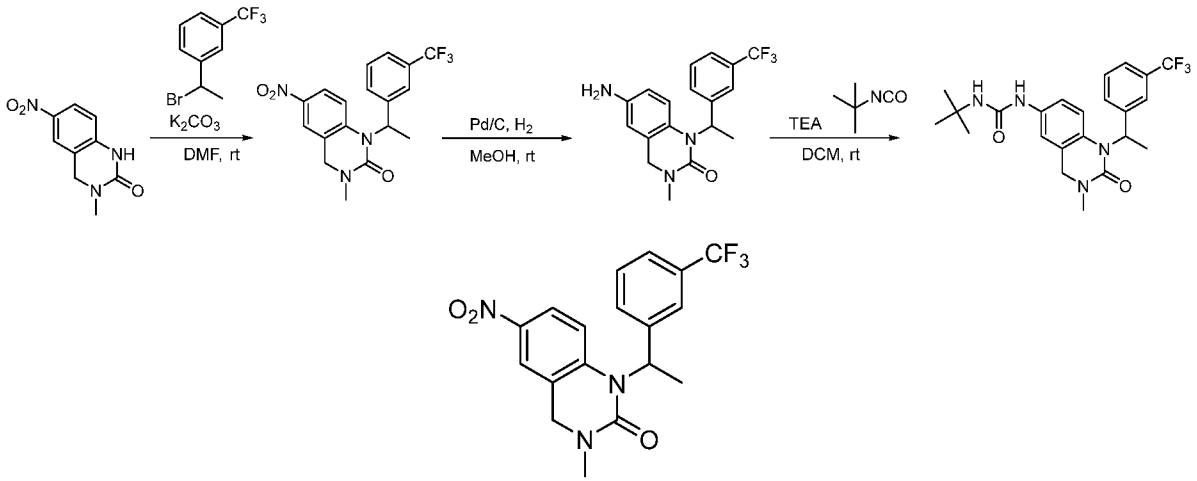


1-(1-benzyl-7-cyano-2-oxo-3,4-dihydroquinolin-6-yl)-3-tert-butylurea

To a stirred solution of 6-amino-1-benzyl-2-oxo-3,4-dihydroquinoline-7-carbonitrile (70 mg, 0.252 mmol, 1 equiv) in DCM/Toluene (2:1,1 mL) was added 2-isocyanato-2-methylpropane (75.07 mg, 0.756 mmol, 3 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 90 °C under air atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by Prep-HPLC using a X Bridge Prep OBD C18 150 mm x 30 mm x 5 μm column (eluent: 26% to 45% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford 1-(1-benzyl-7-cyano-2-oxo-3,4-dihydroquinolin-6-yl)-3-tert-butylurea (3.9 mg, 4.01%) as a white solid. LC/MS (ESI): mass calcd. for $C_{22}H_{24}N_4O_2$: 376.19 m/z, found 377.15 $[M+H]^+$. ^1H NMR (300 MHz, Methanol-d_4) δ 7.82 (s, 1H), 7.35 – 7.31 (m, 2H), 7.24 (t, J = 7.1 Hz, 3H), 7.11 (s, 1H), 5.20 (s, 2H), 3.08 – 3.01 (m, 2H), 2.80 – 2.75 (m, 2H), 1.35 (s, 9H).

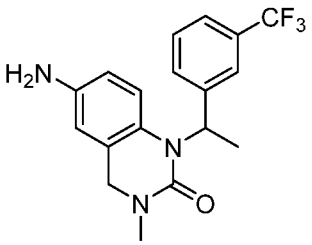
Example 271: 1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea

Synthetic Scheme



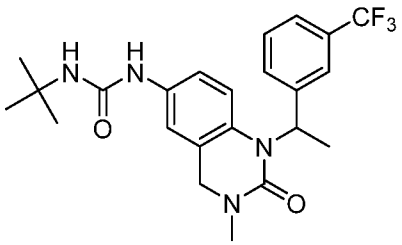
3-methyl-6-nitro-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydroquinazolin-2(1H)-one

To a solution of 3-methyl-6-nitro-1,4-dihydroquinazolin-2-one (200 mg, 0.966 mmol, 1 equiv) in DMF (5mL) was added K_2CO_3 (0.40 g, 2.890 mmol, 3 equiv) and 1-(1-bromoethyl)-3-(trifluoromethyl)benzene (269 mg, 1.06 mmol, 1.1 equiv). The resulting mixture was placed at rt and stirred overnight. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by silica gel column to afford 3-methyl-6-nitro-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydroquinazolin-2(1H)-one (100 mg, 27.31%) as a yellow solid.



6-amino-3-methyl-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydroquinazolin-2(1H)-one

To a solution of 3-methyl-6-nitro-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydroquinazolin-2(1H)-one (100 mg, 0.264 mmol, 1 equiv) in MeOH (10 mL) was added Pd/C (28.0 mg, 10%, 0.026 mmol, 0.1 equiv). The resulting mixture was placed at rt under a hydrogen atmosphere until the starting material was totally consumed by LCMS. The mixture was filtered and concentrated under vacuum to afford 6-amino-3-methyl-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydroquinazolin-2(1H)-one (60 mg, 65.15%) as a yellow solid. MS (ESI): mass calcd. for $C_{18}H_{18}F_3N_3O$, 349.14 m/z, found 350.10 $[M+H]^+$.

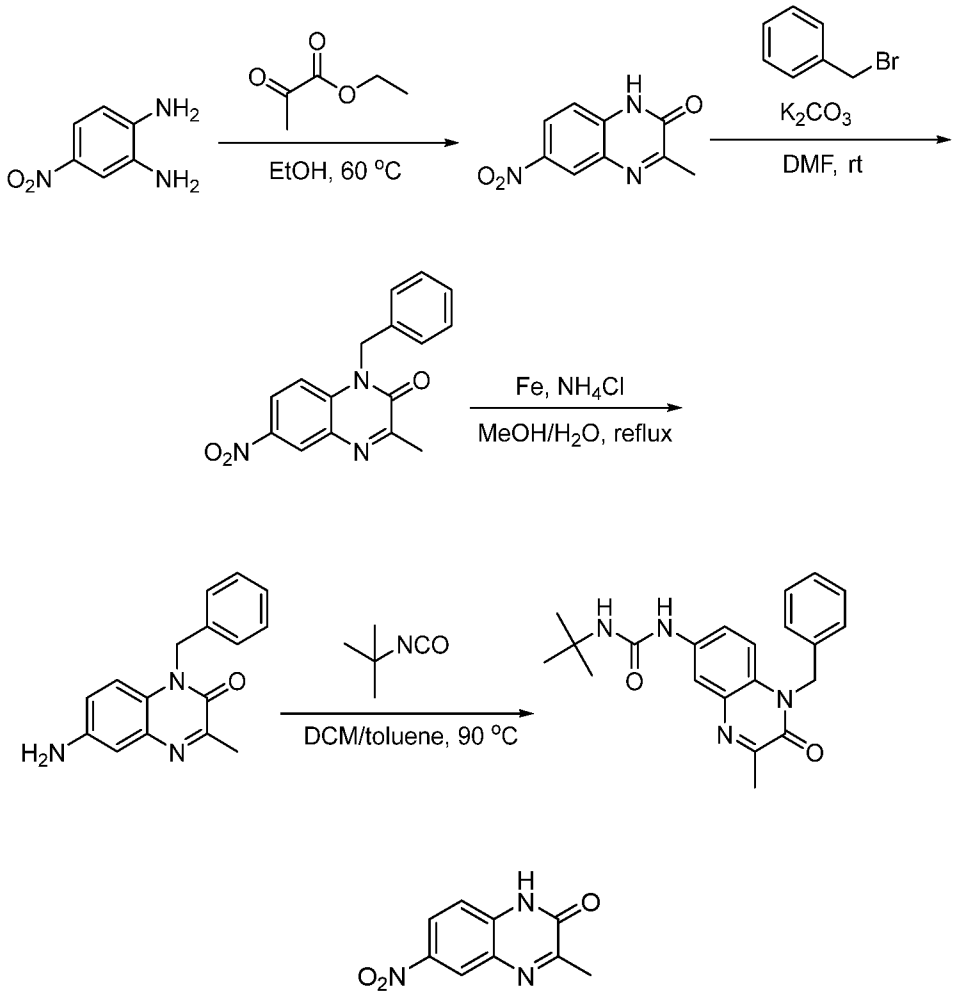


1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea

To a stirred solution of 6-amino-3-methyl-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydroquinazolin-2(1H)-one (100 mg, 0.286 mmol, 1 equiv) in DCM (10 mL) was added 2-isocyanato-2-methylpropane (142 mg, 1.431 mmol, 5 equiv) and TEA (87 mg, 0.859 mmol, 3 equiv) stirred overnight at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 100 mg crude product as a white solid.The compound was separated by preparative HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 73% B in 9 min, 73% B; Wave Length: 254/220 nm; RT1(min): 9.6; Number Of Runs: 0) to afford 1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea (12.6 mg, 9.78%) as a white solid. MS (ESI): mass calcd. for $C_{23}H_{27}F_3N_4O_2$, 448.21 m/z, found 449.05 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.58 (s, 4H), 7.30 (s, 1H), 6.88 (d, J = 8.7 Hz, 1H), 6.40 (d, J = 8.8 Hz, 1H), 5.83 – 5.96 (m, 2H), 4.32 (s, 2H), 2.91 (s, 3H), 1.78 (d, J = 7.0 Hz, 3H), 1.26 (s, 9H).

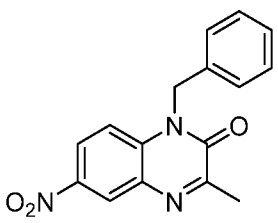
Example 272: 1-(1-benzyl-3-methyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea

Synthetic Scheme



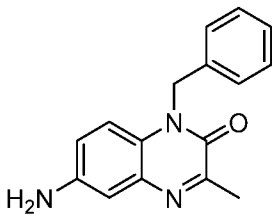
3-methyl-6-nitroquinoxalin-2(1H)-one

To a solution of 2-amino-4-nitroaniline (2 g, 13.060 mmol, 1 equiv) in ethyl alcohol (20 mL) was added ethyl pyruvate (1.82 g, 15.674 mmol, 1.20 equiv). The reaction was stirred at rt for 3 h. Quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 3-methyl-6-nitro-1H-quinoxalin-2-one (1.78 g, 66.43%) as a yellow solid. MS (ESI): mass calcd. for $C_9H_7N_3O_3$: 205.05m/z, found 206.05 $[M+H]^+$



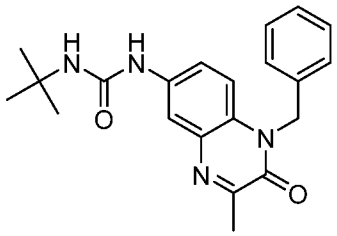
benzyl-3-methyl-6-nitroquinoxalin-2(1H)-one

To a solution of 3-methyl-6-nitro-1H-quinoxalin-2-one (400 mg, 1.950 mmol, 1 equiv) and benzyl bromide (500.17 mg, 2.925 mmol, 1.5 equiv) in dimethylformamide (5 mL) was added K_2CO_3 (814.22 mg, 5.850 mmol, 3 equiv). The reaction was stirred at rt for 3 h. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-benzyl-3-methyl-6-nitroquinoxalin-2-one (212 mg, 36.82%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{13}N_3O_3$: 295.10 m/z, found 296.10 $[M+H]^+$



6-amino-1-benzyl-3-methylquinoxalin-2(1H)-one

To a solution of 1-benzyl-3-methyl-6-nitroquinoxalin-2-one (129 mg, 0.437 mmol, 1 equiv) in water (0.2 mL) and methanol (2 mL) was added iron (243.96 mg, 4.370 mmol, 10 equiv) and NH_4Cl (233.67 mg, 4.370 mmol, 10 equiv). The reaction was stirred at 60 °C for 3 h. After cooling down to rt, the reaction was quenched with water (5 mL) and extracted with EA (3 x 5 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-1-benzyl-3-methylquinoxalin-2-one (54.6 mg, 47.11%) as a white solid. LC/MS (ESI): mass calcd. for $C_{16}H_{15}N_3O$: 265.12 m/z, found:266.15 $[M+H]^+$.



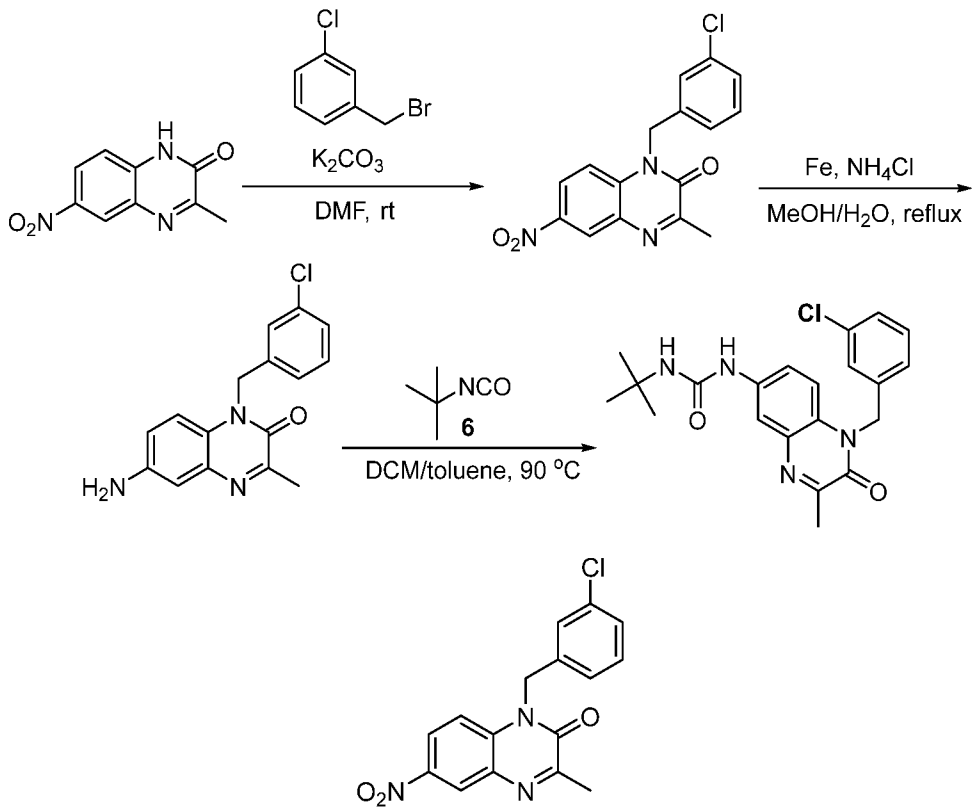
1-(1-benzyl-3-methyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea

To a solution of 6-amino-1-benzyl-3-methylquinoxalin-2-one (55 mg, 0.207 mmol, 1 equiv) in DCM (1 mL)/toluene (0.5 mL) was added 2-isocyanato-2-methylpropane (61.65 mg, 0.621 mmol, 3 equiv). The reaction was stirred at 90 °C for 3 h. After cooling down to rt, the reaction

was quenched with water (5 mL) and extracted with DCM (3 x 5 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column (eluent: 26% to 42% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford the title compound 1-(1-benzyl-3-methyl-2-oxoquinoxalin-6-yl)-3-tert-butylurea (15.3 mg, 20.22%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{21}H_{24}N_4O_2$:364.19 m/z, found:365.05 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 7.84 (s, 1H), 7.23-7.40 (m, 7H), 6.01 (s, 1H), 5.45 (s, 2H), 2.49 (s, 3H), 1.29 (s, 9H).

Example 273: 3-tert-butyl-1-{1-[(3-chlorophenyl)methyl]-3-methyl-2-oxoquinoxalin-6-yl}urea.

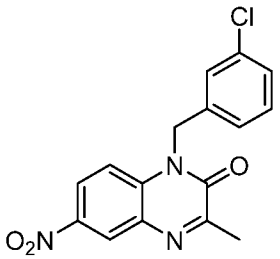
Synthetic Scheme



1-[(3-chlorophenyl) methyl]-3-methyl-6-nitroquinoxalin-2-one

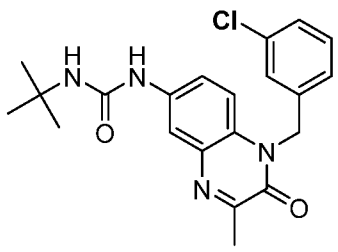
To a stirred solution of 3-methyl-6-nitro-1H-quinoxalin-2-one (400 mg, 1.950 mmol, 1 equiv) and 1-(bromomethyl)-3-chlorobenzene (600.90 mg, 2.925 mmol, 1.5 equiv) in DMF (5 mL) was

added K_2CO_3 (542.81 mg, 3.900 mmol, 2 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere. Quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 1-[(3-chlorophenyl) methyl]-3-methyl-6-nitroquinoxalin-2-one (300 mg, 46.67%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{16}H_{12}ClN_3O_3$: 329.06 m/z, found 330.00 $[M+H]^+$.



6-amino-1-[(3-chlorophenyl) methyl]-3-methylquinoxalin-2-one

To a stirred solution of 1-[(3-chlorophenyl) methyl]-3-methyl-6-nitroquinoxalin-2-one (300 mg, 0.910 mmol, 1 equiv) in MeOH / H_2O (10:1, 4 mL) were added NH_4Cl (486.66 mg, 9.100 mmol, 10 equiv) and Fe (508.08 mg, 9.100 mmol, 10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 60 °C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 6-amino-1-[(3-chlorophenyl) methyl]-3-methylquinoxalin-2-one (240 mg, 88.00%) as a white solid. LC/MS (ESI): mass calcd. for $C_{16}H_{14}ClN_3O$: 299.08 m/z, found 300.00 $[M+H]^+$.

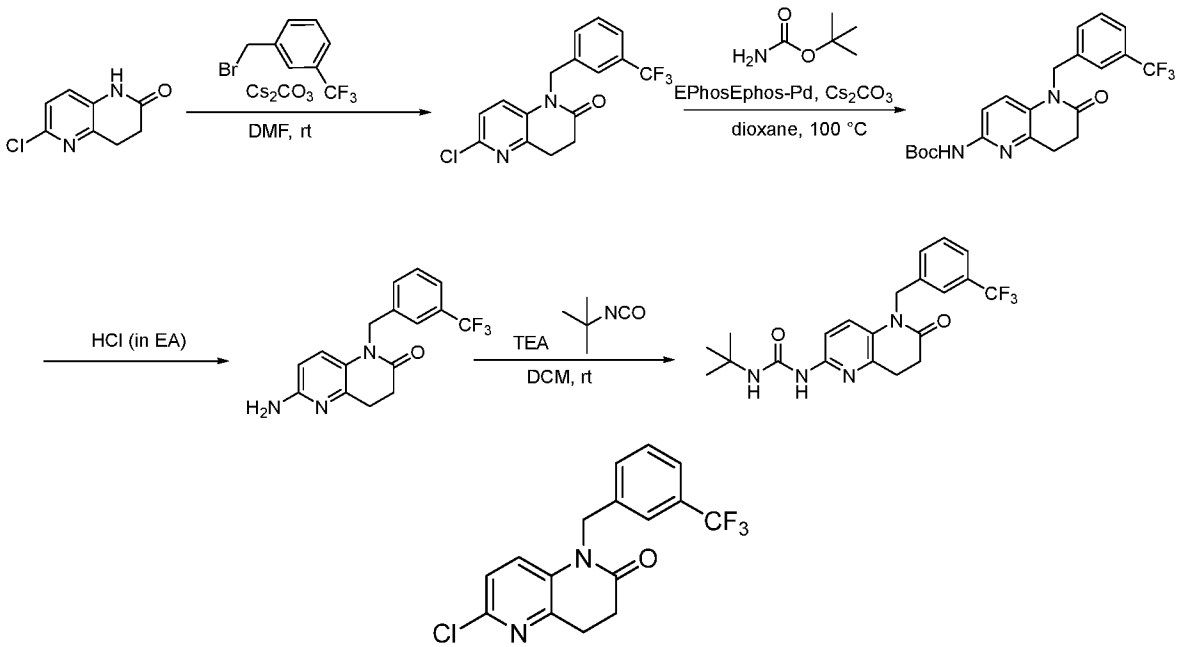


3-tert-butyl-1-{1-[(3-chlorophenyl) methyl]-3-methyl-2-oxoquinoxalin-6-yl} urea

To a stirred solution of 6-amino-1-[(3-chlorophenyl) methyl]-3-methylquinoxalin-2-one (100 mg, 0.334 mmol, 1 equiv) in DCM/Toluene (2:1,1 mL) was added 2-isocyanato-2-methylpropane (99.21 mg, 1.002 mmol, 3 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 90 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by Prep-HPLC using a Xselect CSH OBD C18 150 mm x 30 mm x 5 μm column (eluent: 37% to 62% (v/v) CH_3CN and H_2O with 0.1%FA) to afford 3-tert-butyl-1-{1-[(3-chlorophenyl) methyl]-3-methyl-2-oxoquinoxalin-6-yl}urea (22.4 mg, 16.17%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{21}H_{23}ClN_4O_2$: 398.2 m/z, found 399.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.40 (s, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.38 – 7.28 (m, 6H), 6.02 (s, 1H), 5.45 (s, 2H), 2.49 (s, 3H) 1.30 (s, 9H).

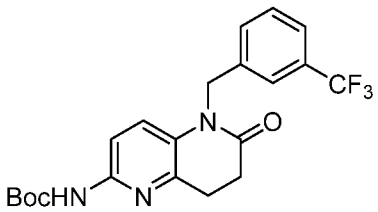
Example 274: 1-(tert-butyl)-3-(6-oxo-5-(3-(trifluoromethyl)benzyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea

Synthetic Scheme



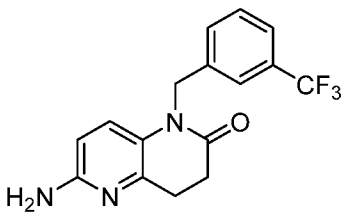
6-chloro-1-(3-(trifluoromethyl)benzyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one

To a stirred solution of 6-chloro-3,4-dihydro-1H-1,5-naphthyridin-2-one (300 mg, 1.643 mmol, 1 equiv) in anhydrous dimethylformamide (5 mL) was added 1-(bromomethyl)-3-(trifluoromethyl)benzene (432 mg, 1.807 mmol, 1.1 equiv) and Cs_2CO_3 (1.6 g, 4.929 mmol, 3 equiv) at rt and stirred for 2 h. After completion of reaction, the reaction mixture was quenched by water (20 mL) and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography with PE/EA (3:1) to afford 6-chloro-1-(3-(trifluoromethyl)benzyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (390 mg, 69.67%) as a light-yellow solid.



tert-butyl (6-oxo-5-(3-(trifluoromethyl)benzyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)carbamate

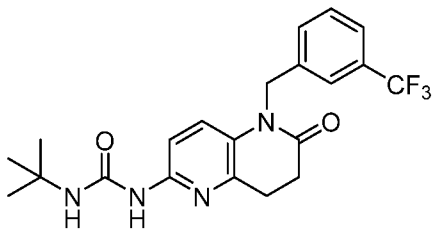
A solution of 6-chloro-1-(3-(trifluoromethyl)benzyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (390 mg, 1.145 mmol, 1 equiv) in 1,4-dioxane (5 mL) was treated with tert-butyl carbamate (269 mg, 2.290 mmol, 2 equiv), Cs_2CO_3 (1.11 g, 3.435 mmol, 3 equiv), EPHOS (61 mg, 0.115 mmol, 0.1 equiv) and EPhos Pd G4 (105 mg, 0.115 mmol, 0.1 equiv) for overnight at 100 °C under nitrogen atmosphere. The reaction mixture was quenched by water (20 mL) and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography with PE/EA (3:1) to afford tert-butyl (6-oxo-5-(3-(trifluoromethyl)benzyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)carbamate (0.5 g, 96.01%) .



6-amino-1-(3-(trifluoromethyl)benzyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one

To a stirred solution of tert-butyl (6-oxo-5-(3-(trifluoromethyl)benzyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)carbamate (350 mg, 0.831 mmol, 1 equiv) in HCl (4N in EA, 10 mL) at rt. The

reaction was stirred for 2 h at rt. The resulting mixture was concentrated under reduced pressure to afford 6-amino-1-(3-(trifluoromethyl)benzyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (300 mg, 112.42%) as a white solid.

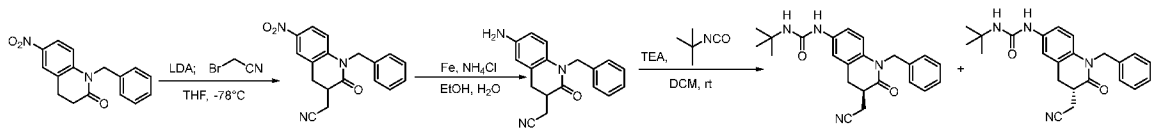


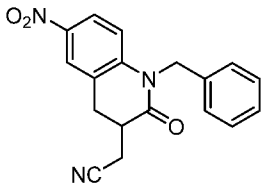
1-(tert-butyl)-3-(6-oxo-5-(3-(trifluoromethyl)benzyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea

A solution of 6-amino-1-(3-(trifluoromethyl)benzyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (50 mg, 0.156 mmol, 1 equiv), TEA (79 mg, 0.780 mmol, 5 equiv) and 2-isocyanato-2-methylpropane (77 mg, 0.780 mmol, 5 equiv) in DCM (5 mL) was stirred for overnight at rt. The mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA (46%-57%) to afford crude products. The residue was purified by reversed-phase flash chromatography with the following conditions Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% B to 65% B in 9 min, 65% B; Wave Length: 254/220 nm; RT1(min): 8.0; Number Of Runs: 0 to afford 3-tert-butyl-1-(6-oxo-5-{[3-(trifluoromethyl)phenyl]methyl}-7,8-dihydro-1,5-naphthyridin-2-yl)urea (19.6 mg, 29.91%) as a white solid. MS (ESI):mass calcd. for $C_{21}H_{23}F_3N_4O_2$: 420.18 m/z, found 421.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.89 (s, 1H), 7.91 (s, 1H), 7.66 – 7.58 (m, 2H), 7.54 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.32 (d, J = 8.9 Hz, 1H), 7.13 (d, J = 8.9 Hz, 1H), 5.18 (s, 2H), 2.96 – 3.04 (m, 2H), 2.81 (dd, J = 8.8, 6.2 Hz, 2H), 1.30 (s, 9H).

Example 275: (R)-1-(1-benzyl-3-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

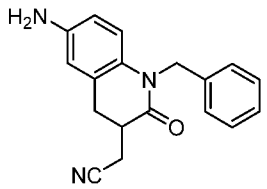
Synthetic Scheme





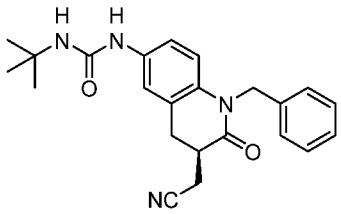
2-(1-benzyl-6-nitro-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)acetonitrile

3-In a 100-mL round bottom flask, to a solution of 1-benzyl-6-nitro-3,4-dihydroquinolin-2-one (300 mg, 1.063 mmol, 1 equiv) in tetrahydrofuran (5 mL) was added dropwise LDA (2M, in THF, 0.63 mL, 1.276 mmol, 1.2 equiv) at -78 °C under N_2 atmosphere. The reaction mixture was stirred at -78 °C for 20 mins. Then a solution of 2-bromoacetonitrile (153 mg, 1.276 mmol, 1.2 equiv) in 3 mL THF was added dropwise and the mixture was stirred for another 30 mins. The reaction was quenched with NH_4Cl (aq., 10 mL), and then the mixture were extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EA (3/1) to afford 2-(1-benzyl 6-nitro-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)acetonitrile (180 mg, 52.71%) as a white solid.



2-(6-amino-1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)acetonitrile

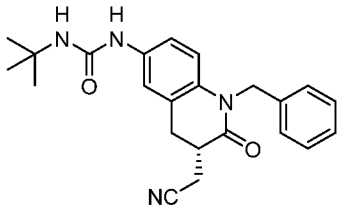
A solution of 2-(1-benzyl-6-nitro-2-oxo-3,4-dihydroquinolin-3-yl)acetonitrile (180 mg, 0.560 mmol, 1 equiv) in EtOH (5 mL) and H_2O (0.5 mL) was added Fe (313 mg, 5.600 mmol, 10 equiv) and NH_4Cl (300 mg, 5.600 mmol, 10 equiv) at rt. The resulting mixture was stirred for overnight at 80 °C. The reaction was quenched with H_2O (10 mL). The resulting mixture was extracted with EA (10 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (3/1) to afford 2-(6-amino-1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)acetonitrile (100 mg, 61.27%) as a brown solid. MS (ESI): mass calcd. for $C_{18}H_{17}N_3O$, 291.14 m/z, found 292.15 $[M+H]^+$.



(R)-1-(1-benzyl-3-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

A solution of 2-(6-amino-1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)acetonitrile (70 mg, 0.240 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (72 mg, 0.720 mmol, 3.0 equiv) and TEA (122 mg, 1.200 mmol, 5.0 equiv) at rt. The resulting mixture was stirred for overnight at rt. The reaction was quenched with H_2O (10 mL). The resulting mixture was extracted with EA (10 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column (PE/EA=2:1) and separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 12 min; Wave Length: 220/254 nm; RT1(min): 6.534; RT2(min): 10.398; Sample Solvent: EtOH--HPLC; Injection Volume: 1.8 mL; Number Of Runs: 4) to afford (R)-1-(1-benzyl-3-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea (18.8 mg, 19.39%) as an off-white solid. MS (ESI): mass calcd. $C_{23}H_{26}N_4O_2$ for: 390.21 m/z, found 391.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.29 – 7.35 (m, 3H), 7.24 – 7.28 (m, 2H), 7.19 – 7.21 (m,1H), 7.01 – 7.06 (m, 1H), 6.79 – 6.86 (m, 1H), 5.97 (s, 1H), 5.03 – 5.20 (m, 2H), 3.05 – 3.15 (m, 1H), 2.83 – 3.02 (m, 4H), 1.26 (s, 9H). And to afford (S)-1-(1-benzyl-3-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea (11.9 mg, 12.66%) as an off-white solid. MS (ESI): mass calcd. $C_{23}H_{26}N_4O_2$ for : 390.21m/z, found 391.15 $[M+H]^+$.^1H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.29 – 7.35 (m, 3H), 7.24 – 7.28 (m, 2H), 7.19 – 7.21 (m,1H), 7.01 – 7.06 (m, 1H), 6.79 – 6.86 (m, 1H), 5.97 (s, 1H), 5.03 – 5.20 (m, 2H), 3.05 – 3.15 (m, 1H), 2.83 – 3.02 (m, 4H), 1.26 (s, 9H).

Example 276: (S)-1-(1-benzyl-3-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

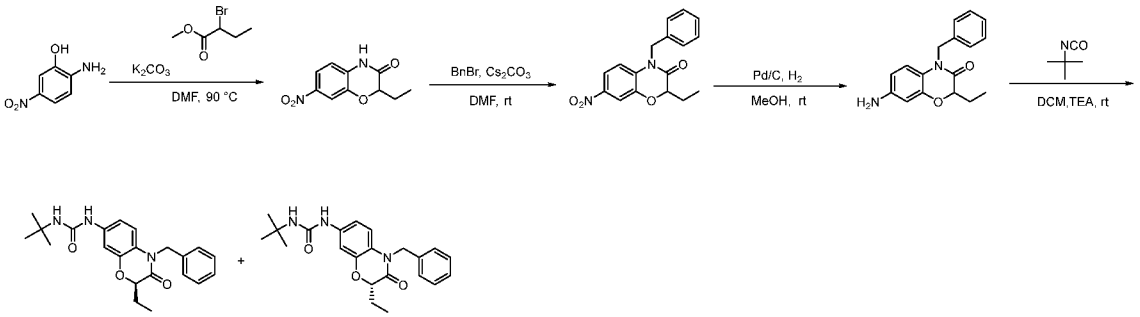


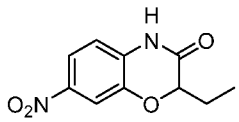
(S)-1-(1-benzyl-3-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

A solution of 2-(6-amino-1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)acetonitrile (70 mg, 0.240 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (72 mg, 0.720 mmol, 3.0 equiv) and TEA (122 mg, 1.200 mmol, 5.0 equiv) at rt. The resulting mixture was stirred for overnight at rt. The reaction was quenched with H_2O (10 mL). The resulting mixture was extracted with EA (10 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column (PE/EA=2:1) and separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 12 min; Wave Length: 220/254 nm; RT1(min): 6.534; RT2(min): 10.398; Sample Solvent: EtOH--HPLC; Injection Volume: 1.8 mL; Number Of Runs: 4) to afford (R)-1-(1-benzyl-3-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea (18.8 mg, 19.39%) as an off-white solid. MS (ESI): mass calcd. $C_{23}H_{26}N_4O_2$ for: 390.21 m/z, found 391.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.29 - 7.35 (m, 3H), 7.24 - 7.28 (m, 2H), 7.19 - 7.21 (m,1H), 7.01 - 7.06 (m, 1H), 6.79 - 6.86 (m, 1H), 5.97 (s, 1H), 5.03 - 5.20 (m, 2H), 3.05 - 3.15 (m, 1H), 2.83 - 3.02 (m, 4H), 1.26 (s, 9H). And to afford (S)-1-(1-benzyl-3-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea (11.9 mg, 12.66%) as an off-white solid. MS (ESI): mass calcd. $C_{23}H_{26}N_4O_2$ for : 390.21m/z, found 391.15 $[M+H]^+$.^1H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.29 - 7.35 (m, 3H), 7.24 - 7.28 (m, 2H), 7.19 - 7.21 (m,1H), 7.01 - 7.06 (m, 1H), 6.79 - 6.86 (m, 1H), 5.97 (s, 1H), 5.03 - 5.20 (m, 2H), 3.05 - 3.15 (m, 1H), 2.83 - 3.02 (m, 4H), 1.26 (s, 9H).

Example 277: (R)-1-(4-benzyl-2-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

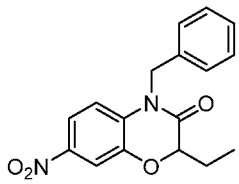
Synthetic Scheme





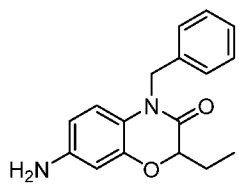
2-ethyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

To a stirred solution of 2-amino-5-nitrophenol (1 g, 6.488 mmol, 1 equiv) in anhydrous dimethylformamide (30 mL) was added K_2CO_3 (2.71 g, 19.464 mmol, 3 equiv) and methyl 2-bromobutanoate (1.41 g, 7.786 mmol, 1.2 equiv) at 0 °C and stirred for 30 min and the mixture is stirred for overnight at 90 °C. The reaction mixture was quenched by addition of water (15 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate filtered and concentrated under reduced pressure. The residue was purified by silica gel column, eluted with PE/EA (3:1) to give 2-ethyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (1.3 g, 90.17%) as a yellow solid.



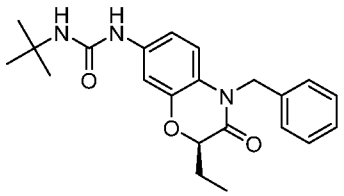
4-benzyl-2-ethyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

To a stirred solution of To a stirred solution of 2-amino-5-nitrophenol (0.5 g, 2.25 mmol, 1 equiv) in anhydrous dimethylformamide (6 mL) was added Cs_2CO_3 (1.5 g, 4.50 mmol, 2 equiv) and BnBr (460 mg, 2.70 mmol, 1.2 equiv) at rt and stirred for 16 h. The reaction mixture was quenched by addition of water (15 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate filtered and concentrated under reduced pressure. The residue was purified by silica gel column, eluted with PE/EA (3:1) to give 4-benzyl-2-ethyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (0.5 g, 71.43%) as a yellow solid.



7-amino-4-benzyl-2-ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of 4-benzyl-2-ethyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (200 mg, 0.640 mmol, 1 equiv) in 15 mL MeOH was added Pd/C (10%, 0.1 g) under nitrogen atmosphere. The mixture was hydrogenated at room temperature for 1 h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in 7-7-amino-4-benzyl-2-ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one (180 mg, 99.56%) as a white solid.

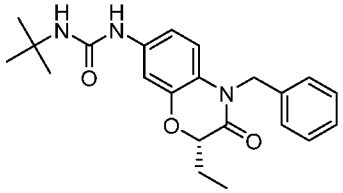


(R) -1-(4-benzyl-2-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

A solution of 7-amino-4-benzyl-2-ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one (150 mg, 0.531 mmol, 1 equiv), TEA (269 mg, 2.655 mmol, 5 equiv) and 2-isocyanato-2-methylpropane (263 mg, 2.655 mmol, 5 equiv) in DCM (10 mL) was stirred for overnight at rt. The reaction mixture was quenched by addition of water (15 mL). The aqueous layer was extracted with DCM (3 x 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate filtered and concentrated under reduced pressure. The residue was purified by silica gel column, eluted with PE/EA (2:1) to give crude product. The residue was purified by Chiral HPLC with the following conditions Column: CHIRALPAK ID, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 16 min; Wave Length: 220/254 nm; RT1(min): 9.531; RT2(min): 12.768; Sample Solvent: EtOH--HPLC; Injection Volume: 0.8 mL; Number Of Runs: 6 to afford (R)-1-(4-benzyl-2-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea (15.5 mg, 7.64%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_3$: 381.21 m/z, found 382.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.20 (d, J = 2.8 Hz, 1H), 7.22 – 7.33 (m, 6H), 6.85 (dd, J = 8.7, 2.8 Hz, 1H), 6.76 – 6.66 (m, 1H), 5.94 (d, J = 2.8 Hz, 1H), 5.10 (t, J = 3.5 Hz, 2H), 4.63 – 4.65 (m, 1H), 1.78 – 1.91 (m, 2H), 1.26 (s, 9H), 1.04 (t, J = 7.4 Hz, 3H). And (S)-1-(4-benzyl-2-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea (13.4 mg, 6.60%) as a white solid.MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_3$: 381.21 m/z, found 382.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.20 (d, J = 2.8 Hz, 1H), 7.22 – 7.33 (m, 6H), 6.85 (dd, J = 8.7, 2.8 Hz, 1H), 6.76 –

6.66 (m, 1H), 5.94 (d, *J* = 2.8 Hz, 1H), 5.10 (t, *J* = 3.5 Hz, 2H), 4.63 – 4.65 (m, 1H), 1.78 – 1.91 (m, 2H), 1.26 (s, 9H), 1.04 (t, *J* = 7.4 Hz, 3H).

Example 278: (S)-1-(4-benzyl-2-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

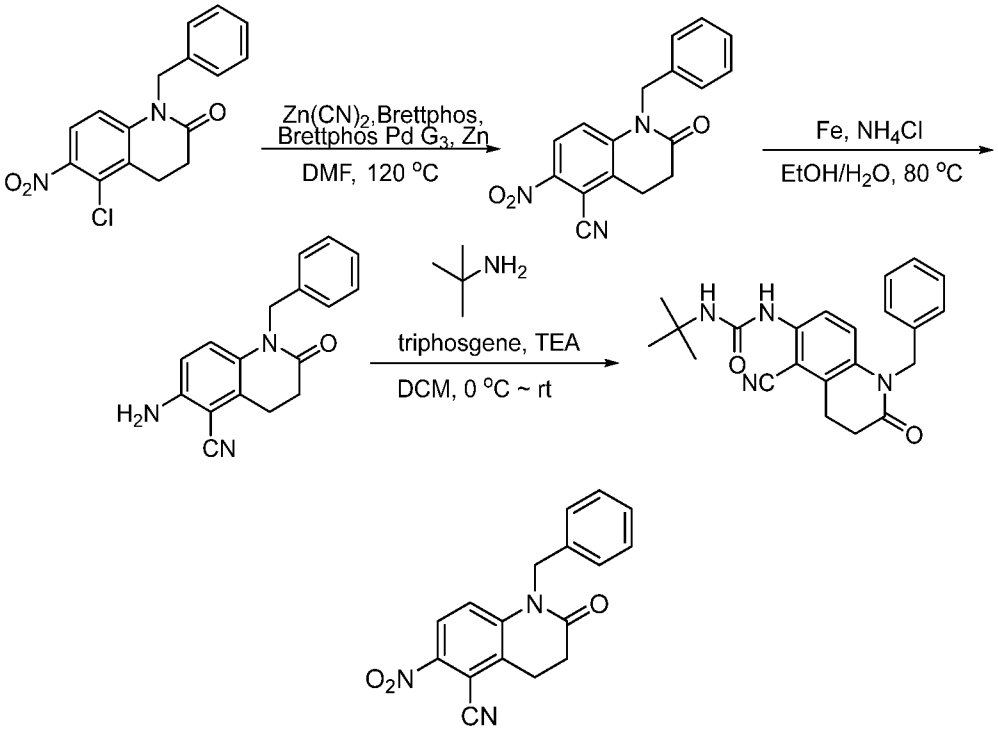


(S)-1-(4-benzyl-2-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

A solution of 7-amino-4-benzyl-2-ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one (150 mg, 0.531 mmol, 1 equiv), TEA (269 mg, 2.655 mmol, 5 equiv) and 2-isocyanato-2-methylpropane (263 mg, 2.655 mmol, 5 equiv) in DCM (10 mL) was stirred for overnight at rt. The reaction mixture was quenched by addition of water (15 mL). The aqueous layer was extracted with DCM (3 x 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate filtered and concentrated under reduced pressure. The residue was purified by silica gel column, eluted with PE/EA (2:1) to give crude product. The residue was purified by Chiral HPLC with the following conditions Column: CHIRALPAK ID, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 16 min; Wave Length: 220/254 nm; RT1(min): 9.531; RT2(min): 12.768; Sample Solvent: EtOH--HPLC; Injection Volume: 0.8 mL; Number Of Runs: 6 to afford (R)-1-(4-benzyl-2-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea (15.5 mg, 7.64%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_3$: 381.21 m/z, found 382.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.20 (d, *J* = 2.8 Hz, 1H), 7.22 – 7.33 (m, 6H), 6.85 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.76 – 6.66 (m, 1H), 5.94 (d, *J* = 2.8 Hz, 1H), 5.10 (t, *J* = 3.5 Hz, 2H), 4.63 – 4.65 (m, 1H), 1.78 – 1.91 (m, 2H), 1.26 (s, 9H), 1.04 (t, *J* = 7.4 Hz, 3H). And (S)-1-(4-benzyl-2-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea (13.4 mg, 6.60%) as a white solid.MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_3$: 381.21 m/z, found 382.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.20 (d, *J* = 2.8 Hz, 1H), 7.22 – 7.33 (m, 6H), 6.85 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.76 – 6.66 (m, 1H), 5.94 (d, *J* = 2.8 Hz, 1H), 5.10 (t, *J* = 3.5 Hz, 2H), 4.63 – 4.65 (m, 1H), 1.78 – 1.91 (m, 2H), 1.26 (s, 9H), 1.04 (t, *J* = 7.4 Hz, 3H).

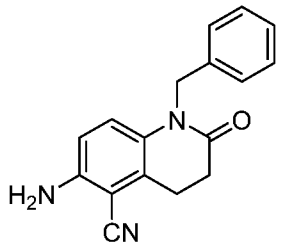
Example 279: 1-(1-benzyl-5-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

Synthetic Scheme



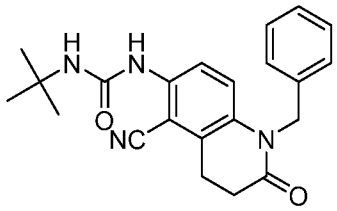
1-benzyl-6-nitro-2-oxo-1,2,3,4-tetrahydroquinoline-5-carbonitrile

To a solution of 1-benzyl-5-chloro-6-nitro-3,4-dihydroquinolin-2-one (180 mg, 0.568 mmol, 1 equiv) in dimethylformamide (2 mL) was added zinc (5.57 mg, 0.085 mmol, 0.15 equiv), zinc cyanide (80.07 mg, 0.682 mmol, 1.2 equiv), Brettphos Pd G_3 (103.03 mg, 0.114 mmol, 0.2 equiv) and Brettphos (61.01 mg, 0.114 mmol, 0.2 equiv). The reaction was stirred at 120 °C under N_2 for 3 h. After cooling down to rt, the reaction was quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-benzyl-6-nitro-2-oxo-3,4-dihydroquinoline-5-carbonitrile (77 mg, 44.09%) as a white solid. LC/MS (ESI): mass calcd. for $C_{17}H_{13}N_3O_3$: 307.10 m/z, found:308.10 $[M+H]^+$.



6-amino-1-benzyl-2-oxo-1,2,3,4-tetrahydroquinoline-5-carbonitrile

To a solution of 1-benzyl-6-nitro-2-oxo-3,4-dihydroquinoline-5-carbonitrile (77 mg, 0.251 mmol, 1 equiv) in ethyl alcohol (20 mL) and water (2 mL) was added iron (140 mg, 2.507 mmol, 10.01 equiv) and NH_4Cl (133 mg, 2.486 mmol, 9.92 equiv). The reaction was stirred at 60 °C for 3 h. After cooling down to rt, the reaction was quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-1-benzyl-2-oxo-3,4-dihydroquinoline-5-carbonitrile (22 mg, 31.66%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{17}H_{15}N_3O$: 277.12 m/z, found:278.10 $[M+H]^+$.



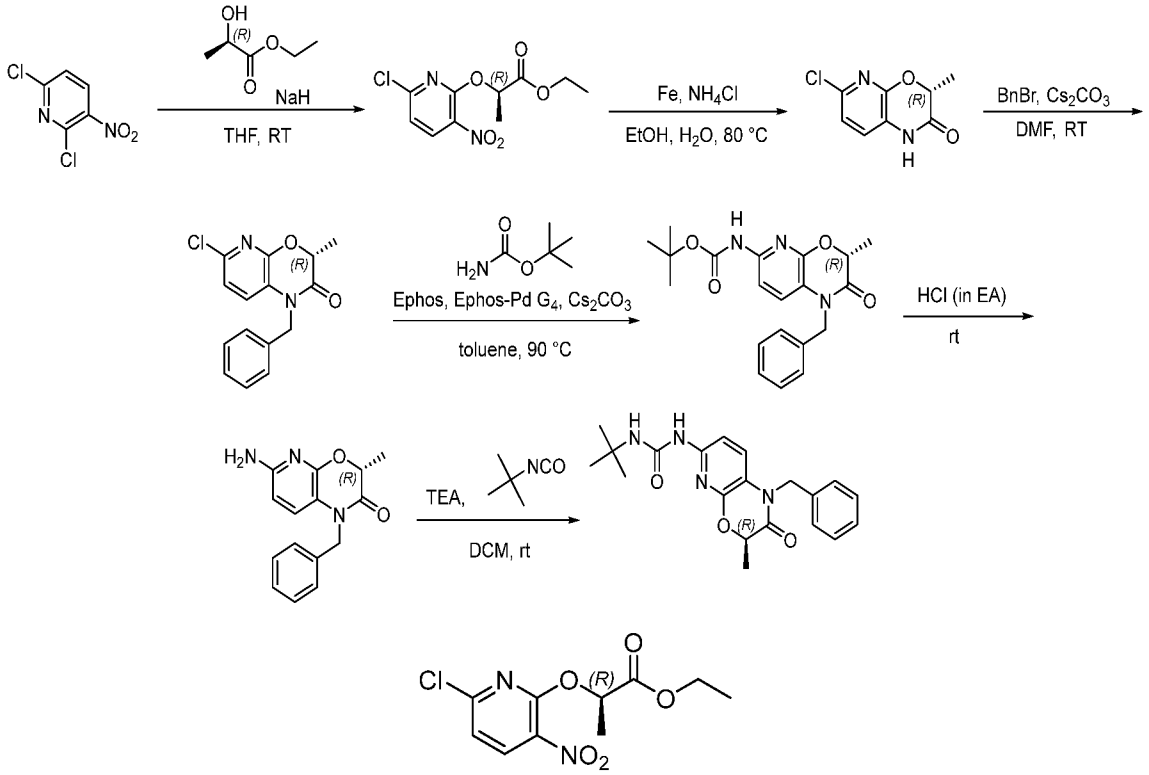
1-(1-benzyl-5-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

To a solution of 6-amino-1-benzyl-2-oxo-3,4-dihydroquinoline-5-carbonitrile (80 mg, 0.288 mmol, 1 equiv) in DCM (4 mL) was added erbumine (42.20 mg, 0.576 mmol, 2 equiv). The reaction was stirred at 0 °C under N_2 for 1 h. The reaction was added TEA (87.57 mg, 0.864 mmol, 3 equiv) and stirred at rt under N_2 for 1 h. The reaction was added 2-methylpropan-2-amine (42.20 mg, 0.576 mmol, 2 equiv) and stirred at rt under N_2 for 1 h. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a Aeris PEPTIDE 5um XB-C18 Axia 21.2 mm X 250 mm, 5 μm column (eluent: 43% to 57% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford the title compound 1-(1-benzyl-5-cyano-2-oxo-3,4-dihydroquinolin-6-yl)-3-tert-butylurea (12.5 mg, 11.48%) as a white solid. LC/MS (ESI): mass calcd. for $C_{22}H_{24}N_4O_2$:376.19 m/z, found:377.05 $[M+H]^+$. ^1H

NMR (300 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.71-7.74 (m, 1H), 7.11-7.36 (m, 6H), 6.80 (s, 1H), 5.14 (s, 2H), 3.06-3.11 (m, 2H), 2.72-2.77 (m, 2H), 1.27 (s, 9H).

Example 280: (R)-1-(1-benzyl-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea

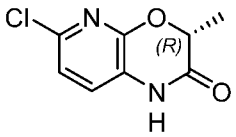
Synthetic Scheme



ethyl (R)-2-((6-chloro-3-nitropyridin-2-yl)oxy)propanoate

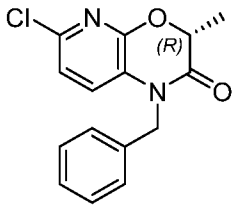
To a solution of 2,6-dichloro-3-nitropyridine (2.0 g, 10.364 mmol, 1 equiv) in tetrahydrofuran (20 mL) was added 60% NaH (0.5 g, 12.437 mmol, 1.2 equiv) at 0 °C. The mixture was stirred for 15 min. ethyl lactate (1.47 g, 12.437 mmol, 1.2 equiv) was added and the mixture was allowed to warm to RT and stirred for 2 h. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 20 mL). The combined organic layers were washed with NaCl (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (5/1) to afford ethyl

(R)-2-((6-chloro-3-nitropyridin-2-yl)oxy)propanoate (2.0 g, 70.26%) as a white solid. MS (ESI): mass calcd. for $C_{10}H_{11}ClN_2O_5$, 274.04 m/z, found 275.05 $[M+H]^+$.



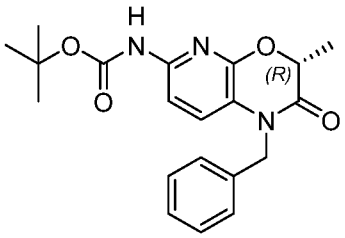
(R)-6-chloro-3-methyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one

A solution of ethyl (R)-2-((6-chloro-3-nitropyridin-2-yl)oxy)propanoate (500 mg, 1.820 mmol, 1 equiv) in EtOH (10 mL) and H_2O (1 mL) was added Fe (2.0 g, 36.400 mmol, 20 equiv) and NH_4Cl (1.9 g, 36.400 mmol, 20 equiv) at rt. The resulting mixture was stirred for overnight at 80 °C. The reaction was quenched with water (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The residue was purified by silica gel column chromatography, eluted with PE/EA (3:1) to afford (R)-6-chloro-3-methyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (300 mg, 82.97%) as a brown solid. MS (ESI): mass calcd. for $C_8H_7ClN_2O_2$, 198.02 m/z, found 199.10 $[M+H]^+$.



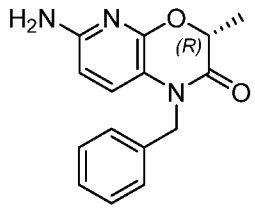
(R)-1-benzyl-6-chloro-3-methyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one

A solution of (R)-6-chloro-3-methyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (300 mg, 1.510 mmol, 1 equiv) in DMF (5 mL) was added BnBr (775 mg, 4.530 mmol, 3.0 equiv) and Cs_2CO_3 (2.0 g, 6.040 mmol, 4.0 equiv) at rt. The resulting mixture was stirred for 2 h at rt. The reaction was quenched with water (20 mL). The resulting mixture was extracted with EA (3 x 20 mL). The combined organic layers were washed with NaCl (aq., 3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (3/1) to afford (R)-1-benzyl-6-chloro-3-methyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (300 mg, 68.79%) as a white solid. MS (ESI): mass calcd. for $C_{15}H_{13}ClN_2O_2$, 288.07 m/z, found 289.15 $[M+H]^+$.



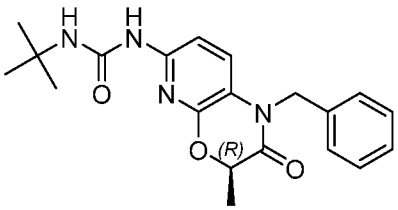
tert-butyl (R)-(1-benzyl-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)carbamate

A solution of (R)-1-benzyl-6-chloro-3-methyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (150 mg, 0.520 mmol, 1 equiv) in dioxane (5 mL) was added tert-butyl carbamate (73 mg, 0.624 mmol, 1.2 equiv), Cs_2CO_3 (338 mg, 1.040 mmol, 2.0 equiv), Ephos (55.5 mg, 0.104 mmol, 0.2 equiv) and Ephos Pd G4 (48.0 mg, 0.052 mmol, 0.1 equiv) at rt. The resulting mixture was stirred for overnight at 90 °C. The resulting was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (3/1) to afford tert-butyl (R)-(1-benzyl-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)carbamate (110 mg, 57.32%) as an off-white solid. MS (ESI): mass calcd. for $C_{20}H_{23}N_3O_4$, 369.17 m/z, found 370.10 $[M+H]^+$.



(R)-6-amino-1-benzyl-3-methyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one

A solution of tert-butyl (R)-(1-benzyl-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)carbamate (100 mg, 0.271 mmol, 1 equiv) in 4N HCl (in EA, 10 mL) at rt. The resulting mixture was stirred for 2 h at rt. The resulting mixture was concentrated under reduced pressure to afford (R)-6-amino-1-benzyl-3-methyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (70 mg, 96.02%) was used in the next step directly without further purification. MS (ESI): mass calcd. for $C_{15}H_{15}N_3O_2$, 269.12 m/z, found 270.20 $[M+H]^+$.

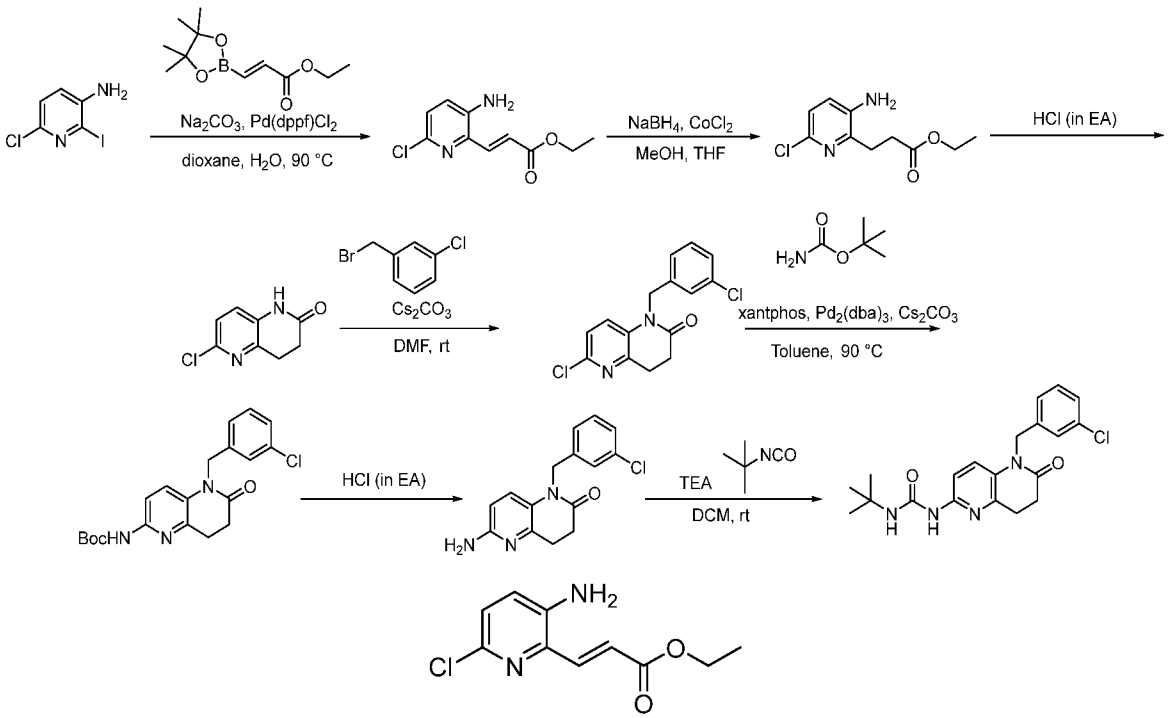


(R)-1-(1-benzyl-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea

A solution of (R)-6-amino-1-benzyl-3-methyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (80 mg, 0.297 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (294 mg, 2.970 mmol, 10 equiv) and TEA (300 mg, 2.970 mmol, 10 equiv) at rt. The resulting mixture was stirred for overnight at rt. The reaction was quenched with water (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1) and C18 column to afford (R)-1-(1-benzyl-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea (28.0 mg, 25.51%) as a white solid. MS (ESI): mass calcd.C20H24N4O3 for: 368.18m/z, found 369.20 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (s, 1H), 7.36 – 7.43 (m, 1H), 7.29 – 7.35 (m, 2H), 7.22 – 7.29 (m, 3H), 7.16 – 7.22 (m, 1H), 7.08 – 7.12 (m, 1H),4.79 – 5.19 (m, 3H), 1.53 (d, J = 6.8 Hz, 3H), 1.29 (s, 9H).

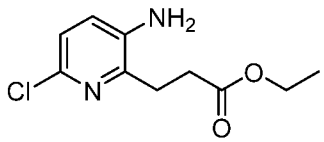
Example 281: 1-(tert-butyl)-3-(5-(3-chlorobenzyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea

Synthetic Scheme



ethyl (E)-3-(3-amino-6-chloropyridin-2-yl)acrylate

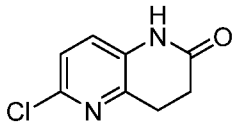
A solution of 6-chloro-2-iodopyridin-3-amine (2.3 g, 9.039 mmol, 1 equiv) ethyl (2E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-enoate (2.0 g, 9.039 mmol, 1 equiv), Na_2CO_3 (2.9 g, 27.117 mmol, 3 equiv) and $Pd(dppf)Cl_2$ (0.66 g, 0.904 mmol, 0.1 equiv) in water (3 mL) and 1,4-dioxane (30 mL) was stirred for overnight at 90 °C under N_2 atmosphere. The mixture was allowed to cool down to rt. The reaction mixture was quenched by water (50 mL) and extracted with EA (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography with PE/EA (3:1) to afford ethyl (E)-3-(3-amino-6-chloropyridin-2-yl)acrylate (1.5 g, 73.22%) as a yellow solid.



ethyl 3-(3-amino-6-chloropyridin-2-yl)propanoate

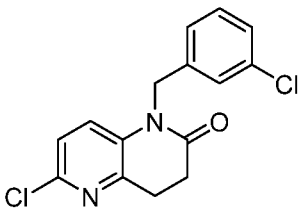
A solution of ethyl (E)-3-(3-amino-6-chloropyridin-2-yl)acrylate (1.4 g, 6.177 mmol, 1 equiv) in methanol (10 mL) and tetrahydrofuran (20 mL) was treated with cobalt(II) chloride (0.40 g, 3.088 mmol, 0.5 equiv) for 30 min at 0 °C under nitrogen atmosphere followed by the addition of $NaBH_4$ (1.17 g, 30.885 mmol, 5 equiv) in portions at 0 °C. The resulting mixture was stirred for additional 1 h at rt. The reaction mixture was quenched by water (20 mL) and extracted with EA (3 x 30 mL).

The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography with PE/EA (2:1) to afford ethyl 3-(3-amino-6-chloropyridin-2-yl)propanoate (1.2 g, 84.96%) as a white solid. MS (ESI): mass calcd. for $C_{10}H_{13}ClN_2O_2$, 228.07 m/z, found 229.10 $[M+H]^+$.



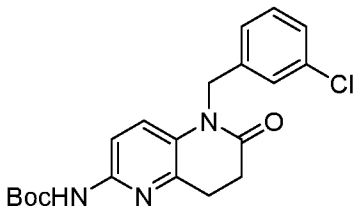
6-chloro-3,4-dihydro-1,5-naphthyridin-2(1H)-one

To a stirred solution of ethyl 3-(3-amino-6-chloropyridin-2-yl)propanoate (1.2 g, 5.248 mmol, 1 equiv) in EA (10 mL), HCl (4N, in EA, 20 mL) was added at rt. The reaction stirred for 2 h. The precipitated solids were collected by filtration and washed with Et_2O (3 x 50 mL). This resulted in6-chloro-3,4-dihydro-1,5-naphthyridin-2(1H)-one (1.08 g, 112.71%) as a white solid. MS (ESI): mass calcd. for $C_8H_7ClN_2O$, 182.02 m/z, found 183.10 $[M+H]^+$.



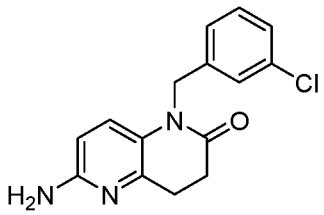
6-chloro-1-(3-chlorobenzyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one

To a stirred solution of 6-chloro-3,4-dihydro-1,5-naphthyridin-2(1H)-one (300 mg, 1.643 mmol, 1 equiv) in anhydrous DMF (20 mL) was added 1-(bromomethyl)-3-chlorobenzene (371 mg, 1.807 mmol, 1.1 equiv) and Cs_2CO_3 (1.6 g, 4.929 mmol, 3 equiv) at rt and stirred for 2 h. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography with PE/EA (3:1) to afford 6-chloro-1-(3-chlorobenzyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (293 mg, 58.06%) as a light-yellow solid. MS (ESI): mass calcd. for $C_{15}H_{12}Cl_2N_2O$, 306.03 m/z, found 307.00 $[M+H]^+$.



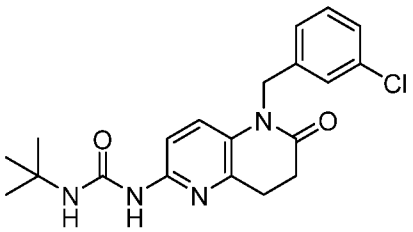
tert-butyl (5-(3-chlorobenzyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)carbamate

To a stirred solution of 6-chloro-1-(3-chlorobenzyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (210 mg, 0.684 mmol, 1 equiv) in anhydrous toluene (15 mL) was added Cs_2CO_3 (670 mg, 2.052 mmol, 3 equiv) tert-butyl carbamate (160 mg, 1.368 mmol, 2 equiv), XantPhos (40 mg, 0.068 mmol, 0.1 equiv) $Pd_2(dba)_3$ (63 mg, 0.068 mmol, 0.1 equiv) at 90 °C and stirred for overnight. After completion of reaction, the reaction mixture was concentrated under reduced pressure to give crude product which was further purified by column chromatography (PE/EA=2:1) afford desired compound tert-butyl (5-(3-chlorobenzyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)carbamate (204 mg, 76.93%) as a yellow semi-solid. MS (ESI): mass calcd. for $C_{20}H_{22}ClN_3O_3$, 387.13 m/z, found 388.20 $[M+H]^+$.



6-amino-1-(3-chlorobenzyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one

To a stirred solution of tert-butyl (5-(3-chlorobenzyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)carbamate (220 mg, 0.567 mmol, 1 equiv) in EA (5 mL), HCl (4N, in EA, 10 mL) was added at rt. The reaction stirred for 2 h. The resulting mixture was concentrated under reduced pressure to afford 6-amino-1-(3-chlorobenzyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (250 mg, 153.17%) as a white solid. MS (ESI): mass calcd. for $C_{15}H_{14}ClN_3O$, 287.08 m/z, found 288.20 $[M+H]^+$.



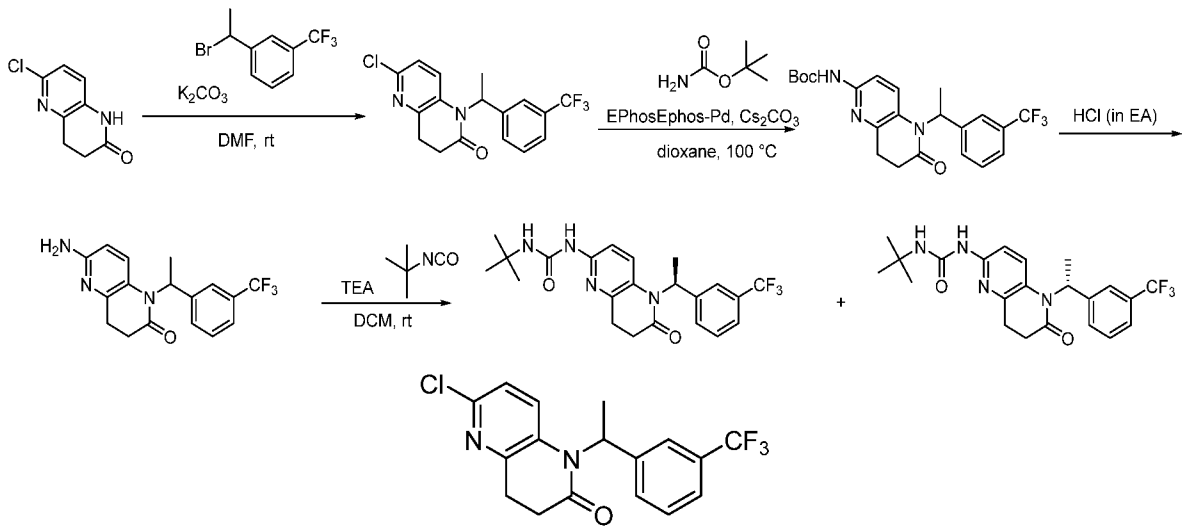
1-(tert-butyl)-3-(5-(3-chlorobenzyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea

A solution of 6-amino-1-(3-chlorobenzyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (100 mg, 0.348 mmol, 1 equiv), TEA (176 mg, 1.740 mmol, 5 equiv) and 2-isocyanato-2-methylpropane (172 mg, 1.740 mmol, 5 equiv) in DCM (10 mL) was stirred for overnight at rt. The reaction was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted

with EA (55%-62%) to afford crude products. The residue was purified by reversed-phase flash chromatography with the following conditions Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 55% B in 10 min; Wave Length: 254/220 nm; RT1(min): 9.8; Number Of Runs: 3 to) afford 1-(tert-butyl)-3-(5-(3-chlorobenzyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea (26.2 mg, 19.44%) as a white solid. MS (ESI): mass calcd. for $C_{20}H_{23}ClN_4O_2$: 386.15 m/z, found 387.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.81 (s, 1H), 7.94 (s, 1H), 7.11 – 7.36 (m, 6H), 5.08 (s, 2H), 2.97 (dd, J = 8.8, 6.2 Hz, 2H), 2.78 (dd, J = 8.7, 6.2 Hz, 2H), 1.30 (s, 9H).

Example 282: (S)-1-(tert-butyl)-3-(6-oxo-5-(1-(3-(trifluoromethyl)phenyl)ethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea

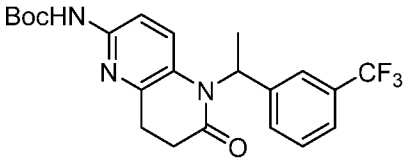
Synthetic Scheme



6-chloro-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one

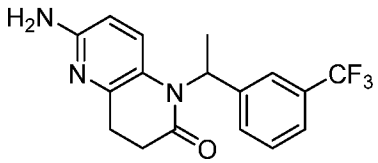
To a solution of 6-chloro-3,4-dihydro-1H-1,5-naphthyridin-2-one (400 mg, 2.190 mmol, 1 equiv) in DMF (10 mL) was added K_2CO_3 (908 mg, 6.571 mmol, 3 equiv) and 1-(1-bromoethyl)-3-(trifluoromethyl)benzene (831 mg, 3.286 mmol, 1 equiv). The resulting mixture was placed at rt and stirred overnight until the starting material was totally consumed by LCMS. The mixture was diuted with EtOAc (50 mL), washed with water (3 x 30 mL), brine (2 x 30 mL) and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-

100% ethyl acetate/petroleum ether) to afford 6-chloro-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (300 mg, 38.29%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{14}ClF_3N_2O$ 354.07 m/z, found 355.05 $[M+H]^+$.



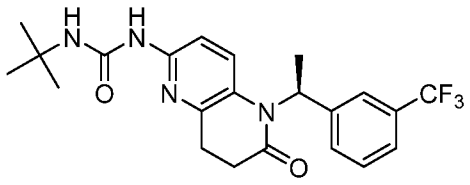
tert-butyl (6-oxo-5-(1-(3-(trifluoromethyl)phenyl)ethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)carbamate

To a solution of 6-chloro-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (300 mg, 0.846 mmol, 1 equiv) in dioxane (10 mL) was added tert-butyl carbamate (198.1 mg, 1.691 mmol, 2 equiv), Ephos (45.2 mg, 0.085 mmol, 0.1 equiv), EPhos Pd G4 (77.6 mg, 0.085 mmol, 0.1 equiv) and Cs_2CO_3 (826.5 mg, 2.537 mmol, 3 equiv). The resulting mixture was placed at 100 °C under a nitrogen atmosphere and stirred overnight until the starting material was totally consumed by LCMS, The reaction mixture was quenched by water and extracted with EA (3 x 20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford tert-butyl (6-oxo-5-(1-(3-(trifluoromethyl)phenyl)ethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)carbamate (200 mg, 54.31%) as a yellow solid. MS (ESI): mass calcd. for $C_{22}H_{24}F_3N_3O_3$, 435.18 m/z, found 436.15 $[M+H]^+$.



6-amino-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one

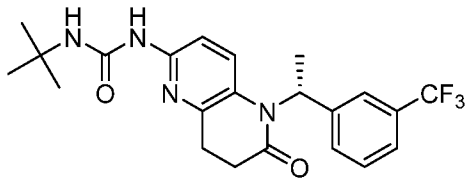
To a solution of tert-butyl (6-oxo-5-(1-(3-(trifluoromethyl)phenyl)ethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)carbamate (20 mg, 0.046 mmol, 1 equiv) in HCl (4N, in EA, 2 mL). The resulting mixture was placed at rt and stirred overnight until the starting material was totally consumed by LCMS. The reaction mixture was concentrated under vacuum to yield 6-amino-1-{1-[3-(trifluoromethyl)phenyl]ethyl}-3,4-dihydro-1,5-naphthyridin-2-one (100 mg, 61.75%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{16}F_3N_3O$, 335.12 m/z, found 336.05 $[M+H]^+$.



(S)-1-(tert-butyl)-3-(6-oxo-5-(1-(3-(trifluoromethyl)phenyl)ethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea

To a stirred solution of 6-amino-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (100 mg, 0.298 mmol, 1 equiv) in DCM (10.00 mL) was added 2-isocyanato-2-methylpropane (147.8 mg, 1.491 mmol, 5 equiv) and TEA (90.5 mg, 0.895 mmol, 3 equiv) stirred overnight at rt. The reaction progress was monitored by LCMS. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 100 mg crude product as a white solid. The compound was separated by Chiral-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 73% B in 9 min, 73% B; Wave Length: 254/220 nm; RT1(min): 9.6; Number Of Runs: 0) to afford (S)-1-(tert-butyl)-3-(6-oxo-5-(1-(3-(trifluoromethyl)phenyl)ethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea (11.7 mg, 8.86%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{25}F_3N_4O_2$, 434.19 m/z, found 435.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.89 (s, 1H), 7.96 (s, 1H), 7.52 – 7.67 (m, 4H), 6.96 – 7.07 (m, 2H), 6.08 (d, J = 7.3 Hz, 1H), 2.61 – 3.06 (m, 4H), 1.74 (d, J = 7.1 Hz, 3H), 1.30 (s, 9H). And another isomer (R)-1-(tert-butyl)-3-(6-oxo-5-(1-(3-(trifluoromethyl)phenyl)ethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea (9.1 mg, 6.96%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{25}F_3N_4O_2$, 434.19 m/z, found 435.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.89 (s, 1H), 7.96 (s, 1H), 7.52 – 7.67 (m, 4H), 6.96 – 7.07 (m, 2H), 6.08 (d, J = 7.3 Hz, 1H), 2.61 – 3.06 (m, 4H), 1.74 (d, J = 7.1 Hz, 3H), 1.30 (s, 9H).

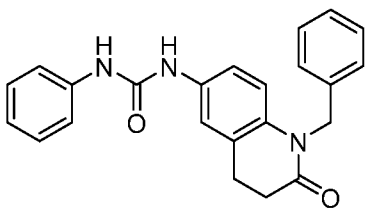
Example 283: (R)-1-(tert-butyl)-3-(6-oxo-5-(1-(3-(trifluoromethyl)phenyl)ethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea



(R)-1-(tert-butyl)-3-(6-oxo-5-(1-(3-(trifluoromethyl)phenyl)ethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea

To a stirred solution of 6-amino-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (100 mg, 0.298 mmol, 1 equiv) in DCM (10.00 mL) was added 2-isocyanato-2-methylpropane (147.8 mg, 1.491 mmol, 5 equiv) and TEA (90.5 mg, 0.895 mmol, 3 equiv) stirred overnight at rt. The reaction progress was monitored by LCMS. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 100 mg crude product as a white solid. The compound was separated by Chiral-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 73% B in 9 min, 73% B; Wave Length: 254/220 nm; RT1(min): 9.6; Number Of Runs: 0) to afford (S)-1-(tert-butyl)-3-(6-oxo-5-(1-(3-(trifluoromethyl)phenyl)ethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea (11.7 mg, 8.86%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{25}F_3N_4O_2$, 434.19 m/z, found 435.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.89 (s, 1H), 7.96 (s, 1H), 7.52 – 7.67 (m, 4H), 6.96 – 7.07 (m, 2H), 6.08 (d, J = 7.3 Hz, 1H), 2.61 – 3.06 (m, 4H), 1.74 (d, J = 7.1 Hz, 3H), 1.30 (s, 9H). And another isomer (R)-1-(tert-butyl)-3-(6-oxo-5-(1-(3-(trifluoromethyl)phenyl)ethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea (9.1 mg, 6.96%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{25}F_3N_4O_2$, 434.19 m/z, found 435.10 $[M+H]^+$. $_1H$ NMR (300 MHz, DMSO-d_6) δ 8.89 (s, 1H), 7.96 (s, 1H), 7.52 – 7.67 (m, 4H), 6.96 – 7.07 (m, 2H), 6.08 (d, J = 7.3 Hz, 1H), 2.61 – 3.06 (m, 4H), 1.74 (d, J = 7.1 Hz, 3H), 1.30 (s, 9H).

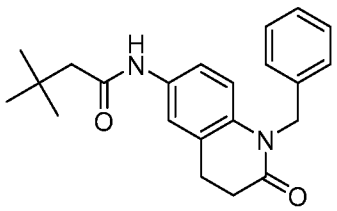
Example 284: 3-(1-benzyl-2-oxo-3,4-dihydroquinolin-6-yl)-1-phenylurea



3-(1-benzyl-2-oxo-3,4-dihydroquinolin-6-yl)-1-phenylurea

To a stirred solution of 6-amino-1-benzyl-3,4-dihydroquinolin-2-one (150 mg, 0.594 mmol, 1 equiv) in DCM (2 mL) was added triphosgene (59.98 mg, 0.202 mmol, 0.34 equiv) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at 0°C under nitrogen atmosphere. To the above mixture was added triethylamine (180.47 mg, 1.782 mmol, 3 equiv) in portions at room temperature. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. To the above mixture was added aniline (55.36 mg, 0.594 mmol, 1 equiv) in portions at 0 °C. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by Prep-HPLC using a X Bridge Prep OBD C18 150 mm x 30 mm x 5 μm column (eluent: 26% to 45% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford 3-(1-benzyl-2-oxo-3,4-dihydroquinolin-6-yl)-1-phenylurea (37.5 mg, 16.92%) as a white solid. LC/MS (ESI): mass calcd. for $C_{23}H_{21}N_3O_2$:371.2 m/z, found:372.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.55 (s, 1H), 7.43 – 7.41 (m, 3H), 7.31 – 7.21 (m, 8H), 7.01 – 6.89 (m, 1H), 6.84 (d, J = 8.7 Hz, 1H), 5.12 (s, 2H), 2.93 (m, 2H), 2.69 (m, 2H).

Example 285: N-(1-benzyl-2-oxo-3,4-dihydroquinolin-6-yl)-3,3-dimethylbutanamide



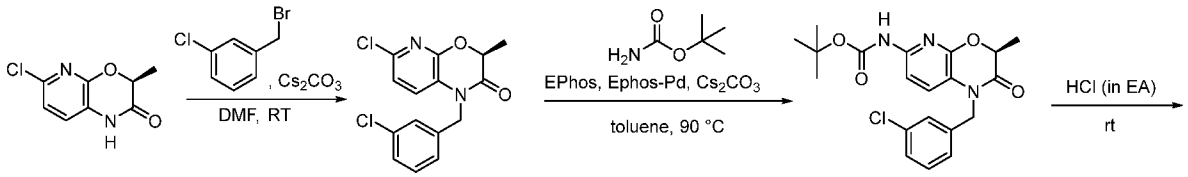
N-(1-benzyl-2-oxo-3,4-dihydroquinolin-6-yl)-3,3-dimethylbutanamide

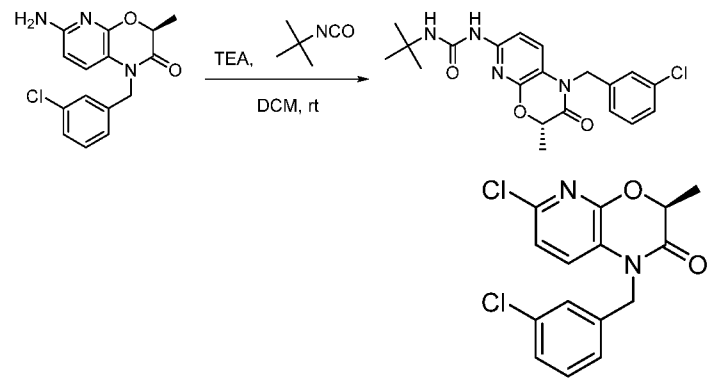
To a stirred solution of 3,3-dimethylbutanamide (35.15 mg, 0.305 mmol, 1.1 equiv) and HATU (137.13 mg, 0.360 mmol, 1.3 equiv) in DMF (1 mL) were added 6-amino-1-benzyl-3,4-dihydroquinolin-2-one (70 mg, 0.277 mmol, 1 equiv) and DIEA (107.57 mg, 0.831 mmol, 3 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude

product was purified by Prep-HPLC using a X Bridge Prep OBD C18 150 mm x 30 mm x 5 μm column (eluent: 26% to 42% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford N-(1-benzyl-2-oxo-3,4-dihydroquinolin-6-yl)-3,3-dimethylbutanamide (47.6 mg, 48.80%) as a white solid.LC/MS (ESI): mass calcd. for $C_{22}H_{26}N_2O_2$:350.2 m/z, found:351.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 9.69 (s, 1H), 7.51 (d, J = 2.1 Hz, 1H), 7.33 – 7.19 (m, 6H), 6.84 (d, J = 8.7 Hz, 1H), 5.11 (s, 2H), 2.92 – 2.88 (m, 2H), 2.69 – 2.64 (m, 2H), 2.13 (s, 2H), 0.99 (s, 9H).

Example 286: (S)-1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea

Synthetic Scheme

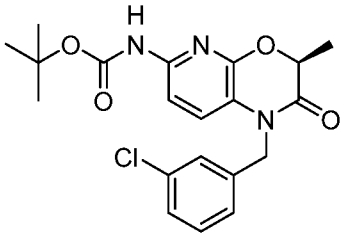




(S)-6-chloro-1-(3-chlorobenzyl)-3-methyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one

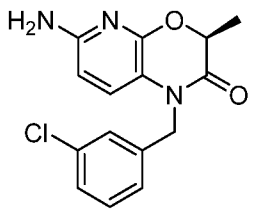
A solution of (S)-6-chloro-3-methyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (100 mg, 0.503 mmol, 1 equiv) in DMF (5 mL) was added 1-(bromomethyl)-3-chlorobenzene (155 mg, 0.754 mmol, 1.5 equiv) and Cs_2CO_3 (492 mg, 1.509 mmol, 3.0 equiv) at rt. The resulting mixture was stirred for 2h at rt. The reaction mixture was quenched by ice water (5 mL) and extracted with EA (3 x 5 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column, eluted with

PE/EA (3:1) to afford (S)-6-chloro-1-(3-chlorobenzyl)-3-methyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (150 mg, 92.19%) as a white solid. MS (ESI): mass calcd. for $C_{15}H_{12}Cl_2N_2O_2$, 322.03 m/z, found 323.00 $[M+H]^+$.



tert-butyl (S)-(1-(3-chlorobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)carbamate

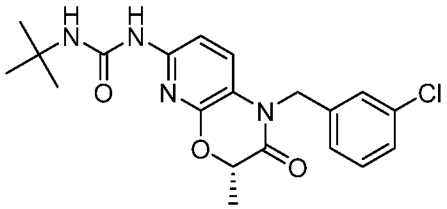
A solution of (S)-6-chloro-1-(3-chlorobenzyl)-3-methyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (150 mg, 0.464 mmol, 1 equiv) in toluene (5 mL) was added tert-butyl carbamate (70 mg, 0.603 mmol, 1.3 equiv), Cs_2CO_3 (453 mg, 1.392 mmol, 3.0 equiv), Ephos (49 mg, 0.093 mmol, 0.2 equiv) and EPhos Pd G4 (42 mg, 0.046 mmol, 0.1 equiv) at rt. The resulting mixture was stirred for overnight at 90 °C under N_2. After cooled to room temperature the reaction mixture was quenched by water (5 mL) and extracted with EA (3 x 5 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column, eluted with PE/EA (3:1) to afford tert-butyl (S)-(1-(3-chlorobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)carbamate (160 mg, 85.35%) as yellow oil. MS (ESI): mass calcd. for $C_{20}H_{22}ClN_3O_4$, 403.13 m/z, found 404.20 $[M+H]^+$.



(S)-6-amino-1-(3-chlorobenzyl)-3-methyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one

A solution of tert-butyl (S)-(1-(3-chlorobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)carbamate (150 mg, 0.371 mmol, 1 equiv) in EA (5 mL), 2N HCl (in EA, 5 mL) was added into the reaction at rt. The resulting mixture was stirred for 2 h at rt. The resulting mixture was concentrated under reduced pressure. The crude product (S)-6-amino-1-(3-chlorobenzyl)-3-methyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (80 mg, 70.91%) was used in the

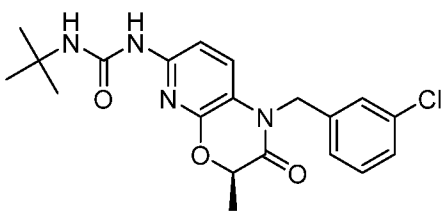
next step directly without further purification. MS (ESI): mass calcd. for $C_{15}H_{14}ClN_3O_2$, 303.08 m/z, found 304.15 $[M+H]^+$.



(S)-1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea

A solution of (S)-6-amino-1-(3-chlorobenzyl)-3-methyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (80 mg, 0.263 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (261 mg, 2.630 mmol, 10 equiv) and TEA (266 mg, 2.630 mmol, 10 equiv) at rt. The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water (10 mL) and extracted with DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude was purified by flash chromatography with PE/EA (1:1) and Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Flow rate: 60 mL/min; Gradient: 30% B to 60% B in 7 min, 60% B; Wave Length: 254/220 nm; RT1(min): 6.7; Number Of Runs: 0) to afford (S)-1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea (19.6 mg, 17.86%) as a white solid. MS (ESI): mass calcd. $C_{20}H_{23}ClN_4O_3$ for: 402.15m/z, found 403.05 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 7.29 – 7.41 (m, 4H), 7.17 – 7.26 (m, 2H), 7.09 (s, 1H), 5.02 – 5.16(m, 3H), 1.53 (d, J = 6.8 Hz, 3H), 1.28 (s, 9H).

Example 287: (R)-1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea

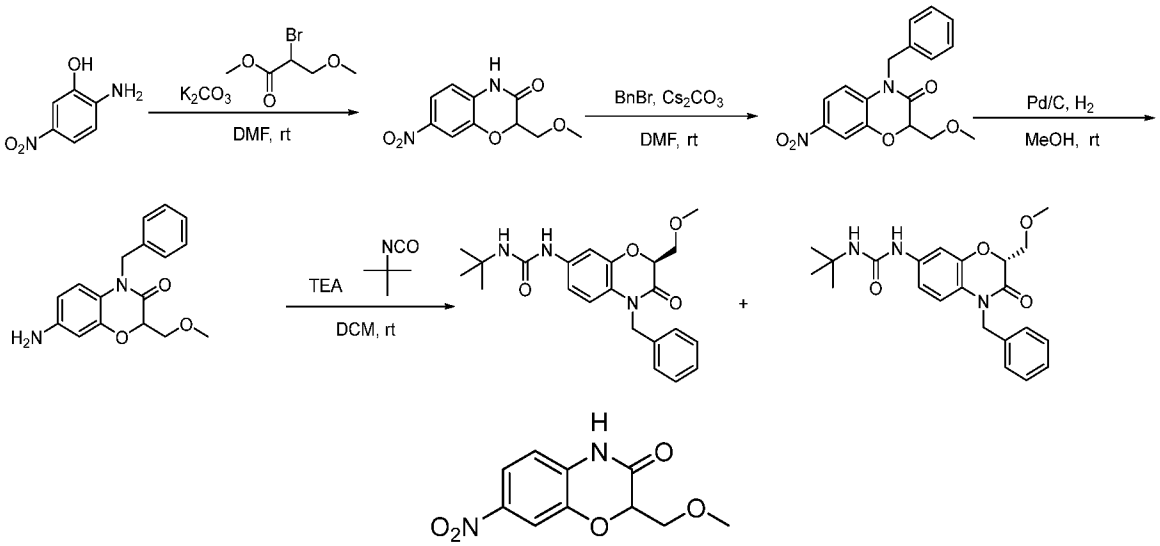


(R)-1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea

A solution of (R)-6-amino-1-(3-chlorobenzyl)-3-methyl-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (60 mg, 0.198 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (195 mg, 1.980 mmol, 10 equiv) and TEA (199 mg, 1.980 mmol, 10 equiv) at rt. The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water (10 mL) and extracted with DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude was purified by flash chromatography with PE/EA (1:1) and Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Flow rate: 60 mL/min; Gradient: 30% B to 60% B in 7 min, 60% B; Wave Length: 254/220 nm; RT1(min): 6.7; Number Of Runs: 0) to afford (R)-1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea (12.1 mg, 14.76%) as a white solid. MS (ESI): mass calcd. $C_{20}H_{23}ClN_4O_3$ for: 402.15m/z, found 403.05$[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 7.29 – 7.41 (m, 4H), 7.17 – 7.26 (m, 2H), 7.09 (s, 1H), 5.02 – 5.16(m, 3H), 1.53 (d, J = 6.8 Hz, 3H), 1.28 (s, 9H).

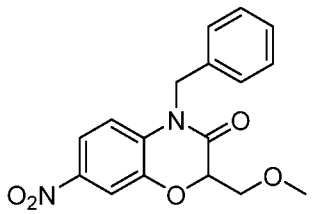
Example 288: (S)-1-(4-benzyl-2-(methoxymethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

Synthetic Scheme



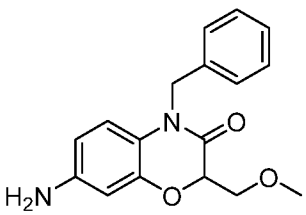
2-(methoxymethyl)-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

A solution of 2-amino-5-nitrophenol (300 mg, 1.946 mmol, 1 equiv) in dimethylformamide (5 mL) was added Cs_2CO_3 (1.9 g, 5.838 mmol, 3.0 equiv) and methyl 2-bromo-3-methoxypropanoate (460.2 mg, 2.335 mmol, 1.2 equiv) at rt. The resulting mixture was stirred for overnight at 90 °C. The reaction mixture was quenched by water (5 mL) and extracted with EA (3 x 10 mL). The combined organic layers were washed with NaCl (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (3/1) to afford 2-(methoxymethyl)-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (200 mg, 43.14%) as a white solid. MS (ESI): mass calcd. for $C_{10}H_{10}N_2O_5$ 238.06 m/z, found 239.10 $[M+H]^+$.



4-benzyl-2-(methoxymethyl)-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

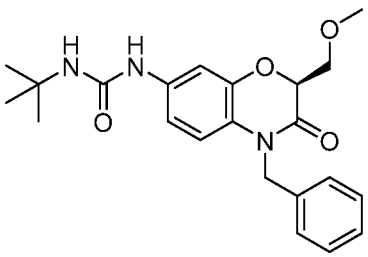
A solution of 2-(methoxymethyl)-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (150 mg, 0.630 mmol, 1 equiv) in dimethylformamide (5 mL) was added BnBr (323.1 mg, 1.890 mmol, 3.0 equiv) and Cs_2CO_3 (615.5 mg, 1.890 mmol, 3.0 equiv) at rt. The resulting mixture was stirred for 2h at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 10 mL). The combined organic layers were washed with NaCl (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (3/1) to afford 4-benzyl-2-(methoxymethyl)-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (130 mg, 62.88%) as a white solid. MS (ESI): mass calcd. for C17H16N2O5, 328.11 m/z, found 329.05 $[M+H]^+$.



7-amino-4-benzyl-2-(methoxymethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of 4-benzyl-2-(methoxymethyl)-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (130 mg, 0.396 mmol, 1 equiv) in methanol (5 mL) was added Pd/C (10%, 421.3 mg, 3.960 mmol, 10 equiv) under nitrogen atmosphere. The mixture was hydrogenated at room temperature for 30 min

under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. The crude product 7-amino-4-benzyl-2-(methoxymethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (100 mg, 84.65%) was used in the next step directly without further purification. MS (ESI): mass calcd. for $C_{17}H_{18}N_2O_3$, 298.13 m/z, found 353.10 $[M+H]^+$.

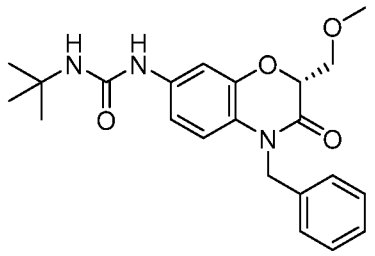


(S)-1-(4-benzyl-2-(methoxymethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

A solution of 7-amino-4-benzyl-2-(methoxymethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (70 mg, 0.235 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (232.6 mg, 2.350 mmol, 10 equiv) and Et_3N (237.4 mg, 2.350 mmol, 10 equiv) at rt. The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 20 mL). The combined organic layers were washed with NaCl (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product 40 mg was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 23 min; Wave Length: 220/254 nm; RT1(min): 13.384; RT2(min): 18.251; Sample Solvent: EtOH--HPLC; Injection Volume: 0.6 mL; Number Of Runs: 7) to afford (S)-1-(4-benzyl-2-(methoxymethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea (20.0 mg, 21.32%) as a white solid. MS (ESI): mass calcd. $C_{22}H_{27}N_3O_4$ for: 397.20m/z, found 398.15 [M+H]+. ^1H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.29 – 7.42 (m, 2H), 7.19 – 7.29 (m, 4H), 6.71 – 6.88 (m, 1H), 6.57 – 6.71 (m, 1H), 5.94 (s, 1H), 5.10 – 5.31 (m, 1H), 4.89 – 5.10 (m, 2H), 3.71 – 3.81 (m, 2H), 3.30 (s, 3H), 1.25 (s, 9H). And to afford (R)-1-(4-benzyl-2-(methoxymethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea (20.5 mg, 21.91%) as a white solid. MS (ESI): mass calcd. $C_{22}H_{27}N_3O_4$ for : 397.20m/z, found 398.15$[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.29 – 7.42 (m, 2H), 7.19 – 7.29 (m, 4H), 6.71 – 6.88 (m, 1H), 6.57 – 6.71 (m, 1H),

5.94 (s, 1H), 5.10 – 5.31 (m, 1H), 4.89 – 5.10 (m, 2H), 3.71 – 3.81 (m, 2H), 3.30 (s, 3H), 1.25 (s, 9H).

Example 289: (R)-1-(4-benzyl-2-(methoxymethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea



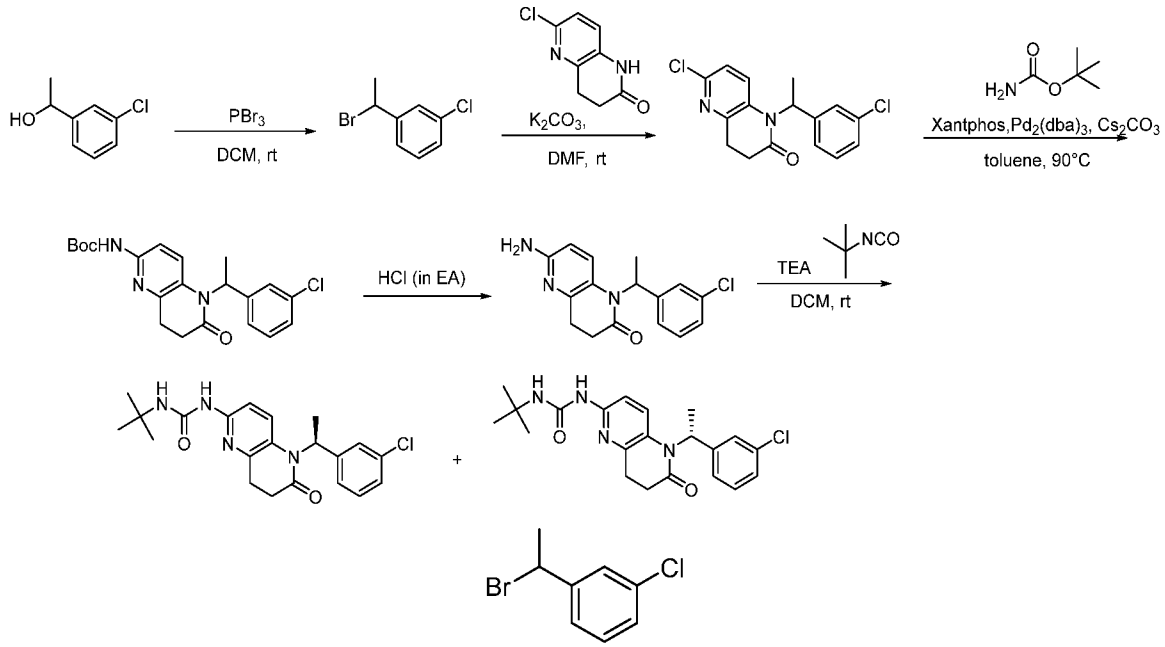
(R)-1-(4-benzyl-2-(methoxymethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

A solution of 7-amino-4-benzyl-2-(methoxymethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (70 mg, 0.235 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (232.6 mg, 2.350 mmol, 10 equiv) and Et3N (237.4 mg, 2.350 mmol, 10 equiv) at rt. The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 20 mL). The combined organic layers were washed with NaCl (20 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The crude product 40 mg was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 23 min; Wave Length: 220/254 nm; RT1(min): 13.384; RT2(min): 18.251; Sample Solvent: EtOH--HPLC; Injection Volume: 0.6 mL; Number Of Runs: 7) to afford (S)-1-(4-benzyl-2-(methoxymethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea (20.0 mg, 21.32%) as a white solid. MS (ESI): mass calcd. C22H27N3O4 for: 397.20m/z, found 398.15 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.19 (s, 1H), 7.29 – 7.42 (m, 2H), 7.19 – 7.29 (m, 4H), 6.71 – 6.88 (m, 1H), 6.57 – 6.71 (m, 1H), 5.94 (s, 1H), 5.10 – 5.31 (m, 1H), 4.89 – 5.10 (m, 2H), 3.71 – 3.81 (m, 2H), 3.30 (s, 3H), 1.25 (s, 9H). And to afford (R)-1-(4-benzyl-2-(methoxymethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea (20.5 mg, 21.91%) as a white solid. MS (ESI): mass calcd. C22H27N3O4 for : 397.20m/z, found 398.15[M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.19 (s, 1H), 7.29 – 7.42 (m, 2H), 7.19 – 7.29 (m, 4H), 6.71 – 6.88 (m, 1H), 6.57 – 6.71 (m,

1H), 5.94 (s, 1H), 5.10 – 5.31 (m, 1H), 4.89 – 5.10 (m, 2H), 3.71 – 3.81 (m, 2H), 3.30 (s, 3H), 1.25 (s, 9H).

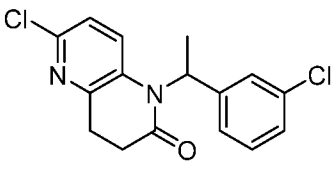
Example 290: (S)-1-(tert-butyl)-3-(5-(1-(3-chlorophenyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea

Synthetic Scheme



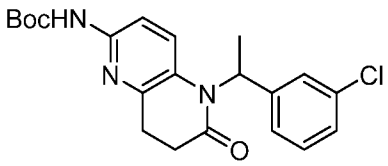
1-(1-bromoethyl)-3-chlorobenzene

To a solution of 1-(3-chlorophenyl)ethan-1-ol (500 mg, 3.193 mmol, 1 equiv) in DCM (15 mL) was added PBr_3 (950.6 mg, 3.512 mmol, 1.1 equiv) at 0 °C. The resulting mixture was placed at 0°C and stirred overnight until the starting material was totally consumed by TLC. The reaction mixture was quenched by ice water (10 mL) and extracted with EA (3 x 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column, eluted with PE/EA (3:1) to afford 1-(1-bromoethyl)-3-chlorobenzene (400 mg,57.08%) as a yellow oil.



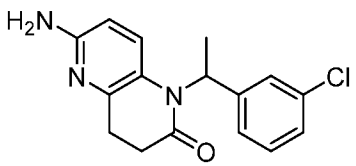
6-chloro-1-(1-(3-chlorophenyl)ethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one

To a solution of 1-(1-bromoethyl)-3-chlorobenzene (249.5 mg, 1.367 mmol, 1 equiv) in DMF (10 mL) was added K_2CO_3 (566.6 mg, 4.100 mmol, 3 equiv) and 1-(1-bromoethyl)-3-chlorobenzene (300 mg, 1.367 mmol, 1 equiv). The resulting mixture was placed at rt and stirred overnight until the starting material was totally consumed by LCMS. The reaction mixture was quenched by ice water (10 mL) and extracted with EA (3 x 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column, eluted with PE/EA (3:1) to afford 6-chloro-1-(1-(3-chlorophenyl)ethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (200 mg, 45.26%) as a yellow solid.MS (ESI): mass calcd. for $C_{16}H_{14}Cl_2N_2O$ 320.05 m/z, found 321.05 $[M+H]^+$.



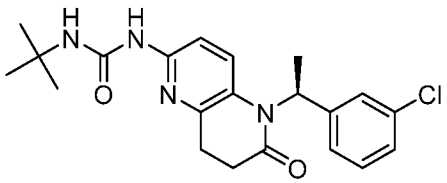
tert-butyl (5-(1-(3-chlorophenyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)carbamate

To a solution of 6-chloro-1-(1-(3-chlorophenyl)ethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (200 mg, 0.623 mmol, 1 equiv) in toluene (15 mL) was added tert-butyl carbamate (87.5 mg, 0.747 mmol, 1.2 equiv), Xantphos (36.0 mg, 0.062 mmol, 0.1 equiv), $Pd_2(dba)_3$ (57.0 mg, 0.062 mmol, 0.1 equiv) and Cs_2CO_3 (608.6 mg, 1.868 mmol, 3 equiv). The resulting mixture was placed at 90°C under a nitrogen atmosphere and stirred overnight until the starting material was totally consumed by LCMS. After cooled to room temperature the reaction mixture was quenched by ice water (10 mL) and extracted with EA (3 x 20 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column, eluted with PE/EA to afford tert-butyl (5-(1-(3-chlorophenyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)carbamate (140 mg, 53.72%) as a yellow solid.MS (ESI): mass calcd. for $C_{21}H_{24}ClN_3O_3$, 401.15 m/z, found 402.10 $[M+H]^+$.



6-amino-1-(1-(3-chlorophenyl)ethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one

To a solution of tert-butyl (5-(1-(3-chlorophenyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)carbamate (20 mg, 0.050 mmol, 1 equiv) in HCl (in EA) (2 mL). The resulting mixture was placed at rtand stirred overnight. The reaction mixture was concentrated under vacuum to yield 6-amino-1-(1-(3-chlorophenyl)ethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (80 mg, 60.87%) as a yellow solid.MS (ESI): mass calcd. for $C_{16}H_{16}ClN_3O$, 301.10 m/z, found 302.05 $[M+H]^+$.

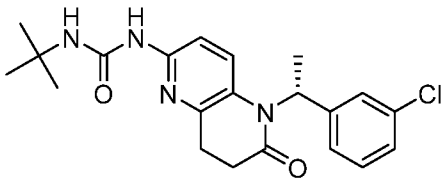


(S)-1-(tert-butyl)-3-(5-(1-(3-chlorophenyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea

To a stirred solution of 6-amino-1-(1-(3-chlorophenyl)ethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (80 mg, 0.265 mmol, 1 equiv) in DCM (10 mL) was added 2-isocyanato-2-methylpropane (131.4 mg, 1.325 mmol, 5 equiv) and TEA (80.4 mg, 0.795 mmol, 3 equiv) stirred overnight at rt. The reaction progress was monitored by LCMS. The reaction mixture was quenched by water (10 mL) and extracted with DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude was purified by flash chromatography with PE/EA and Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 73% B in 9 min, 73% B; Wave Length: 254/220 nm; RT1(min): 9.6; Number Of Runs: 0) and Chiral Prep-HPLC (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 13 min; Wave Length: 220/254 nm; RT1(min): 9.187; RT2(min): 10.914; Sample Solvent: EtOH--HPLC; Injection Volume: 1.2 mL; Number Of Runs: 4) to afford (S)-1-(tert-butyl)-3-(5-(1-(3-chlorophenyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea (3.6 mg, 3.38%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{25}ClN_4O_2$, 400.17 m/z, found 435.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.88 (s, 1H), 8.00 (s, 1H), 7.28 – 7.42 (m, 3H), 7.23 (d, J = 7.5Hz, 1H),

6.99 (q, J = 9.0 Hz, 2H), 6.07 (q, J = 7.1 Hz, 1H), 2.90 – 3.02 (m, 2H), 2.76 – 2.82 (m, 1H), 2.63 – 2.70 (m, 1H), 1.68 (d, J = 7.2 Hz, 3H), 1.30 (s, 9H). And another isomer to afford (R)-1-(tert-butyl)-3-(5-(1-(3-chlorophenyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea (5.2 mg, 4.89%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{25}ClN_4O_2$, 400.17 m/z, found 435.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.88 (s, 1H), 8.00 (s, 1H), 7.28 – 7.42 (m, 3H), 7.23 (d, J = 7.5Hz, 1H), 6.99 (q, J = 9.0 Hz, 2H), 6.07 (q, J = 7.1 Hz, 1H), 2.90 – 3.02 (m, 2H), 2.76 – 2.82 (m, 1H), 2.63 – 2.70 (m, 1H), 1.68 (d, J = 7.2 Hz, 3H), 1.30 (s, 9H).

Example 291: (R)-1-(tert-butyl)-3-(5-(1-(3-chlorophenyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea



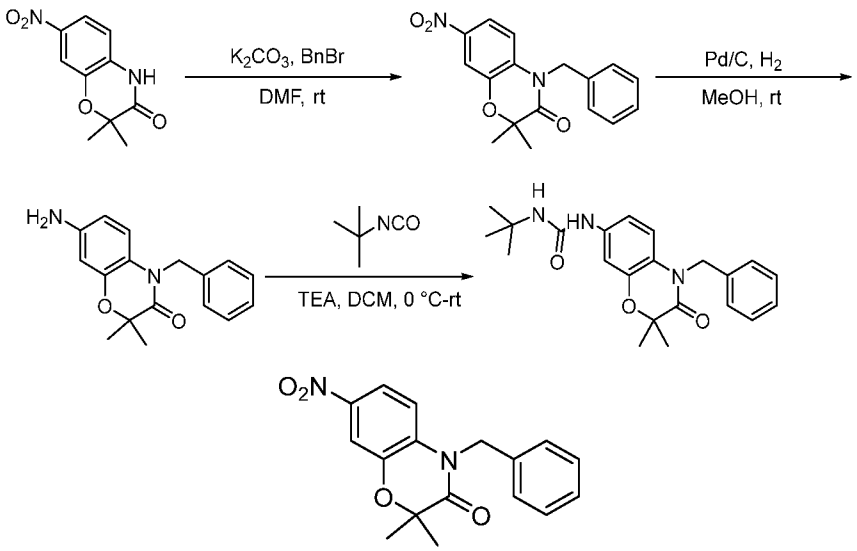
(R)-1-(tert-butyl)-3-(5-(1-(3-chlorophenyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea

To a stirred solution of 6-amino-1-(1-(3-chlorophenyl)ethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (80 mg, 0.265 mmol, 1 equiv) in DCM (10 mL) was added 2-isocyanato-2-methylpropane (131.4 mg, 1.325 mmol, 5 equiv) and TEA (80.4 mg, 0.795 mmol, 3 equiv) stirred overnight at rt. The reaction progress was monitored by LCMS. The reaction mixture was quenched by water (10 mL) and extracted with DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude was purified by flash chromatography with PE/EA and Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 73% B in 9 min, 73% B; Wave Length: 254/220 nm; RT1(min): 9.6; Number Of Runs: 0) and Chiral Prep-HPLC (Column: CHIRALPAK IF, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 13 min; Wave Length: 220/254 nm; RT1(min): 9.187; RT2(min): 10.914; Sample Solvent: EtOH--HPLC; Injection Volume: 1.2 mL; Number Of Runs: 4) to afford (S)-1-(tert-butyl)-3-(5-(1-(3-chlorophenyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea (3.6 mg, 3.38%) as a

white solid. MS (ESI): mass calcd. for $C_{21}H_{25}ClN_4O_2$, 400.17 m/z, found 435.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.88 (s, 1H), 8.00 (s, 1H), 7.28 – 7.42 (m, 3H), 7.23 (d, J = 7.5Hz, 1H), 6.99 (q, J = 9.0 Hz, 2H), 6.07 (q, J = 7.1 Hz, 1H), 2.90 – 3.02 (m, 2H), 2.76 – 2.82 (m, 1H), 2.63 – 2.70 (m, 1H), 1.68 (d, J = 7.2 Hz, 3H), 1.30 (s, 9H). And another isomer to afford (R)-1-(tert-butyl)-3-(5-(1-(3-chlorophenyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea (5.2 mg, 4.89%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{25}ClN_4O_2$, 400.17 m/z, found 435.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.88 (s, 1H), 8.00 (s, 1H), 7.28 – 7.42 (m, 3H), 7.23 (d, J = 7.5Hz, 1H), 6.99 (q, J = 9.0 Hz, 2H), 6.07 (q, J = 7.1 Hz, 1H), 2.90 – 3.02 (m, 2H), 2.76 – 2.82 (m, 1H), 2.63 – 2.70 (m, 1H), 1.68 (d, J = 7.2 Hz, 3H), 1.30 (s, 9H).

Example 292: 1-(4-benzyl-2,2-dimethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

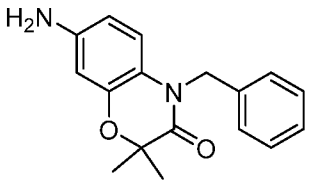
Synthetic Scheme



4-benzyl-2,2-dimethyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

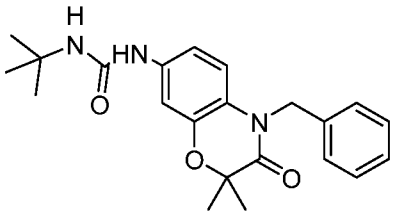
To a stirred solution of 2,2-dimethyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (300 mg, 1.350 mmol, 1 equiv) in anhydrous DMF (10 mL) was added K_2CO (373 mg, 2.700 mmol, 2 equiv) and BnBr (346 mg, 2.025 mmol, 1.5 equiv) at rt. The reaction mixture was stirred for 1.5 h at rt. After completion of reaction, the reaction mixture was quenched by addition of water (15 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate filtered and concentrated under

reduced pressure. The residue was purified by silica gel column, eluted with PE/EA (3:1) to give 4-benzyl-2,2-dimethyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (420 mg, 99.60%) as a yellow oil. MS (ESI): mass calcd. for $C_{17}H_{16}N_2O_4$: 312.11, found: 313.20 $[M+H]^+$.



7-amino-4-benzyl-2,2-dimethyl-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of 4-benzyl-2,2-dimethyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (420 mg, 1.345 mmol, 1 equiv) in MeOH (15 mL) was added Pd/C under N_2 atmosphere. The reaction was stirred at room temperature for 2.5 h under H_2 atmosphere. The reaction was filtered. The filtrate was concentrated to give 7-amino-4-benzyl-2,2-dimethyl-2H-benzo[b][1,4]oxazin-3(4H)-one (340 mg, 87.11%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{18}N_2O_2$: 282.14, found: 283.10$[M+H]^+$.



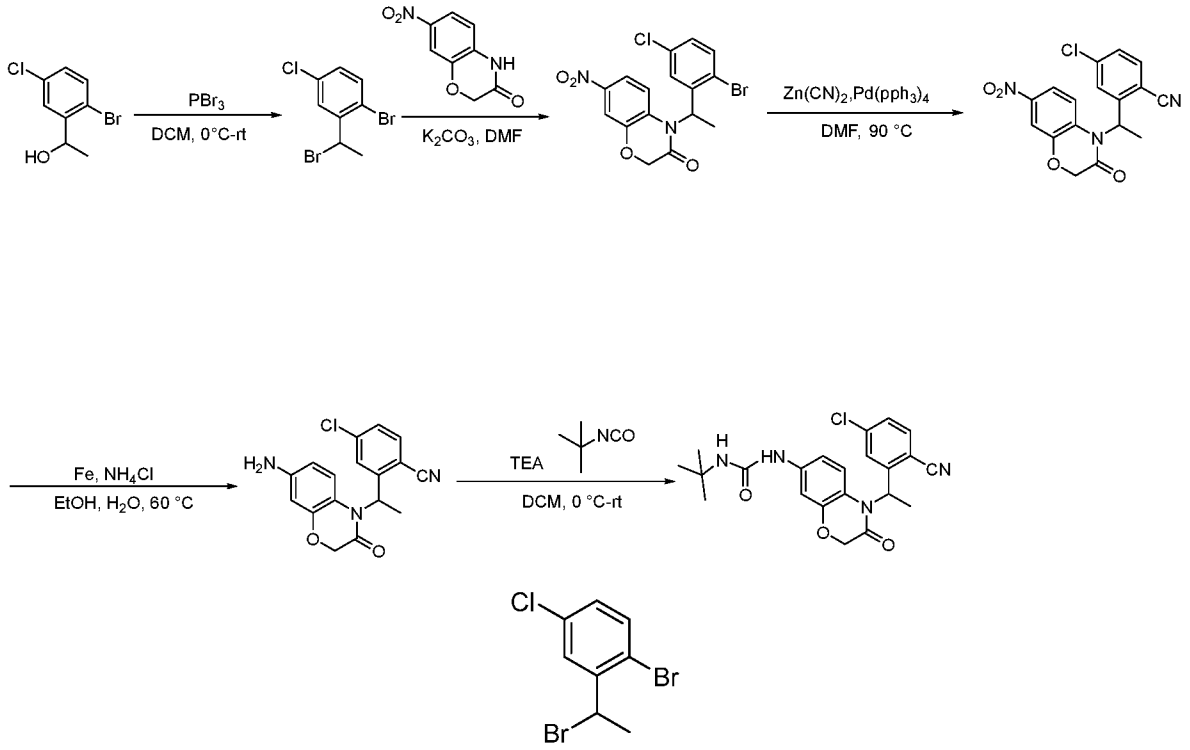
1-(4-benzyl-2,2-dimethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

To a mixture of 7-amino-4-benzyl-2,2-dimethyl-2H-benzo[b][1,4]oxazin-3(4H)-one (110 mg, 0.390 mmol, 1 equiv) and TEA (236 mg, 2.340 mmol, 6 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (232 mg, 2.340 mmol, 6 equiv) at 0°C. The reaction was stirred for overnight at rt. The reaction mixture was quenched by water (10 mL) and extracted with DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by silica gel column (PE/EA 1:1) and Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm) to give 1-(4-benzyl-2,2-dimethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea (21.7 mg, 14.53%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_3$, 381.21 m/z, found 382.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6)

δ 8.20 (s, 1H), 7.31 – 7.35 (m, 2H), 7.20 – 7.26 (m, 4H), 6.83 (d, *J* = 8.7 Hz, 1H), 6.72 (dd, *J* = 8.7, 2.3 Hz, 1H), 5.94 (s, 1H), 5.08 (s, 2H), 1.46 (s, 6H), 1.26 (s, 9H).

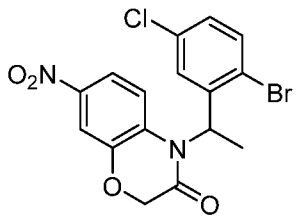
Example 293: 1-(tert-butyl)-3-(4-(1-(5-chloro-2-cyanophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

Synthetic Scheme



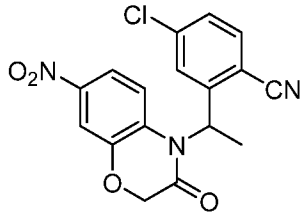
1-bromo-2-(1-bromoethyl)-4-chlorobenzene

To a mixture of 1-(2-bromo-5-chlorophenyl)ethan-1-ol (300 mg, 1.047 mmol, 1 equiv) in DCM (5 mL) was added PBr_3 (567 mg, 2.094 mmol, 2 equiv) at 0 °C. The reaction was stirred for overnight at rt. The reaction mixture was quenched by ice water (10 mL) and the pH value of the aqueous phase was adjusted to 8 with $NaHCO_3$ (aq.). The mixture was extracted with DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by silica gel column, eluted with PE/EA (20:1) to give 1-bromo-2-(1-bromoethyl)-4-chlorobenzene (218 mg, 69.76%) as yellow oil.



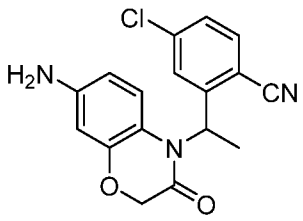
4-(1-(2-bromo-5-chlorophenyl)ethyl)-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

To a mixture of 7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (87 mg, 0.447 mmol, 1 equiv) and K_2CO_3 (187 mg, 1.340 mmol, 3 equiv) in DMF (5 mL). 1-Bromo-2-(1-bromoethyl)-4-chlorobenzene (200 mg, 0.670 mmol, 1.5 equiv) was added into the solution. The resulting solution was stirred for overnight at rt. The reaction mixture was quenched by water (10 mL) and extracted with DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum The residue was purified by silica gel column, eluted with PE/EA (3:1) to afford 4-(1-(2-bromo-5-chlorophenyl)ethyl)-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (150 mg, 81.55%) as a yellow solid.



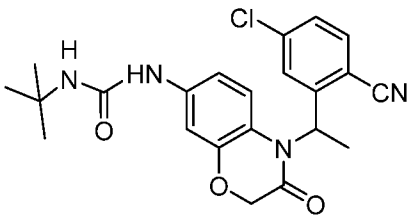
4-chloro-2-(1-(7-nitro-3-oxo-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)ethyl)benzonitrile

A solution of 4-(1-(2-bromo-5-chlorophenyl)ethyl)-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (150 mg, 0.360 mmol, 1 equiv) in DMF (3 mL) was added $Zn(CN)_2$ (106 mg, 0.90 mmol, 2.5 equiv) and $Pd(PPh_3)_4$ (42 mg, 0.036 mmol, 0.1 equiv) at rt. The resulting mixture was maintained under nitrogen and stirred at 90 °C for overnight. After cooling down to rt, the reaction was quenched with water (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography eluted with PE/EA (2:1) to afford 4-chloro-2-(1-(7-nitro-3-oxo-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)ethyl)benzonitrile (100 mg, 77.52%). LC/MS: mass calcd. for $C_{17}H_{12}ClN_3O_4$: 357.05, found: 358.00 $[M+H]^+$.



2-(1-(7-amino-3-oxo-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)ethyl)-4-chlorobenzonitrile

To a mixture of 4-chloro-2-(1-(7-nitro-3-oxo-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)ethyl)benzonitrile (50 mg, 0.140 mmol, 1 equiv) in EtOH (10 mL) and water (2 mL). Fe (78 mg, 1.400 mmol, 10 equiv) and NH_4Cl (74.76 mg, 1.400 mmol, 10 equiv) were added into the mixture. The resulting solution was stirred at 60 °C for 1 h. The resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography with PE/EA (1:1) to afford 2-(1-(7-amino-3-oxo-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)ethyl)-4-chlorobenzonitrile (33 mg, 72.04%) as a yellow solid. LC/MS: mass calcd. for $C_{17}H_{14}ClN_3O_2$, 327.08 m/z, found 328.15 $[M+H]^+$.



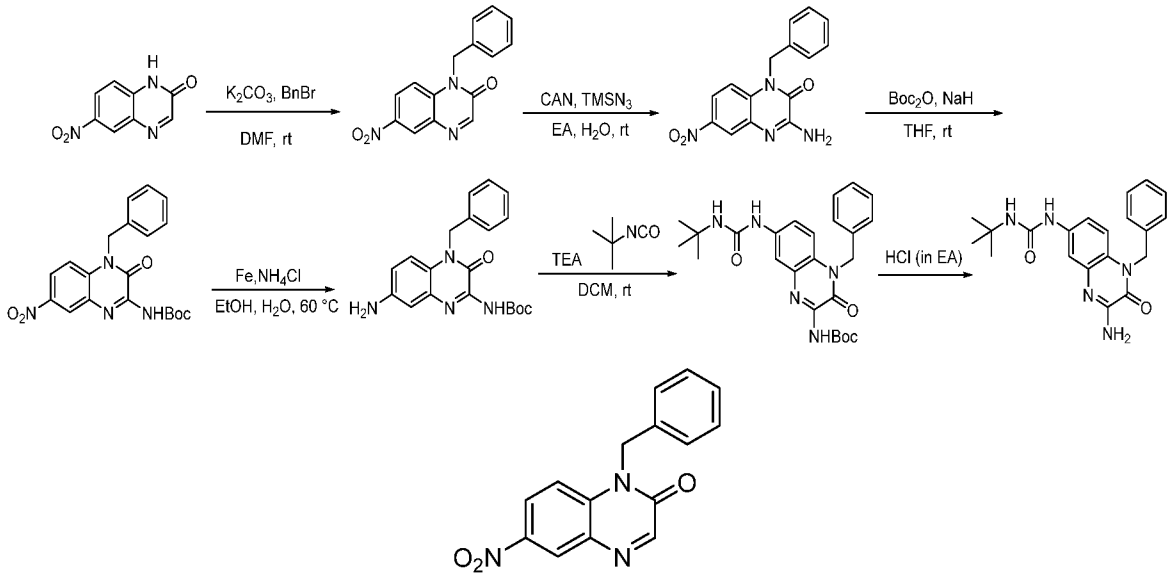
1-(tert-butyl)-3-(4-(1-(5-chloro-2-cyanophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a mixture of 2-(1-(7-amino-3-oxo-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)ethyl)-4-chlorobenzonitrile (33 mg, 0.101 mmol, 1 equiv) and TEA (21 mg, 0.202 mmol, 2 equiv) in DCM (4 mL) was added 2-isocyanato-2-methylpropane (30 mg, 0.303 mmol, 3 equiv) at 0 °C. The reaction was stirred for overnight at rt. The reaction mixture was quenched by water (10 mL) and extracted with DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel column with PE/EA (1:1) and Prep-HPLC (Column: XBridge Prep Phenyl OBD Column, 19*150 mm, 5μm; Mobile Phase A: Water(50 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 57% B in 10 min, 57% B; Wave Length: 254/220 nm) to give 1-(tert-butyl)-3-(4-(1-(5-chloro-2-cyanophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea (4.7 mg, 10.92%) as a white solid. LC/MS: mass calcd. for $C_{22}H_{23}ClN_4O_3$, 426.15 m/z, found 427.05

$[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.79 – 7.84 (m, 2H), 7.58 (dd, J = 8.3, 2.0 Hz, 1H), 7.13 (d, J = 2.3 Hz, 1H), 6.88 (d, J = 8.9 Hz, 1H), 6.77 (dd, J = 8.8, 2.4 Hz, 1H), 5.91 – 5.93 (m, 2H), 4.54 (s, 2H), 1.82 (d, J = 7.0 Hz, 3H), 1.26 (s, 9H).

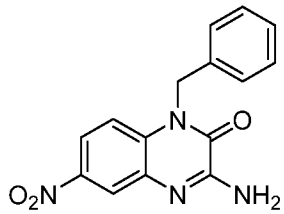
Example 294: 1-(3-amino-1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea

Synthetic Scheme



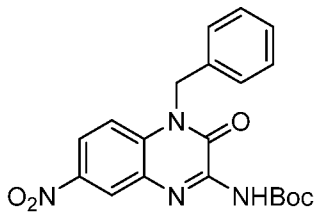
1-benzyl-6-nitroquinoxalin-2(1H)-one

To a solution of 6-nitro-1H-quinoxalin-2-one (3 g, 15.695 mmol, 1 equiv) in DMF (50 mL) was added K_2CO_3 (6.51 g, 47.104 mmol, 3 equiv) and BnBr (4.03 g, 23.562 mmol, 1.5 equiv). The resulting mixture was placed at rt and stirred overnight until the starting material was totally consumed by LCMS, The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 50 mL). The combined organic layers were washed with NaCl (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (3/1) to afford 1-benzyl-6-nitroquinoxalin-2(1H)-one (3 g, 65.14%) as a yellow solid.MS (ESI): mass calcd. for $C_{15}H_{11}N_3O_3$ 281.08 m/z, found 282.05 $[M+H]^+$.



3-amino-1-benzyl-6-nitroquinoxalin-2(1H)-one

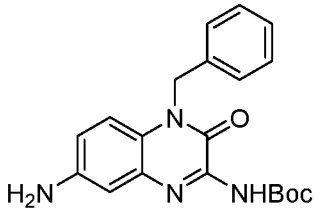
An oven-dried Schlenk tube was charged with 1-benzyl-6-nitroquinoxalin-2(1H)-one (1 g, 3.555 mmol, 1.0 equiv), CAN (2.93 g, 5.325 mmol, 1.5 equiv) and a magnetic stirring bar, and then was purged with nitrogen for three times. EtOAc (36 mL) and H_2O (128.1 mg, 7.111 mmol, 2.0 equiv) were added in turn via respective syringes, and the mixture was stirred at 20 °C in water bath. Then, $TMSN_3$ (1.23 g, 10.676 mmol, 3.0 equiv) was added in turn via a syringe, and the mixture was stirred under the previous conditions until the substrate was consumed (monitored by TLC, about 10 hour). The mixture was added with CH_2Cl_2 (200 mL) and saturated aqueous Na_2CO_3 (200 mL). The organic layer was isolated and the remaining aqueous phase was further extracted with CH_2Cl_2 (150 mL × 2). The combined organic phase was washed with 0.3 M HCl (100 mL × 2), and adjusted pH to 8 by the addition of saturated aqueous Na2CO3, followed by extraction with CH_2Cl_2 (150 mL × 3). The received organic phase was washed with saturated brine (200 mL). The organic layer was dried over Na_2SO_4, and then filtered. The filtrate was evaporated under reduced pressure, and the resulting residue was purified by column chromatography on neutral aluminum oxide (petroleum ether/ethyl acetate, in some cases, 5-10 vol % triethylamine is helpful.) to afford 3-amino-1-benzyl-6-nitroquinoxalin-2(1H)-one (300 mg, 24.48%) as a yellow solid.MS (ESI): mass calcd. for $C_{15}H_{12}N_4O_3$, 296.09 m/z, found 297.10 $[M+H]^+$.



tert-butyl (4-benzyl-7-nitro-3-oxo-3,4-dihydroquinoxalin-2-yl)carbamate

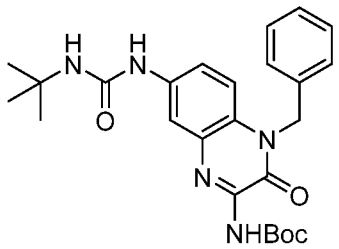
In a 100 mL round bottom flask, to a solution of 3-amino-1-benzyl-6-nitroquinoxalin-2(1H)-one (300 mg, 1.013 mmol, 1 equiv) in THF (10 mL) was added 60% NaH (60.7 mg, 1.519 mmol, 1.5 equiv) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0°C for 0.5 h .

Then a solution of Boc_2O (331.4 mg, 1.519 mmol, 1.5 equiv) in 5 mL THF was added dropwise and the mixture was stirred for another 120 mins. The reaction was quenched with water/sat. NH_4Cl (40 mL), and then the mixture was extracted with ether/EtOAc (2 × 30mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford tert-butyl (4-benzyl-7-nitro-3-oxo-3,4-dihydroquinoxalin-2-yl)carbamate (200 mg, 49.45%) as a yellow solid.MS (ESI): mass calcd. for $C_{20}H_{20}N_4O_5$, 396.14 m/z, found 397.10 [M+H]+ .



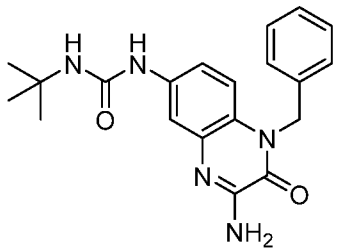
tert-butyl (7-amino-4-benzyl-3-oxo-3,4-dihydroquinoxalin-2-yl)carbamate

To a solution of tert-butyl (4-benzyl-7-nitro-3-oxo-3,4-dihydroquinoxalin-2-yl)carbamate (200 mg, 0.505 mmol, 1 equiv) in EtOH (10 mL) and H_2O (2.5 mL) was added Fe (281.7 mg, 5.045 mmol, 10 equiv) and NH_4Cl (269.8 mg, 5.045 mmol, 10 equiv).The resulting mixture was stirred for overnight at 60 °C. The reaction progress was monitored by LCMS, the reaction mixture was quenched by water and extracted with EA (3 × 20 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford tert-butyl (7-amino-4-benzyl-3-oxo-3,4-dihydroquinoxalin-2-yl)carbamate (100 mg, 46.83%) as a yellow solid.MS (ESI): mass calcd. for $C_{20}H_{22}N_4O_3$, 366.17 m/z, found 367.10 $[M+H]^+$.



tert-butyl (4-benzyl-7-(3-(tert-butyl)ureido)-3-oxo-3,4-dihydroquinoxalin-2-yl)carbamate

To a stirred solution of tert-butyl (7-amino-4-benzyl-3-oxo-3,4-dihydroquinoxalin-2-yl)carbamate (90 mg, 0.246 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (121.7 mg, 1.228 mmol, 5 equiv) and TEA (74.5 mg, 0.737 mmol, 3 equiv) stirred overnight at rt. The reaction progress was monitored by LCMS. The reaction mixture was quenched by water and extracted with EA (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford tert-butyl (4-benzyl-7-(3-(tert-butyl)ureido)-3-oxo-3,4-dihydroquinoxalin-2-yl)carbamate (30 mg, 25.68%) as a yellow solid.MS (ESI): mass calcd. for $C_{25}H_{31}N_5O_4$, 465.24 m/z, found 466.15 $[M+H]^+$.

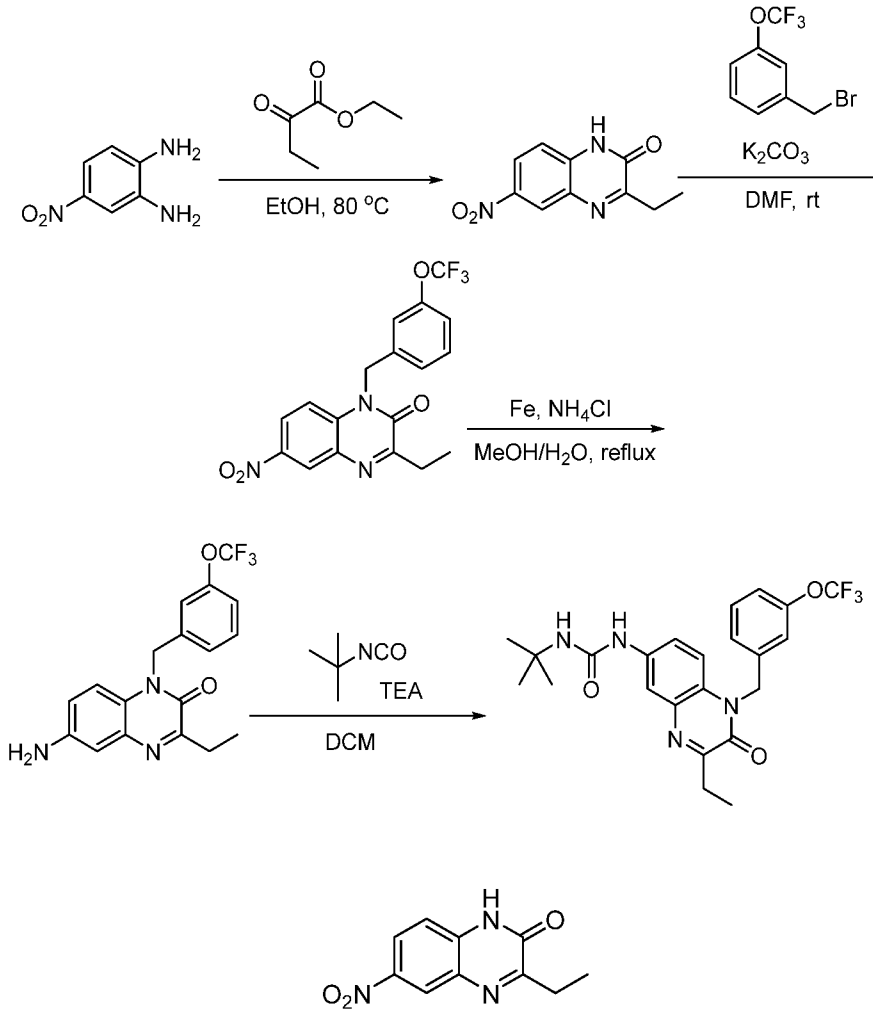


1-(3-amino-1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea

To a stirred solution of tert-butyl (4-benzyl-7-(3-(tert-butyl)ureido)-3-oxo-3,4-dihydroquinoxalin-2-yl)carbamate (30 mg, 0.064 mmol, 1 equiv)in HCl (in EA) (10 mL) stirred 2 h at rt. The reaction mixture was concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-100% ethyl acetate/petroleum ether) to afford 30 mg crude product as a white solid. The compound was separated by preparative HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 73% B in 9 min, 73% B; Wave Length: 254/220 nm; RT1(min): 9.6; Number Of Runs: 0) to afford 1-(3-amino-1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea (9.3 mg, 29.89%) as a yellow solid.MS (ESI): mass calcd. for $C_{20}H_{23}N_5O_2$, 365.19 m/z, found 366.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.55 (br, 2H), 8.43 (s, 1H), 7.69 (d, J = 2.3 Hz, 1H), 7.21 – 7.37 (m, 5H), 7.15 (d, J = 9.1 Hz, 1H), 7.04 (dd, J = 9.0, 2.4 Hz, 1H), 6.03 (s, 1H), 5.44 (s, 2H), 1.28 (s, 9H).

Example 295: 1-(tert-butyl)-3-(3-ethyl-2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea

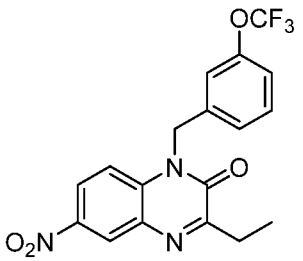
Synthetic Scheme



3-ethyl-6-nitroquinoxalin-2(1H)-one

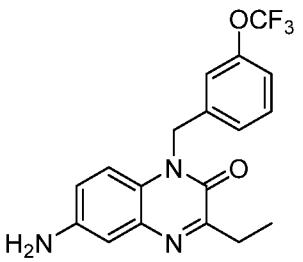
To a solution of 2-amino-4-nitroaniline (2 g, 13.060 mmol, 1 equiv) in ethyl alcohol (30 mL) was added ethyl 2-oxobutanoate (2.039 g, 15.667 mmol, 1.20 equiv). The reaction was stirred at 80 °C for 3 h. The mixture was allowed to cool down to rt. Quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give tert-butyl 3-ethyl-6-nitro-1H-quinoxalin-2-one (2.5 g, 87.33%) as a red solid. MS (ESI): mass calcd. for $C_{10}H_9N_3O_3$: 219.06 m/z, found 220.10 $[M+H]^+$

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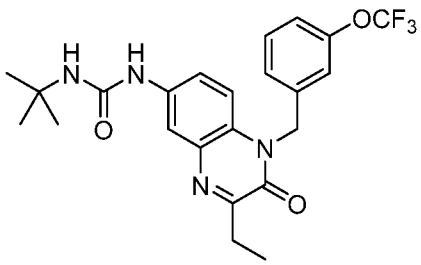
3-ethyl-6-nitro-1-(3-(trifluoromethoxy)benzyl)quinoxalin-2(1H)-one

To a solution of 3-ethyl-6-nitro-1H-quinoxalin-2-one (700 mg, 3.193 mmol, 1 equiv) and 1-(bromomethyl)-3-(trifluoromethoxy)benzene (2443.30 mg, 9.579 mmol, 3 equiv) in DMF (10 mL) was added K_2CO_3 (1333.70 mg, 9.579 mmol, 3 equiv). The reaction was stirred at rt for 3 h. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 3-ethyl-6-nitro-1-{[3-(trifluoromethoxy)phenyl]methyl}quinoxalin-2-one (819 mg, 65.20%) as a red solid. LC/MS: mass calcd. for $C_{18}H_{14}F_3N_3O_4$: 393.09, found: 394.05 $[M+H]^+$.



6-amino-3-ethyl-1-(3-(trifluoromethoxy)benzyl)quinoxalin-2(1H)-one

To a solution of 3-ethyl-6-nitro-1-{[3-(trifluoromethoxy)phenyl]methyl}quinoxalin-2-one (400 mg, 1.017 mmol, 1 equiv) in methanol (15 mL) and water (1.5 mL) was added iron (567.93 mg, 10.170 mmol, 10 equiv) and NH_4Cl (543.98 mg, 10.170 mmol, 10 equiv). The reaction was stirred at 60 °C for 3 h. The mixture was allowed to cool down to rt. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-3-ethyl-1-{[3-(trifluoromethoxy)phenyl]methyl}quinoxalin-2-one (300 mg, 81.19%) as a white solid. LC/MS (ESI): mass calcd. for $C_{18}H_{16}F_3N_3O_2$: 363.12 m/z, found:364.05 $[M+H]^+$.

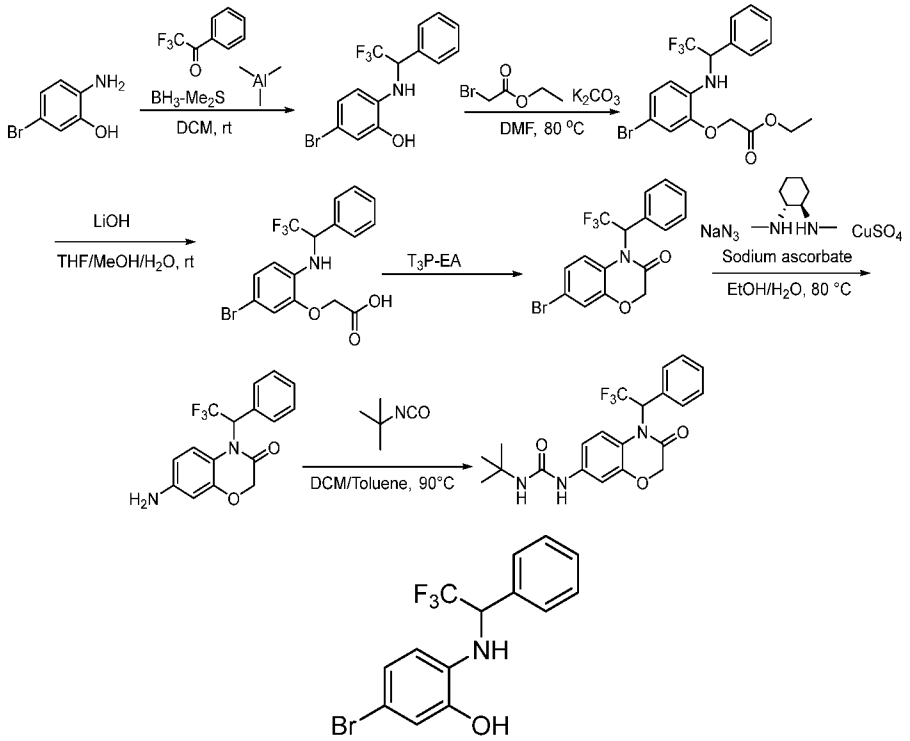


1-(tert-butyl)-3-(3-ethyl-2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea

To a solution of 6-amino-3-ethyl-1-{[3-(trifluoromethoxy)phenyl]methyl}quinoxalin-2-one (100 mg, 0.275 mmol, 1 equiv) and 2-isocyanato-2-methylpropane (81.85 mg, 0.825 mmol, 3 equiv) in DCM (3 mL) was added TEA (83.55 mg, 0.825 mmol, 3 equiv). The reaction was stirred at rt for 3 h. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm(eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-(3-ethyl-2-oxo-1-{[3-(trifluoromethoxy)phenyl]methyl}quinoxalin-6-yl)urea (25.1 mg, 19.69%) as a white solid. LC/MS (ESI): mass calcd. for $C_{23}H_{25}F_3N_4O_3$:462.19 m/z, found:461.00 $[M-H]^-$. ^{19}F NMR (282 MHz, DMSO) δ -56.69.^1H NMR (300 MHz, DMSO-d_6) δ 8.40 (s, 1H), 7.96 (m, 1H), 7.45 (m, 1H), 7.18 – 7.38 (m, 5H), 6.03 (s, 1H), 5.50 (s, 2H), 2.89 (m, 2H), 1.26-1.30 (m, 12H).

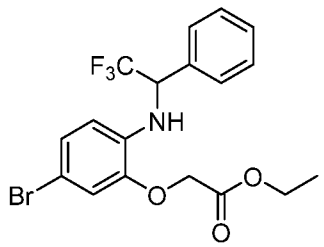
Example 296: 1-(tert-butyl)-3-(3-oxo-4-(2,2,2-trifluoro-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

Synthetic Scheme



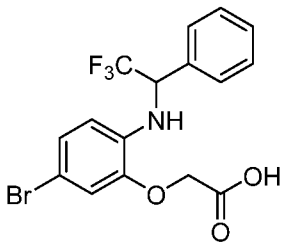
5-bromo-2-((2,2,2-trifluoro-1-phenylethyl)amino)phenol

To a solution of 2-amino-5-bromophenol (1 g, 5.318 mmol, 1 equiv) and trifluoroacetophenone (0.93 g, 5.318 mmol, 1 equiv) in DCM (20 mL) was added trimethylaluminium (1.15 g, 15.954 mmol, 3 equiv) under N_2. The reaction was stirred at rt under N_2 for 15h. To the above mixture was added BH_3-Me_2S (10.64 mL, 10.636 mmol, 2 equiv, 1.0 M in THF). The resulting mixture was stirred for additional 2h at rt. The reaction was quenched by dropwise addition of 20% aqueos NaOH and the vaqueous layer was extracted with DCM (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 5-bromo-2-[(2,2,2-trifluoro-1-phenylethyl)amino]phenol (1.5 g, 81.48%) as an orange oil. MS (ESI): mass calcd. for $C_{14}H_{11}BrF_3NO$: 345.00 m/z, found 346.05, 348.05 $[M+H, M+H+2]^+$.



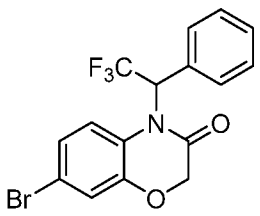
ethyl 2-(5-bromo-2-((2,2,2-trifluoro-1-phenylethyl)amino)phenoxy)acetate

To a solution of 5-bromo-2-[(2,2,2-trifluoro-1-phenylethyl)amino]phenol (400 mg, 1.156 mmol, 1 equiv) in DMF/H_2O(10:1, 11 mL) was added ethyl bromoacetate (231.58 mg, 1.387 mmol, 1.2 equiv) and K_2CO_3 (321.74 mg, 2.312 mmol, 2 equiv). The reaction was stirred at 80 °C for 1h. After cooling down to rt, the reaction was quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give ethyl 2-{5-bromo-2-[(2,2,2-trifluoro-1-phenylethyl)amino]phenoxy}acetate (400 mg, 80.08%) as an orange solid. MS (ESI): mass calcd. for $C_{18}H_{17}BrF_3NO_3$: 431.03 m/z, found 432.05, 434.05 [M+H, M+H+2]$^+$.



2-(5-bromo-2-((2,2,2-trifluoro-1-phenylethyl)amino)phenoxy)acetic acid

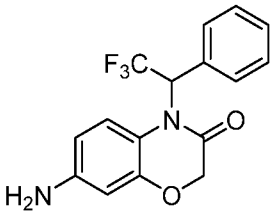
To a solution ofethyl 2-{5-bromo-2-[(2,2,2-trifluoro-1-phenylethyl)amino]phenoxy}acetate (240 mg, 0.555 mmol, 1 equiv) in THF/EtOH/H_2O(1:1:1 , 15 mL) was added LiOH (66.49 mg, 2.775 mmol, 5 equiv). The reaction was stirred at rt for 1h. The mixture was acidified to pH = 5 with 1N HCl. Diluted with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. This resulted in 5-bromo-2-[(2,2,2-trifluoro-1-phenylethyl)amino]phenoxyacetic acid (200 mg, 89.12%) as a white oil. MS (ESI): mass calcd. for $C_{16}H_{13}BrF_3NO_3$: 403.00 m/z, found:404.00, 406.00 [M+H, M+H+2]$^+$.



7-bromo-4-(2,2,2-trifluoro-1-phenylethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

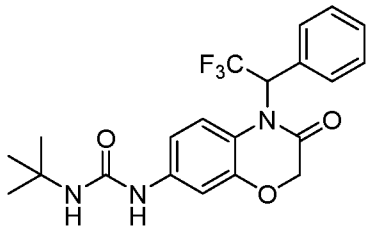
To a solution of 5-bromo-2-[(2,2,2-trifluoro-1-phenylethyl)amino]phenoxyacetic acid (200 mg, 0.495 mmol, 1 equiv) in EA (10 mL) was added T_3P (3 mL, 50% in EA). The reaction was stirred at rt for 1h. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue

was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-bromo-4-(2,2,2-trifluoro-1-phenylethyl)-2H-1,4-benzoxazin-3-one (140 mg, 73.27%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{11}BrF_3NO_2$: 384.99 m/z, found 385.90, 387.90 $[M+H, M+H+2]^+$.



7-amino-4-(2,2,2-trifluoro-1-phenylethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of 7-bromo-4-(2,2,2-trifluoro-1-phenylethyl)-2H-1,4-benzoxazin-3-one (140 mg, 0.363 mmol, 1 equiv) in EtOH/ H_2O (4:1, 10 mL) was added (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (30.94 mg, 0.218 mmol, 0.6 equiv), $CuSO_4$ (57.86 mg, 0.363 mmol, 1 equiv), azidosodium (70.71 mg, 1.089 mmol, 3 equiv) and sodium ascorbate (144.37 mg, 0.726 mmol, 2 equiv). The reaction was stirred at 80°C under N_2 for 3h. After cooling down to rt, the reaction was quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-amino-4-(2,2,2-trifluoro-1-phenylethyl)-2H-1,4-benzoxazin-3-one (70 mg, 59.91%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{13}F_3N_2O_2$: 322.09 m/z, found 323.05 $[M+H]^+$.



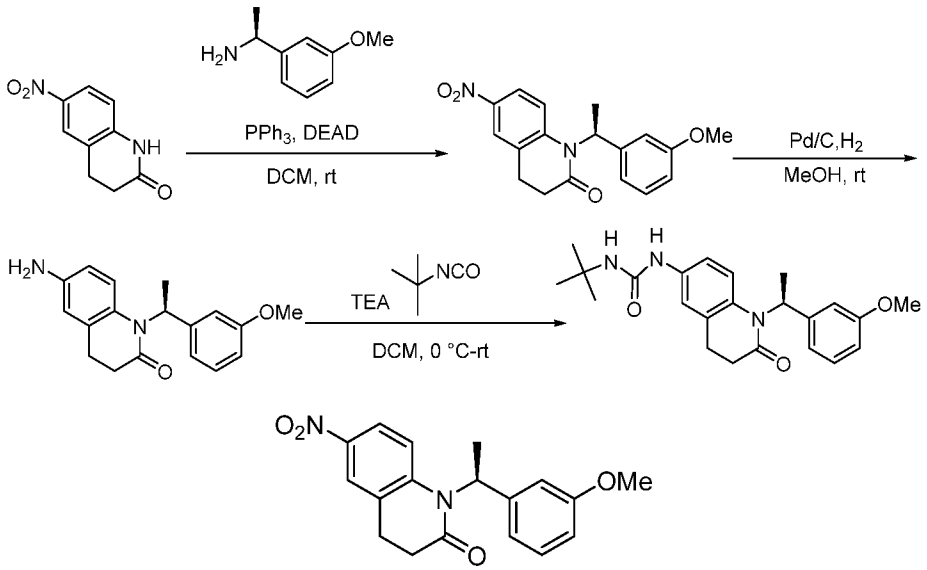
1-(tert-butyl)-3-(3-oxo-4-(2,2,2-trifluoro-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a solution of 7-amino-4-(2,2,2-trifluoro-1-phenylethyl)-2H-1,4-benzoxazin-3-one (90 mg, 0.279 mmol, 1 equiv) in DCM/Toluene (2:1, 7.5 mL) was added 2-isocyanato-2-methylpropane (166.10 mg, 1.674 mmol, 6 equiv).The reaction was stirred at 90 °C under N_2 for 3h. After cooling down to rt, the reaction was quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Shield RP18 OBD

Column, 30*150 mm, 5μm column (eluent: 45% to 67% (v/v) CH_3CN and Water (10 mmol/L NH_4HCO_3)) to afford the title compound 3-tert-butyl-1-[3-oxo-4-(2,2,2-trifluoro-1-phenylethyl)-2H-1,4-benzoxazin-7-yl]urea (22.3 mg, 18.95%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{22}F_3N_3O_3$: 421.16 m/z, found 422.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.03 – 8.30 (m, 1H), 7.37 – 7.60 (m, 5H), 7.15 – 7.30 (m, 1H), 6.78 – 6.96 (m, 1H), 6.56 – 6.78 (m, 2H), 5.80 – 6.06 (m, 1H), 4.68 – 4.88 (m, 2H), 1.20 – 1.39 (m, 9H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -63.7904.

Example 297: (S)-1-(tert-butyl)-3-(1-(1-(3-methoxyphenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

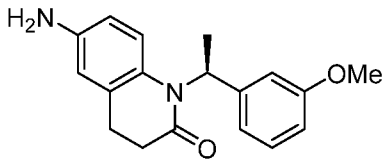
Synthetic Scheme



(S)-1-(1-(3-methoxyphenyl)ethyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one

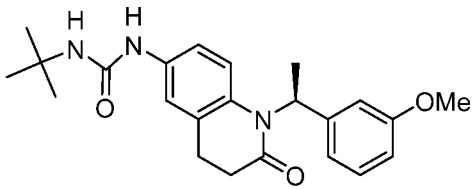
To a solution of (1R)-1-(3-methoxyphenyl)ethanol (238 mg, 1.561 mmol, 1 equiv) in DCM (6 mL) was added 6-nitro-3,4-dihydro-1H-quinolin-2-one (300 mg, 1.561 mmol, 1 equiv), triphenylphosphine (409 mg, 1.561 mmol, 1 equiv) and DEAD (272 mg, 1.561 mmol, 1 equiv) at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred overnight at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography with PE/EA (3:1) to afford (S)-

1-(1-(3-methoxyphenyl)ethyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (160 mg, 21.86%) as a yellow solid. MS (ESI): mass calcd. for $C_{18}H_{18}N_2O_4$, 326.13 m/z, found 327.10 $[M+H]^+$.



(S)-6-amino-1-(1-(3-methoxyphenyl)ethyl)-3,4-dihydroquinolin-2(1H)-one

To a mixture of (S)-1-(1-(3-methoxyphenyl)ethyl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (160 mg, 0.490 mmol, 1 equiv) in methanol (20 mL) was added Pd/C (10%) under nitrogen atmosphere. The mixture was hydrogenated at room temperature for 1 h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in (S)-6-amino-1-(1-(3-methoxyphenyl)ethyl)-3,4-dihydroquinolin-2(1H)-one (100 mg, 68.82%) as a white soild. MS (ESI): mass calcd. for $C_{18}H_{20}N_2O_2$, 296.15 m/z, found 297.15 $[M+H]^+$.



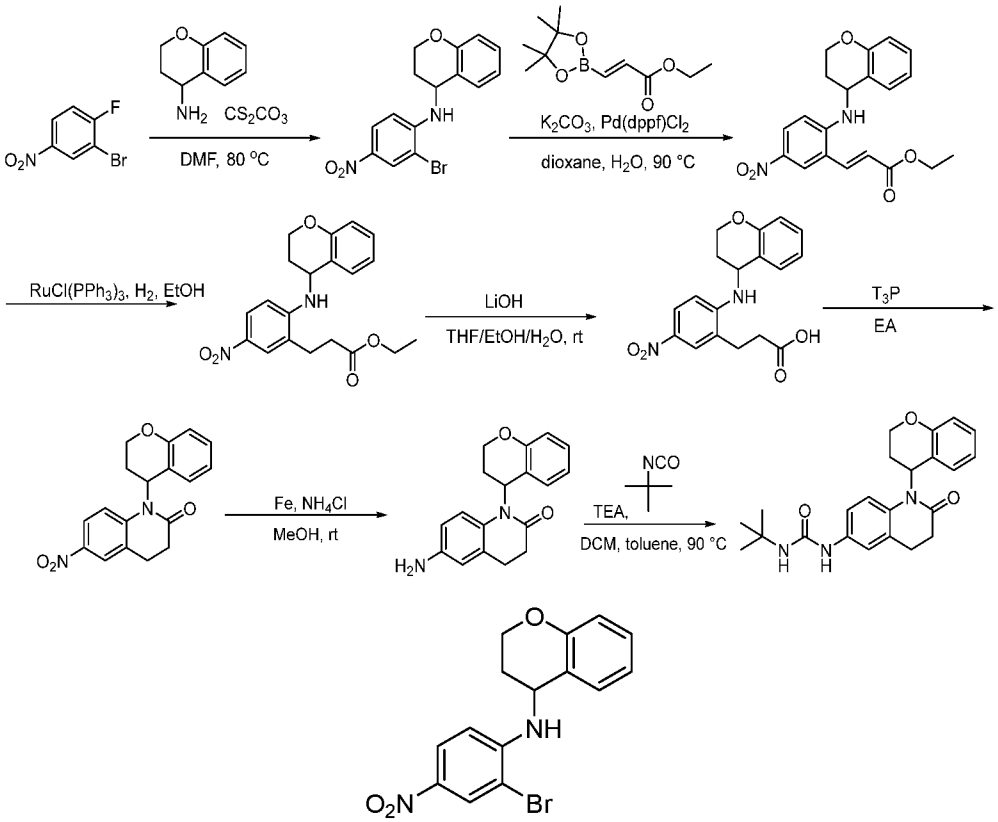
(S)-1-(tert-butyl)-3-(1-(1-(3-methoxyphenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a mixture of (S)-6-amino-1-(1-(3-methoxyphenyl)ethyl)-3,4-dihydroquinolin-2(1H)-one (100 mg, 0.337 mmol, 1 equiv) and TEA (68 mg, 0.674 mmol, 2 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (100 mg, 1.011 mmol, 3 equiv) at 0 °C. The reaction was stirred for overnight at rt. The reaction mixture was quenched by water (10 mL) and extracted with DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude was purified by flash chromatography with PE/EA (1:1) and Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 37% B to 59% B in 10 min, 59% B; Wave Length: 254/220 nm) to give (S)-1-(tert-butyl)-3-(1-(1-(3-methoxyphenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea (31.1 mg, 23.24%) as a white solid. MS (ESI): mass calcd. for $C_{23}H_{29}N_3O_3$, 395.22 m/z, found 396.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.25 (t, J = 7.9

Hz, 1H), 6.88 – 6.74 (m, 4H), 6.49 (d, *J* = 8.8 Hz, 1H), 6.12 (q, *J* = 7.1 Hz, 1H), 5.91 (s, 1H), 3.72 (s, 3H), 2.76 – 2.84 (m, 2H), 2.56 – 2.63 (m, 2H), 1.66 (d, *J* = 7.1 Hz, 3H), 1.25 (s, 9H).

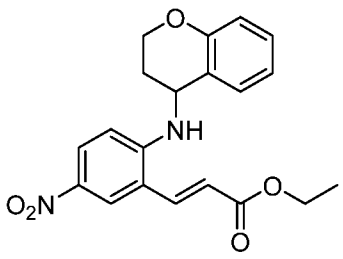
Example 298: 1-(tert-butyl)-3-(1-(chroman-4-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

Synthetic Scheme



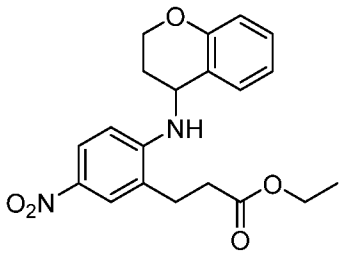
N-(2-bromo-4-nitrophenyl)chroman-4-amine

To a stirred mixture of 2-bromo-1-fluoro-4-nitrobenzene (1.5 g, 6.818 mmol, 1 equiv) and 3,4-dihydro-2H-1-benzopyran-4-amine (1.02 g, 6.818 mmol, 1 equiv) in DMF (20 mL) was added Cs_2CO_3 (4.44 g, 13.636 mmol, 2 equiv) at 25°C under air atmosphere. The resulting mixture was stirred for 2h at room temperature. Desired product could be detected by LCMS. The mixture was diluted with water (50 mL). The resulting mixture was extracted with EA (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue obtained was purified by silica gel chromatography (0-100% ethyl acetate/petroleum ether) to afford N-(2-bromo-4-nitrophenyl)chroman-4-amine (900 mg, 37.8%) as a white solid. MS (ESI): mass calcd. for $C_{15}H_{13}BrN_2O_3$: 348.00 m/z, found 349.00 $[M+H]^+$.



ethyl (E)-3-(2-(chroman-4-ylamino)-5-nitrophenyl)acrylate

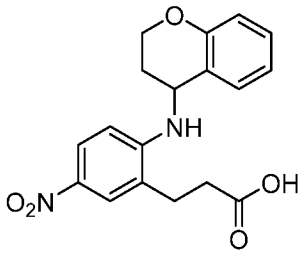
To a stirred mixture of N-(2-bromo-4-nitrophenyl)chroman-4-amine (465 mg, 1.332 mmol, 1 equiv) and ethyl (2E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-enoate (451.60 mg, 1.998 mmol, 1.5 equiv) in dioxane (15 mL) and H2O (1.5 mL) was added K_2CO_3 (552.13 mg, 3.996 mmol, 3 equiv) and $Pd(dppf)Cl_2$ (97.44 mg, 0.133 mmol, 0.1 equiv) at 25°C under air atmosphere. The resulting mixture was stirred for 2h at 90 degrees C under nitrogen. Desired product could be detected by LCMS. The mixture was diluted with water (30 mL). The resulting mixture was extracted with EA (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue obtained was purified by silica gel chromatography (0-100% ethyl acetate/petroleum ether) to afford ethyl (E)-3-(2-(chroman-4-ylamino)-5-nitrophenyl)acrylate (480 mg, 97.84%) as a white solid. MS (ESI): mass calcd. for $C_{20}H_{20}N_2O_5$: 368.14 m/z, found 369.15 $[M+H]^+$.



ethyl 3-(2-(chroman-4-ylamino)-5-nitrophenyl)propanoate

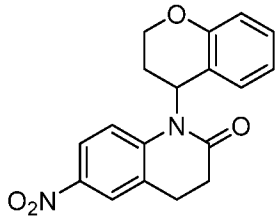
To a stirred mixture of ethyl (E)-3-(2-(chroman-4-ylamino)-5-nitrophenyl)acrylate (400 mg, 1.086 mmol, 1 equiv) in EtOH (5 mL) was added $RuCl(PPh_3)_2$ (399.05 mg, 0.434 mmol, 0.40 equiv) at 25 degrees C under air atmosphere. The resulting mixture was stirred for 2h at room temperature under hydrogen. Desired product could be detected by LCMS. The resulting mixture was filtered, and the filter cake was washed with EtOH (4 x 10 mL). The filtrate was concentrated under reduced pressure. The residue obtained was purified by silica gel chromatography (0-100% ethyl acetate/petroleum ether) to afford ethyl 3-(2-(chroman-4-ylamino)-5-nitrophenyl)propanoate (190

mg, 47.24%) as a white solid. MS (ESI): mass calcd. for $C_{30}H_{42}N_4O_4$: 370.15 m/z, found 371.15 $[M+H]^+$.



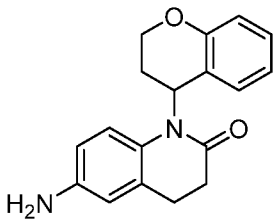
3-(2-(chroman-4-ylamino)-5-nitrophenyl)propanoic acid

To a stirred mixture of ethyl 3-(2-(chroman-4-ylamino)-5-nitrophenyl)propanoate (160 mg, 0.432 mmol, 1 equiv) in H_2O (1 mL), EtOH (1 mL) and THF (1 mL) was added LiOH (31.04 mg, 1.296 mmol, 3 equiv) at 0 degrees C under air atmosphere. The resulting mixture was stirred for 2h at room temperature. Desired product could be detected by LCMS. The mixture was basified to PH = 5 with 2N HCl and diluted with water (20 mL). The resulting mixture was extracted with EA (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 3-(2-(chroman-4-ylamino)-5-nitrophenyl)propanoic acid (120 mg, 81.15%) as a white solid. MS (ESI): mass calcd. for $C_{18}H_{18}N_2O_5$: 342.12 m/z, found 341.00 $[M-H]^-$.



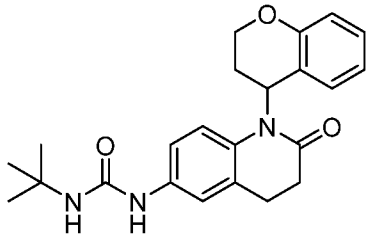
1-(chroman-4-yl)-6-nitro-3,4-dihydroquinolin-2(1H)-one

The 3-(2-(chroman-4-ylamino)-5-nitrophenyl)propanoic acid (110 mg, 0.321 mmol, 1 equiv) was dissolved in T_3P (2 mL) and EA (2 mL) at 0 degrees C under air atmosphere. The resulting mixture was stirred for 2h at room temperature. Desired product could be detected by LCMS. The mixture was diluted with water (10 mL). The resulting mixture was extracted with EA (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% ethyl acetate/petroleum ether) to afford 1-(chroman-4-yl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (100 mg, 95.96%) as a white solid. MS (ESI): mass calcd. for $C_{18}H_{16}N_2O_4$: 324.11 m/z, found 325.05$[M+H]^+$.



6-amino-1-(chroman-4-yl)-3,4-dihydroquinolin-2(1H)-one

To a stirred mixture of 1-(chroman-4-yl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (100 mg, 0.308 mmol, 1 equiv) in MeOH (5 mL) was added Fe (172.18 mg, 3.080 mmol, 10 equiv) and NH_4Cl (164.92 mg, 3.080 mmol, 10 equiv) at room temperature under air atmosphere. The resulting mixture was stirred for 2h at 80 degrees C. Desired product could be detected by LCMS. After cooling down to room temperature, the mixture was diluted with water (10 mL). The resulting mixture was extracted with EA (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% ethyl acetate/petroleum ether) to afford the 6-amino-1-(chroman-4-yl)-3,4-dihydroquinolin-2(1H)-one (50 mg, 55.09%) as a white solid. MS (ESI): mass calcd. for $C_{18}H_{18}N_2O_2$: 294.14 m/z, found 295.05$[M + H]^+$.

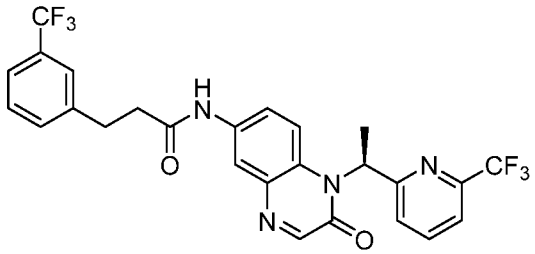


1-(tert-butyl)-3-(1-(chroman-4-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a stirred mixture of 6-amino-1-(chroman-4-yl)-3,4-dihydroquinolin-2(1H)-one (50 mg, 0.170 mmol, 1 equiv) and 2-isocyanato-2-methylpropane (84.20 mg, 0.850 mmol, 5 equiv) in DCM (2 mL) and toluene (0.5 mL) was added TEA (85.94 mg, 0.850 mmol, 5 equiv) dropwise at room temperature under air atmosphere. The resulting mixture was stirred for 2h at 90 degrees C. Desired product could be detected by LCMS. After cooling down to room temperature, the mixture was diluted with water (10 mL). The resulting mixture was extracted with EA (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a X Bridge Prep OBD C18 150 mm x 30 mm x 5μm column (eluent: 26% to 42% (v/v) CH3CN and H_2O with 10 mmol /L NH_4HCO_3) to afford the 1-(tert-butyl)-3-(1-(chroman-4-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea (7.2 mg,

10.72%) as a white solid. MS (ESI): mass calcd. for $C_{23}H_{27}N_3O_3$: 393.21 m/z, found 394.05[M +H] $^+$. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.34 (d, J = 2.5 Hz, 1H), 7.04 – 7.15 (m, 1H), 6.71 – 6.90 (m, 4H), 6.08 – 6.68 (m, 2H), 5.92 (s, 1H), 4.39 (d, J = 10.8 Hz, 1H), 4.19 – 4.33 (m, 1H), 2.78 – 2.89 (m, 2H), 2.58 – 2.69 (m, 3H), 1.92 (s, 1H), 1.24 (s, 9H).

Example 299: (S)-N-(2-oxo-1-(1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)phenyl)propanamide

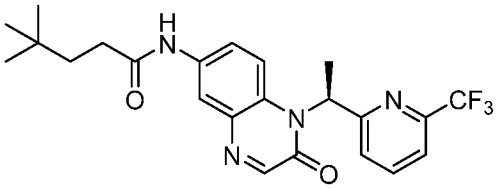


(S)-N-(2-oxo-1-(1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)phenyl)propanamide

To a solution of 3-[3-(trifluoromethyl)phenyl]propanoic acid (43.07 mg, 0.197 mmol, 1.1 equiv) in DMF (5 mL) was added 6-amino-1-[(1S)-1-[6-(trifluoromethyl)pyridin-2-yl]ethyl]quinoxalin-2-one (60 mg, 0.179 mmol, 1 equiv), HATU (88.72 mg, 0.233 mmol, 1.3 equiv) and DIEA (69.59 mg, 0.537 mmol, 3 equiv) at 0 °C. The reaction was stirred at rt for 1h. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound N-{2-oxo-1-[(1S)-1-[6-(trifluoromethyl)pyridin-2-yl]ethyl]quinoxalin-6-yl}-3-[3-(trifluoromethyl)phenyl]propanamide (28.4 mg, 29.61%) as a yellow solid. MS (ESI): mass calcd. for $C_{26}H_{20}F_6N_4O_2$: 534.15 m/z, found:535.15 [M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.25 (s, 1H), 8.10 – 8.20 (m, 1H), 7.95 – 8.10 (m, 1H), 7.77 – 7.86 (m, 1H), 7.50 – 7.70 (m, 6H), 7.00 – 7.50 (m, 1H), 6.55 (s, 1H), 2.97 – 3.11 (m, 2H), 2.62 – 2.77 (m, 2H), 1.90 – 1.98 (m, 3H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -60.9926, -66.5643.

Example 300: (S)-4,4-dimethyl-N-(2-oxo-1-(1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)pentanamide

Synthetic Scheme

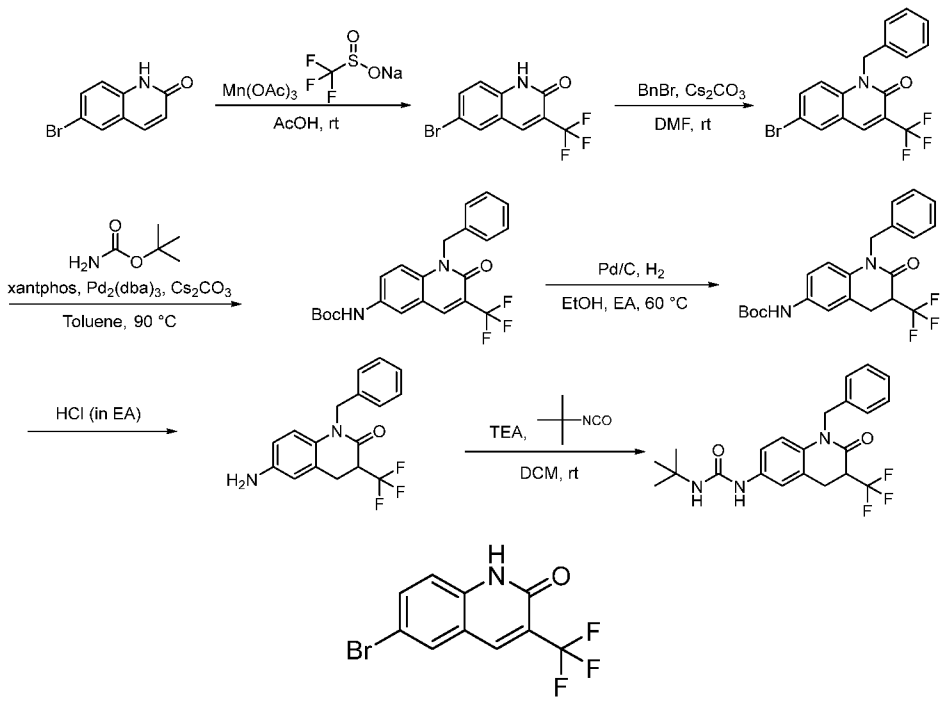


(S)-4,4-dimethyl-N-(2-oxo-1-(1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)pentanamide

To a solution of 4,4-dimethyl valeric acid (25.70 mg, 0.197 mmol, 1.1 equiv) in DMF (5 mL) was added 6-amino-1-[(1S)-1-[6-(trifluoromethyl)pyridin-2-yl]ethyl]quinoxalin-2-one (60 mg, 0.179 mmol, 1 equiv), HATU (88.72 mg, 0.233 mmol, 1.3 equiv) and DIEA (69.59 mg, 0.537 mmol, 3 equiv) at 0°C. The reaction was stirred at rt for 1h. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XSelect CSH Fluoro Phenyl, 30*150 mm, 5μm column (eluent: 33% to 56% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 4,4-dimethyl-N-{2-oxo-1-[(1S)-1-[6-(trifluoromethyl)pyridin-2-yl]ethyl]quinoxalin-6-yl}pentanamide (31.9 mg, 39.81%) as a yellow solid. MS (ESI): mass calcd. for $C_{23}H_{25}F_3N_4O_2$: 446.19 m/z, found:447.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.12 – 8.30 (m, 2H), 7.93 – 8.10 (m, 1H), 7.70 – 7.85 (m, 1H), 7.50 – 7.70 (m, 2H), 6.98 – 7.45 (m, 1H), 6.30 – 6.64 (m, 1H), 2.15 – 2.37 (m, 2H), 1.81 – 2.00 (m, 3H), 1.40 – 1.60 (m, 2H), 0.90 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -66.5505.

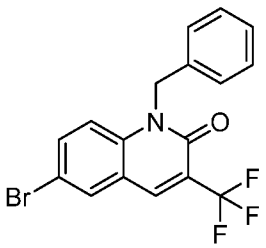
Example 301: 1-(1-benzyl-2-oxo-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

Synthetic Scheme



6-bromo-3-(trifluoromethyl)quinolin-2(1H)-one

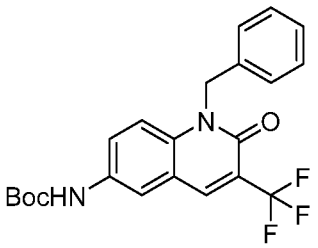
6-bromoquinolin-2(1H)-one (1.0 g, 4.46 mmol, 1.0 equiv), $Mn(OAc)_3.2H_2O$ (3.59 g, 17.84 mmol, 4.0 equiv) and sodium trifluoromethanesulfinate (1.57 g, 13.87 mmol, 3.0 equiv) were dissolved in glacial acetic acid (25 mL), and the reaction was stirred at 25 °C for 24 hours. Water (100 mL) was added to the system, the mixture was extracted with ethyl acetate (100 mL × 2), the organic phases were combined, washed with saturated saline (100 mL), dried over anhydrous sodium sulfate, filtered, the filtrate was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (PE/EA=3:1) to obtain 6-bromo-3-(trifluoromethyl)quinolin-2(1H)-one (0.5 g, 38.46%) as a yellow solid. MS (ESI): mass calcd. for $C_{10}H_5BrF_3NO$, 290.95 m/z, found 292.15 $[M+H]^+$.



1-benzyl-6-bromo-3-(trifluoromethyl)quinolin-2(1H)-one

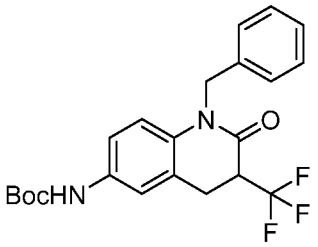
A solution of 6-bromo-3-(trifluoromethyl)quinolin-2(1H)-one (480 mg, 1.64 mmol, 1 equiv) in DMF (5 mL) was added BnBr (0.8 g, 4.90 mmol, 3.0 equiv) and Cs_2CO_3 (2.1 g, 6.560 mmol, 4.0

equiv) at rt. The resulting mixture was stirred for 2 h at rt. The reaction was quenched with water (20 mL). The resulting mixture was extracted with EA (3 x 30 mL). The combined organic layers were washed with NaCl (aq., 3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (3/1) to afford 1-benzyl-6-bromo-3-(trifluoromethyl)quinolin-2(1H)-one (400 mg, 63.89%%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{11}BrF_3NO$, 381.00 m/z, found 382.15 $[M+H]^+$.



tert-butyl (1-benzyl-2-oxo-3-(trifluoromethyl)-1,2-dihydroquinolin-6-yl)carbamate

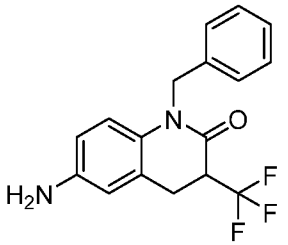
A solution of 1-benzyl-6-bromo-3-(trifluoromethyl)quinolin-2(1H)-one (0.2 g, 0.524 mmol, 1 equiv) in toluene (5 mL) was treated with tert-butyl carbamate (123 mg, 1.04 mmol, 2 equiv), Cs_2CO_3 (0.5 g, 1.57 mmol, 3 equiv), XantPhos (30 mg, 0.052 mmol, 0.1 equiv) and $Pd_2(dba)_3$ (48 mg, 0.052 mmol, 0.1 equiv) for overnight at 90 °C under nitrogen atmosphere. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography with PE/EA (3:1) to afford tert-butyl (1-benzyl-2-oxo-3-(trifluoromethyl)-1,2-dihydroquinolin-6-yl)carbamate (120 mg, 54.79%). MS (ESI): mass calcd. for $C_{22}H_{21}F_3N_2O_3$, 418.15.00 m/z, found 419.10 $[M+H]^+$.



tert-butyl (1-benzyl-2-oxo-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)carbamate

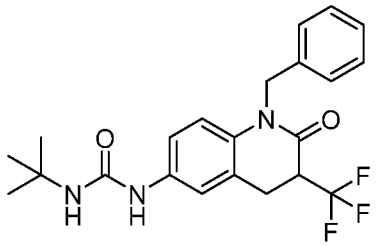
To a solution of tert-butyl (1-benzyl-2-oxo-3-(trifluoromethyl)-1,2-dihydroquinolin-6-yl)carbamate (90 mg, 0.215 mmol, 1 equiv) in EtOH (5 mL) and HOAc (1 mL) was added Pd/C (50 mg) under nitrogen atmosphere. The resulting mixture was placed at 60 °C under a hydrogen

atmosphere (50 bar) until the starting material was totally consumed by LCMS. The mixture was filtered and concentrated under vacuum to afford tert-butyl (1-benzyl-2-oxo-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)carbamate (90 mg crude) as a white solid.



6-amino-1-benzyl-3-(trifluoromethyl)-3,4-dihydroquinolin-2(1H)-one

To a stirred solution of tert-butyl (1-benzyl-2-oxo-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)carbamate (90 mg crude) in HCl (4N in EA, 3 mL) at rt. The reaction was stirred for 2 h at rt. The resulting mixture was concentrated under reduced pressure to afford 6-amino-1-benzyl-3-(trifluoromethyl)-3,4-dihydroquinolin-2(1H)-one (80 mg crude) as a white solid.

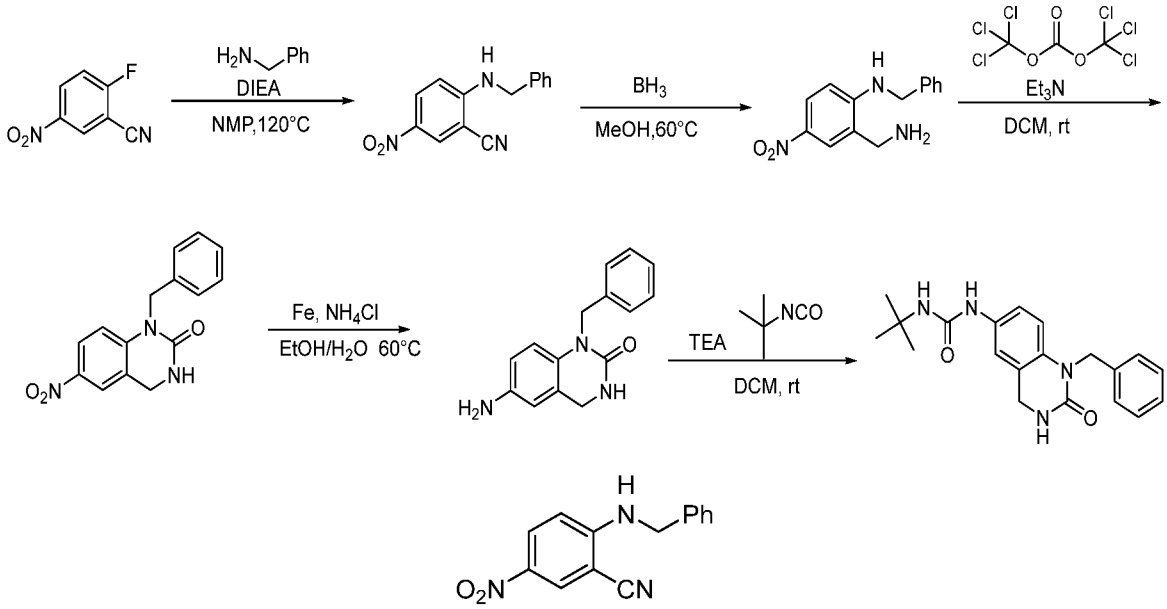


1-(1-benzyl-2-oxo-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

A solution of 6-amino-1-benzyl-3-(trifluoromethyl)-3,4-dihydroquinolin-2(1H)-one (80 mg crude), TEA (80 mg) and 2-isocyanato-2-methylpropane (80 mg) in DCM (5 mL) was stirred for overnight at rt. The mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA (46%-57%) and C18 column to afford 1-(1-benzyl-2-oxo-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea (2.7 mg) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{24}F_3N_3O_2$: 419.18 m/z, found 420.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.39 (d, J = 2.5 Hz, 1H), 7.28 – 7.37 (m, 2H), 7.18 – 7.28 (m, 3H), 7.05 (dd, J = 8.8, 2.5 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 5.96 (s, 1H), 5.08 – 5.18(m, 2H), 4.01 – 4.12 (m, 1H), 3.06 – 3.23 (m, 2H), 1.26 (s, 9H).

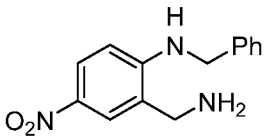
Example 302: 1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-3-(tert-butyl)urea

Synthetic Scheme



2-(benzylamino)-5-nitrobenzonitrile

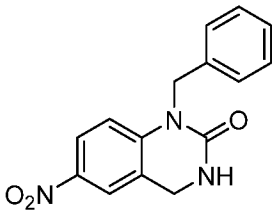
A solution of 2-fluoro-5-nitrobenzonitrile (2.0 g, 12.040 mmol, 1 equiv) in NMP (20 mL) was added benzylamine (1.94 g, 18.060 mmol, 1.5 equiv) and DIEA (3.11 g, 24.080 mmol, 2.0 equiv). The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 20mL). The combined organic layers were washed with NaCl (3 x 20mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (3/1) to afford 2-(benzylamino)-5-nitrobenzonitrile (2.2 g, 72.15%) as an off-white solid. LC/MS: mass calcd. for $C_{14}H_{11}N_3O_2$: 253.09, found: 254.10 $[M+H]^+$.



2-(aminomethyl)-N-benzyl-4-nitroaniline

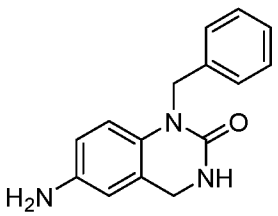
A solution of 2-(benzylamino)-5-nitrobenzonitrile (500 mg, 1.974 mmol, 1 equiv) in methanol (5 mL) was added borane (54.61 mg, 3.948 mmol, 2.0 equiv) at 0°C. The resulting mixture was stirred for overnight at 60 °C. The reaction mixture was quenched by water (5 mL) and extracted with EA (3 x 10mL). The combined organic layers were washed with NaCl (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (3/1) to afford 2-

(aminomethyl)-N-benzyl-4-nitroaniline (300 mg, 59.06%) as colorless oil. LC/MS: mass calcd. for $C_{14}H_{15}N_3O_2$: 257.12, found: 258.10$[M+H]^+$.



1-benzyl-6-nitro-3,4-dihydroquinazolin-2(1H)-one

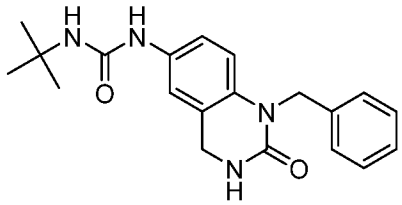
A solution of 2-(aminomethyl)-N-benzyl-4-nitroaniline (130 mg, 0.505 mmol, 1 equiv) in DCM (3 mL) was added triphosgene (45.0 mg, 0.151 mmol, 0.3 equiv) and triethylamine (127.8 mg, 1.262 mmol, 2.5 equiv). The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water (5 mL) and extracted with EA (3 x 10 mL). The combined organic layers were washed with NaCl (3 x 10mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (3/1) to afford 1-benzyl-6-nitro-3,4-dihydroquinazolin-2(1H)-one (37 mg, 25.85%) as a white solid. LC/MS: mass calcd. for $C_{15}H_{13}N_3O_3$: 283.10, found: 284.05 $[M+H]^+$.



6-amino-1-benzyl-3,4-dihydroquinazolin-2(1H)-one

A solution of 1-benzyl-6-nitro-3,4-dihydroquinazolin-2(1H)-one (32 mg, 0.113 mmol, 1 equiv) in EtOH (3 mL)/H_2O (0.3 mL) was added Fe (63.1 mg, 1.130 mmol, 10 equiv) and NH_4Cl (60.4 mg, 1.130 mmol, 10 equiv). The resulting mixture was stirred for 1h at 60 °C. The reaction mixture was quenched by water (5 mL) and extracted with EA (3 x 5mL). The combined organic layers were washed with NaCl (3 x 5mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (1/1) to afford 6-amino-1-benzyl-3,4-dihydroquinazolin-

2(1H)-one (20 mg, 69.90%) as an off-white solid. LC/MS: mass calcd. for $C_{15}H_{15}N_3O$: 253.12, found: 254.20 $[M+H]^+$.

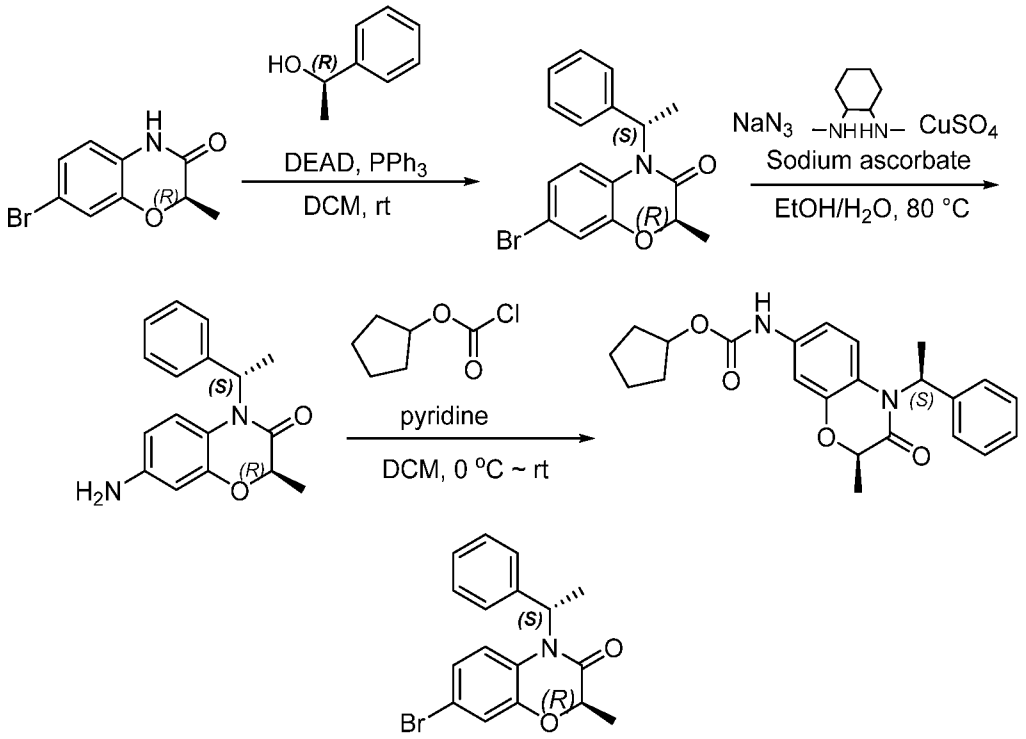


1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-3-(tert-butyl)urea

A solution of 6-amino-1-benzyl-3,4-dihydroquinazolin-2(1H)-one (20 mg, 0.079 mmol, 1 equiv) in DCM (26.8 mg, 0.316 mmol, 4.0 equiv) was added 2-isocyanato-2-methylpropane (23.5 mg, 0.237 mmol, 3.0 equiv) and TEA (3 mL) at rt. The resulting mixture was stirred for overnight at rt. The reaction mixture was quenched by water (5 mL) and extracted with EA (5 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product 30 mg was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9; Number Of Runs: 0) to affored 1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-3-(tert-butyl)urea (3.0 mg, 10.77%) as a white solid. MS (ESI): mass calcd. $C_{20}H_{24}N_4O_2$ for: 352.19 m/z, found 353.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.27 – 7.35 (m, 3H),7.24 – 7.19(m, 3H), 7.09 (s, 1H), 6.89 (dd, J = 8.8, 2.5 Hz, 1H), 6.57 (d, J = 8.8 Hz, 1H), 5.90 (s, 1H), 5.00 (s, 2H), 4.33 (s, 2H), 1.25 (s, 9H).

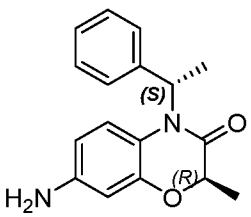
Example 303: cyclopentyl ((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)carbamate

Synthetic Scheme



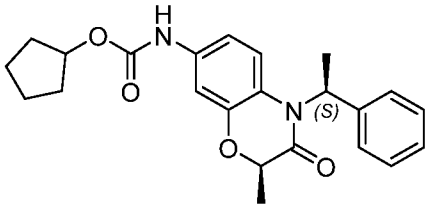
(R)-7-bromo-2-methyl-4-((S)-1-phenylethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a stirred mixture of (R)-7-bromo-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one (1 g, 4.131 mmol, 1 equiv) and (R)-1-phenylethan-1-ol (555.14 mg, 4.544 mmol, 1.1 equiv) in DCM (20 mL) was added PPh_3 (1.63 g, 6.197 mmol, 1.5 equiv) at 25°C under air atmosphere. The resulting mixture was stirred at room temperature under nitrogen. After 30 min, the DEAD (719.44 mg, 4.131 mmol, 1 equiv) was added to the mixture. The resulting mixture was stirred for 2h at room temperature under nitrogen. Desired product could be detected by LCMS. The mixture was diluted with water (50 mL). The resulting mixture was extracted with EA (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue obtained was purified by silica gel chromatography (0-50% ethyl acetate/petroleum ether) to afford the (R)-7-bromo-2-methyl-4-((S)-1-phenylethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (1 g, 69.92%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{16}BrNO_2$: 345.04 m/z, found 346.05 $[M+H]^+$.



(R)-7-amino-2-methyl-4-((S)-1-phenylethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a stirred mixture of (R)-7-bromo-2-methyl-4-((S)-1-phenylethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (1 g, 2.432 mmol, 1 equiv) in EtOH (8 mL) and H_2O (2 mL) was added NaN_3 (452.37 mg, 7.296 mmol, 3 equiv), N1,N2-dimethylcyclohexane-1,2-diamine (207.54 mg, 1.459 mmol, 0.6 equiv) , $CuSO_4$ (388.10 mg, 2.432 mmol, 1 equiv) and sodium ascorbate (968.37 mg, 4.864 mmol, 2 equiv) at 25°C under air atmosphere. The resulting mixture was stirred for 2h at 80 degrees C under nitrogen. Desired product could be detected by LCMS. After cooling down to room temperature, the mixture was diluted with water (30 mL). The resulting mixture was extracted with EA (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue obtained was purified by silica gel chromatography (0-100% ethyl acetate/petroleum ether) to afford the (R)-7-amino-2-methyl-4-((S)-1-phenylethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (300 mg, 43.70%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{18}N_2O_2$: 282.14 m/z, found 283.15 $[M+H]^+$.



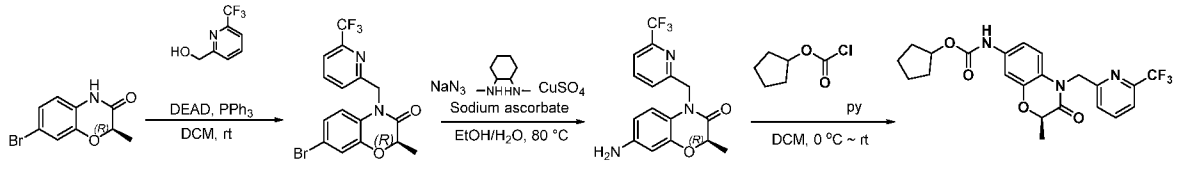
cyclopentyl ((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)carbamate

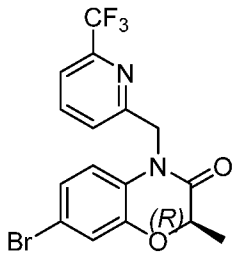
To a stirred mixture of (R)-7-amino-2-methyl-4-((S)-1-phenylethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (80 mg, 0.283 mmol, 1 equiv) and cyclopentyl carbonochloridate (126.31 mg, 0.849 mmol, 3 equiv) in DCM (3 mL) was added pyridine (67.24 mg, 0.849 mmol, 3 equiv) dropwise at 0 degrees C under air atmosphere. The resulting mixture was stirred for 2h at room temperature. Desired product could be detected by LCMS. The mixture was diluted with water (10 mL). The resulting mixture was extracted with EA (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a X Bridge Prep OBD C18 150 mm x 30 mm x 5μm column (eluent: 51% to 73% (v/v) CH_3CN and H_2O with 10 mmol /L NH_4HCO_3) to afford the cyclopentyl ((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)carbamate (14.3 mg, 12.73%) as a white solid. MS (ESI): mass calcd. for $C_{23}H_{26}N_2O_4$: 394.19 m/z, found 395.10 $[M+H]^+$. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.50 (s, 1H), 7.31 – 7.41 (m, 2H), 7.20 – 7.31 (m, 3H),

7.20 (d, J = 2.4 Hz, 1H), 6.81 – 6.91 (m, 1H), 6.67 (d, J = 8.9 Hz, 1H), 6.03 – 6.16 (m, 1H), 5.00 – 5.10 (m, 1H), 4.70 – 4.82 (m, 1H), 1.79 – 1.94 (m, 2H), 1.71 – 1.78 (m, 3H), 1.49 – 1.70 (m, 6H), 1.45 (d, J = 6.8 Hz, 3H).

Example 304: cyclopentyl N-[(2R)-2-methyl-3-oxo-4-{[6-(trifluoromethyl)pyridin-2-yl]methyl}-2H-1,4-benzoxazin-7-yl]carbamate

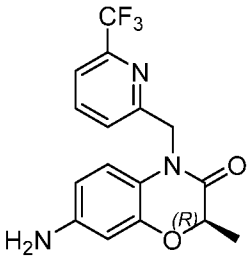
Synthetic Scheme





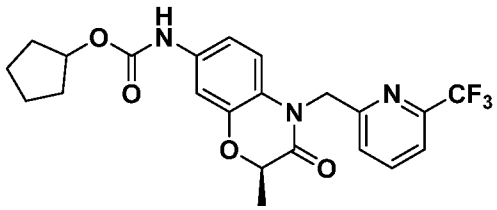
(2R)-7-bromo-2-methyl-4-{[6-(trifluoromethyl)pyridin-2-yl]methyl}-2H-1,4-benzoxazin-3-one

To a solution of (2R)-7-bromo-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (500 mg, 2.066 mmol, 1 equiv) in DCM (10 mL) was added [6-(trifluoromethyl)pyridin-2-yl]methanol (439.02 mg, 2.479 mmol, 1.2 equiv) and PPh_3 (812.65 mg, 3.099 mmol, 1.5 equiv). After the mixture was stirred at rt for 1 h, then DEAD (539.58 mg, 3.099 mmol, 1.5 equiv) was added at 0 °C. The reaction was stirred at 25 °C for 2 h. Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-bromo-2-methyl-4-{[6-(trifluoromethyl)pyridin-2-yl]methyl}-2H-1,4-benzoxazin-3-one (410 mg, 49.48%) as a white solid. MS(ESI): mass calcd. for $C_{16}H_{12}BrF_3N_2O_2$:400.00 m/z, found:401.00, 403.00 $[M+H, M+H+2]^+$.



(2R)-7-amino-2-methyl-4-{[6-(trifluoromethyl)pyridin-2-yl]methyl}-2H-1,4-benzoxazin-3-one

To a solution of (2R)-7-bromo-2-methyl-4-{[6-(trifluoromethyl)pyridin-2-yl]methyl}-2H-1,4-benzoxazin-3-one (600 mg, 1.287 mmol, 1 equiv) in EtOH (10 mL) and H_2O (1 mL) were added N1,N2-dimethylcyclohexane-1,2-diamine (109.84 mg, 0.772 mmol, 0.6 equiv) and $CuSO_4$ (205.41 mg, 1.287 mmol, 1 equiv), sodium ascorbate (512.53 mg, 2.574 mmol, 2 equiv). The reaction was stirred at 80 °C for 2 h. The mixture was allowed to cool down to room temperature. Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-2-methyl-4-{[6-(trifluoromethyl)pyridin-2-yl]methyl}-2H-1,4-benzoxazin-3-one (290 mg, 66.80%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{14}F_2N_3O_2$:337.10 m/z, found:338.10 $[M+H]^+$.



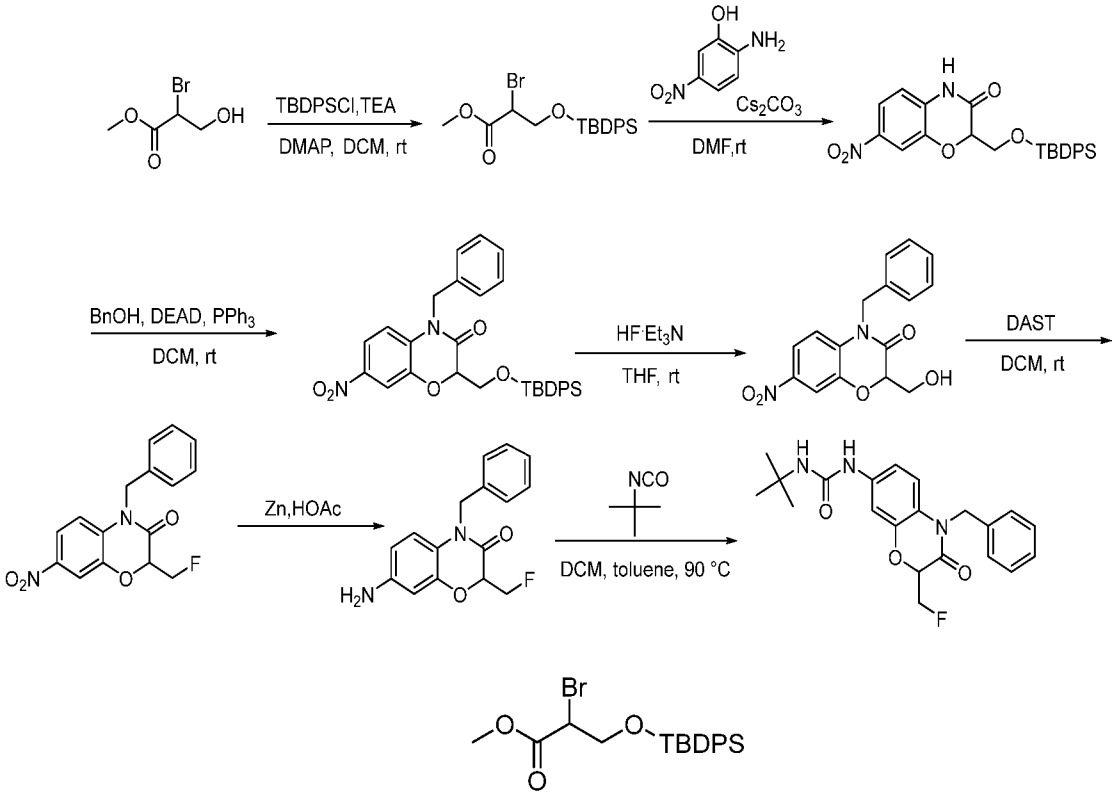
cyclopentyl N-[(2R)-2-methyl-3-oxo-4-{[6-(trifluoromethyl)pyridin-2-yl]methyl}-2H-1,4-benzoxazin-7-yl]carbamate

To a solution of (2R)-7-amino-2-methyl-4-{[6-(trifluoromethyl)pyridin-2-yl]methyl}-2H-1,4-benzoxazin-3-one (80 mg, 0.237 mmol, 1 equiv) in DCM (5 mL) was added cyclopentyl carbonochloridate (52.86 mg, 0.355 mmol, 1.5 equiv) and pyridine (56.28 mg, 0.711 mmol, 3 equiv) at 0 °C. The reaction was stirred at 25 °C for 2 h. Quenched with water (30 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 30*150 mm, 5μm column (eluent: 26% to 42% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford the title compound cyclopentyl N-[(2R)-2-methyl-3-oxo-4-

{[6-(trifluoromethyl)pyridin-2-yl]methyl}-2H-1,4-benzoxazin-7-yl]carbamate (24.7 mg, 23.14%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{22}F_3N_3O_4$:449.16 m/z, found:450.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 9.54 (s, 1H), 8.03 – 8.11 (m, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.22 (s, 1H), 7.01 (d, J = 9.4 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 5.25 (s, 2H), 5.04-5.09 (m, 1H), 4.80 – 4.90 (m, 1H), 1.80 – 1.88 (m, 3H), 1.61 – 1.70 (m, 5H), 1.47 (d, J = 6.7 Hz, 3H). ^{19}F NMR (376 MHz, DMSO) δ -66.56.

Example 305: 1-[4-benzyl-2-(fluoromethyl)-3-oxo-2H-1,4-benzoxazin-7-yl]-3-tert-butylurea

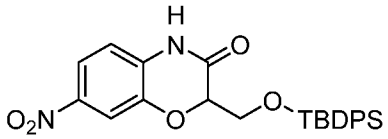
Synthetic Scheme



methyl 2-bromo-3-[(tert-butyldiphenylsilyl)oxy]propanoate

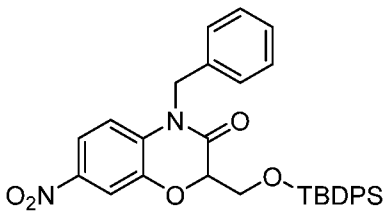
To a stirred solution of methyl 2-bromo-3-hydroxypropanoate (3 g, 16.393 mmol, 1 equiv) in DCM (30 mL) was added TBDPSCl (6.76 g, 24.590 mmol, 1.5 equiv), TEA (4.98 g, 49.179 mmol, 3 equiv) and DMAP (0.20 g, 1.639 mmol, 0.1 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at room temperature under air atmosphere. The reaction was monitored by LCMS. Quenched with water (150 mL) and extracted with DCM (3 x 150 mL). The combined extracts were washed with water, brine, dried

over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford methyl 2-bromo-3-[(tert-butyldiphenylsilyl)oxy] propanoate (6.5 g, 94.1%) as a yellow oil. LC/MS (ESI): mass calcd. for $C_{20}H_{25}BrO_3Si$: 420.1 m/z, found:421.1, 423.1 $[M+H, M+H+2]^+$.



2-{[(tert-butyldiphenylsilyl)oxy]methyl}-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one

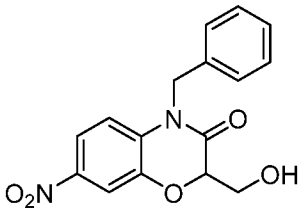
To a stirred solution of methyl 2-bromo-3-[(tert-butyldiphenylsilyl)oxy]propanoate (8 g, 18.984 mmol, 1 equiv) in DMF(80 mL) was added 2-amino-5-nitrophenol (2.93 g, 18.984 mmol, 1 equiv) and K_2CO_3 (5.25 g, 37.968 mmol, 2 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 80 °C under air atmosphere. The reaction was monitored by LCMS. After cooling down to rt, the reaction was quenched with water (400 mL) and extracted with EA (3 x 300 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 2-{[(tert-butyldiphenylsilyl)oxy]methyl}-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (2.8 g, 31.88%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{25}H_{26}N_2O_5Si$:462.2 m/z, found:461.2 $[M+H]^+$.



4-benzyl-2-{[(tert-butyldiphenylsilyl)oxy]methyl}-7-nitro-2H-1,4-benzoxazin-3-one

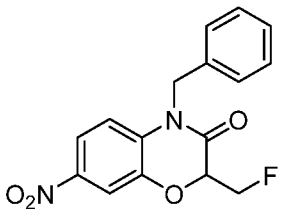
To a stirred solution of 2-{[(tert-butyldiphenylsilyl)oxy]methyl}-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (1.2 g, 2.594 mmol, 1 equiv) and benzyl alcohol (0.28 g, 2.594 mmol, 1 equiv) in DCM was added PPh_3 (0.68 g, 2.594 mmol, 1 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. To the above mixture was added DEAD (0.68 g, 3.891 mmol, 1.5 equiv) in portions at 0 °C. The resulting mixture was stirred for additional 2 h at room temperature. The reaction was monitored by LCMS. Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and

concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 4-benzyl-2-{[(tert-butyldiphenylsilyl)oxy]methyl}-7-nitro-2H-1,4-benzoxazin-3-one (800 mg, 55.80%) as a yellow oil. LC/MS (ESI): mass calcd. for $C_{32}H_{32}N_2O_5Si$:552.2 m/z, found:551.3 $[M+H]^+$.



4-benzyl-2-(hydroxymethyl)-7-nitro-2H-1,4-benzoxazin-3-one

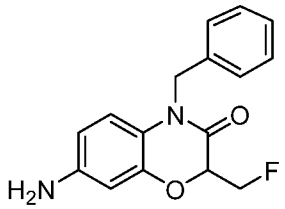
To a stirred solution of 4-benzyl-2-{[(tert-butyldiphenylsilyl)oxy]methyl}-7-nitro-2H-1,4-benzoxazin-3-one (800 mg, 1.447 mmol, 1 equiv) in THF (8 mL) was added $Et_3N.3HF$ (350.02 mg, 2.171 mmol, 1.5 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 3 h at room temperature under air atmosphere. The reaction was monitored by LCMS. Quenched with water (40 mL) and extracted with EA (3 x 40 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 4-benzyl-2-(hydroxymethyl)-7-nitro-2H-1,4-benzoxazin-3-one (320 mg, 70.34%) as a yellow oil. LC/MS (ESI): mass calcd. for $C_{16}H_{14}N_2O_5$:314.1 m/z, found:315.2 $[M+H]^+$.



4-benzyl-2-(fluoromethyl)-7-nitro-2H-1,4-benzoxazin-3-one

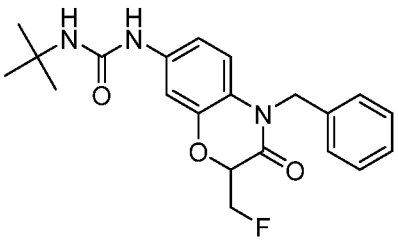
To a stirred solution of 4-benzyl-2-(hydroxymethyl)-7-nitro-2H-1,4-benzoxazin-3-one (320 mg, 1.018 mmol, 1 equiv) in DCM (3 mL) was added DAST (328.23 mg, 2.036 mmol, 2 equiv) dropwise at 0 °C under air atmosphere. The resulting mixture was stirred for 3 h at 0 °C under air atmosphere. The reaction was monitored by LCMS. Quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 4-benzyl-2-(fluoromethyl)-7-nitro-2H-1,4-benzoxazin-3-one

(130 mg, 40.37%) as a yellow oil. LC/MS (ESI): mass calcd. for $C_{16}H_{13}FN_2O_4$:316.1 m/z, found:317.20 $[M+H]^+$.



7-amino-4-benzyl-2-(fluoromethyl)-2H-1,4-benzoxazin-3-one

To a stirred solution of 4-benzyl-2-(fluoromethyl)-7-nitro-2H-1,4-benzoxazin-3-one (130 mg, 0.411 mmol, 1 equiv) in AcOH (1.5 mL) was added Zn (268.72 mg, 4.110 mmol, 10 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 3 h at room temperature under air atmosphere. The reaction was monitored by LCMS. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. This resulted in 7-amino-4-benzyl-2-(fluoromethyl)-2H-1,4-benzoxazin-3-one (130 mg, 110.47%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{16}H_{15}FN_2O_2$:286.1 m/z, found:287.20 $[M+H]^+$.



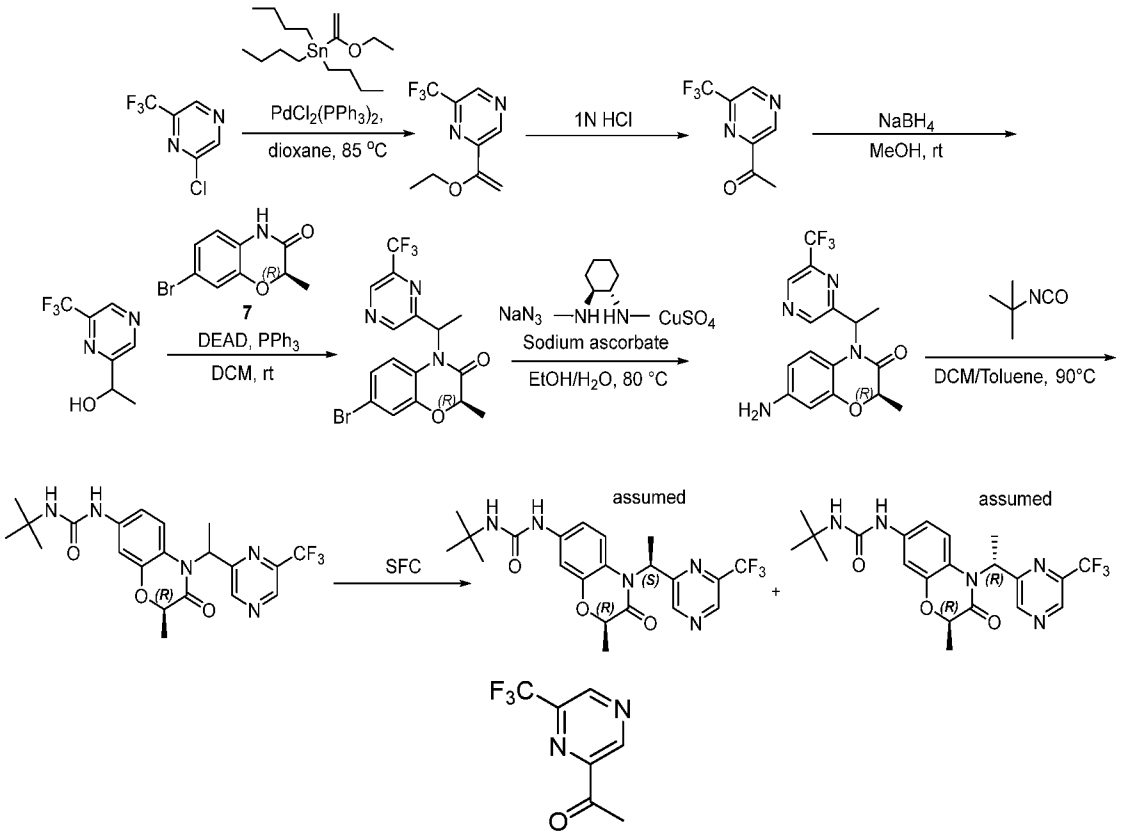
1-[4-benzyl-2-(fluoromethyl)-3-oxo-2H-1,4-benzoxazin-7-yl]-3-tert-butylurea

To a stirred solution of 7-amino-4-benzyl-2-(fluoromethyl)-2H-1,4-benzoxazin-3-one (120 mg, 0.419 mmol, 1 equiv) in DCM/Toluene (2:1, 1.5 mL) was added 2-isocyanato-2-methylpropane (124.65 mg, 1.257 mmol, 3 equiv) dropwise at room temperature under air atmosphere. The resulting mixture was stirred overnight at 90 °C under air atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by Prep-HPLC using YMC-Actus Tiart ExRS C18 150 mm x 30 mm x 5 μm column (eluent: 23% to 40% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford 1-[4-benzyl-2-(fluoromethyl)-3-oxo-2H-1,4-benzoxazin-7-yl]-3-tert-butylurea (13.7 mg, 8.25%) as a white

solid. LC/MS (ESI): mass calcd. for $C_{21}H_{24}FN_3O_3$:385.2 m/z, found:386.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 7.35 – 7.21 (m, 6H), 6.83 (d, J = 8.8 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 5.97 (s, 1H), 5.21 – 4.81 (m, 5H), 1.26 (s, 9H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -231.52.

Example 306 and Example 307: 1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethyl)pyrazin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea and 1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-(6-(trifluoromethyl)pyrazin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

Synthetic Scheme



1-(6-(trifluoromethyl)pyrazin-2-yl)ethan-1-one

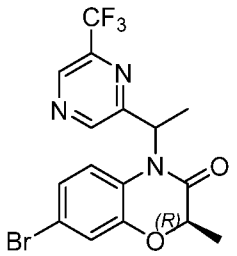
To a solution of 2-chloro-6-(trifluoromethyl)pyrazine (1 g, 5.479 mmol, 1 equiv) and bis(triphenylphosphine) palladium chloride (0.38 g, 0.548 mmol, 0.1 equiv) in dioxane (10 mL) was added tributyl(1-ethoxyethenyl)stannane (2.97 g, 8.219 mmol, 1.5 equiv) under N_2. The reaction was stirred at 85 °C under N_2 for 3h. The mixture was allowed to cool down to rt, and to the above mixture was added 1 N HCl (5 mL, 16.456 mmol). The resulting mixture was stirred for

additional 1h at rt. Quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-[6-(trifluoromethyl)pyrazin-2-yl]ethanone (640 mg, 60.21%) as a yellow oil. MS (ESI): mass calcd. for $C_7H_5F_3N_2O$: 190.04 m/z, found 191.00$[M+H]^+$.



1-(6-(trifluoromethyl)pyrazin-2-yl)ethan-1-ol

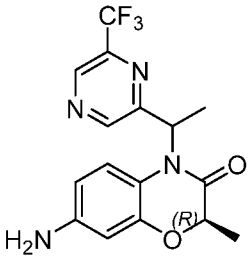
To a solution of 1-[6-(trifluoromethyl)pyrazin-2-yl]ethanone (600 mg, 3.156 mmol, 1 equiv) in MeOH (10 mL) was added $NaBH_4$ (358.15 mg, 9.468 mmol, 3 equiv) at 0 °C. The reaction was stirred at rt for 1h. Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-[6-(trifluoromethyl)pyrazin-2-yl]ethanol (210 mg, 34.63%) as a yellow oil. MS (ESI): mass calcd. for $C_7H_7F_3N_2O$: 192.05 m/z, found 193.15 $[M+H]^+$.



(2R)-7-bromo-2-methyl-4-(1-(6-(trifluoromethyl)pyrazin-2-yl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

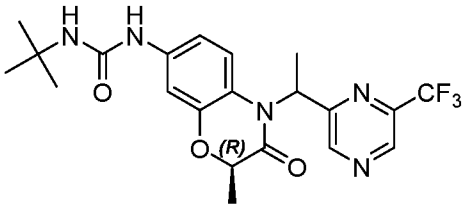
To a solution of 1-[6-(trifluoromethyl)pyrazin-2-yl]ethanol (200 mg, 1.041 mmol, 1 equiv) in DCM (10 mL) was added (2R)-7-bromo-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (251.97 mg, 1.041 mmol, 1 equiv) and PPh_3 (409.53 mg, 1.561 mmol, 1.5 equiv). The reaction was stirred at rt under N_2 for 0.5h. To the above mixture was added DEAD (271.92 mg, 1.561 mmol, 1.5 equiv) at 0 °C. The resulting mixture was stirred for additional 1h at rt. Quenched with water (30 mL) and extracted with DCM (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-bromo-2-methyl-4-{1-[6-(trifluoromethyl)pyrazin-

2-yl]ethyl}-2H-1,4-benzoxazin-3-one (162 mg, 37.39%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{13}BrF_3N_3O_2$: 415.01 m/z, found:415.90, 417.90 $[M+H, M+H+2]^+$.



(2R)-7-amino-2-methyl-4-(1-(6-(trifluoromethyl)pyrazin-2-yl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

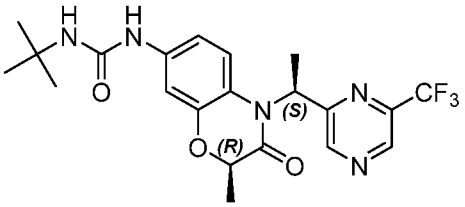
To a solution of (2R)-7-bromo-2-methyl-4-{1-[6-(trifluoromethyl)pyrazin-2-yl]ethyl}-2H-1,4-benzoxazin-3-one (150 mg, 0.360 mmol, 1 equiv) in EtOH/H_2O(4:1, 10 mL) was added (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (30.76 mg, 0.216 mmol, 0.6 equiv), azidosodium (70.29 mg, 1.080 mmol, 3 equiv), $CuSO_4$(57.52 mg, 0.360 mmol, 1 equiv) and sodium ascorbate (143.52 mg, 0.720 mmol, 2 equiv). The reaction was stirred at 80°C under N_2 for 3h. After cooling down to rt, the reaction was quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-2-methyl-4-{1-[6-(trifluoromethyl)pyrazin-2-yl]ethyl}-2H-1,4-benzoxazin-3-one (100 mg, 78.75%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{15}F_3N_4O_2$: 352.11 m/z, found 353.10 $[M+H]^+$.

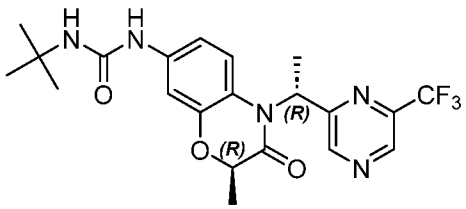


1-(tert-butyl)-3-((2R)-2-methyl-3-oxo-4-(1-(6-(trifluoromethyl)pyrazin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a solution of (2R)-7-amino-2-methyl-4-{1-[6-(trifluoromethyl)pyrazin-2-yl]ethyl}-2H-1,4-benzoxazin-3-one (100 mg, 0.284 mmol, 1 equiv) in DCM/Toluene(2:1, 15 mL) was added 2-isocyanato-2-methylpropane (281.37 mg, 2.840 mmol, 10 equiv). The reaction was stirred at 90 °C under N_2 for 3h. After cooling down to rt, the reaction was quenched with water (100 mL) and extracted with DCM (3 x 100 mL). The combined extracts were washed with water, brine, dried

over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm column (eluent: 41% to 63% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-[(2R)-2-methyl-3-oxo-4-{1-[6-(trifluoromethyl)pyrazin-2-yl]ethyl}-2H-1,4-benzoxazin-7-yl]urea (40 mg, 31.21%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{24}F_3N_5O_3$: 451.18 m/z, found 452.00 $[M+H]^+$.



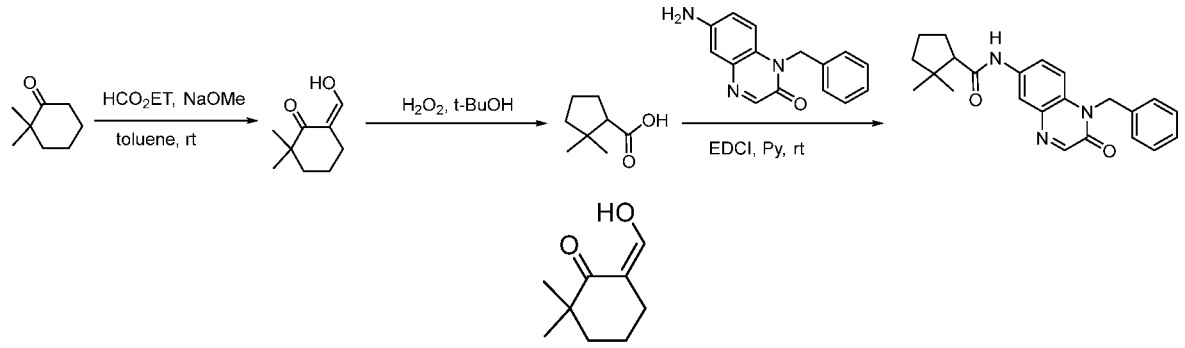


1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethyl)pyrazin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea and 1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-(6-(trifluoromethyl)pyrazin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

A sample of 3-tert-butyl-1-[(2R)-2-methyl-3-oxo-4-{1-[6-(trifluoromethyl)pyrazin-2-yl]ethyl}-2H-1,4-benzoxazin-7-yl]urea (40 mg) was separated by chiral-HPLC using a CHIRALPAK IE, 2*25 cm, 5 μm column (eluent: 90% to 90% (v/v) HEX: DCM=3: 1(0.3% IPAmine) and IPA) to yield first example 3-tert-butyl-1-[(2R)-2-methyl-3-oxo-4-[(1S)-1-[6-(trifluoromethyl)pyrazin-2-yl]ethyl]-2H-1,4-benzoxazin-7-yl]urea (16.3 mg, 40.75%) as a white solid. MS(ESI): mass calcd. for $C_{21}H_{24}F_3N_5O_3$: 451.18 m/z, found: 452.05 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 9.00 (s, 1H), 8.25 (s, 1H), 7.25 (d, J = 2.3 Hz, 1H), 6.77 – 6.90 (m, 2H), 6.00 – 6.05 (m, 1H), 5.93 – 5.99 (m, 1H), 4.67 – 4.70 (m, 1H), 1.75 – 1.85 (m, 3H), 1.36 – 1.41 (m, 3H), 1.28 (s, 9H).^{19}F NMR (376 MHz, DMSO) δ(ppm): -66.4059. And to yield second example 3-tert-butyl-1-[(2R)-2-methyl-3-oxo-4-[(1R)-1-[6-(trifluoromethyl)pyrazin-2-yl]ethyl]-2H-1,4-benzoxazin-7-yl]urea (15 mg, 37.50%) as a white solid. MS(ESI): mass calcd. for $C_{21}H_{24}F_3N_5O_3$: 451.18 m/z, found: 452.05 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.08 (s, 1H), 8.98 (s, 1H), 8.25 (s, 1H), 7.24 (d, J = 2.4 Hz, 1H), 6.89 – 7.00 (m, 1H), 6.74 – 6.89 (m, 1H), 5.87 – 6.10 (m, 2H), 4.60 – 4.75 (m, 1H), 1.80 – 1.87 (m, 3H), 1.36 – 1.44 (m, 3H), 1.28 (s, 9H).^{19}F NMR (376 MHz, DMSO) δ(ppm): -66.3907.

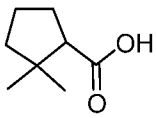
Example 308: N-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-2,2-dimethylcyclopentane-1-carboxamide

Synthetic Scheme



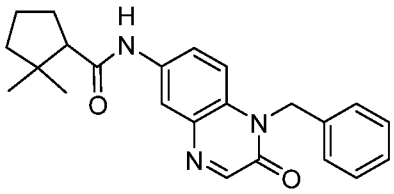
(Z)-6-(hydroxymethylene)-2,2-dimethylcyclohexan-1-one

A solution of sodium methoxide (406 mg, 7.528 mmol, 1.9 equiv) in toluene (8 mL) was treated with 2,2-dimethylcyclohexan-1-one (500 mg, 3.962 mmol, 1 equiv).The solution was stirred at rt for 30 min. Ethyl formate (733 mg, 9.905 mmol, 2.5 equiv) was added into the reaction. The solution was stirred at rt for 12 h. The mixture was acidified to pH 7 with 2N HCl. The reaction mixture was quenched by ice water (20 mL) and extracted with DCM (3 x 20 mL).The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (0-60% EA/PE) to afford (Z)-6-(hydroxymethylene)-2,2-dimethylcyclohexan-1-one (300 mg, 49.10%) as white solid. MS (ESI): mass calcd. for $C_9H_{14}O_2$, 154.10 m/z, found 153.00 $[M-H]^-$.



2,2-dimethylcyclopentane-1-carboxylic acid

A solution of (Z)-6-(hydroxymethylene)-2,2-dimethylcyclohexan-1-one (300 mg, 0.065 mmol, 1 equiv) in 2-methyl-2-propanol (6 mL) was treated with hydrogen peroxide (0.6 mL, 0.235 mmol, 3.63 equiv). The solution was stirred at rt for overnight. The mixture was acidified to pH 5 with $NaHCO_3$ (aq.). The reaction mixture was quenched by ice water (20 mL) and extracted with Et_2O (3 x 20 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to yield a crude product 2,2-dimethylcyclopentane-1-carboxylic acid (70 mg, 25.36%) as white oil. MS (ESI): mass calcd. for $C_8H_{14}O_2$, 142.10 m/z, found 141.00 $[M-H]^-$.

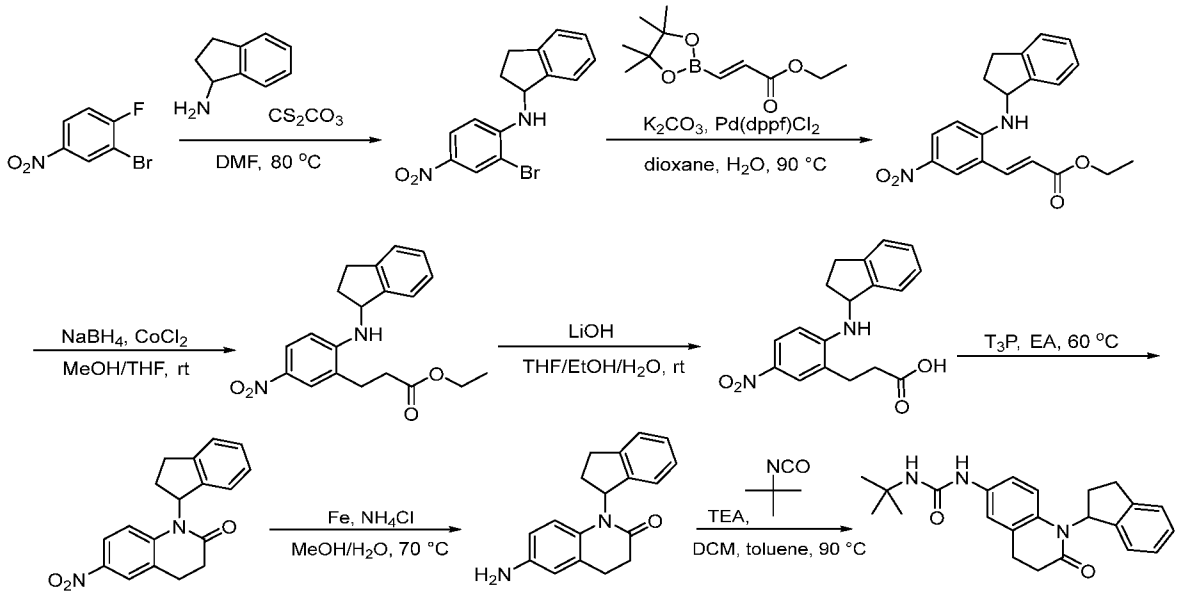


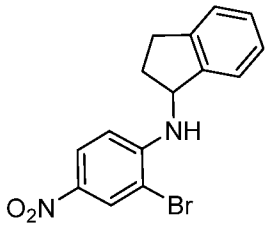
N-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-2,2-dimethylcyclopentane-1-carboxamide

To a mixture of 2,2-dimethylcyclopentane-1-carboxylic acid (70 mg, 0.492 mmol, 1 equiv) and 6-amino-1-benzylquinoxalin-2-one (123 mg, 0.492 mmol, 1 equiv) in pyridine (5 mL) was stirred ,and added EDCI (189 mg, 0.984 mmol, 2 equiv). The reaction was stirred at rt for 4 h. The resulting mixture was concentrated under vacuum. The crude product was purified by reverse phase flash with the following conditions to afford N-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-2,2-dimethylcyclopentane-1-carboxamide (21.4 mg, 11.55%) as yellow solid. MS (ESI): mass calcd. for $C_{23}H_{25}N_3O_2$, 375.19 m/z, found 376.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.35 (s, 1H), 8.22 (d, J = 2.4 Hz, 1H), 7.71 (dd, J = 9.1, 2.5 Hz, 1H), 7.43 (d, J = 9.0 Hz, 1H), 7.29 – 7.37 (m, 2H), 7.25 – 7.27 (m, 3H), 5.47 (s, 2H), 2.46 (t, J = 7.7 Hz, 1H), 1.96 – 2.03 (m, 1H), 1.80 – 1.89 (m, 1H), 1.70 – 1.75 (m, 1H), 1.60 – 1.64 (m, 1H), 1.51 – 1.56 (m, 1H), 1.36 – 1.45 (m, 1H), 1.10 (s, 3H), 0.91 (s, 3H).

Example 309: 1-(tert-butyl)-3-(1-(2,3-dihydro-1H-inden-1-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

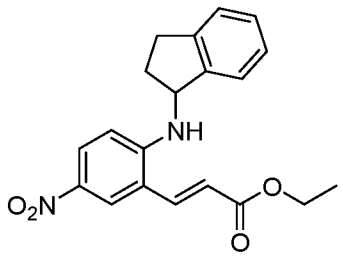
Synthetic Scheme





N-(2-bromo-4-nitrophenyl)-2,3-dihydro-1H-inden-1-amine

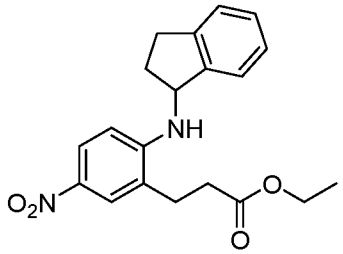
To a stirred mixture of 2-bromo-1-fluoro-4-nitrobenzene (4.3 g, 19.546 mmol, 1 equiv) and 2,3-dihydro-1H-inden-1-amine (2.60 g, 19.546 mmol, 1 equiv) in DMF (50 mL) was added Cs_2CO_3 (15.92 g, 48.865 mmol, 2.5 equiv) in portions at 25°C under air atmosphere. The resulting mixture was stirred for 2 h at 80 °C. Desired product could be detected by LCMS. The mixture was diluted with water (200 mL). The resulting mixture was extracted with EA (3 x 200 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford N-(2-bromo-4-nitrophenyl)-2,3-dihydro-1H-inden-1-amine (3.6 g, 55.28%) as a white solid. LC/MS (ESI): mass calcd. for $C_{15}H_{13}BrN_2O_2$: 332.02 m/z, found 334.90 [M+H, M+H+2] $^+$.



ethyl (E)-3-(2-((2,3-dihydro-1H-inden-1-yl)amino)-5-nitrophenyl)acrylate

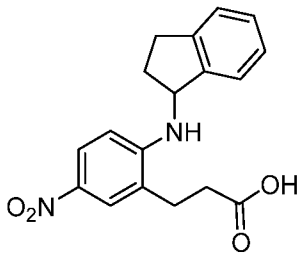
To a stirred mixture of N-(2-bromo-4-nitrophenyl)-2,3-dihydro-1H-inden-1-amine (1.5 g, 4.502 mmol, 1 equiv) and ethyl (2E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-enoate (1.53 g, 6.753 mmol, 1.5 equiv) in dioxane (15 mL) and H_2O (1.5 mL) was added K_2CO_3 (1.56 g, 11.255 mmol, 2.5 equiv) and $Pd(dppf)Cl_2$ (329.42 mg, 0.450 mmol, 0.1 equiv) in portions at 25°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 90 °C under N_2. Desired product could be detected by LCMS. After cooling down to rt, the mixture was diluted with water (100 mL). The resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted

with PE / EA (0-100%) to afford ethyl (E)-3-(2-((2,3-dihydro-1H-inden-1-yl)amino)-5-nitrophenyl)acrylate (630 mg, 39.71%) as a white solid. LC/MS (ESI): mass calcd. for $C_{20}H_{20}N_2O_4$: 352.14 m/z, found 353.15 $[M+H]^+$.



ethyl 3-(2-((2,3-dihydro-1H-inden-1-yl)amino)-5-nitrophenyl)propanoate

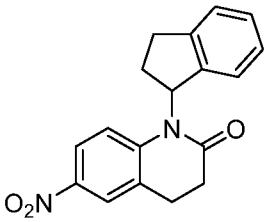
To a stirred mixture of ethyl (E)-3-(2-((2,3-dihydro-1H-inden-1-yl)amino)-5-nitrophenyl)acrylate (610 mg, 1.731 mmol, 1 equiv) and $CoCl_2$ (112.37 mg, 0.866 mmol, 0.5 equiv) in MeOH (0.5 mL) and THF (10 mL) was added $NaBH_4$ (130.97 mg, 3.462 mmol, 2 equiv) in portions at 0 °C under N_2 atmosphere. The resulting mixture was stirred for 2 h at room temperature. Desired product could be detected by LCMS. The mixture was diluted with water (50 mL). The resulting mixture was extracted with EA (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford ethyl 3-(2-((2,3-dihydro-1H-inden-1-yl)amino)-5-nitrophenyl)propanoate (200 mg, 35.89%) as a white solid. LC/MS (ESI): mass calcd. for $C_{18}H_{18}N_2O_4$: 354.16 m/z, found 355.15 $[M+H]^+$.



3-(2-((2,3-dihydro-1H-inden-1-yl)amino)-5-nitrophenyl)propanoic acid

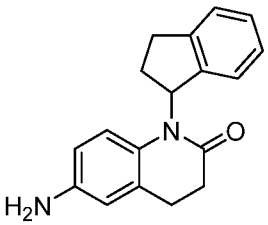
To a stirred mixture of ethyl 3-(2-((2,3-dihydro-1H-inden-1-yl)amino)-5-nitrophenyl)propanoate (210 mg, 0.593 mmol, 1 equiv) in THF (2 mL), EtOH (2 mL) and H_2O (2 mL) was added LiOH (42.57 mg, 1.779 mmol, 3 equiv) at 0 °C under air atmosphere. The resulting mixture was stirred for 2 h at room temperature. Desired product could be detected by LCMS. The mixture was basified to PH = 5 with 2N HCl and diluted with water (20 mL). The resulting mixture was

extracted with EA (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 3-(2-((2,3-dihydro-1H-inden-1-yl)amino)-5-nitrophenyl)propanoic acid (180 mg, 93.08%) as a white solid. LC/MS (ESI): mass calcd. for $C_{25}H_{34}N_4O_2$: 326.13 m/z, found 327.15 [M+H] +.



1-(2,3-dihydro-1H-inden-1-yl)-6-nitro-3,4-dihydroquinolin-2(1H)-one

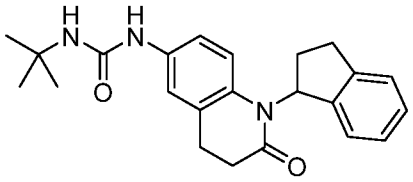
To a stirred mixture of 3-(2-((2,3-dihydro-1H-inden-1-yl)amino)-5-nitrophenyl)propanoic acid (170 mg, 0.521 mmol, 1 equiv) in T_3P (1 mL) at 0 °C under air atmosphere. The resulting mixture was stirred for 2 h at room temperature. Desired product could be detected by LCMS. The mixture was diluted with water (10 mL). The resulting mixture was extracted with EA (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% ethyl acetate/petroleum ether) to afford the 1-(2,3-dihydro-1H-inden-1-yl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (150 mg, 93.39%) as a white solid. LC/MS (ESI): mass calcd. for $C_{18}H_{16}N_2O_3$: 308.12 m/z, found 309.05[M+H] $^+$.



6-amino-1-(2,3-dihydro-1H-inden-1-yl)-3,4-dihydroquinolin-2(1H)-one

To a stirred mixture of 1-(2,3-dihydro-1H-inden-1-yl)-6-nitro-3,4-dihydroquinolin-2(1H)-one (170 mg, 0.551 mmol, 1 equiv) in MeOH (2 mL) and H_2O (0.2 mL) was added Fe (307.90 mg, 5.510 mmol, 10 equiv) and NH_4Cl (294.91 mg, 5.510 mmol, 10 equiv) in portions at room temperature nder air atmosphere. The resulting mixture was stirred for 2 h at 70 °C. Desired product could be detected by LCMS. After cooling down to rt, the mixture was diluted with water (10 mL). The resulting mixture was extracted with EA (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue

obtained was purified by silica gel chromatography (0-20% ethyl acetate/petroleum ether) to afford the 6-amino-1-(2,3-dihydro-1H-inden-1-yl)-3,4-dihydroquinolin-2(1H)-one (120 mg, 78.19%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{18}H_{18}N_2O$: 278.14 m/z, found 279.15[M+H] $^+$.

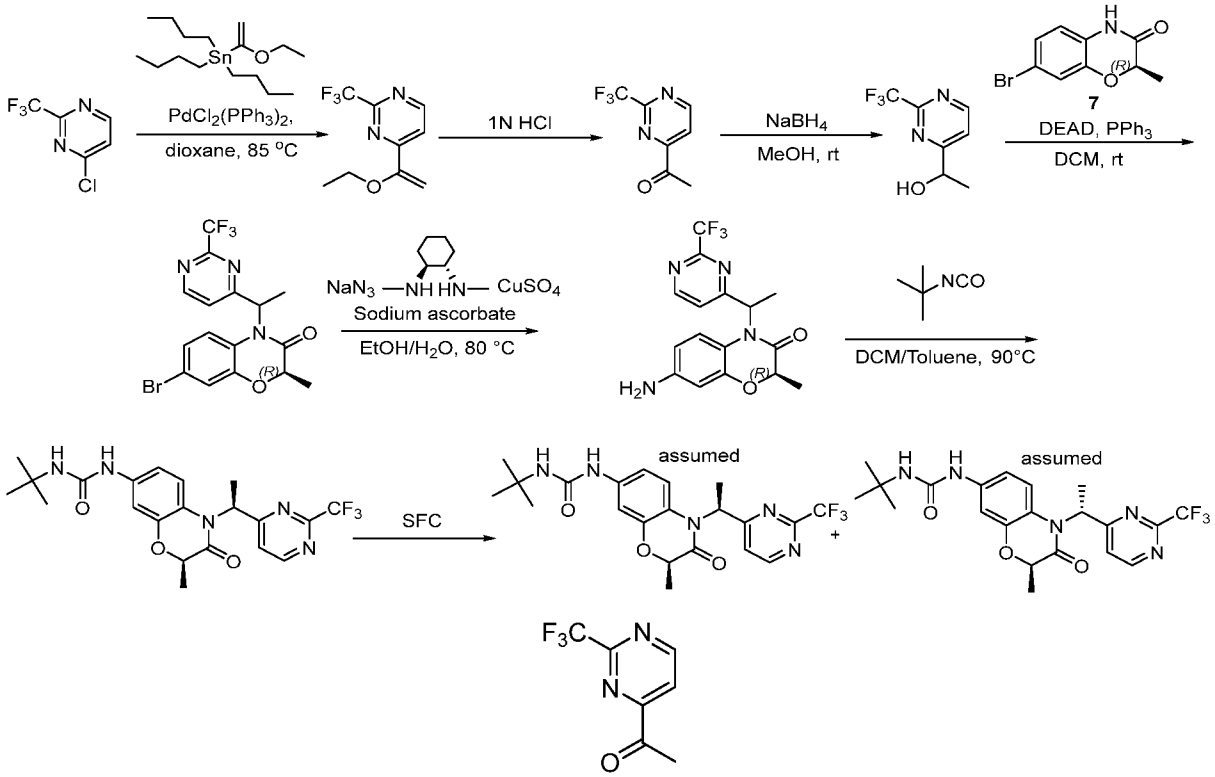


1-(tert-butyl)-3-(1-(2,3-dihydro-1H-inden-1-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

To a stirred mixture of 6-amino-1-(2,3-dihydro-1H-inden-1-yl)-3,4-dihydroquinolin-2(1H)-one (110 mg, 0.395 mmol, 1 equiv) in DCM/Toluene (2:1, 2mL) was added 2-isocyanato-2-methylpropane (117.53 mg, 1.185 mmol, 3 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2h at 90°C. Desired product could be detected by LCMS. After cooling down to rt, the mixture was diluted with water (10 mL). The resulting mixture was extracted with DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by preparative HPLC using a X Bridge Prep OBD C18 150 mm x 30 mm x 5μm column (eluent: 35% to 65% (v/v) CH_3CN and H_2O with 10 mmol /L NH_4HCO_3) to afford the 1-(tert-butyl)-3-(1-(2,3-dihydro-1H-inden-1-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea (31.6 mg, 21.16%) as a white solid. LC/MS (ESI): mass calcd. for $C_{23}H_{27}N_3O_2$: 377.21 m/z, found 378.15[M +H] $^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.32 – 7.29 (m, 2H), 7.20 (t, J = 7.3 Hz, 1H), 7.10 (t, J = 7.3 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.36 (s, 2H), 5.92 (m, 1H), 3.15 – 3.11 (m, 1H), 2.98 – 2.94 (m, 1H), 2.85 – 2.80 (m, 2H), 2.57 – 2.55 (m, 2H), 2.43 – 2.27 (m, 2H), 1.25 (s, 9H).

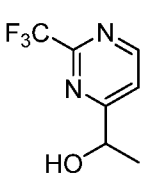
Example 310 and Example 311: 1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(2-(trifluoromethyl)pyrimidin-4-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea and 1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-(2-(trifluoromethyl)pyrimidin-4-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

Synthetic Scheme



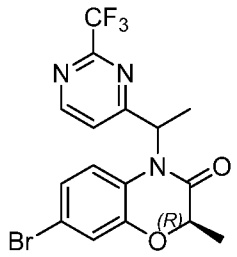
1-(2-(trifluoromethyl)pyrimidin-4-yl)ethan-1-one

To a solution of 4-chloro-2-(trifluoromethyl)pyrimidine (1 g, 5.479 mmol, 1 equiv) and bis(triphenylphosphine) palladium chloride (0.38 g, 0.548 mmol, 0.1 equiv) in dioxane (10 mL) was added tributyl(1-ethoxyethenyl)stannane (2.97 g, 8.219 mmol, 1.5 equiv) under N_2. The reaction was stirred at 85 °C under N_2 for 3h. The mixture was allowed to cool down to rt., and to the above mixture was added 1 N HCl (5 mL). The resulting mixture was stirred for additional 1h at rt. Quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-[2-(trifluoromethyl)pyrimidin-4-yl]ethanone (500 mg, 47.04%) as a yellow oil. MS (ESI): mass calcd. for $C_7H_5F_3N_2O$: 190.04 m/z, found 191.45 $[M+H]^+$



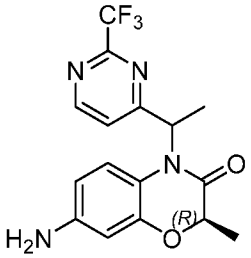
1-(2-(trifluoromethyl)pyrimidin-4-yl)ethan-1-ol

To a solution of 1-[2-(trifluoromethyl)pyrimidin-4-yl]ethanone (640 mg, 3.366 mmol, 1 equiv) in MeOH (10 mL) was added $NaBH_4$ (382.03 mg, 10.098 mmol, 3 equiv) at 0 °C. The reaction was stirred at rt for 1h. Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. This resulted in 1-[2-(trifluoromethyl)pyrimidin-4-yl]ethanol (400 mg, 58.75%) as a yellow oil. LCMS showed the desired product was generated and the reaction was not worked up. MS (ESI): mass calcd. for $C_7H_7F_3N_2O$: 192.05 m/z, found 193.00 $[M+H]^+$.



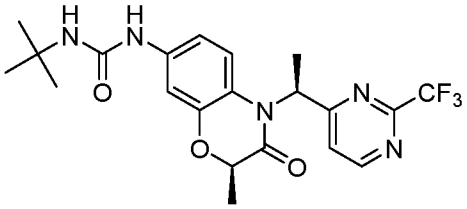
(2R)-7-bromo-2-methyl-4-(1-(2-(trifluoromethyl)pyrimidin-4-yl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of 1-[2-(trifluoromethyl)pyrimidin-4-yl]ethanol (270 mg, 1.405 mmol, 1 equiv) in DCM (10 mL) was added (2R)-7-bromo-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (340.16 mg, 1.405 mmol, 1 equiv) and PPh3 (552.87 mg, 2.107 mmol, 1.5 equiv). The reaction was stirred at rt under N_2 for 0.5h. To the above mixture was added DEAD (367.09 mg, 2.107 mmol, 1.5 equiv) at 0 °C. The resulting mixture was stirred for additional 1h at rt. Quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, water in ACN, 65% to 75% gradient in 10 min; detector, UV 254 nm. This resulted in (2R)-7-bromo-2-methyl-4-{1-[2-(trifluoromethyl)pyrimidin-4-yl]ethyl}-2H-1,4-benzoxazin-3-one (110 mg, 18.81%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{13}BrF_3N_3O_2$: 415.01 m/z, found:415.90,417.90 $[M+H, M+H+2]^+$.



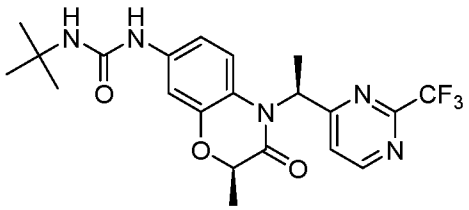
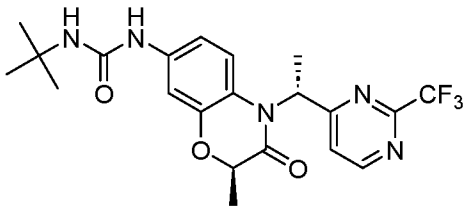
(2R)-7-amino-2-methyl-4-(1-(2-(trifluoromethyl)pyrimidin-4-yl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-7-bromo-2-methyl-4-{1-[2-(trifluoromethyl)pyrimidin-4-yl]ethyl}-2H-1,4-benzoxazin-3-one (180 mg, 0.432 mmol, 1 equiv) in EtOH/H2O (4:1, 10 mL) was added (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (36.91 mg, 0.259 mmol, 0.6 equiv), $CuSO_4$ (69.02 mg, 0.432 mmol, 1 equiv), sodium ascorbate (172.23 mg, 0.864 mmol, 2 equiv) and NaN_3 (84.35 mg, 1.296 mmol, 3 equiv). The reaction was stirred at 80°C under N_2 for 3h. After cooling down to rt, the reaction was quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-2-methyl-4-{1-[2-(trifluoromethyl)pyrimidin-4-yl]ethyl}-2H-1,4-benzoxazin-3-one (70 mg, 45.94%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{15}F_3N_4O_2$: 352.12 m/z, found 353.00 $[M+H]^+$.



1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(2-(trifluoromethyl)pyrimidin-4-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a solution of (2R)-7-amino-2-methyl-4-{1-[2-(trifluoromethyl)pyrimidin-4-yl]ethyl}-2H-1,4-benzoxazin-3-one (70 mg, 0.199 mmol, 1 equiv) in DCM/Toluene (2:1, 7.5 mL) was added 2-isocyanato-2-methylpropane (196.96 mg, 1.990 mmol, 10 equiv). The reaction was stirred at 90 °C under N_2 for 3h. After cooling down to rt, the reaction was quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a YMC-Actus Tiart C18 ExRS Column, 30*150 mm, 5μm column (eluent: 49% to 73% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-[(2R)-2-methyl-3-oxo-4-{1-[2-(trifluoromethyl)pyrimidin-4-yl]ethyl}-2H-1,4-benzoxazin-7-yl]urea (40 mg, 44.59%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{24}F_3N_5O_3$: 451.18 m/z, found 452.15 $[M+H]^+$.

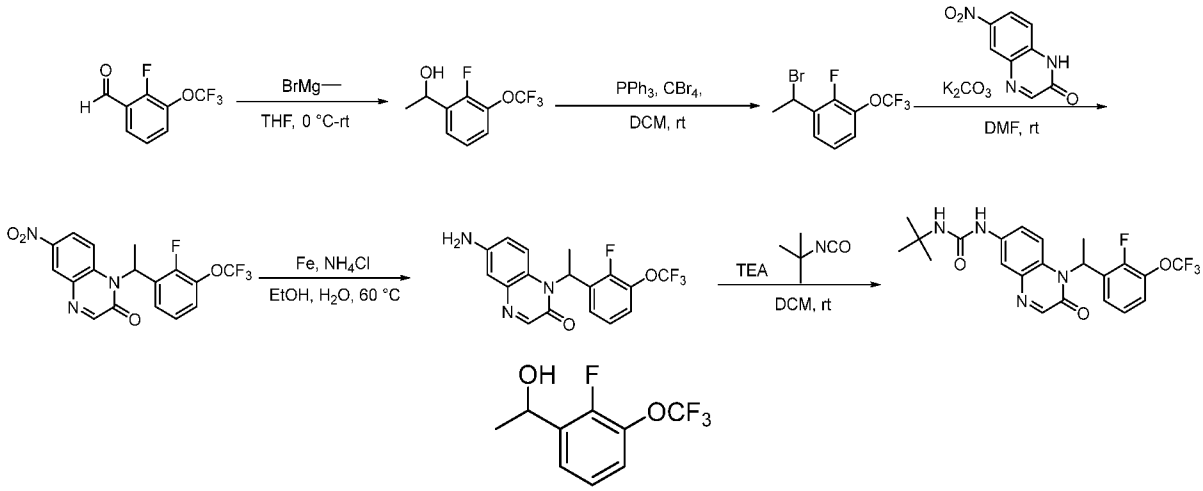



1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(2-(trifluoromethyl)pyrimidin-4-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea and 1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-(2-(trifluoromethyl)pyrimidin-4-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

A sample of 3-tert-butyl-1-[(2R)-2-methyl-3-oxo-4-{1-[2-(trifluoromethyl)pyrimidin-4-yl]ethyl}-2H-1,4-benzoxazin-7-yl]urea (40 mg) was separated by chiral-HPLC using a CHIRALPAK IE, 2*25 cm, 5 μm column (eluent: 10% to 10% (v/v) HEX: DCM=3: 1(0.5% 2M NH_3-MeOH) to yield first example 3-tert-butyl-1-[(2R)-2-methyl-3-oxo-4-[(1S)-1-[2-(trifluoromethyl)pyrimidin-4-yl]ethyl]-2H-1,4-benzoxazin-7-yl]urea (12.8 mg, 32.00%) as a white solid. MS(ESI): mass calcd. for $C_{21}H_{24}F_3N_5O_3$: 451.18 m/z, found: 474.15 $[M+Na]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.81 - 9.10 (m, 1H), 8.26 (s, 1H), 7.59 – 7.90 (m, 1H), 7.16 – 7.34 (m, 1H), 6.58 – 7.03 (m, 2H), 5.78 – 6.01 (m, 2H), 4.65 – 4.80 (m, 1H), 1.78 (d, J = 6.9 Hz, 3H), 1.39 (d, J = 6.7 Hz, 3H), 1.27 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -69.1379. And to yield second example 3-tert-butyl-1-[(2R)-2-methyl-3-oxo-4-[(1R)-1-[2-(trifluoromethyl)pyrimidin-4-yl]ethyl]-2H-1,4-benzoxazin-7-yl]urea (13.7 mg, 34.25%) as a white solid. MS(ESI): mass calcd. for $C_{21}H_{24}F_3N_5O_3$: 451.18 m/z, found: 452.05 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.90 - 9.10 (m, 1H), 8.26 (s, 1H), 7.63 – 7.94 (m, 1H), 7.15 – 7.36 (m, 1H), 6.65 – 7.00 (m, 2H), 5.98 (m, 1H), 5.80 – 5.95 (m, 1H), 4.68 – 4.72 (m, 1H), 1.70 – 1.86 (m, 3H), 1.33 – 1.45 (m, 3H), 1.27 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -69.1481.

Example 312: 1-(tert-butyl)-3-(1-(1-(2-fluoro-3-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

Synthetic Scheme

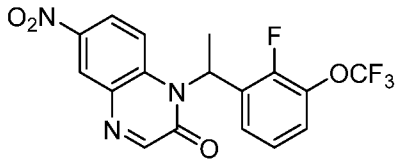


1-(2-fluoro-3-(trifluoromethoxy)phenyl)ethan-1-ol

To a stirring solution 2-fluoro-3-(trifluoromethoxy)benzaldehyde (500 mg, 2.403 mmol, 1 equiv) in tetrahydrofuran (10 mL) was added a solution of methylmagnesium bromide (2 M in THF, 1.8 mL, 3.604 mmol, 1.5 equiv) at 0 °C. The mixture was stirred at room temperature for 5 h. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 30 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude was purified by silica gel column with PE/EA (4:1) to afford 1-(2-fluoro-3-(trifluoromethoxy)phenyl)ethan-1-ol (500 mg, 92.84%) as a yellow solid.

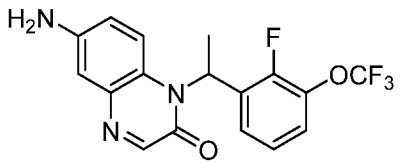
1-(1-bromoethyl)-2-fluoro-3-(trifluoromethoxy)benzene

To a stirring solution 1-(2-fluoro-3-(trifluoromethoxy)phenyl)ethan-1-ol (100 mg, 0.446 mmol, 1 equiv) in DCM (2 mL) was added a solution of CBr_4 (163 mg, 0.491 mmol, 1.1 equiv) in 0 °C and PPh_3 (129 mg, 0.491 mmol, 1.1 equiv) at 0 °C . The mixture was stirred at room temperature for 5 h. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude was purified by silica gel column with PE/EA (5:1) to afford 1-(1-bromoethyl)-2-fluoro-3-(trifluoromethoxy)benzene (100 mg, 78.09%) as a yellow solid.



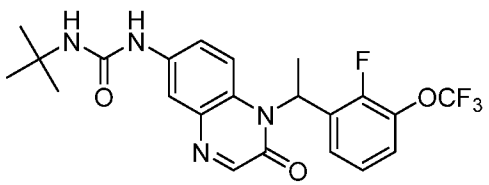
1-(1-(2-fluoro-3-(trifluoromethoxy)phenyl)ethyl)-6-nitroquinoxalin-2(1H)-one

To a stirring solution 6-nitroquinoxalin-2(1H)-one (67 mg, 0.348 mmol, 1 equiv) in DMF (5 mL) was added K_2CO_3 (146 mg, 1.044 mmol, 3 equiv) and 1-(1-bromoethyl)-2-fluoro-3-(trifluoromethoxy)benzene (100 mg, 0.348 mmol, 1 equiv). The mixture was stirred at room temperature for 5 h. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude was purified by silica gel column with PE/EA (3:1) to afford 1-(1-(2-fluoro-3-(trifluoromethoxy)phenyl)ethyl)-6-nitroquinoxalin-2(1H)-one (40 mg, 28.90%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{11}F_4N_3O_4$: 397.07 found: 398.10 $[M+H]^+$.



6-amino-1-(1-(2-fluoro-3-(trifluoromethoxy)phenyl)ethyl)quinoxalin-2(1H)-one

To a stirring solution 1-(1-(2-fluoro-3-(trifluoromethoxy)phenyl)ethyl)-6-nitroquinoxalin-2(1H)-one (40 mg, 0.101 mmol, 1 equiv) in EtOH (2 mL) and H_2O (0.5 mL) was added Fe (27 mg, 0.479 mmol, 4.74 equiv) and NH_4Cl (27 mg, 0.500 mmol, 4.95 equiv). The mixture was stirred for 2 h at 60 °C. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude was purified by silica gel column with PE/EA (1:1) to afford 6-amino-1-(1-(2-fluoro-3-(trifluoromethoxy)phenyl)ethyl)quinoxalin-2(1H)-one (30 mg, 81.12%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{13}F_4N_3O_2$: 367.07 found: 368.10 $[M+H]^+$.

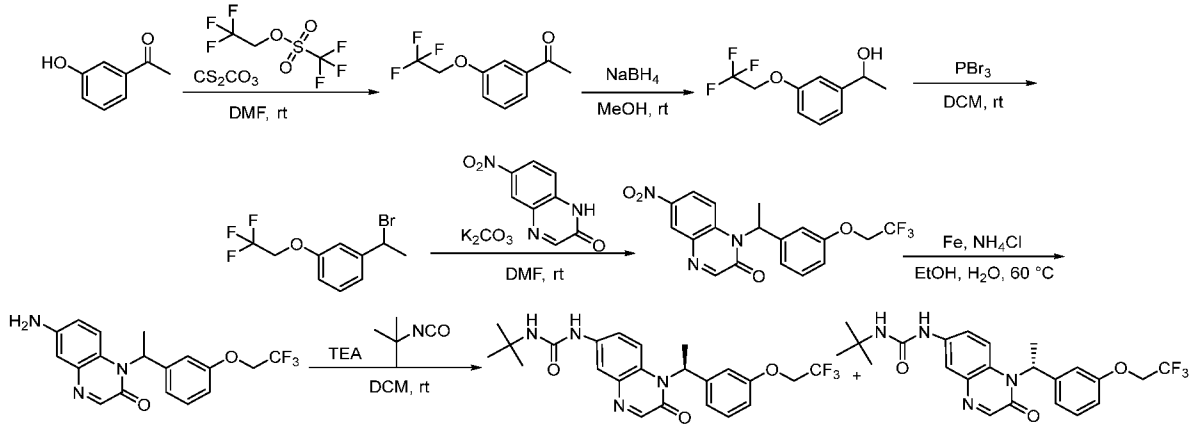


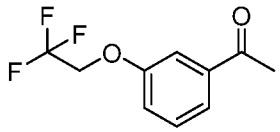
1-(tert-butyl)-3-(1-(1-(2-fluoro-3-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

To a stirring solution 6-amino-1-(1-(2-fluoro-3-(trifluoromethoxy)phenyl)ethyl)quinoxalin-2(1H)-one (30 mg, 0.082 mmol, 1 equiv) in DCM (2 mL) was added 2-isocyanato-2-methylpropane (30 mg, 0.303 mmol, 3.71 equiv) and TEA (40 mg, 0.395 mmol, 4.84 equiv). The mixture was stirred at room temperature for 16 h. The reaction mixture was quenched by water (10 mL) and extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude was purified by silica gel column with PE/EA (1:1) and Prep-HPLC (Column: XBridge Prep OBD C18, 30*150 mm, 5.0 μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate: 60 mL/min; Gradient: 30% B to 60% B in 7min ; Wave Length: 254/220 nm; RT1(min): 10.7; Number Of Runs: 3) to afford 1-(tert-butyl)-3-(1-(1-(2-fluoro-3-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea (9.5 mg, 24.79%) as a yellow solid. MS (ESI): mass calcd. for $C_{22}H_{22}F_4N_4O_3$: 466.15 found: 467.00$[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.14 (s, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.73 (t, J = 7.4 Hz, 1H), 7.44 – 7.54 (m,3H), 7.37 (t, J = 8.2 Hz, 1H), 6.54 (s, 1H), 6.04 (s, 1H), 1.89 (d, J = 7.0 Hz, 3H), 1.29 (s, 9H).

Example 313: (S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

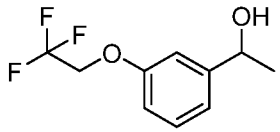
Synthetic Scheme





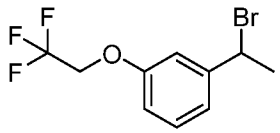
1-(3-(2,2,2-trifluoroethoxy)phenyl)ethan-1-one

To a stirred solution of 3-hydroxyacetophenone (1.5 g, 11.017 mmol, 1 equiv) was added dimethylformamide (15 mL) followed by catalytic amount of 2,2,2-trifluoroethyl trifluoromethanesulfonate (3.84 g, 16.526 mmol, 1.5 equiv) and at room temperature. The reaction mixture was stirred at room temperature for a period of 3h. After completion of reaction, the reaction mixture was quenched by water (30 mL) and extracted with EA (3 x 30 mL).The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford desired 1-(3-(2,2,2-trifluoroethoxy)phenyl)ethan-1-one (1.5 g, 62.40%) . MS (ESI): mass calcd. for $C_{10}H_9F_3O_2$: 218.175 m/z, found: 219.15 [M+H]+.



1-(3-(2,2,2-trifluoroethoxy)phenyl)ethan-1-ol

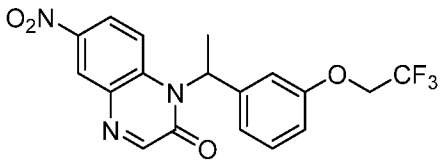
To a solution of 1-(3-(2,2,2-trifluoroethoxy)phenyl)ethan-1-one (2.2 g, 10.249 mmol, 1 equiv) in methanol (30 mL) was added $NaBH_4$ (0.77 g, 20.498 mmol, 2 equiv)) at 0 °C. The mixture was stirred for 30 min. The reaction mixture was quenched by water (20 mL) and extracted with EA (3 x 100 mL). Then, the combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (1:1) to afford 1-(3-(2,2,2-trifluoroethoxy)phenyl)ethan-1-ol (1.23 g, 54.68%) as a yellow oil.



1-(1-bromoethyl)-3-(2,2,2-trifluoroethoxy)benzene

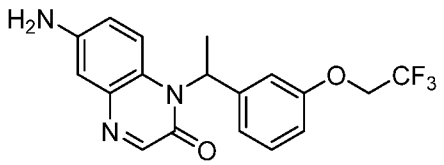
To a solution of 1-(3-(2,2,2-trifluoroethoxy)phenyl)ethan-1-ol (1.0 g, 4.542 mmol, 1 equiv) in methylene chloride (20 mL) the mixture was 0 °C then added phosphorus tribromide (6.15 g, 22.710 mmol, 5.0 equiv) slowly, the mixture was warmed to room temperature stirred at room

temperature for 3 h. The reaction mixture was quenched by ice-water and extracted with EA (3 x 50 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 1-(1-bromoethyl)-3-(2,2,2-trifluoroethoxy)benzene (725 mg, 56.39%) as a yellow oil.



6-nitro-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)quinoxalin-2(1H)-one

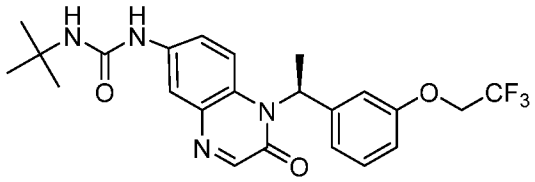
To a solution of 1-(1-bromoethyl)-3-(2,2,2-trifluoroethoxy)benzene (430 mg, 1.519 mmol, 1 equiv) in dimethylformamide (10 mL) was added potassium methaneperoxoate potassium (634 mg, 4.557 mmol, 3 equiv) at room temperature. Then 6-nitro-1H-quinoxalin-2-one (290 mg, 1.519 mmol, 1 equiv) was added at room temperature. The reaction was stirred at room temperature for 6h. The reaction mixture was quenched by water and extracted with EA (3 x 100 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (1:1) to afford 6-nitro-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)quinoxalin-2(1H)-one (380 mg, 63.60%). MS (ESI): mass calcd. for C18H14F3N3O4: 393.322 m/z, found:394.20 [M+H]+.



6-amino-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)quinoxalin-2(1H)-one

To a stirred solution of6-nitro-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)quinoxalin-2(1H)-one (50 mg, 0.127 mmol, 1 equiv) in methanol (10 mL) and water (2 mL) was added iron (71 mg, 1.27 mmol, 10 equiv) followed by catalytic amount of NH_4Cl (67 mg, 1.27 mmol, 10 equiv) at room temperature. The reaction mixture was stirred at 60 °C for a period of 0.5 h. The reaction mixture was quenched by water (20 mL) and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum

to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (1:1) to afford desired 6-amino-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)quinoxalin-2(1H)-one (30 mg, 64.93%). MS (ESI): mass calcd. for C18H16F3N3O2: 363.34 m/z, found:364.20 [M+H]+.

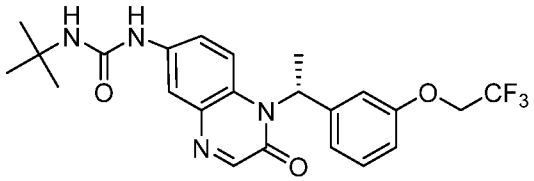


(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

To a stirring solution 6-amino-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)quinoxalin-2(1H)-one (200 mg, 0.550 mmol, 1 equiv) in DCM (5 mL) was added a solution of 2-isocyanato-2-methylpropane (272 mg, 2.750 mmol, 5 equiv) and TEA (557 mg, 5.500 mmol, 10 equiv). The mixture was stirred at room temperature for 16 h. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by C18 column (eluent: CH_3CN and H_2O), Prep-HPLC (Column: XBridge Prep OBD C18, 30*150 mm, 5.0 μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate: 60 mL/min; Gradient: 30% B to 60% B in 7min) and Chiral-HPLC (Column: (R, R)-WHELK-01-Kromasil 5*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 30; Wave Length: 220/254 nm; RT1(min): 21.321; RT2(min): 28.591; Injection Volume: 0.9 mL; Number Of Runs: 5) to afford (S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea (8.2 mg, 3.21%) as a yellow solid. MS (ESI): mass calcd. for $C_{23}H_{25}F_3N_4O_3$: 462.18 m/z, found: 463.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.26 (s, 1H), 7.93 (d, J = 2.5 Hz, 1H), 7.23 – 7.36 (m, 2H), 7.05 (br, 1H), 6.94 – 7.01 (m, 2H), 6.90 (d, J = 7.8 Hz, 1H), 6.57 (br, 1H), 6.03 (s, 1H), 4.76 (q, J = 8.9 Hz, 2H), 1.87 (d, J = 7.1 Hz, 3H), 1.28 (s, 9H). And another isomer (R)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea as a yellow solid (6 mg, 2.35%) as a yellow solid. MS (ESI): mass calcd. for $C_{23}H_{25}F_3N_4O_3$: 462.18 m/z, found: 463.15 [M+H]+. ^1H NMR (300 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.26 (s, 1H), 7.93 (d,

J = 2.5 Hz, 1H), 7.23 – 7.36 (m, 2H), 7.05 (br, 1H), 6.94 – 7.01 (m, 2H), 6.90 (d, J = 7.8 Hz, 1H), 6.57 (br, 1H), 6.03 (s, 1H), 4.76 (q, J = 8.9 Hz, 2H), 1.87 (d, J = 7.1 Hz, 3H), 1.28 (s, 9H).

Example 314: (R)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

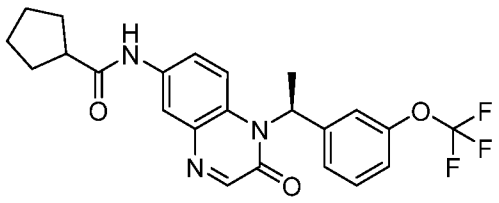


(R)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

To a stirring solution 6-amino-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)quinoxalin-2(1H)-one (200 mg, 0.550 mmol, 1 equiv) in DCM (5 mL) was added a solution of 2-isocyanato-2-methylpropane (272 mg, 2.750 mmol, 5 equiv) and TEA (557 mg, 5.500 mmol, 10 equiv). The mixture was stirred at room temperature for 16 h. The mixture was concentrated to dryness under reduced pressure to provide the crude product, which was purified by C18 column (eluent: CH_3CN and H_2O), Prep-HPLC (Column: XBridge Prep OBD C18, 30*150 mm, 5.0 μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate: 60 mL/min; Gradient: 30% B to 60% B in 7min) and Chiral-HPLC (Column: (R, R)-WHELK-01-Kromasil 5*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 30; Wave Length: 220/254 nm; RT1(min): 21.321; RT2(min): 28.591; Injection Volume: 0.9 mL; Number Of Runs: 5) to afford (S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea (8.2 mg, 3.21%) as a yellow solid. MS (ESI): mass calcd. for $C_{23}H_{25}F_3N_4O_3$: 462.18 m/z, found: 463.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.26 (s, 1H), 7.93 (d, J = 2.5 Hz, 1H), 7.23 – 7.36 (m, 2H), 7.05 (br, 1H), 6.94 – 7.01 (m, 2H), 6.90 (d, J = 7.8 Hz, 1H), 6.57 (br, 1H), 6.03 (s, 1H), 4.76 (q, J = 8.9 Hz, 2H), 1.87 (d, J = 7.1 Hz, 3H), 1.28 (s, 9H). And another isomer (R)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea as a yellow solid (6 mg, 2.35%) as a yellow solid. MS (ESI): mass calcd. for $C_{23}H_{25}F_3N_4O_3$: 462.18 m/z, found: 463.15 [M+H]+. ^1H NMR (300 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.26 (s, 1H), 7.93 (d,

J = 2.5 Hz, 1H), 7.23 – 7.36 (m, 2H), 7.05 (br, 1H), 6.94 – 7.01 (m, 2H), 6.90 (d, J = 7.8 Hz, 1H), 6.57 (br, 1H), 6.03 (s, 1H), 4.76 (q, J = 8.9 Hz, 2H), 1.87 (d, J = 7.1 Hz, 3H), 1.28 (s, 9H).

Example 315: (S)-N-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)cyclopentanecarboxamide

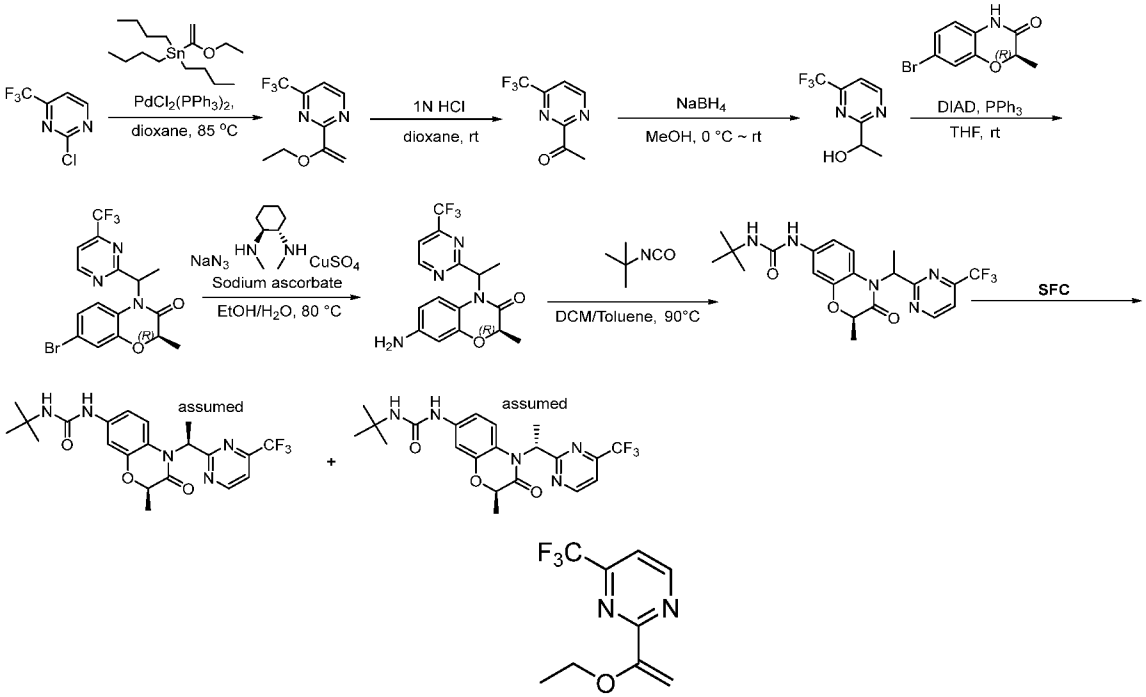


(S)-N-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)cyclopentanecarboxamide

To a stirring solution 6-amino-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one (40 mg, 0.115 mmol, 1 equiv) in pyridine (3 mL) was added a solution of cyclopentanecarboxylic acid (16.99 mg, 0.150 mmol, 1.3 equiv) and EDCI (33 mg, 0.173 mmol, 1.5 equiv). The mixture was stirred at room temperature for 16 h. The mixture was concentrated and purified by C18 column (eluent: CH_3CN and H_2O) to afford (S)-N-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)cyclopentanecarboxamide (32.3 mg, 19.32%) as a yellow solid. MS (ESI): mass calcd. for : $C_{23}H_{22}F_3N_3O_3$: 445.44 m/z, found: 446.10 [M+H]+. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.07 (s, 1H), 8.27 (s, 1H), 8.19 (d, J = 2.5 Hz, 1H), 7.59 (d, J = 9.1 Hz, 1H), 7.47 (t, J = 8.1 Hz, 1H), 7.30 (d, J = 4.9 Hz, 4H), 7.17 (s, 1H), 6.58 (s, 1H), 2.74 – 2.79 (m, 1H), 1.83 – 1.88 (m, 5H), 1.56 –1.68 (m, 4H), 1.45 – 1.53 (m, 2H).

Example 316 and Example 317: 1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(4-(trifluoromethyl)pyrimidin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea and 1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-(4-(trifluoromethyl)pyrimidin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

Synthetic Scheme



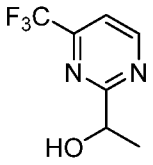
2-(1-ethoxyvinyl)-4-(trifluoromethyl)pyrimidine

To a solution of 2-chloro-4-(trifluoromethyl)pyrimidine (5 g, 27.393 mmol, 1 equiv) in dioxane (70 mL) was added tributyl(1-ethoxyethenyl)stannane (14.84 g, 41.090 mmol, 1.5 equiv) and bis(triphenylphosphane) dichloropalladium (1.92 g, 2.739 mmol, 0.1 equiv). The resulting mixture was maintained under nitrogen and stirred at 90 °C for 3 h. After cooling down to rt, the reaction was quenched with water (150 mL). The resulting mixture was extracted with ethyl acetate (3 x 150 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% ethyl acetate/petroleum ether) to afford the 2-(1-ethoxyvinyl)-4-(trifluoromethyl)pyrimidine (5 g, 83.66%) as a yellow solid.LC/MS: mass calcd. for $C_8H_8F_3N_2O$: 218.07 m/z, found: 219.00 $[M+H]^+$.

1-(4-(trifluoromethyl)pyrimidin-2-yl)ethan-1-one

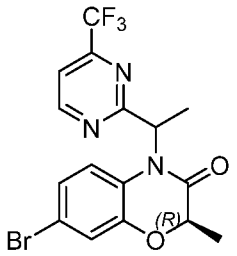
To a solution of 2-(1-ethoxyvinyl)-4-(trifluoromethyl)pyrimidine (1.5 g, 6.875 mmol, 1 equiv) in dioxane (70 mL) was added 1N HCl (15 mL). The resulting mixture was maintained under air and

stirred at rt for 3 h. The reaction was quenched with water (100 mL). The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% ethyl acetate/petroleum ether) to afford the 1-(4-(trifluoromethyl)pyrimidin-2-yl)ethan-1-one (800 mg, 61.20%) as a yellow oil.LC/MS: mass calcd. for $C_7H_5F_3N_2O$: 190.04 m/z, found: 191.10 $[M+H]^+$.



1-(4-(trifluoromethyl)pyrimidin-2-yl)ethan-1-ol

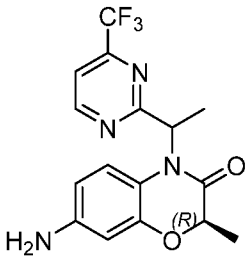
To a solution of 1-(4-(trifluoromethyl)pyrimidin-2-yl)ethan-1-one (2.2 g, 11.571 mmol, 1 equiv) in MeOH (24 mL) was added $NaBH_4$ (656.62 mg, 17.357 mmol, 1.5 equiv) at 0°C. The resulting mixture was maintained under air and stirred at rt for 3 h. The reaction was quenched with water (100 mL). The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% ethyl acetate/petroleum ether) to afford the 1-(4-(trifluoromethyl)pyrimidin-2-yl)ethan-1-ol (1 g, 44.98%) as a yellow oil. LC/MS: mass calcd. for $C_7H_7F_3N_2O$: 192.05 m/z, found: 193.00 $[M+H]^+$.



(2R)-7-bromo-2-methyl-4-(1-(4-(trifluoromethyl)pyrimidin-2-yl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

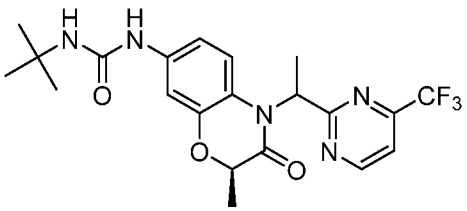
To a solution of 1-(4-(trifluoromethyl)pyrimidin-2-yl)ethan-1-ol (300 mg, 1.561 mmol, 1 equiv) in THF (5 mL) was added (R)-7-bromo-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one (377.96 mg, 1.561 mmol, 1 equiv) and PPh_3 (614.30 mg, 2.341 mmol, 1.5 equiv). The reaction was stirred at rt under N_2 for 0.5h. To the above mixture was added DIAD (473.58 mg, 2.341 mmol, 1.5 equiv) at 0 °C. The resulting mixture was stirred for additional 1h at rt. The reaction was quenched with water (30 mL). The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The organic

layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% ethyl acetate/petroleum ether) to afford the (2R)-7-bromo-2-methyl-4-(1-(4-(trifluoromethyl)pyrimidin-2-yl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (550 mg, 84.64%) as a yellow oil. LC/MS: mass calcd. for $C_{16}H_{13}BrF_3N_3O_2$: 415.01 m/z, found: 416.00, 418.00 $[M+H, M+H+2]^+$.



(2R)-7-amino-2-methyl-4-(1-(4-(trifluoromethyl)pyrimidin-2-yl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

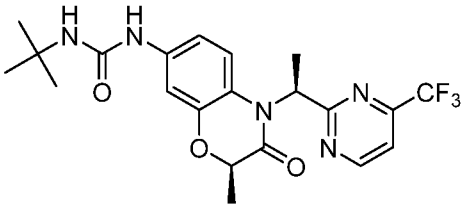
To a solution of 6-nitro-1-[(1S)-1-[6-(trifluoromethoxy)pyridin-2-yl]ethyl]quinoxalin-2-one (540 mg, 1.122 mmol, 1 equiv) in EtOH (4 mL) and H_2O (1 mL) was added (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (95.77 mg, 0.673 mmol, 0.6 equiv), $CuSO_4$ (179.10 mg, 1.122 mmol, 1 equiv), sodium ascorbate (446.88 mg, 2.244 mmol, 2 equiv) and sodium azide (218.86 mg, 3.366 mmol, 3 equiv). The reaction was stirred at 80 °C for 1h. After cooling down to rt, the filtrate was quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-2-methyl-4-(1-(4-(trifluoromethyl)pyrimidin-2-yl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (360 mg, 91.06%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{15}F_3N_4O_2$: 352.11 m/z, found 352.95 $[M+H]^+$.

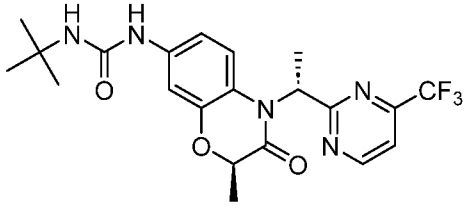


1-(tert-butyl)-3-((2R)-2-methyl-3-oxo-4-(1-(4-(trifluoromethyl)pyrimidin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a solution of (2R)-7-amino-2-methyl-4-{1-[4-(trifluoromethyl)pyrimidin-2-yl]ethyl}-2H-1,4-benzoxazin-3-one (280 mg, 0.795 mmol, 1 equiv) in DCM (10 mL) was added TEA (482.53 mg,

4.770 mmol, 6 equiv) and 2-isocyanato-2-methylpropane (787.85 mg, 7.950 mmol, 10 equiv). The reaction was stirred at rt under N_2 for 3h.Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Shield RP 18 OBD Column, 30*150 mm, 5μm column (eluent: 39% to 69% (v/v) CH_3CN and Water (10mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$)) to afford the title compound 3-tert-butyl-1-[(2R)-2-methyl-3-oxo-4-{1-[4-(trifluoromethyl)pyrimidin-2-yl]ethyl}-2H-1,4-benzoxazin-7-yl]urea (80 mg, 22.30%) as a white solid. LC/MS (ESI): mass calcd. for $C_{21}H_{24}F_3N_5O_3$:451.18 m/z, found:452.15 $[M+H]^+$.





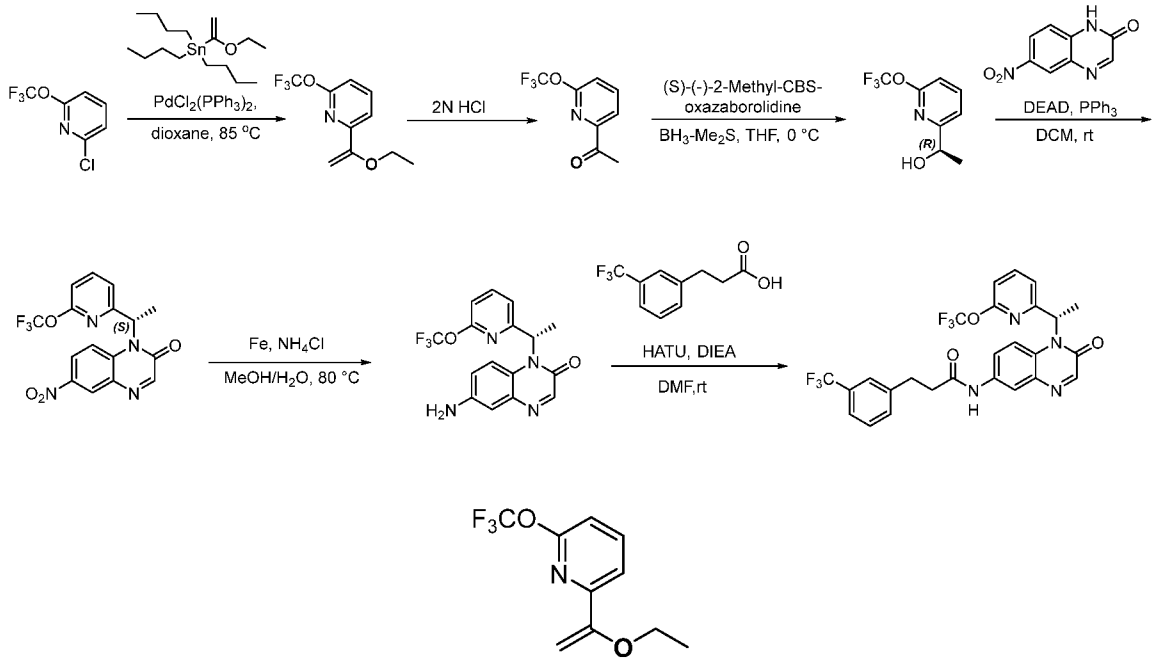
1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(4-(trifluoromethyl)pyrimidin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea and 1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-(4-(trifluoromethyl)pyrimidin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

A sample of 3-tert-butyl-1-[(2R)-2-methyl-3-oxo-4-{1-[4-(trifluoromethyl)pyrimidin-2-yl]ethyl}-2H-1,4-benzoxazin-7-yl]urea (80 mg) was separated by chiral-HPLC using a CHIRALPAK IF 2*25 cm, 5 μm column (eluent: 25% to 25% (v/v) EtOH and Hex(0.5% 2M NH_3-MeOH) to yield first enantiomer example 3-tert-butyl-1-[(2R)-2-methyl-3-oxo-4-[(1S)-1-[4-(trifluoromethyl)pyrimidin-2-yl]ethyl]-2H-1,4-benzoxazin-7-yl]urea (29.9 mg, 37.38%) as a white solid. MS(ESI): mass calcd. for $C_{21}H_{24}F_3N_5O_3$: 451.18 m/z, found: 452.05 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.16 (d, J = 5.0 Hz, 1H), 8.25 (s, 1H), 7.91 (d, J = 5.1 Hz, 1H), 7.23 (d, J = 2.3 Hz, 1H), 6.88 – 7.00 (m, 1H), 6.70 – 6.88 (m, 1H), 5.96 (s, 1H), 5.81 – 5.13 (m, 1H), 4.61 (q, J = 6.7 Hz, 1H), 1.82 (d, J = 6.9 Hz, 3H), 1.34 (d, J = 6.7 Hz, 3H), 1.28 (s, 9H).^{19}F NMR (376 MHz, DMSO) δ(ppm): -68.7349. and to yield second enantiomer example 3-tert-butyl-1-[(2R)-2-methyl-3-oxo-4-[(1R)-1-[4-(trifluoromethyl)pyrimidin-2-yl]ethyl]-2H-1,4-benzoxazin-7-yl]urea (25.9 mg, 32.38%) as a white solid. MS(ESI): mass calcd. for $C_{21}H_{24}F_3N_5O_3$: 451.18 m/z, found: 452.05 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.16 (d, J = 5.0 Hz, 1H), 8.22 (s, 1H), 7.92 (d, J = 5.1 Hz, 1H), 7.23 (d, J = 2.2 Hz, 1H), 6.45 – 7.00 (m, 2H), 5.98 – 6.06 (m, 1H), 5.95 (s, 1H),

4.33 – 4.72 (m, 1H), 1.81 (d, J = 7.0 Hz, 3H), 1.36 (d, J = 6.8 Hz, 3H), 1.27 (s, 9H).^{19}F NMR (376 MHz, DMSO) δ(ppm): -68.7105.

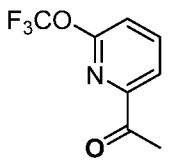
Example 318: (S)-N-(2-oxo-1-(1-(6-(trifluoromethoxy)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)phenyl)propanamide

Synthetic Scheme



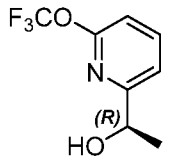
2-(1-ethoxyvinyl)-6-(trifluoromethoxy)pyridine

To a solution of 2-chloro-6-(trifluoromethoxy)pyridine (1 g, 5.062 mmol, 1 equiv) and $Pd(PPh_3)_2Cl_2$ (0.36 g, 0.506 mmol, 0.1 equiv) in dioxane (10 mL) was added tributyl(1-ethoxyethenyl)stannane (2.74 g, 7.593 mmol, 1.5 equiv) under N_2. The reaction was stirred at 85 °C under N_2 for 1h. After cooling down to rt, the reaction was quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. This resulted in 2-(1-ethoxyethenyl)-6-(trifluoromethoxy)pyridine (1 g, 84.71%) as a white oil. MS (ESI): mass calcd. for $C_{10}H_{10}F_3NO_2$: 233.07 m/z, found 233.95 $[M+H]^+$.



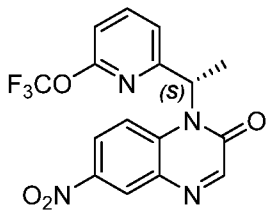
1-(6-(trifluoromethoxy)pyridin-2-yl)ethan-1-one

To a solution of 2-(1-ethoxyethenyl)-6-(trifluoromethoxy)pyridine (1 g, 4.288 mmol, 1 equiv) in dioxane (10 mL) was added 2N HCl (5 mL) .The reaction was stirred at rt for 1 day. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-[6-(trifluoromethoxy)pyridin-2-yl]ethanone (0.75 g, 75.26%) as a white oil. MS (ESI): mass calcd. for $C_8H_6F_3NO_2$: 205.04 m/z, found 205.95 $[M+H]^+$.



(R)-1-(6-(trifluoromethoxy)pyridin-2-yl)ethan-1-ol

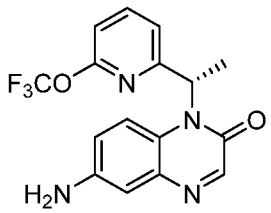
To a solution of (3aS)-1-methyl-3,3-diphenyl-hexahydropyrrolo[1,2-c][1,3,2]oxazaborole (162.14 mg, 0.585 mmol, 0.2 equiv) in THF (10 mL) was added BH_3-Me_2S (333.26 mg, 4.387 mmol, 1.5 equiv) and 1-[6-(trifluoromethoxy)pyridin-2-yl]ethanone (600 mg, 2.925 mmol, 1 equiv) at 0 °C. The reaction was stirred at 0 °C for 1h. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (1R)-1-[6-(trifluoromethoxy)pyridin-2-yl]ethanol (260 mg, 42.91%) as a white oil. MS (ESI): mass calcd. for $C_8H_8F_3NO_2$: 207.05 m/z, found:208.10 $[M+H]^+$.



(S)-6-nitro-1-(1-(6-(trifluoromethoxy)pyridin-2-yl)ethyl)quinoxalin-2(1H)-one

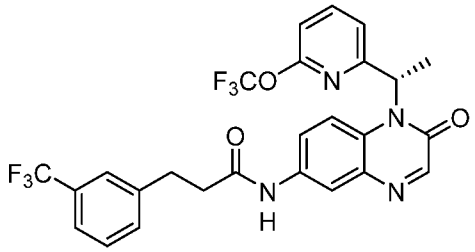
To a solution of (1R)-1-[6-(trifluoromethoxy)pyridin-2-yl]ethanol (240 mg, 1.159 mmol, 1 equiv) in DCM (10 mL) was added 6-nitro-1H-quinoxalin-2-one (221.46 mg, 1.159 mmol, 1 equiv) and PPh_3 (455.83 mg, 1.739 mmol, 1.5 equiv). The reaction was stirred at rt under N_2 for 0.5 h. To the above mixture was added DEAD (302.66 mg, 1.739 mmol, 1.5 equiv) at 0 °C. The resulting mixture was stirred for additional 1h at rt. Quenched with water (20 mL) and extracted with DCM

(3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-nitro-1-[(1S)-1-[6-(trifluoromethoxy)pyridin-2-yl]ethyl]quinoxalin-2-one (100 mg, 22.70%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{11}F_3N_4O_4$: 380.07 m/z, found 380.95 $[M+H]^+$.



(S)-6-amino-1-(1-(6-(trifluoromethoxy)pyridin-2-yl)ethyl)quinoxalin-2(1H)-one

To a solution of 6-nitro-1-[(1S)-1-[6-(trifluoromethoxy)pyridin-2-yl]ethyl]quinoxalin-2-one (1 g, 2.630 mmol, 1 equiv) in MeOH/H_2O (10:1, 11 mL) was added Fe (1.47 g, 26.300 mmol, 10 equiv) and NH_4Cl (1.41 g, 26.300 mmol, 10 equiv). The reaction was stirred at 80 °C for 1h. The mixture was allowed to cool down to rt. the resulting mixture was filtered, the filter cake was washed with MeOH (3x20 mL). The filtrate was concentrated under reduced pressure. Diluted with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-1-[(1S)-1-[6-(trifluoromethoxy)pyridin-2-yl]ethyl]quinoxalin-2-one (460 mg, 49.94%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{13}F_3N_4O_2$: 350.10 m/z, found 351.00 $[M+H]^+$.



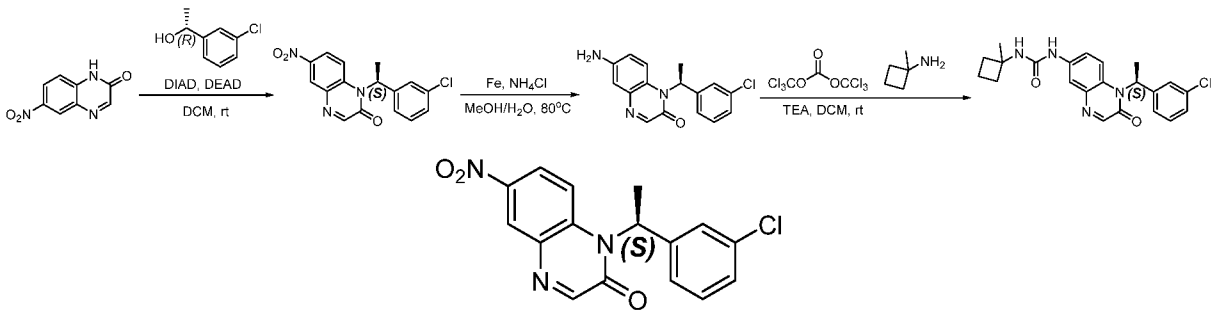
(S)-N-(2-oxo-1-(1-(6-(trifluoromethoxy)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)phenyl)propanamide

To a solution of 6-amino-1-[(1S)-1-[6-(trifluoromethoxy)pyridin-2-yl]ethyl]quinoxalin-2-one (90 mg, 0.257 mmol, 1 equiv) in DMF (10 mL) was added 3-[3-(trifluoromethyl)phenyl]propanoic acid (61.66 mg, 0.283 mmol, 1.1 equiv), HATU (127.00 mg, 0.334 mmol, 1.3 equiv) and DIEA (99.62 mg, 0.771 mmol, 3 equiv) at 0 °C. Quenched with water (30 mL) and extracted with EA (3

x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm column (eluent: 43% to 73% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound N-{2-oxo-1-[(1S)-1-[6-(trifluoromethoxy)pyridin-2-yl]ethyl]quinoxalin-6-yl}-3-[3-(trifluoromethyl)phenyl]propanamide (62.6 mg, 44.26%) as a yellow solid.LC/MS (ESI): mass calcd. for $C_{26}H_{20}F_6N_4O_3$:550.14 m/z, found:551.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H), 8.24 (s, 1H), 8.14 (d, J = 2.5 Hz, 1H), 7.85 – 8.09 (m, 1H), 7.46 – 7.80 (m, 6H), 7.39 – 7.46 (m, 1H), 7.09 – 7.20 (m, 1H), 6.22 – 6.74 (m, 1H), 2.94 – 3.11 (m, 2H), 2.60 – 2.78 (m, 2H), 1.89 (d, J = 7.0 Hz, 3H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -55.3657, -60.9601, -61.0139.

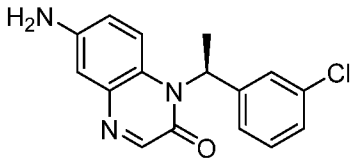
Example 319: (S)-1-(1-(1-(3-chlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1-methylcyclobutyl)urea

Synthetic Scheme



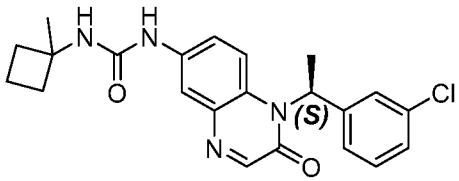
(S)-1-(1-(3-chlorophenyl)ethyl)-6-nitroquinoxalin-2(1H)-one

To a solution of 6-nitro-1H-quinoxalin-2-one (852 mg, 4.457 mmol, 1 equiv) in DCM (10 mL) was added (1R)-1-(3-chlorophenyl)ethanol (698.06 mg, 4.457 mmol, 1 equiv) and PPh_3 (1753.68 mg, 6.685 mmol, 1.5 equiv). The reaction was stirred at rt under N_2 for 0.5h. To the above mixture was added DEAD (1164.41 mg, 6.685 mmol, 1.5 equiv) at 0°C. The resulting mixture was stirred for additional 1h at rt. Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-[(1S)-1-(3-chlorophenyl)ethyl]-6-nitroquinoxalin-2-one (200 mg, 13.47%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{12}ClN_3O_3$: 329.06 m/z, found 329.95 $[M+H]^+$.



(S)-6-amino-1-(1-(3-chlorophenyl)ethyl)quinoxalin-2(1H)-one

To a solution of 1-[(1S)-1-(3-chlorophenyl)ethyl]-6-nitroquinoxalin-2-one (190 mg, 0.576 mmol, 1 equiv) in MeOH/H_2O (10:1, 11 mL) was added Fe (321.79 mg, 5.760 mmol, 10 equiv) and NH_4Cl (308.22 mg, 5.760 mmol, 10 equiv). The reaction was stirred at 80 °C for 1h. After cooling down to rt, the resulting mixture was filtered, the filter cake was washed with MeOH (3 x 20 mL). The filtrate was concentrated under reduced pressure. Diluted with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-1-[(1S)-1-(3-chlorophenyl)ethyl]quinoxalin-2-one (100 mg, 57.90%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{14}ClN_3O$: 299.08 m/z, found 300.00 $[M+H]^+$.



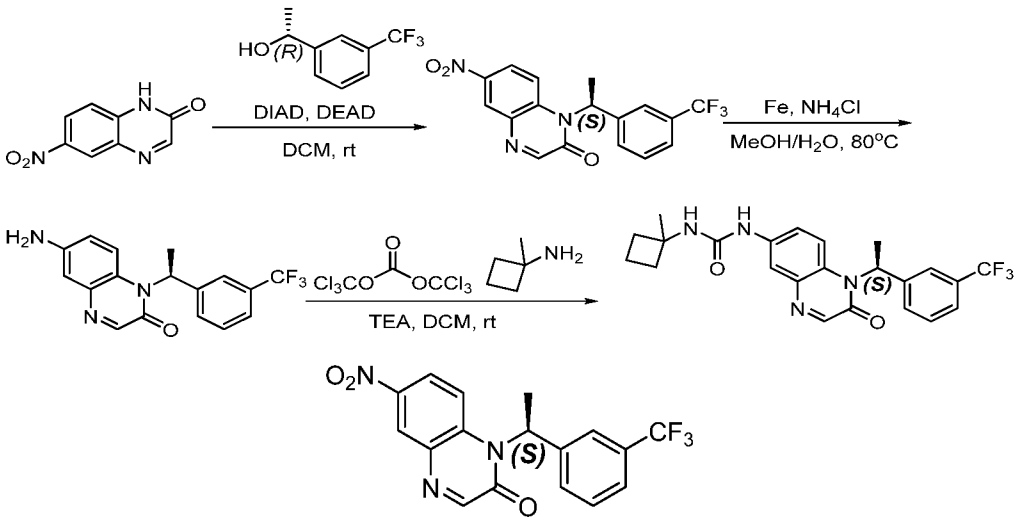
(S)-1-(1-(1-(3-chlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1-methylcyclobutyl)urea

To a solution of 6-amino-1-[(1S)-1-(3-chlorophenyl)ethyl]quinoxalin-2-one (90 mg, 0.300 mmol, 1 equiv) in DCM (10 mL) was added triphosgene (35.64 mg, 0.120 mmol, 0.4 equiv) under N_2 at 0 °C. The reaction was stirred at 0 °C under N_2 for 1h. Then, to the above mixture was added TEA (91.15 mg, 0.900 mmol, 3 equiv) under N_2 at 0 °C. The resulting mixture was stirred for additional 1h at rt. Then, 1-methylcyclobutan-1-amine (51.13 mg, 0.600 mmol, 2 equiv) was added. The reaction was stirred at rt for 1h. Quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Shield RP 18 OBD Column, 30*150 mm, 5μm column (eluent: 36% to 66% (v/v) CH_3CN and Water (10mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$)) to afford the title compound 1-{1-[(1S)-1-(3-chlorophenyl)ethyl]-2-oxoquinoxalin-6-yl}-3-(1-methylcyclobutyl)urea (27.7 mg, 22.45%) as a yellow solid.LC/MS

(ESI): mass calcd. for $C_{22}H_{23}ClN_4O_2$:410.15 m/z, found:411.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.25 (s, 1H), 7.96 (d, J = 2.5 Hz, 1H), 7.27 – 7.41 (m, 4H), 7.21 (d, J = 6.9 Hz, 1H), 6.93 – 7.16 (m, 1H), 6.55 (s, 1H), 6.33 (s, 1H), 2.18 – 2.33 (m, 2H), 1.86 – 1.94 (m, 5H), 1.70 – 1.82 (m, 2H), 1.39 (s, 3H).

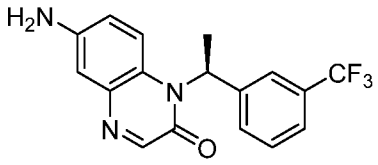
Example 320: (S)-1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

Synthetic Scheme



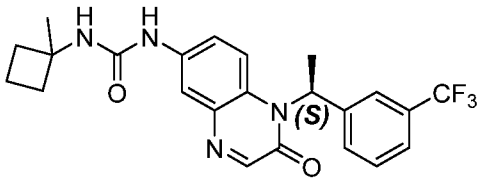
(S)-6-nitro-1-(1-(3-(trifluoromethyl)phenyl)ethyl)quinoxalin-2(1H)-one

To a solution of 6-nitro-1H-quinoxalin-2-one (704 mg, 3.683 mmol, 1 equiv) in DCM (10 mL) was added (1R)-1-[3-(trifluoromethyl)phenyl]ethanol (700.39 mg, 3.683 mmol, 1 equiv) and PPh_3 (1449.05 mg, 5.524 mmol, 1.5 equiv). The reaction was stirred at rt under N_2 for 0.5h. To the above mixture was added DEAD (962.14 mg, 5.524 mmol, 1.5 equiv) at 0°C. The resulting mixture was stirred for additional 1h at rt. Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-nitro-1-[(1S)-1-[3-(trifluoromethyl)phenyl]ethyl]quinoxalin-2-one (200 mg, 14.35%) as a yellow oil. MS (ESI): mass calcd. for $C_{17}H_{12}F_3N_3O_3$: 363.08 m/z, found 364.00 $[M+H]^+$.



(S)-6-amino-1-(1-(3-(trifluoromethyl)phenyl)ethyl)quinoxalin-2(1H)-one

To a solution of 6-nitro-1-[(1S)-1-[3-(trifluoromethyl)phenyl]ethyl]quinoxalin-2-one (190 mg, 0.523 mmol, 1 equiv) in MeOH/H_2O (10:1, 11 mL) was added Fe (292.06 mg, 5.230 mmol, 10 equiv) and NH_4Cl (279.75 mg, 5.230 mmol, 10 equiv). The reaction was stirred at 80 °C for 1h. After cooling down to rt, the resulting mixture was filtered, the filter cake was washed with MeOH (3x20 mL). The filtrate was concentrated under reduced pressure. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-1-[(1S)-1-[3-(trifluoromethyl)phenyl]ethyl]quinoxalin-2-one (96 mg, 55.07%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{14}F_3N_3O$: 333.11 m/z, found 334.00 $[M+H]^+$.



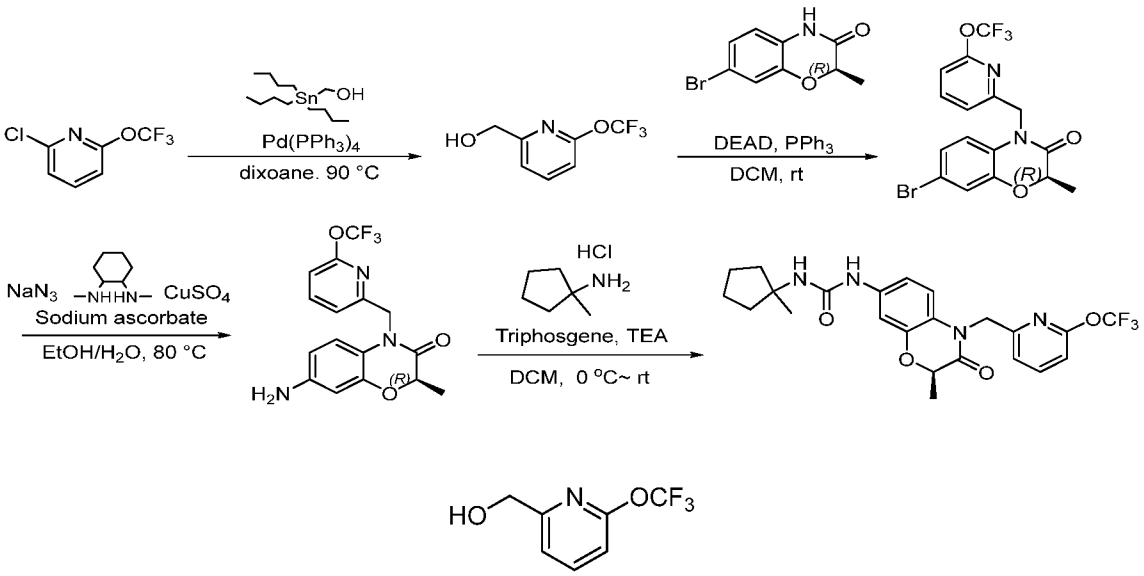
(S)-1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

To a solution of 6-amino-1-[(1S)-1-[3-(trifluoromethyl)phenyl]ethyl]quinoxalin-2-one (80 mg, 0.240 mmol, 1 equiv) in DCM (10 mL) was added triphosgene (28.49 mg, 0.096 mmol, 0.4 equiv) under N_2 at 0 °C. The reaction was stirred at 0 °C under N_2 for 1h. Then, to the above mixture was added TEA (72.86 mg, 0.720 mmol, 3 equiv) under N_2 at 0 °C. The resulting mixture was stirred for additional 1h at rt. Then, to the above mixture was added 1-methylcyclobutan-1-amine (40.87 mg, 0.480 mmol, 2 equiv). The reaction was stirred at rt for 1h. Quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Shield RP 18 OBD Column, 30*150 mm, 5μm column (eluent: 36% to 66% (v/v) CH_3CN and Water(10mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$) to afford the title compound 3-(1-methylcyclobutyl)-1-{2-oxo-1-[(1S)-1-[3-(trifluoromethyl)phenyl]ethyl]quinoxalin-6-yl}urea

(22.2 mg, 20.81%) as a yellow solid. MS (ESI): mass calcd. for $C_{23}H_{23}F_3N_4O_2$: 444.18 m/z, found:445.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.24 (s, 1H), 7.96 (d, J = 2.5 Hz, 1H), 7.50 – 7.70 (m, 4H), 7.35 (s, 1H), 6.90 – 7.27 (m, 1H), 6.40 – 6.78 (m, 1H), 6.33 (s, 1H), 2.21 – 2.33 (m, 2H), 1.85 – 1.97 (m, 5H), 1.71 – 1.80 (m, 2H), 1.88 – 1.72 (m, 2H), 1.39 (s, 3H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -60.8769.

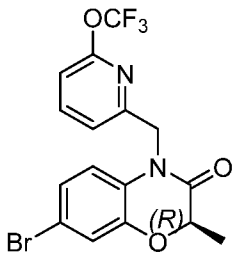
Example 321: (R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethoxy)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea

Synthetic Scheme



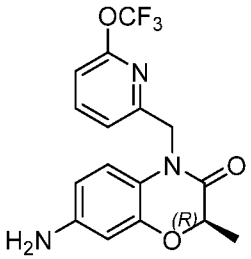
(6-(trifluoromethoxy)pyridin-2-yl)methanol

To a solution of 2-chloro-6-(trifluoromethoxy)pyridine (800 mg, 4.050 mmol, 1 equiv) in dioxane (8.0 mL) was added (tripropylstannyl)methanol (1694.91 mg, 6.075 mmol, 1.5 equiv) and $Pd(PPh_3)_4$ (467.99 mg, 0.405 mmol, 0.1 equiv). The reaction was stirred at 90 °C under N_2 for 12 h. The mixture was allowed to cool down to rt. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give [6-(trifluoromethoxy)pyridin-2-yl]methanol (500 mg, 63.93%) as a white solid. MS (ESI): mass calcd. for $C_7H_6F_3NO_2$: 193.04 m/z, found 194.05 $[M+H]^+$.



(R)-7-bromo-2-methyl-4-((6-(trifluoromethoxy)pyridin-2-yl)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

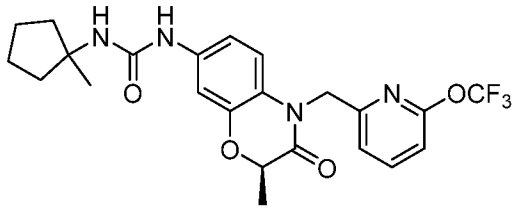
A solution of (2R)-7-bromo-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (451.24 mg, 1.864 mmol, 1.2 equiv) in DCM (5.0 mL) was treated with [6-(trifluoromethoxy)pyridin-2-yl]methanol (300 mg, 1.553 mmol, 1 equiv) and PPh_3 (611.17 mg, 2.329 mmol, 1.5 equiv) for 1h at rt under nitrogen atmosphere followed by the addition of DEAD (270.53 mg, 1.553 mmol, 1 equiv) dropwise at 0°C. The resulting mixture was stirred for 2h at rt under N_2 atmosphere. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-bromo-6-fluoro-2-methyl-4-[(1S)-1-phenylethyl]-2H-1,4-benzoxazin-3-one (195 mg, 46.41%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{12}BrF_3N_2O_3$: 416.00 m/z, found 416.95, 418.95 $[M+H, M+H+2]^+$.



(R)-7-amino-2-methyl-4-((6-(trifluoromethoxy)pyridin-2-yl)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-7-bromo-2-methyl-4-{[6-(trifluoromethoxy)pyridin-2-yl]methyl}-2H-1,4-benzoxazin-3-one (180 mg, 0.373 mmol, 1 equiv) in EtOH (3 mL)/H_2O (0.3 mL) was added N1,N2-dimethylcyclohexane-1,2-diamine (31.86 mg, 0.224 mmol, 0.6 equiv), $CuSO_4$(59.58 mg, 0.373 mmol, 1 equiv), sodium ascorbate (148.66 mg, 0.746 mmol, 2 equiv) and NaN_3 (72.80 mg, 1.119 mmol, 3 equiv). The reaction was stirred at 90 °C under N_2 for 2 h. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column

chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-2-methyl-4-{[6-(trifluoromethoxy)pyridin-2-yl]methyl}-2H-1,4-benzoxazin-3-one (91 mg, 69.00%) as a white solid. LC/MS (ESI): mass calcd. for $C_{16}H_{14}F_3N_3O_3$: 353.10 m/z, found:354.00 $[M+H]^+$.

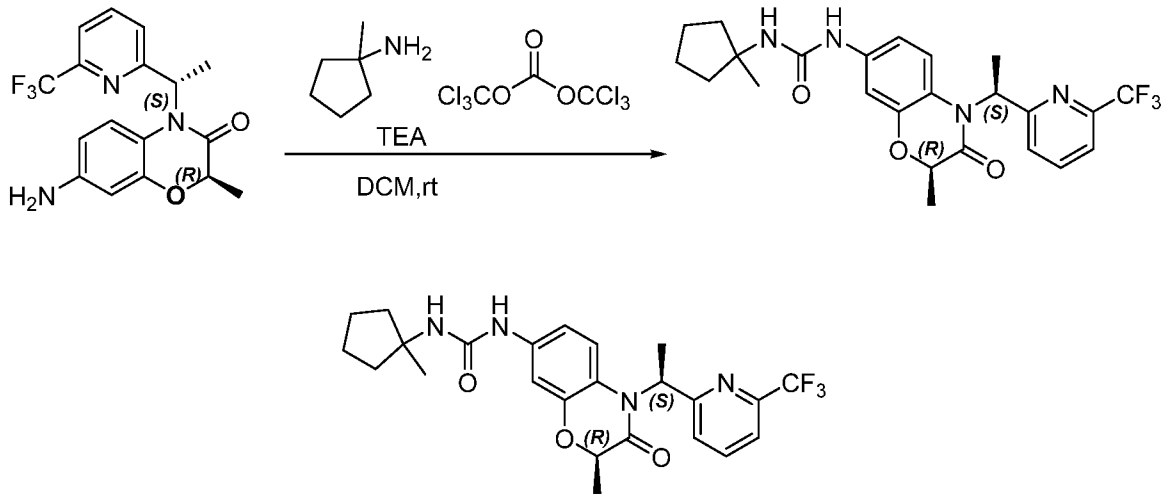


(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethoxy)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea

To a solution of (2R)-7-amino-2-methyl-4-{[6-(trifluoromethoxy)pyridin-2-yl]methyl}-2H-1,4-benzoxazin-3-one (85 mg, 0.241 mmol, 1 equiv) in DCM (3 mL) was added Triphosgene (71.39 mg, 0.241 mmol, 1 equiv). The reaction was stirred at 0 °C under N_2 for 1 h. The reaction was added TEA (194.77 mg, 1.928 mmol, 8 equiv) and stirred at 0 °C under N_2 for 1 h. The reaction was added 1-methyl-cyclopentanamine (95.44 mg, 0.964 mmol, 4 equiv) and stirred at rt under N_2 for 1 h. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a YMC-Actus Triart C18 ExRS 150 mm x 30 mm x 5 μm column (eluent: 49% to 73% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford the title compound 1-[(2R)-2-methyl-3-oxo-4-{[6-(trifluoromethoxy)pyridin-2-yl]methyl}-2H-1,4-benzoxazin-7-yl]-3-(1-methylcyclopentyl)urea (35.8 mg, 31.05%) as a white solid. LC/MS (ESI): mass calcd. for $C_{23}H_{25}F_3N_4O_4$:478.18 m/z, found:479.05 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.96-7.99 (m, 1H), 7.29-7.32 (m, 1H), 7.22-7.23 (m, 1H), 7.15-7.17 (m, 1H), 6.82-6.85 (m, 1H), 6.74-7.78 (m, 1H), 6.02 (s, 1H), 5.14 (s, 2H), 4.73-7.79 (m, 1H), 1.87-1.89 (m, 2H), 1.56-1.62 (m, 4H), 1.44-1.54 (m, 5H), 1.34 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ-55.06.

Example 322: 1-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea

Synthetic Scheme

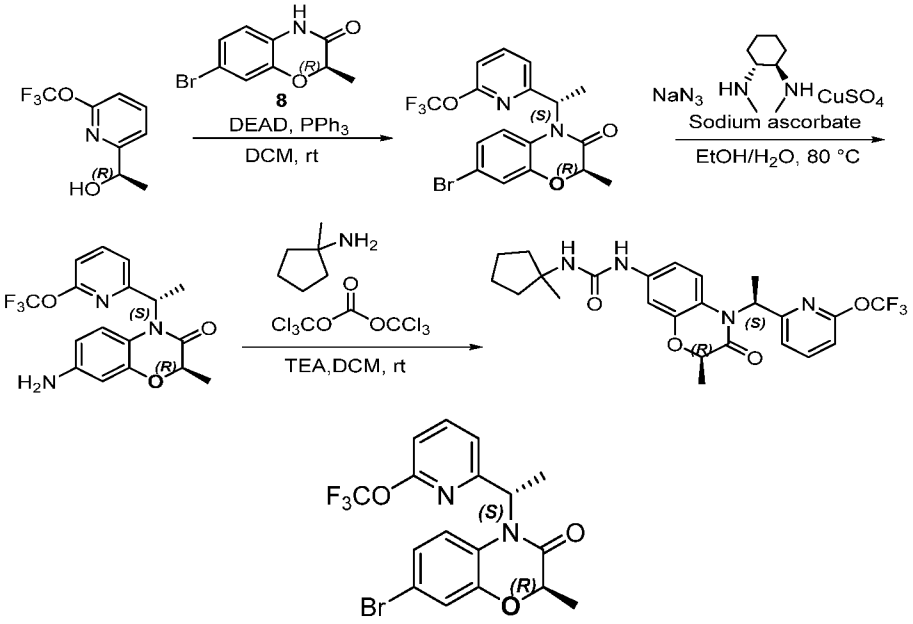


1-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea

To a solution of (2R)-7-amino-2-methyl-4-[(1S)-1-[6-(trifluoromethyl)pyridin-2-yl]ethyl]-2H-1,4-benzoxazin-3-one (70 mg, 0.199 mmol, 1 equiv) in DCM (5 mL) was added triphosgene (23.65 mg, 0.080 mmol, 0.4 equiv) under N_2 at 0 °C. The reaction was stirred at 0 °C under N_2 for 1h. Then, to the above mixture was added TEA (60.49 mg, 0.597 mmol, 3 equiv) under N_2 at 0 °C. The resulting mixture was stirred for additional 1h at rt. Then, 1-methyl-cyclopentanamine (39.52 mg, 0.398 mmol, 2 equiv) was added. The reaction was stirred at rt for 1h. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Shield RP 18 OBD Column, 30*150 mm, 5μm column (eluent: 48% to 78% (v/v) CH_3CN and H_2O (10mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$)) to afford the title compound 1-[(2R)-2-methyl-3-oxo-4-[(1S)-1-[6-(trifluoromethyl)pyridin-2-yl]ethyl]-2H-1,4-benzoxazin-7-yl]-3-(1-methylcyclopentyl)urea (16.7 mg, 17.59%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{24}H_{27}F_3N_4O_3$:476.20 m/z, found:477.05 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.97 – 8.11 (m, 1H), 7.70 – 7.90 (m, 1H), 7.52 – 7.67 (m, 1H), 7.23 (d, J = 1.9 Hz, 1H), 6.63 – 6.80 (m, 2H), 5.95 – 6.15 (m, 2H), 4.63 – 4.80 (m, 1H), 1.84 – 1.99 (m, 2H), 1.74 – 1.84 (m, 3H), 1.57 – 1.69 (m, 4H), 1.47 – 1.54 (m, 2H), 1.37 – 1.42 (m, 3H), 1.33 (s, 3H).^{19}F NMR (282 MHz, DMSO) δ(ppm): -66.560.

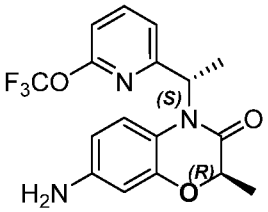
Example 323: 1-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethoxy)pyridin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea

Synthetic Scheme



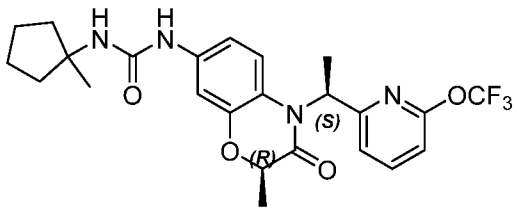
(R)-7-bromo-2-methyl-4-((S)-1-(6-(trifluoromethoxy)pyridin-2-yl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (1R)-1-[6-(trifluoromethoxy)pyridin-2-yl]ethanol (300 mg, 1.448 mmol, 1 equiv) in DCM (10 mL) was added (2R)-7-bromo-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (350.57 mg, 1.448 mmol, 1 equiv) and PPh_3 (569.78 mg, 2.172 mmol, 1.5 equiv). The reaction was stirred at rt under N_2 for 0.5h. To the above mixture was added DEAD (378.32 mg, 2.172 mmol, 1.5 equiv) at 0°C. The resulting mixture was stirred for additional 1h at rt. Quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give(2R)-7-bromo-2-methyl-4-[(1S)-1-[6-(trifluoromethoxy)pyridin-2-yl]ethyl]-2H-1,4-benzoxazin-3-one (220 mg, 35.23%) as a yellow solid. LC/MS: mass calcd. for $C_{17}H_{14}BrF_3N_2O_3$: 430.01, found: 430.95, 432.95 $[M+H, M+H+2]^+$.



(R)-7-amino-2-methyl-4-((S)-1-(6-(trifluoromethoxy)pyridin-2-yl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-7-bromo-2-methyl-4-[(1S)-1-[6-(trifluoromethoxy)pyridin-2-yl]ethyl]-2H-1,4-benzoxazin-3-one (210 mg, 0.487 mmol, 1 equiv) in EtOH/H2O (4:1, 10 mL) was added (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (41.56 mg, 0.292 mmol, 0.6 equiv), $CuSO_4$ (77.73 mg, 0.487 mmol, 1 equiv), azidosodium (94.98 mg, 1.461 mmol, 3 equiv) and sodium ascorbate (193.94 mg, 0.974 mmol, 2 equiv). The reaction was stirred at 80°C under N_2 for 3h. After cooling down to rt, the reaction was quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-2-methyl-4-[(1S)-1-[6-(trifluoromethoxy)pyridin-2-yl]ethyl]-2H-1,4-benzoxazin-3-one (130 mg, 72.67%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{16}F_3N_3O_3$: 367.11 m/z, found 368.05 $[M+H]^+$.



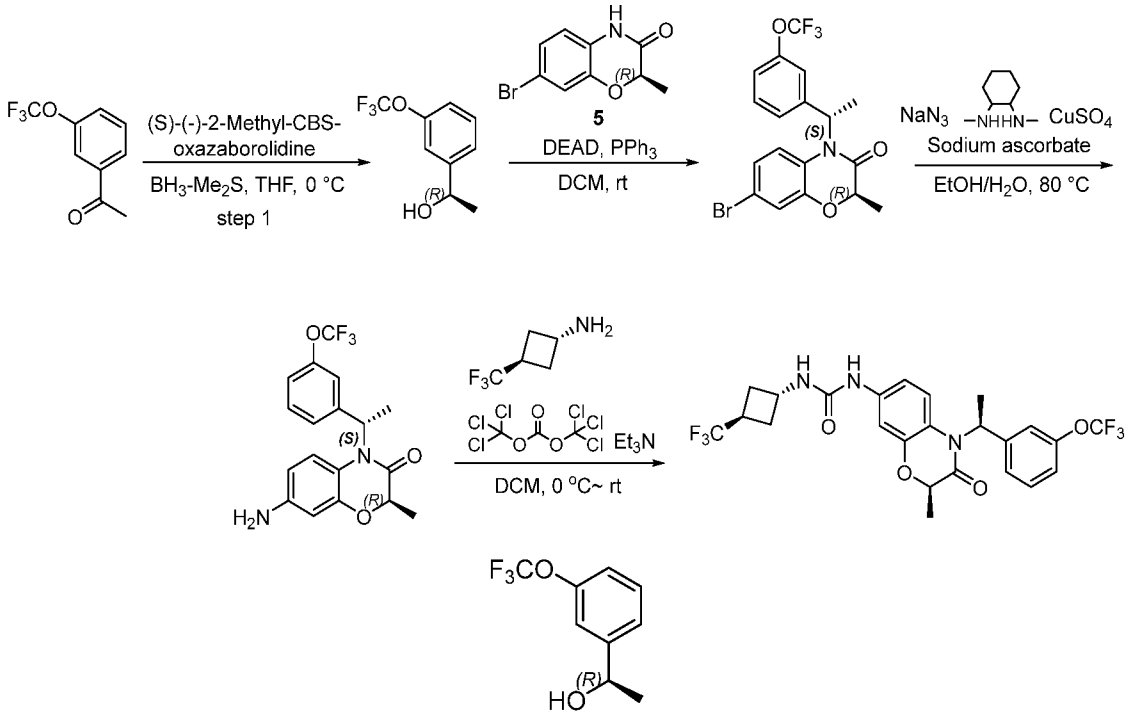
1-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethoxy)pyridin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea

To a solution of (2R)-7-amino-2-methyl-4-[(1S)-1-[6-(trifluoromethoxy)pyridin-2-yl]ethyl]-2H-1,4-benzoxazin-3-one (60 mg, 0.163 mmol, 1 equiv) in DCM (5 mL) was added triphosgene (19.39 mg, 0.065 mmol, 0.4 equiv) under N_2 at 0 °C. The reaction was stirred at 0 °C under N_2 for 1h. To the above mixture was added TEA (49.59 mg, 0.489 mmol, 3 equiv) under N_2 at 0 °C. The resulting mixture was stirred for additional 1h at rt. Then, 1-methyl-cyclopentanamine (32.40 mg, 0.326 mmol, 2 equiv) was added. The reaction was stirred at rt for 1h. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column30*150 mmm column (eluent: 30% to 55% (v/v) CH_3CN and Water (10 mmol/L NH_4HCO_3)) to afford the title compound 1-[(2R)-2-methyl-3-oxo-4-[(1S)-1-[6-(trifluoromethoxy)pyridin-2-yl]ethyl]-2H-1,4-benzoxazin-7-yl]-3-(1-methylcyclopentyl)urea (23.1 mg, 28.72%) as a white solid. LC/MS (ESI): mass calcd. for $C_{24}H_{27}F_3N_4O_4$: 492.20 m/z, found:493.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.19 (s, 1H), 8.00 (t, J = 7.9 Hz, 1H), 7.35 (d, J = 7.7 Hz, 1H), 7.10 – 7.20 (m, 2H), 6.60 – 6.78 (m, 2H), 5.90 – 6.11 (m, 2H), 4.55 –

4.80 (m, 1H), 1.81 – 2.00 (m, 2H), 1.75 (d, J = 7.1 Hz, 3H), 1.45 – 1.70 (m, 6H), 1.38 – 1.45 (s, 3H), 1.25 – 1.38 (m, 3H). ^{19}F NMR (282 MHz, DMSO) δ (ppm): -55.093

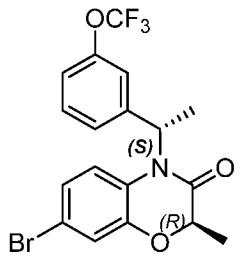
Example 324: 1-((R)-2-methyl-3-oxo-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-((1r,3R)-3-(trifluoromethyl)cyclobutyl)urea

Synthetic Scheme



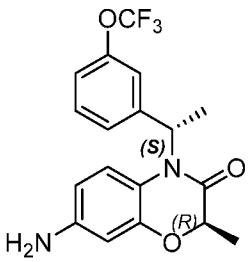
(R)-1-(3-(trifluoromethoxy)phenyl)ethan-1-ol

To a solution of BH_3-Me_2S (279 mg, 3.676 mmol, 1.5 equiv) and (S)-(-)-2-Methyl-CBS-oxazaborolidine (135 mg, 0.490 mmol, 0.2 equiv) in THF (6 mL) was added 1-(3-(trifluoromethoxy)phenyl)ethan-1-one (500 mg, 2.450 mmol, 1 equiv) at 0 °C. The resulting mixture was stirred for 2 h at 0 °C. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography with PE/EA (3:1) to afford (R)-1-(3-(trifluoromethoxy)phenyl)ethan-1-ol (0.4 g, 80.00%) as a yellow oil.



(R)-7-bromo-2-methyl-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

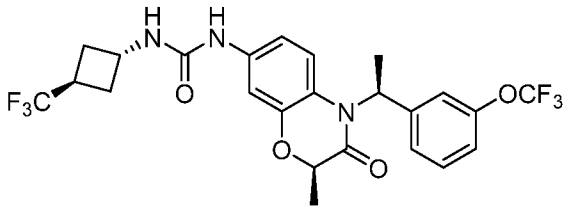
To a solution of (R)-1-(3-(trifluoromethoxy)phenyl)ethan-1-ol (0.4 g, 1.942 mmol, 1 equiv) in DCM (6 mL) was added (R)-7-bromo-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one (469 mg, 1.942 mmol, 1 equiv), triphenylphosphine (510mg, 1.942 mmol, 1 equiv) and DEAD (338 mg, 1.942 mmol, 1 equiv) at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred overnight at rt. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography with PE/EA (3:1) to afford (R)-7-bromo-2-methyl-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (0.3 g, 36.06%) as a yellow solid.



(R)-7-amino-2-methyl-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (R)-7-bromo-2-methyl-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (0.3 g, 0.699 mmol, 1 equiv) in EtOH (6 mL) & H_2O (2 mL) was added sodium ascorbate (28 mg, 0.140 mmol, 0.2 equiv), N^1,N^2-dimethylcyclohexane-1,2-diamine (20 mg , 0.140 mmol, 0.2 equiv), $CuSO_4$ (23 mg , 0.14 mmol, 0.2 equiv) and NaN_3 (136 mg, 2.097 mmol, 3 equiv) at rt. The resulting mixture was stirred 4 h at 80 °C. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography with PE/EA (1:1) to afford (R)-7-amino-

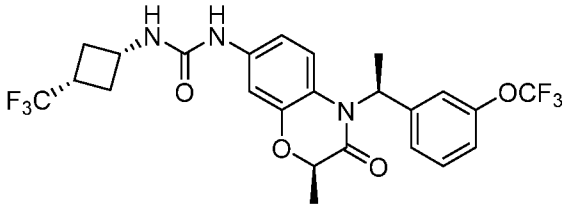
2-methyl-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (166 mg, 65.02%) as a yellow solid.



1-((R)-2-methyl-3-oxo-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-((1r,3R)-3-(trifluoromethyl)cyclobutyl)urea

To a mixture of (R)-7-amino-2-methyl-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (60 mg, 0.163 mmol, 1 equiv) in DCM (4 mL) was stirred under nitrogen atmosphere and added triphosgene (15 mg, 0.149 mmol, 0.3 equiv) at 0 °C. The reaction was stirred at rt for 1 h. TEA (41 mg, 0.407 mmol, 2.5 equiv) was added into the mixture at 0 °C. The reaction was stirred at rt for 1 h. (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine (23 mg, 0.163 mmol, 1.0 equiv) was added into the mixture at 0 °C. The reaction was stirred at rt for 1 h. The reaction mixture was quenched by 1N hydrochloric acid (5 mL) and extracted with DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford 1-((R)-2-methyl-3-oxo-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-((1r,3R)-3-(trifluoromethyl)cyclobutyl)urea (25.5 mg, 29.44%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{23}F_6N_3O4$: 531.15 m/z, found: 532.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.45 (s, 1H), 7.40 – 7.60 (m, 1H), 7.19 – 7.40 (m, 4H), 6.72 – 6.85 (m, 1H), 6.62 – 6.72 (m, 1H), 6.52 – 6.62 (m, 1H), 5.96 – 6.19 (m, 1H), 4.66 – 4.85 (m, 1H), 4.13 – 4.31 (m,1H), 2.91 – 3.18 (m,1H), 2.31 – 2.43 (m,2H), 2.15 – 2.31 (m, 2H), 1.68 – 1.87 (m, 3H), 1.38 – 1.48 (m, 3H).

Example 325: 1-((R)-2-methyl-3-oxo-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-((1s,3S)-3-(trifluoromethyl)cyclobutyl)urea



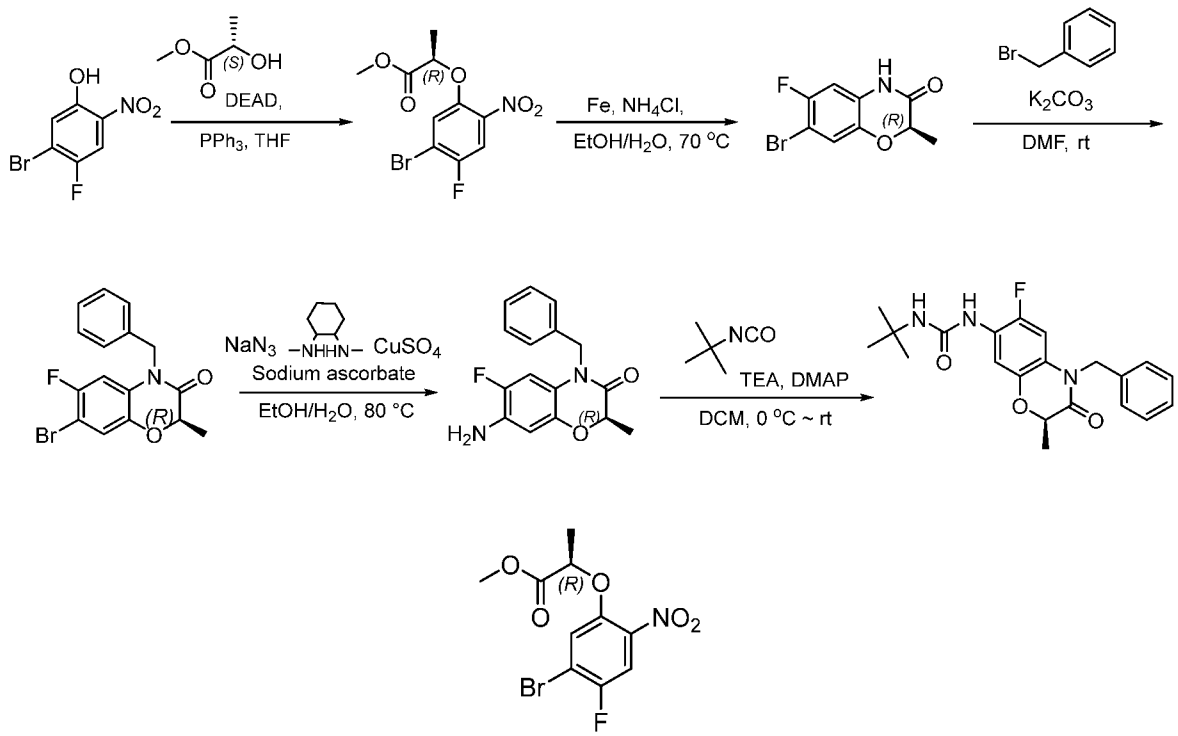
1-((R)-2-methyl-3-oxo-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-((1s,3S)-3-(trifluoromethyl)cyclobutyl)urea

To a mixture of (R)-7-amino-2-methyl-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (60 mg, 0.163 mmol, 1 equiv) in DCM (4 mL) was stirred under nitrogen atmosphere and added

triphosgene (15 mg, 0.149 mmol, 0.3 equiv) at 0 °C. The reaction was stirred at rt for 1 h. TEA (41 mg, 0.407 mmol, 2.5 equiv) was added into the mixture at 0 °C. The reaction was stirred at rt for 1 h. (1s,3s)-3-(trifluoromethyl)cyclobutan-1-amine (23 mg, 0.163 mmol, 1.0 equiv) was added into the mixture at 0 °C. The reaction was stirred at rt for 1 h. The reaction mixture was quenched by 1N hydrochloric acid (5 mL) and extracted with DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford 1-((R)-2-methyl-3-oxo-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-((1s,3S)-3-(trifluoromethyl)cyclobutyl)urea (30.5 mg, 35.20%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{23}F_6N_3O4$: 531.15 m/z, found: 532.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.32 (s, 1H), 7.40 – 7.60 (m, 1H), 7.19 – 7.22 (m, 4H), 6.72 – 6.85 (m, 1H), 6.62 – 6.72 (m, 1H), 6.52 – 6.62 (m, 1H), 5.96 – 6.19 (m, 1H), 4.66 – 4.85 (m, 1H), 4.02 – 4.22 (m,1H), 2.79 – 2.98 (m,1H), 2.35 – 2.49 (m,2H), 1.85 – 2.05 (m, 2H), 1.72 – 1.85 (m, 3H), 1.38 – 1.46 (m, 3H).

Example 326: (R)-1-(4-benzyl-6-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

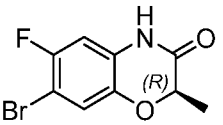
Synthetic Scheme



methyl (R)-2-(5-bromo-4-fluoro-2-nitrophenoxy)propanoate

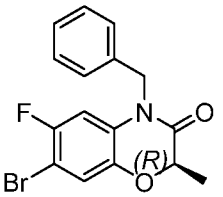
A solution of 5-bromo-4-fluoro-2-nitrophenol (1 g, 4.237 mmol, 1 equiv), methyl (2S)-2-hydroxypropanoate (0.66 g, 6.356 mmol, 1.5 equiv) and PPh_3 (1.67 g, 6.356 mmol, 1.5 equiv) in

THF (10 mL) was stirred for 1 h at rt under N_2 atmosphere. To the above mixture was added DEAD (1.11 g, 6.356 mmol, 1.5 equiv) dropwise over 10 min at 0°C. The resulting mixture was stirred for additional 2h at rt. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give methyl (2R)-2-(5-bromo-4-fluoro-2-nitrophenoxy)propanoate (1.21 g, 88.66%) as a white solid. MS (ESI): mass calcd. for $C_{10}H_9BrFNO_5$: 320.96 m/z, found 322.05, 324.05[M+H, M+H+2]$^+$.



(R)-7-bromo-6-fluoro-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

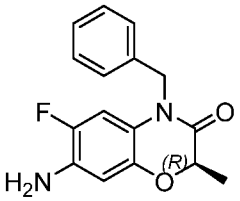
To a solution of methyl (2R)-2-(5-bromo-4-fluoro-2-nitrophenoxy)propanoate (1.2 g, 3.726 mmol, 1 equiv) in EtOH (12.0 mL)/H_2O(1.2 mL) was added Fe (2.1 g, 37.260 mmol, 10 equiv) and NH_4Cl (2.0 g, 37.260 mmol, 10 equiv). The reaction was stirred at 70°C for 3 h. The mixture was allowed to cool down to rt. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-bromo-6-fluoro-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (900 mg, 92.89%) as a white solid. MS (ESI): mass calcd. for $C_9H_7BrFNO_2$: 258.96 m/z, found 260.06, 262.06 [M+H, M+H+2]$^+$.



(R)-4-benzyl-7-bromo-6-fluoro-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

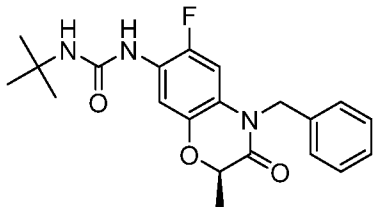
To a solution of (2R)-7-bromo-6-fluoro-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (250 mg, 0.961 mmol, 1 equiv) in DMF (3 mL) was added benzyl bromide (493.26 mg, 2.883 mmol, 3 equiv) and K_2CO_3 (401.48 mg, 2.883 mmol, 3 equiv). The reaction was stirred at rt for 1 h. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified

by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-4-benzyl-7-bromo-6-fluoro-2-methyl-2H-1,4-benzoxazin-3-one (250 mg, 74.26%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{13}BrFNO_2$: 349.01 m/z, found 349.95, 351.95 $[M+H, M+H+2]^+$.



(R)-7-amino-4-benzyl-6-fluoro-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-4-benzyl-7-bromo-6-fluoro-2-methyl-2H-1,4-benzoxazin-3-one (240 mg, 0.578 mmol, 1 equiv) in EtOH (5 mL)/H_2O (1 mL) was added N1,N2-dimethylcyclohexane-1,2-diamine (49.33 mg, 0.347 mmol, 0.6 equiv), $CuSO_4$(92.25 mg, 0.578 mmol, 1 equiv), sodium ascorbate (230.19 mg, 1.156 mmol, 2 equiv), and NaN_3 (112.74 mg, 1.734 mmol, 3 equiv). The reaction was stirred at 80 °C under N_2 for 2 h. The mixture was allowed to cool down to rt. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-4-benzyl-6-fluoro-2-methyl-2H-1,4-benzoxazin-3-one (150 mg, 90.64%) as a white solid. LC/MS (ESI): mass calcd. for $C_{16}H_{15}FN_2O_2$: 286.11 m/z, found: 287.20 $[M+H]^+$.



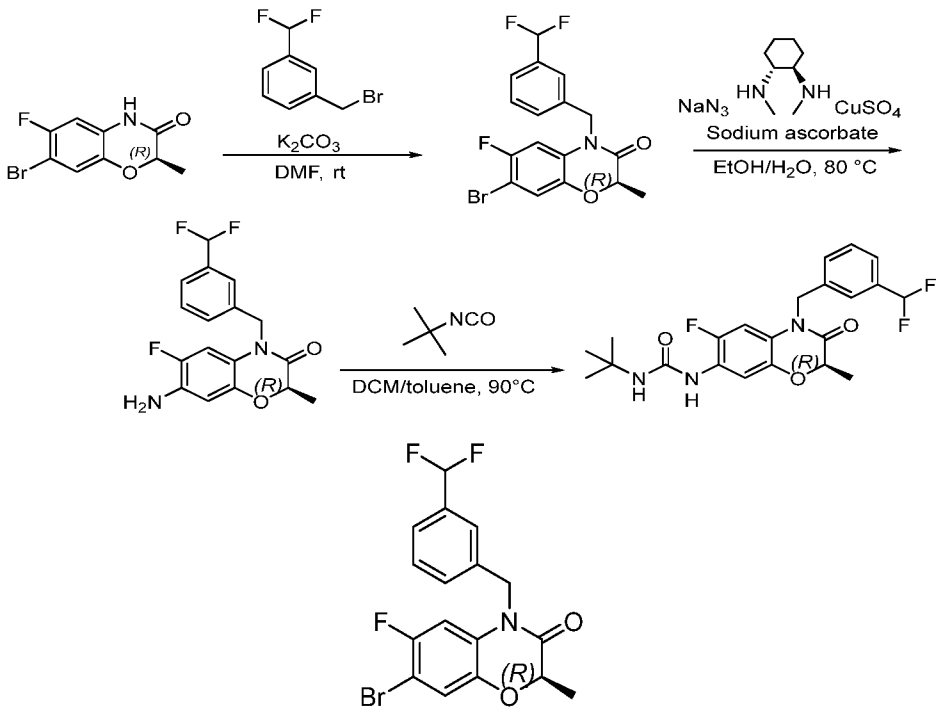
(R)-1-(4-benzyl-6-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

To a solution of (2R)-7-amino-4-benzyl-6-fluoro-2-methyl-2H-1,4-benzoxazin-3-one (130 mg, 0.454 mmol, 1 equiv) and DMAP (5.55 mg, 0.045 mmol, 0.1 equiv) in DCM (3 mL) was added 2-isocyanato-2-methylpropane (135.04 mg, 1.362 mmol, 3 equiv) and TEA (137.84 mg, 1.362 mmol, 3 equiv). The reaction was stirred at rt for 24 h. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a YMC-Actus Triart C18 ExRS 150 mm x 30 mm x 5 μm column (eluent: 49% to 73% (v/v)

CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford the title compound 1-[(2R)-4-benzyl-6-fluoro-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]-3-tert-butylurea (34.9 mg, 19.74%) as a white solid. LC/MS (ESI): mass calcd. for $C_{21}H_{24}FN_3O_3$: 385.18 m/z, found: 408.10 $[M+Na]^+$. ^{19}F NMR (282 MHz, DMSO) δ -137.66. ^1H NMR (300 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.80-7.83 (d, J = 7.7 Hz, 1H), 7.30 – 7.40 (m, 2H), 7.22 – 7.26 (m, 3H), 6.94 – 6.98 (d, J = 12 Hz, 1H), 6.51 (s, 1H), 5.11 (s, 2H), 4.77 – 4.84 (m, 1H), 1.46 – 1.48 (d, J = 6 Hz, 3H), 1.27 (s, 9H).

Example 327: (R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-6-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

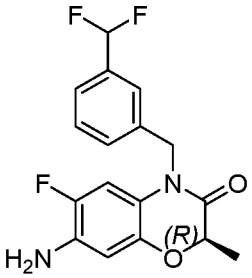
Synthetic Scheme



(R)-7-bromo-4-(3-(difluoromethyl)benzyl)-6-fluoro-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

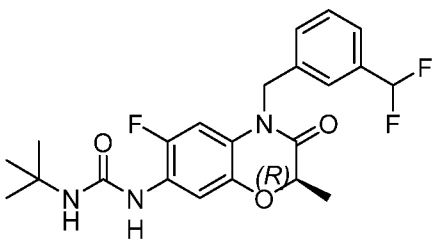
To a solution of (2R)-7-bromo-6-fluoro-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (250 mg, 0.961 mmol, 1 equiv) in DMF (10 mL) was added 1-(bromomethyl)-3-(difluoromethyl)benzene (637.48 mg, 2.883 mmol, 3 equiv) and K_2CO_3 (401.48 mg, 2.883 mmol, 3 equiv). The reaction was stirred at rt for 1h. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to

give(2R)-7-bromo-4-{[3-(difluoromethyl)phenyl]methyl}-6-fluoro-2-methyl-2H-1,4-benzoxazin-3-one (350 mg, 90.98%) as a yellow solid. LC/MS: mass calcd. for $C_{17}H_{13}BrF_3NO_2$:399.01 m/z, found: 399.90, 401.90 $[M+H, M+H+2]^+$.



(R)-7-amino-4-(3-(difluoromethyl)benzyl)-6-fluoro-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-7-bromo-4-{[3-(difluoromethyl)phenyl]methyl}-6-fluoro-2-methyl-2H-1,4-benzoxazin-3-one (340 mg, 0.850 mmol, 1 equiv) in EtOH (8 mL) and H_2O (2 mL) was added (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (72.51 mg, 0.510 mmol, 0.6 equiv), $CuSO_4$ (135.59 mg, 0.850 mmol, 1 equiv), NaN_3 (165.70 mg, 2.550 mmol, 3 equiv) and sodium ascorbate (338.33 mg, 1.700 mmol, 2 equiv). The reaction was stirred at 80 °C under N_2 for 3h. After cooling down to rt, the reaction was quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-4-{[3-(difluoromethyl)phenyl]methyl}-6-fluoro-2-methyl-2H-1,4-benzoxazin-3-one (100 mg, 35.00%) as a yellow solid. LC/MS: mass calcd. for $C_{17}H_{15}F_3N_2O_2$:336.11 m/z, found:337.10 $[M+H]^+$.



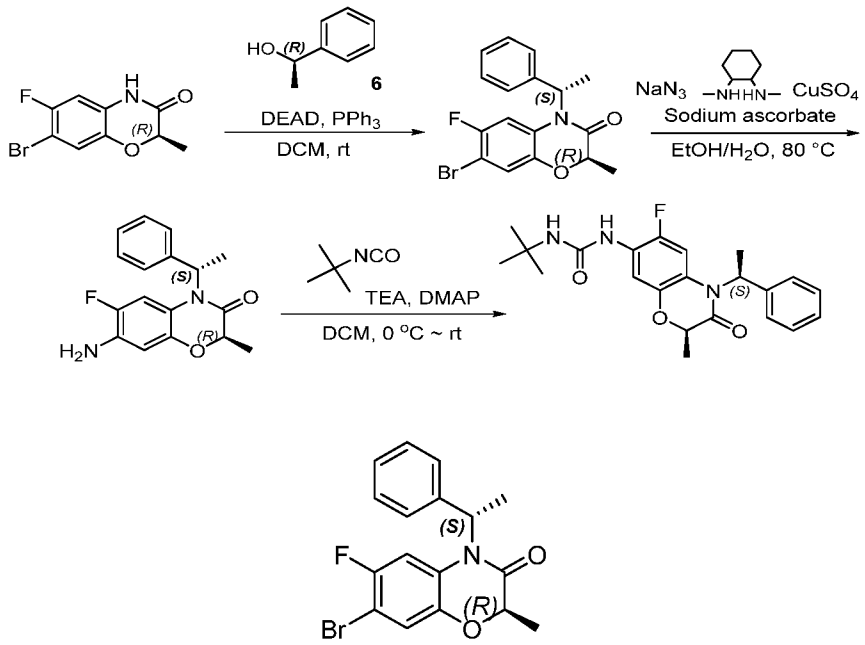
(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-6-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a solution of (2R)-7-amino-4-{[3-(difluoromethyl)phenyl]methyl}-6-fluoro-2-methyl-2H-1,4-benzoxazin-3-one (100 mg, 0.297 mmol, 1 equiv) in DCM (5 mL) and toluene (2.5 mL) was added 2-isocyanato-2-methylpropane (88.43 mg, 0.891 mmol, 3 equiv). The reaction was stirred at 90°C

under N_2 for 3h. After cooling down to rt, the reaction was quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm column (eluent: 42% to 64% (v/v) CH_3CN and Water (10mmol/L NH_4HCO_3)) to afford the title compound 3-tert-butyl-1-[(2R)-4-{[3-(difluoromethyl)phenyl]methyl}-6-fluoro-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]urea (22.9 mg, 17.69%) as a white solid. LC/MS: mass calcd. for $C_{22}H_{24}F_3N_3O_3$:435.18 m/z, found:458.10 $[M+Na]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, J = 2.6 Hz, 1H), 7.84 (d, J = 7.7 Hz, 1H), 7.37 – 7.52 (m, 4H), 6.84 – 7.21 (m, 2H), 6.51 (s, 1H), 5.10 – 5.25 (m, 2H), 4.83 (q, J = 6.7 Hz, 1H), 1.48 (d, J = 6.8 Hz, 3H), 1.27 (s, 9H).^{19}F NMR (376 MHz, DMSO) δ(ppm): -109.7463, -137.0823.

Example 328: 1-(tert-butyl)-3-((R)-6-fluoro-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

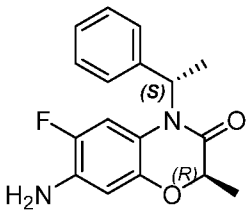
Synthetic Scheme



(R)-7-bromo-6-fluoro-2-methyl-4-((S)-1-phenylethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

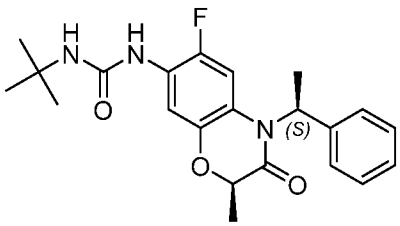
A solution of (2R)-7-bromo-6-fluoro-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (300 mg, 1.154 mmol, 1 equiv) in DCM (5 mL) was treated with 1-phenyl-ethanol (140.93 mg, 1.154 mmol, 1 equiv) and PPh_3 (453.86 mg, 1.731 mmol, 1.5 equiv) for 1h at rt under nitrogen

atmosphere followed by the addition of DEAD (200.90 mg, 1.154 mmol, 1 equiv) dropwise at 0°C. The resulting mixture was stirred for 2h at rt under N_2 atmosphere. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-bromo-6-fluoro-2-methyl-4-[(1S)-1-phenylethyl]-2H-1,4-benzoxazin-3-one (195 mg, 46.41%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{15}BrFNO_2$: 363.03 m/z, found 364.10, 366.10 $[M+H, M+H+2]^+$.



(R)-7-amino-6-fluoro-2-methyl-4-((S)-1-phenylethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-7-bromo-6-fluoro-2-methyl-4-[(1S)-1-phenylethyl]-2H-1,4-benzoxazin-3-one (175 mg, 0.408 mmol, 1 equiv) in EtOH (4 mL)/H_2O (1 mL) was added N1,N2-dimethylcyclohexane-1,2-diamine (34.80 mg, 0.245 mmol, 0.6 equiv), $CuSO_4$ (65.07 mg, 0.408 mmol, 1 equiv), sodium ascorbate (162.36 mg, 0.816 mmol, 2 equiv) and NaN_3 (79.52 mg, 1.224 mmol, 3 equiv). The reaction was stirred at 80°C for 3 h. The mixture was allowed to cool down to rt. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-6-fluoro-2-methyl-4-[(1S)-1-phenylethyl]-2H-1,4-benzoxazin-3-one (60 mg, 49.00%)as a white solid. MS (ESI): mass calcd. for $C_{17}H_{17}FN_2O_2$: 300.13 m/z, found 301.05 $[M+H]^+$.



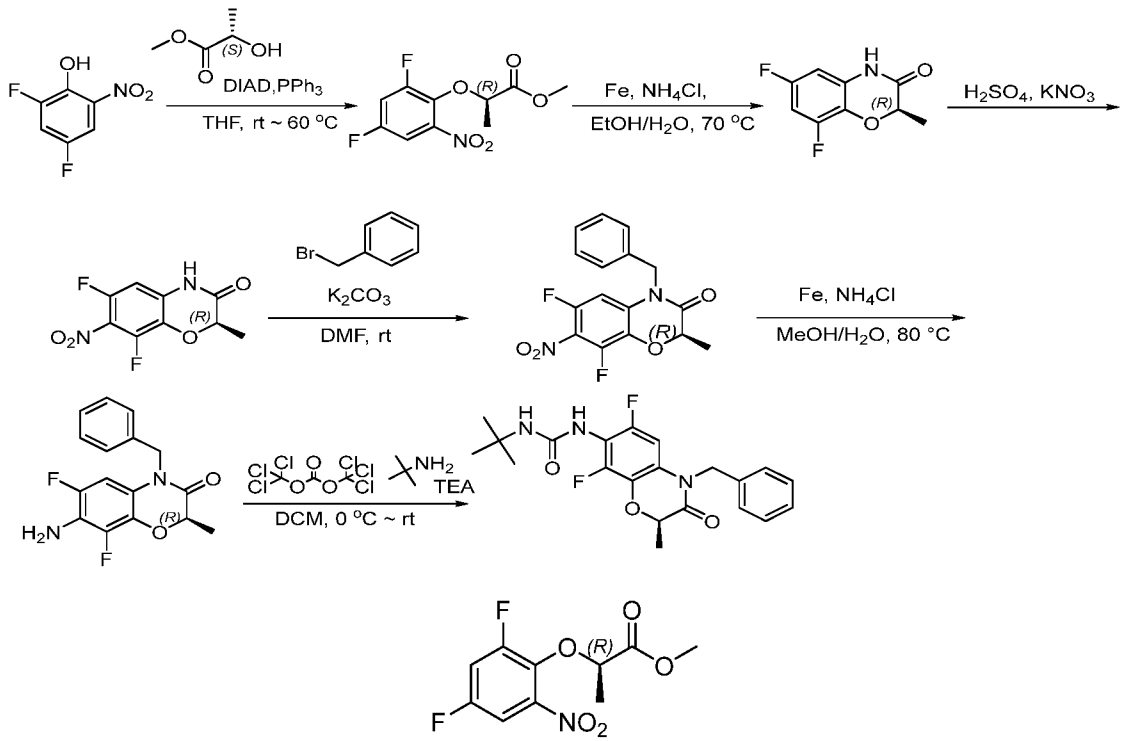
1-(tert-butyl)-3-((R)-6-fluoro-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a solution of (2R)-7-amino-6-fluoro-2-methyl-4-[(1S)-1-phenylethyl]-2H-1,4-benzoxazin-3-one (60 mg, 0.200 mmol, 1 equiv) and 2-isocyanato-2-methylpropane (59.41 mg, 0.600 mmol, 3

equiv) in DCM (3 mL) was added TEA (60.65 mg, 0.600 mmol, 3 equiv) and DMAP (2.44 mg, 0.020 mmol, 0.1 equiv). The reaction was stirred at rt for 24 h. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a YMC-Actus Triart C18 ExRS 150 mm x 30 mm x 5 μm column (eluent: 49% to 73% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-[(2R)-6-fluoro-2-methyl-3-oxo-4-[(1S)-1-phenylethyl]-2H-1,4-benzoxazin-7-yl]urea (14.5 mg, 18.06%) as a white solid. LC/MS (ESI): mass calcd. for $C_{22}H_{26}FN_3O_3$:399.20 m/z, found:400.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.80-7.82 (d, J = 6 Hz, 1H), 7.33 - 7.44 (m, 2H), 7.23 - 7.33 (m, 3H), 6.48 - 6.59 (m, 2H), 6.04 -6.06 (m, 1H), 4.72 - 4.75 (m, 1H), 1.74 - 1.76 (d, J = 6 Hz, 3H), 1.41 -1.44 (d, J = 9 Hz, 3H), 1.26 (s, 9H). ^{19}F NMR (282 MHz, DMSO) δ-137.16.

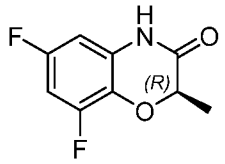
Example 329: (R)-1-(4-benzyl-6,8-difluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

Synthetic Scheme



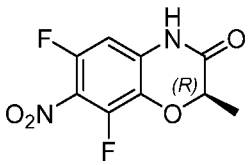
methyl (R)-2-(2,4-difluoro-6-nitrophenoxy)propanoate

To a solution of 2,4-difluoro-6-nitrophenol (2 g, 11.423 mmol, 1 equiv) in THF (20 mL) was added methyl (2S)-2-hydroxypropanoate (1.19 g, 11.423 mmol, 1 equiv) and PPh_3 (4.49 g, 17.134 mmol, 1.5 equiv). The reaction was stirred at rt under N_2 for 0.5h. To the above mixture was added DIAD (2.21 g, 17.134 mmol, 1.5 equiv) at 0°C. The resulting mixture was stirred for additional 1h at 60°C. The reaction was monitored by TLC. After cooling down to rt, the reaction was quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give tmethyl (2R)-2-(2,4-difluoro-6-nitrophenoxy)propanoate (2.5 g, 83.80%) as a white oil. LC/MS: mass calcd. for $C_{10}H_9F_2NO_5$:261.04m/z.



(R)-6,8-difluoro-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

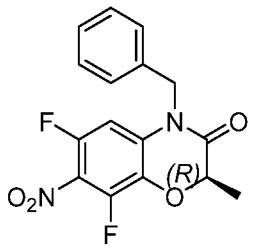
To a solution of methyl (2R)-2-(2,4-difluoro-6-nitrophenoxy)propanoate (2.5 g, 9.572 mmol, 1 equiv) in EtOH (30 mL) and H_2O (3 mL) was added Fe (5.35 g, 95.720 mmol, 10 equiv) and NH_4Cl (5.12 g, 95.720 mmol, 10 equiv). The reaction was stirred at 80 °C for 1h. The mixture was allowed to cool down to rt. The resulting mixture was filtered, the filter cake was washed with EtOH (3 x 100 mL). The filtrate was concentrated under reduced pressure. Diluted with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-6,8-difluoro-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (1.74 g, 91.28%) as white oil. LC/MS: mass calcd. for $C_9H_7F_2NO_2$:199.04 m/z, found:197.90 $[M-H]^-$.



(R)-6,8-difluoro-2-methyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

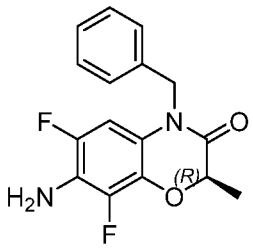
To a solution of (2R)-6,8-difluoro-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (800 mg, 4.017 mmol, 1 equiv) in H_2SO_4 (10 mL) was added KNO_3 (406.12 mg, 4.017 mmol, 1 equiv) at 0°C.

The reaction was stirred at rt for 1h. The reaction was quenched with water/Ice at 0°C. Diluted with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-6,8-difluoro-2-methyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (900 mg, 91.77%) as a yellow solid. LC/MS: mass calcd. for $C_9H_6F_2N_2O_4$:244.03 m/z, found:242.95 $[M-H]^-$.



(R)-4-benzyl-6,8-difluoro-2-methyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

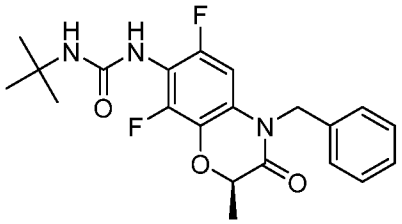
To a solution of (2R)-6,8-difluoro-2-methyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (300 mg, 1.229 mmol, 1 equiv) in DMF (10 mL) was added K_2CO_3 (513.17 mg, 3.687 mmol, 3 equiv) and benzyl bromide (315.24 mg, 1.844 mmol, 1.5 equiv) at 0 °C. The reaction was stirred at rt for 1h. The reaction was monitored by TLC. Quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-4-benzyl-6,8-difluoro-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (390 mg, 94.95%) as a yellow solid.



(R)-7-amino-4-benzyl-6,8-difluoro-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-4-benzyl-6,8-difluoro-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (380 mg, 1.137 mmol, 1 equiv) in MeOH (10 mL) and H_2O (1 mL) was added Fe (634.83 mg, 11.370 mmol, 10 equiv) and NH_4Cl (608.06 mg, 11.370 mmol, 10 equiv). The reaction was stirred at 80 °C for 1h. The mixture was allowed to cool down to rt. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 50 mL). The filtrate was concentrated under reduced pressure.

Quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-4-benzyl-6,8-difluoro-2-methyl-2H-1,4-benzoxazin-3-one (320 mg, 92.51%) as a yellow solid. LC/MS: mass calcd. for $C_{16}H_{14}F_2N_2O_2$: 304.10 m/z, found:305.15 $[M+H]^+$.

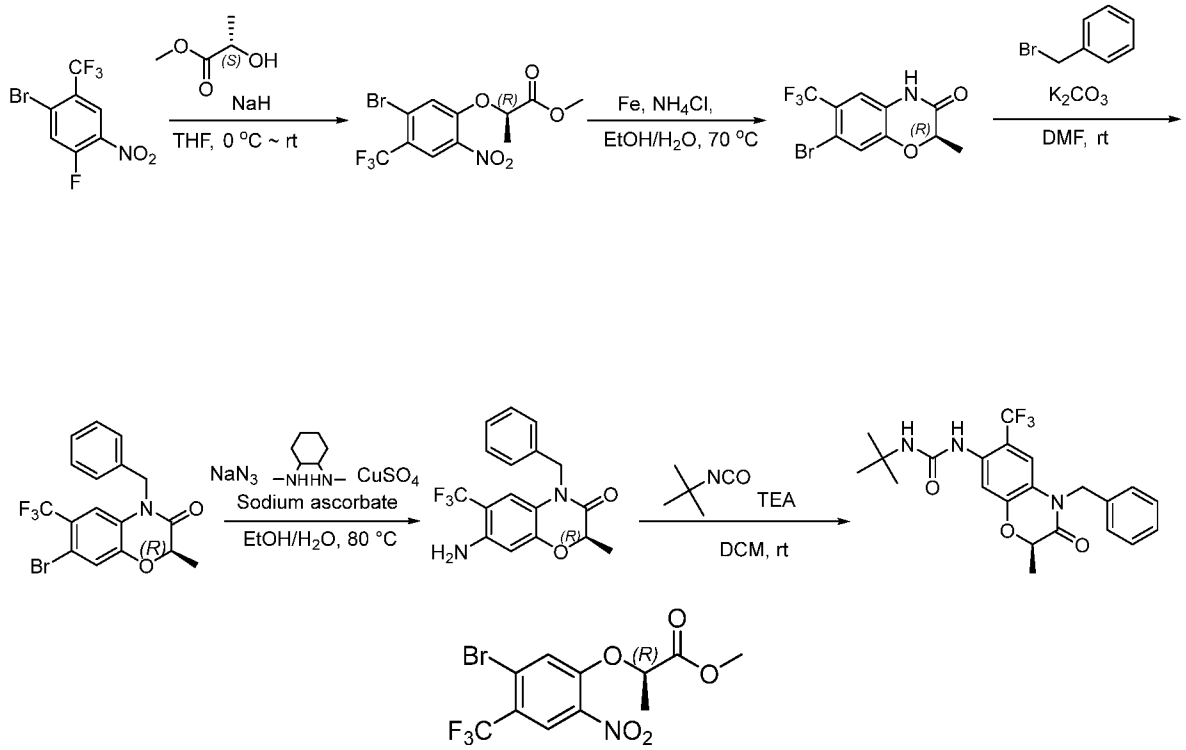


(R)-1-(4-benzyl-6,8-difluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

To a solution of (2R)-7-amino-4-benzyl-6,8-difluoro-2-methyl-2H-1,4-benzoxazin-3-one (280 mg, 0.920 mmol, 1 equiv) in DCM (5 mL) was added triphosgene (109.21 mg, 0.368 mmol, 0.4 equiv) under N_2 at 0 °C. The reaction was stirred at 0 °C under N_2 for 1h. To the above mixture was added TEA (279.34 mg, 2.760 mmol, 3 equiv) at 0°C. The resulting mixture was stirred for additional 1h at rt. Then, to the above mixture was added erbumine (201.90 mg, 2.760 mmol, 3 equiv). The resulting mixture was stirred for additional 1h at rt. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm column (eluent: 36% to 66% (v/v) CH_3CN and Water (10mmol/L NH_4HCO_3)) to afford the title compound 1-[(2R)-4-benzyl-6,8-difluoro-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]-3-tert-butylurea (65.3 mg, 17.26%) as a white solid. LC/MS: mass calcd. for $C_{21}H_{23}F_2N_3O_3$:403.17 m/z, found:404.05 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.50 (s, 1H), 7.31 – 7.39 (m, 2H), 7.26 (td, J = 5.2, 3.0 Hz, 3H), 6.90 (dd, J = 11.4, 1.9 Hz, 1H), 6.15 (s, 1H), 5.09 – 5.23 (m, 2H), 4.98 (q, J = 6.7 Hz, 1H), 1.54 (d, J = 6.7 Hz, 3H), 1.25 (s, 9H).^{19}F NMR (376 MHz, DMSO) δ(ppm): -126.0506, -139.2961.

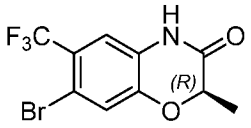
Example 330: (R)-1-(4-benzyl-2-methyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

Synthetic Scheme



methyl (R)-2-(5-bromo-2-nitro-4-(trifluoromethyl)phenoxy)propanoate

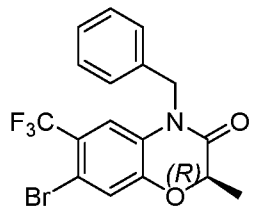
To a stirred solution of methyl (2S)-2-hydroxypropanoate (181 mg, 1.736 mmol, 1 equiv) in THF was added 60% NaH (83.3 mg, 2.083 mmol, 1.2 equiv) at 0 °C. The final reaction mixture was stirred for 30 min at 0 °C. To the above mixture was added 1-bromo-5-fluoro-4-nitro-2-(trifluoromethyl)benzene (500 mg, 1.736 mmol, 1 equiv) at room temperature. The reaction was stirred for 2 h at rt. The reaction was quenched with water (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford methyl (R)-2-(5-bromo-2-nitro-4-(trifluoromethyl)phenoxy)propanoate (410 mg, 63.47%) as a white solid. (ESI): mass calcd. for $C_{11}H_9BrF_3NO_5$: 370.96 m/z, found: 372.09 $[M+H]^+$.



(R)-7-bromo-2-methyl-6-(trifluoromethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

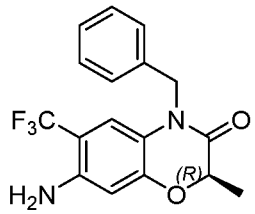
To a mixture of methyl (R)-2-(5-bromo-2-nitro-4-(trifluoromethyl)phenoxy)propanoate (0.4 g, 1.075 mmol, 1 equiv) in EtOH (25 mL) and water (5 mL). Fe (0.6 g, 10.75 mmol, 10 equiv) and NH_4Cl (569 mg, 10.75 mmol, 10 equiv) was added into the mixture. The resulting solution was stirred at 70 °C for 1 h. The reaction was quenched with water (30 mL) at rt. After filtration, the filter cake was washed with EA (3 x 30 mL). The filtrate was added water (30 mL)

and extracted with EA (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford (R)-7-bromo-2-methyl-6-(trifluoromethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one as a light yellow oil. (ESI): mass calcd. for $C_{10}H_7BrF_3NO_2$: 308.96 m/z, found: 310.07 $[M+H]^+$.



(R)-4-benzyl-7-bromo-2-methyl-6-(trifluoromethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

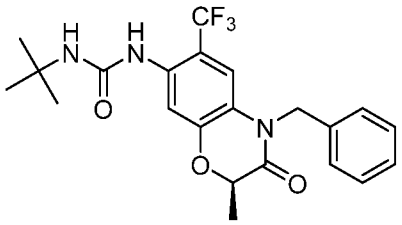
A solution of (R)-7-bromo-2-methyl-6-(trifluoromethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (300 mg, 0.968 mmol, 1 equiv) and benzyl bromide (248 mg, 1.452 mmol, 1.5 equiv) and K_2CO_3 (404 mg, 2.904 mmol, 3 equiv) in DMF was stirred for 3 h at room temperature. The reaction was quenched with water (10 mL) at room temperature. The aqueous layer was extracted with EtOAc (3 x 10 mL). The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford (R)-4-benzyl-7-bromo-2-methyl-6-(trifluoromethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (310 mg, 80.06%) as a white solid. (ESI): mass calcd. for $C_{17}H_{13}BrF_3NO_2$: 399.01 m/z, found: 400.19 $[M+H]^+$.



(R)-7-amino-4-benzyl-2-methyl-6-(trifluoromethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (R)-4-benzyl-7-bromo-2-methyl-6-(trifluoromethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (279 mg, 0.699 mmol, 1 equiv) in EtOH (6 mL) & H_2O (2 mL) was added sodium ascorbate (28 mg, 0.140 mmol, 0.2 equiv), N^1,N^2-dimethylcyclohexane-1,2-diamine (20 mg , 0.140 mmol, 0.2 equiv), $CuSO_4$ (23 mg , 0.14 mmol, 0.2 equiv) and NaN_3 (136 mg, 2.097 mmol, 3 equiv) at rt. The resulting mixture was stirred 4 h at 80 °C. The reaction mixture was quenched by water (10 mL) and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography with PE/EA (1:1) to afford (R)-7-amino-4-benzyl-

2-methyl-6-(trifluoromethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (177 mg, 75.51%) as a yellow oil. (ESI): mass calcd. for $C_{17}H_{15}F_3N_2O_2$: 336.10 m/z, found: 337.11 $[M+H]^+$.

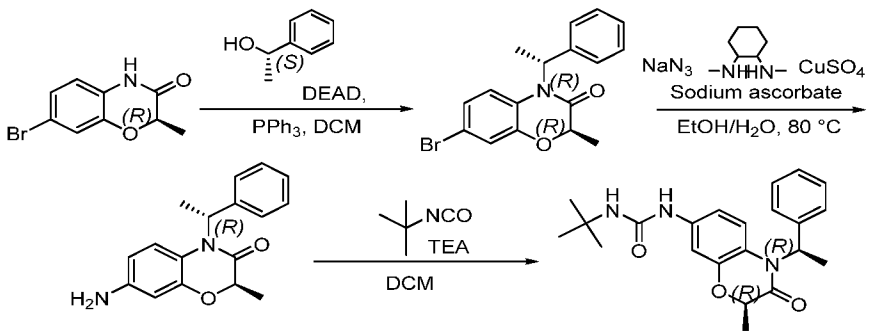


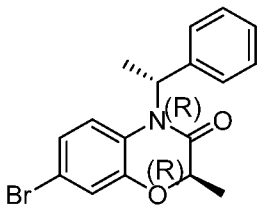
(R)-1-(4-benzyl-2-methyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

To a mixture of 2-(1-(7-amino-3-oxo-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)ethyl)-4-chlorobenzonitrile (34 mg, 0.101 mmol, 1 equiv) and TEA (21 mg, 0.202 mmol, 2 equiv) in DCM (4 mL) was added 2-isocyanato-2-methylpropane (30 mg, 0.303 mmol, 3 equiv) at 0 °C. The reaction was stirred for overnight at rt. The reaction mixture was quenched by water (10 mL) and extracted with DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel column with PE/EA (1:1) and Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10mmol/L NH_4HCO_3+0.05%NH_3H_2O), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 50% B to 72% B in 7 min; Wave Length: 254nm/220nm nm; RT1(min): 6.07) to afford (R)-1-(4-benzyl-2-methyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea (15 mg, 34.09%) as a white solid. (ESI): mass calcd. for $C_{22}H_{24}F_3N_3O_3$: 435.18 m/z, found: 436.18 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 (s, 1H), 7.57 (s, 1H), 7.33 – 7.41 (m, 2H), 7.21 – 7.30 (m, 3H), 7.12 (s, 1H), 6.94 (s, 1H), 5.13 – 5.28 (m, 2H), 4.92 – 5.03 (m, 1H), 1.51 – 1.59 (m, 3H), 1.27 (s, 9H).

Example 331: 1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

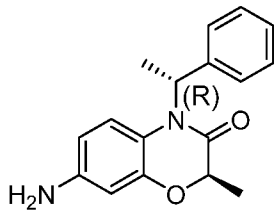
Synthetic Scheme





(R)-7-bromo-2-methyl-4-((R)-1-phenylethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

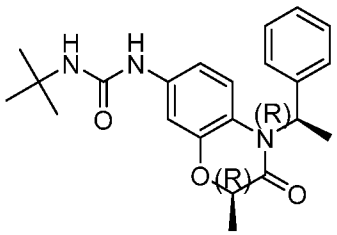
A solution of (2R)-7-bromo-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (600 mg, 2.479 mmol, 1 equiv) in DCM (10 mL) was treated with (S)-1-phenylethanol (454.20 mg, 3.719 mmol, 1.5 equiv) and PPh_3 (975.18 mg, 3.719 mmol, 1.5 equiv) for 1h at rt under nitrogen atmosphere followed by the addition of DEAD (647.49 mg, 3.719 mmol, 1.5 equiv) dropwise at 0°C. The resulting mixture was stirred for 2h at rt under N_2 atmosphere. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-bromo-2-methyl-4-[(1R)-1-phenylethyl]-2H-1,4-benzoxazin-3-one (400 mg, 46.61%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{16}BrNO_2$: 345.04 m/z, found 346.00, 348.00 $[M+H, M+H+2]^+$.



(R)-7-amino-2-methyl-4-((R)-1-phenylethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-7-bromo-2-methyl-4-[(1R)-1-phenylethyl]-2H-1,4-benzoxazin-3-one (390 mg, 0.948 mmol, 1 equiv) in EtOH (4 mL) was added N1,N2-dimethylcyclohexane-1,2-diamine (80.94 mg, 0.569 mmol, 0.6 equiv), $CuSO_4$ (151.36 mg, 0.948 mmol, 1 equiv), sodium ascorbate

(377.66 mg, 1.896 mmol, 2 equiv) and NaN_3 (184.96 mg, 2.844 mmol, 3 equiv). The reaction was stirred at 80 °C under N_2 for 1h. The mixture was allowed to cool down to rt. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-2-methyl-4-[(1R)-1-phenylethyl]-2H-1,4-benzoxazin-3-one (250 mg, 93.37%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{18}N_2O_2$: 282.14 m/z, found 283.10 $[M+H]^+$.

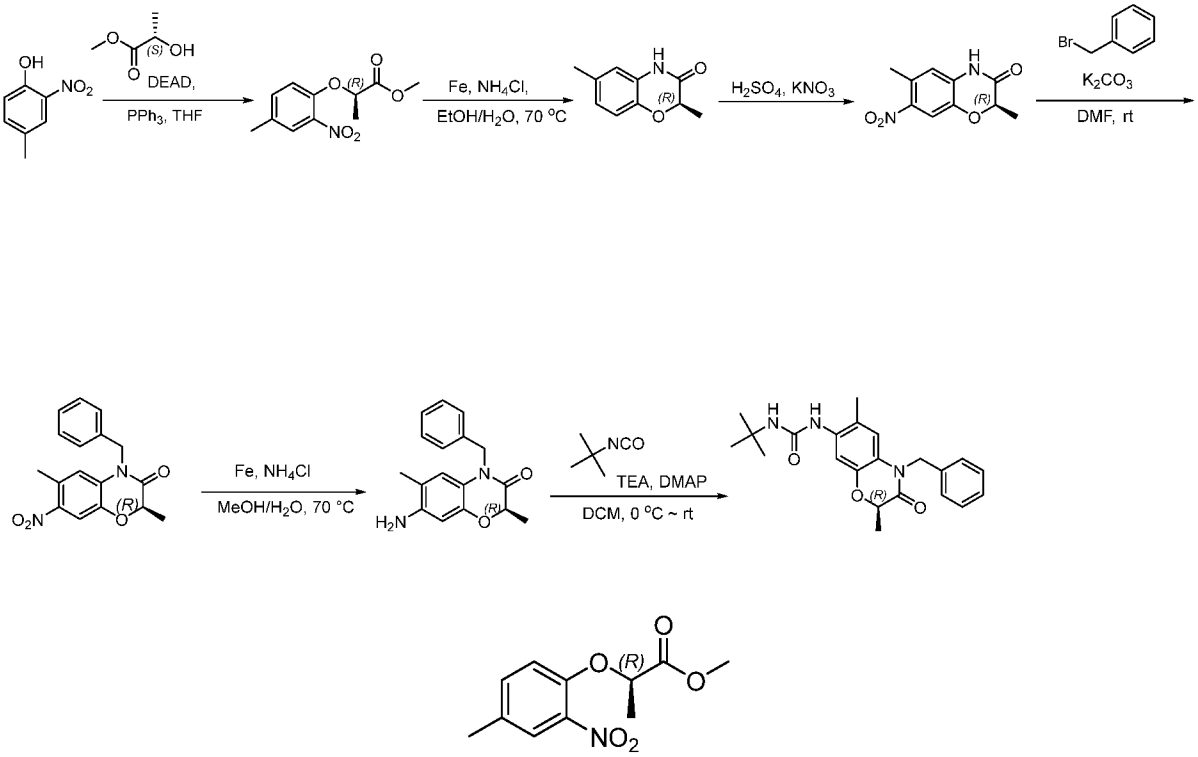


1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a solution of (2R)-7-amino-2-methyl-4-[(1R)-1-phenylethyl]-2H-1,4-benzoxazin-3-one (294 mg, 1.041 mmol, 1 equiv) and 2-isocyanato-2-methylpropane (309.68 mg, 3.123 mmol, 3 equiv) in DCM (10 mL) was added TEA (316.11 mg, 3.123 mmol, 3 equiv) and DMAP (12.72 mg, 0.104 mmol, 0.1 equiv). The reaction was stirred at rt for 24 h. Quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a YMC-Actus Triart C18 ExRS 150 mm x 30 mm x 5 μm column (eluent: 49% to 73% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-[(2R)-2-methyl-3-oxo-4-[(1R)-1-phenylethyl]-2H-1,4-benzoxazin-7-yl]urea (58.6 mg, 14.53%) as a white solid. LC/MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_3$:381.21 m/z, found:382.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.25 – 7.39 (m, 6H), 6.62-6.63 (m, 1H), 6.60-6.61 (m, 1H), 6.15-6.17 (m, 1H), 5.94 (s, 1H), 4.69-4.75 (m, 1H), 1.66-1.69 (d, J = 9.0 Hz, 3H), 1.46-1.48 (d, J = 6.0 Hz, 3H), 1.26 (s, 9H).

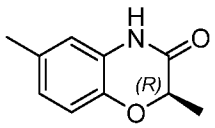
Example 332: (R)-1-(4-benzyl-2,6-dimethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

Synthetic Scheme



methyl (2R)-2-(4-methyl-2-nitrophenoxy)propanoate

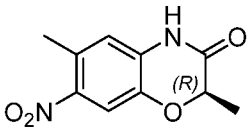
To a solution of 2-nitro-P-cresol (1 g, 6.530 mmol, 1 equiv) in THF (15 mL) was added methyl (2S)-2-hydroxypropanoate (0.82 g, 7.836 mmol, 1.2 equiv) and PPh_3 (2.57 g, 9.795 mmol, 1.5 equiv) under N_2 at 0°C. The reaction was stirred at 0 degrees C for 0.5 h. Then DEAD (1.71 g, 9.795 mmol, 1.5 equiv) was added at 0°C. The reaction was stirred at 60 degrees C for 2 h. The mixture was allowed to cool down to room temperature. Quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give methyl (2R)-2-(4-methyl-2-nitrophenoxy)propanoate (1.3 g, 83.22%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{11}H_{13}NO_5$:239.08 m/z, found:240.05 $[M+H]^+$.



(2R)-2,6-dimethyl-2,4-dihydro-1,4-benzoxazin-3-one

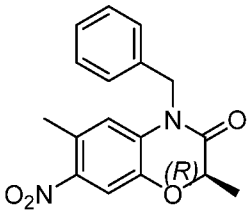
To a solution of methyl (2R)-2-(4-methyl-2-nitrophenoxy)propanoate (700 mg, 2.926 mmol, 1 equiv) in EtOH (10 mL) and H_2O (2 mL) was added Fe (1.63 g, 29.260 mmol, 10 equiv) and

NH_4Cl (1.57 g, 29.260 mmol, 10 equiv). The reaction was stirred at 70 degrees C for 2 h. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 50 mL). The filtrate was concentrated under reduced pressure. Quenched with water (100 mL) and extracted with DCM (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-2,6-dimethyl-2,4-dihydro-1,4-benzoxazin-3-one (450 mg, 86.79%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{10}H_{11}NO_2$:177.08 m/z, found:178.15 $[M+H]^+$.



(2R)-2,6-dimethyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one

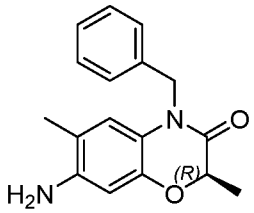
To a solution of (2R)-2,6-dimethyl-2,4-dihydro-1,4-benzoxazin-3-one (420 mg, 2.370 mmol, 1 equiv) in H_2SO_4 (5 mL) was added KNO_3 (311.52 mg, 3.081 mmol, 1.3 equiv) at 0°C. The reaction was stirred at 0 degrees C for 1 h. Quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-2,6-dimethyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (160 mg, 30.38%) as a yellow solid. TLC showed the desired product was generated.



(2R)-4-benzyl-2,6-dimethyl-7-nitro-2H-1,4-benzoxazin-3-one

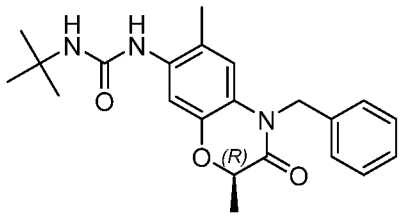
To a solution of (2R)-2,6-dimethyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (160 mg, 0.720 mmol, 1 equiv) in DMF (5 mL) was added benzyl bromide (160.11 mg, 0.936 mmol, 1.3 equiv) and K_2CO_3 (300.73 mg, 2.160 mmol, 3 equiv). The reaction was stirred at 25 degrees C for 16 h. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-4-benzyl-2,6-

dimethyl-7-nitro-2H-1,4-benzoxazin-3-one (200 mg, 88.93%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{17}H_{16}N_2O_4$:312.11 m/z, found:310.95 $[M-H]^-$.



(2R)-7-amino-4-benzyl-2,6-dimethyl-2H-1,4-benzoxazin-3-one

To a solution of (2R)-4-benzyl-2,6-dimethyl-7-nitro-2H-1,4-benzoxazin-3-one (190 mg, 0.608 mmol, 1 equiv) in MeOH (4 mL) and H_2O (1 mL) was added Fe (339.73 mg, 6.080 mmol, 10 equiv) and NH_4Cl (325.40 mg, 6.080 mmol, 10 equiv). The reaction was stirred at 70 degrees C for 2 h. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed with DCM (3 x 50 mL). The filtrate was concentrated under reduced pressure. Diluted with water (40 mL) and extracted with DCM (3 x 40 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-4-benzyl-2,6-dimethyl-2H-1,4-benzoxazin-3-one (130 mg, 75.69%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{17}H_{18}N_2O_2$:282.14 m/z, found:283.10 $[M+H]^+$.



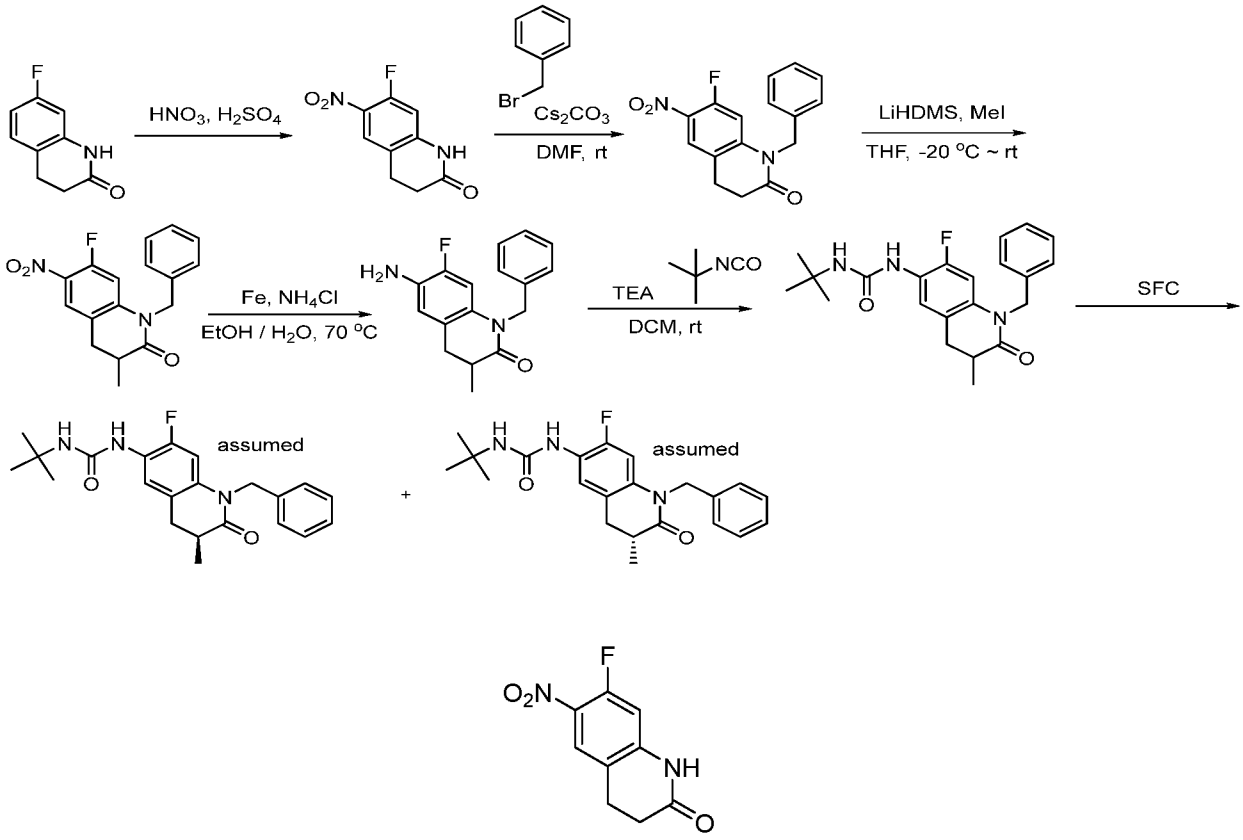
(R)-1-(4-benzyl-2,6-dimethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

To a solution of (R)-7-amino-4-benzyl-2,6-dimethyl-2H-benzo[b][1,4]oxazin-3(4H)-one (150 mg, 0.531 mmol, 1 equiv) in DCM (5 mL) was added NEt_3 (322.61 mg, 3.186 mmol, 6 equiv) , 2-isocyanato-2-methylpropane (210.69 mg, 2.124 mmol, 4 equiv) and DMAP (6.49 mg, 0.053 mmol, 0.1 equiv) at 0°C. The reaction was stirred at 25 °C for 48 hours. Quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge C18 Column 250 mm x 19 mm x 5 μm column (eluent: 53% to 80% (v/v) CH_3CN and

H_2O with 10 mmol/L NH_4HCO_3) to give the (R)-1-(4-benzyl-2,6-dimethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea (63.1 mg, 30.91%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{27}N_3O_3$: 381.2 m/z, found 382.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.65 (s, 1H), 7.40 (s, 1H), 7.30 – 7.36 (m, 2H), 7.21 – 7.27 (m, 3H), 6.82 (s, 1H), 6.48 (s, 1H), 5.10 (s, 2H), 4.76 (q, J = 6.7 Hz, 1H), 2.03 (s, 3H), 1.46 (d, J = 6.7 Hz, 3H), 1.28 (s, 9H).

Example 333 and Example 334: (S)-1-(1-benzyl-7-fluoro-3-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea and (R)-1-(1-benzyl-7-fluoro-3-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

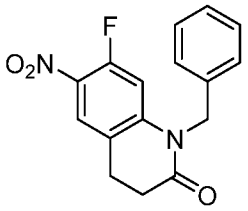
Synthetic Scheme



7-fluoro-6-nitro-3,4-dihydroquinolin-2(1H)-one

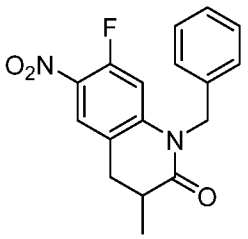
To a solution of 7-fluoro-3,4-dihydro-1H-quinolin-2-one (1 g, 6.054 mmol, 1 equiv) in H_2SO_4 (10 mL) was added HNO_3 (0.38 g, 6.054 mmol, 1 equiv) at 0°C. The reaction was stirred at 0°C for 1 h. Quenched with ice water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The

residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-fluoro-6-nitro-3,4-dihydro-1H-quinolin-2-one (1.1 g, 86.45%) as a white solid. MS (ESI): mass calcd. for $C_9H_7FN_2O_3$: 210.04 m/z, found 209.05 $[M-H]^-$.



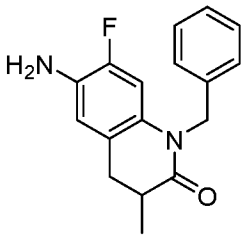
1-benzyl-7-fluoro-6-nitro-3,4-dihydroquinolin-2(1H)-one

To a solution of 7-fluoro-6-nitro-3,4-dihydro-1H-quinolin-2-one (1.1 g, 5.234 mmol, 1 equiv) in DMF (10 mL) was added benzyl bromide (2.68 g, 15.702 mmol, 3 equiv) and Cs_2CO_3(5.13 g, 15.702 mmol, 3 equiv). The reaction was stirred at rt for 3 h. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-benzyl-7-fluoro-6-nitro-3,4-dihydroquinolin-2-one (1.4 g, 89.07%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{13}FN_2O_3$: 300.09 m/z, found 300.95 $[M+H]^+$.



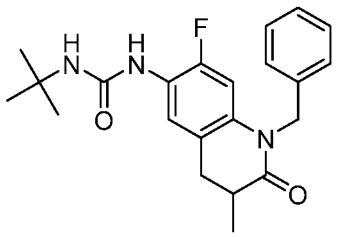
1-benzyl-7-fluoro-3-methyl-6-nitro-3,4-dihydroquinolin-2(1H)-one

A solution of 1-benzyl-7-fluoro-6-nitro-3,4-dihydroquinolin-2-one (600 mg, 1.998 mmol, 1 equiv) in tetrahydrofuran (6 mL) was treated with LiHDMS (401.20 mg, 2.398 mmol, 1.2 equiv) for 1 h at -78°C under nitrogen atmosphere followed by the addition of MeI (283.60 mg, 1.998 mmol, 1 equiv) dropwise at -78°C. The resulting mixture was stirred for 1 h at rt under N_2 atmosphere. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-benzyl-7-fluoro-3-methyl-6-nitro-3,4-dihydroquinolin-2-one (275 mg, 43.79%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{15}FN_2O_3$: 314.11 m/z, found 315.10 $[M+H]^+$.



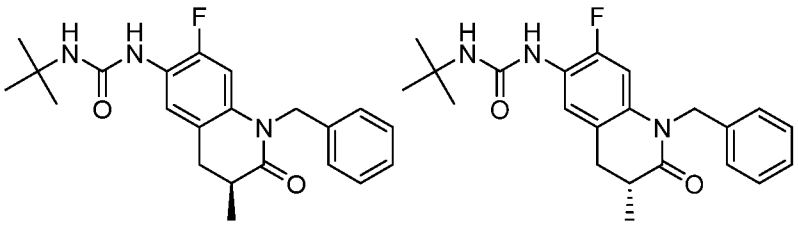
6-amino-1-benzyl-7-fluoro-3-methyl-3,4-dihydroquinolin-2(1H)-one

To a solution of 1-benzyl-7-fluoro-3-methyl-6-nitro-3,4-dihydroquinolin-2-one (270 mg, 0.859 mmol, 1 equiv) in EtOH (5 mL)/H_2O (0.5 mL) was added Fe (479.71 mg, 8.590 mmol, 10 equiv) and NH_4Cl (459.48 mg, 8.590 mmol, 10 equiv). The reaction was stirred at 70°C for 3 h. The mixture was allowed to cool down to rt. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-1-benzyl-7-fluoro-3-methyl-3,4-dihydroquinolin-2-one (220 mg, 90.07%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{17}FN_2O$: 284.13 m/z, found 285.10 $[M+H]^+$.



1-(1-benzyl-7-fluoro-3-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

To a solution of 6-amino-1-benzyl-7-fluoro-3-methyl-3,4-dihydroquinolin-2-one (210 mg, 0.739 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (219.65 mg, 2.217 mmol, 3 equiv) and TEA (224.21 mg, 2.217 mmol, 3 equiv). The reaction was stirred at rt for 24 h. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 1-(1-benzyl-7-fluoro-3-methyl-2-oxo-3,4-dihydroquinolin-6-yl)-3-tert-butylurea (70 mg, 24.72%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{26}FN_3O_2$: 383.20 m/z, found 382.00 $[M-H]^-$.

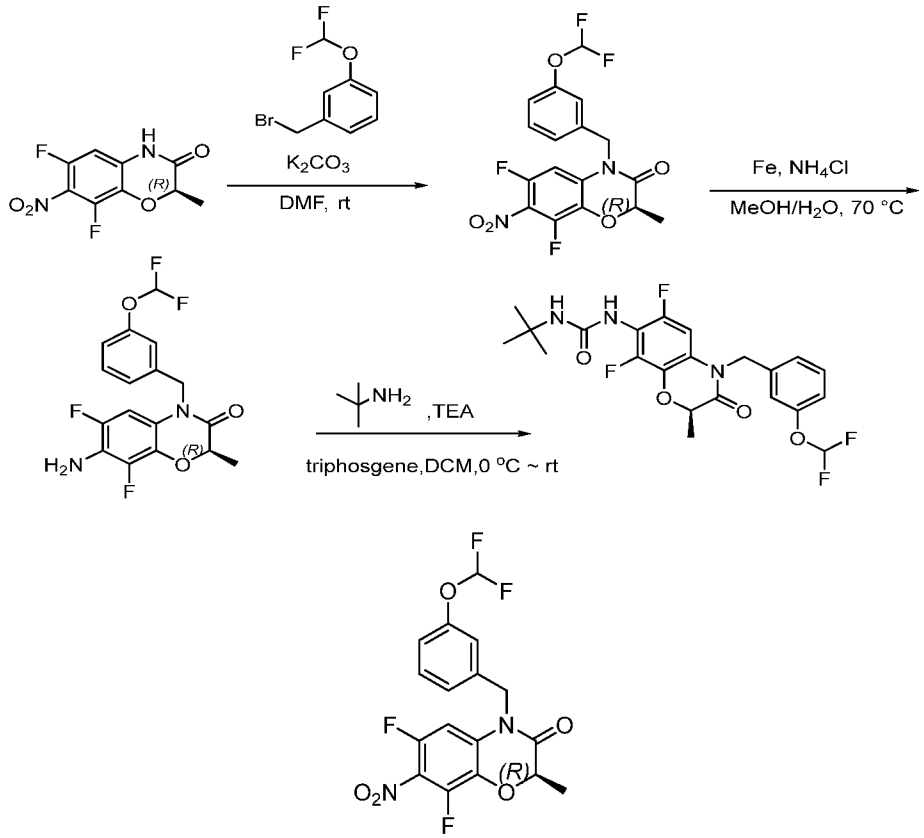


(S)-1-(1-benzyl-7-fluoro-3-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea and (R)-1-(1-benzyl-7-fluoro-3-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

A sample of 1-(1-benzyl-7-fluoro-3-methyl-2-oxo-3,4-dihydroquinolin-6-yl)-3-tert-butylurea (70 mg, 0.183 mmol, 1 equiv) was separated by CHIRALPAK IG, 5*25 cm, 5 μm (eluent: 30% to 30% (v/v) Hex(0.1% 2M NH_3-MeOH)—HPLC and EtOH to yield 1-[(3S)-1-benzyl-7-fluoro-3-methyl-2-oxo-3,4-dihydroquinolin-6-yl]-3-tert-butylurea (29.3 mg, 41.21%) (first enantiomer to elute, labelled *S) MS (ESI): mass calcd. for $C_{22}H_{26}FN_3O_2$: 383.20 m/z, found 382.00 $[M-H]^-$. ^1H NMR (300 MHz, DMSO-d_6) δ 7.92-7.95 (m, 2H), 7.27 – 7.38 (m, 2H), 7.15 – 7.27 (m, 3H), 6.75-6.79 (d, J = 12 Hz, 1H), 6.43 (s, 1H), 5.10 (s, 2H), 2.91-2.95 (d, J = 12 Hz, 1H), 2.59 – 2.74 (m, 2H), 1.27 (s, 9H), 1.15 – 1.19 (m, 3H). ^{19}F NMR (282 MHz, DMSO) δ-131.68 and 1-[(3R)-1-benzyl-7-fluoro-3-methyl-2-oxo-3,4-dihydroquinolin-6-yl]-3-tert-butylurea (18.6 mg, 26.42%) (second enantiomer to elute, labelled *R) MS (ESI): mass calcd. for $C_{22}H_{26}FN_3O_2$: 383.20 m/z, found 382.00 $[M-H]^-$. ^1H NMR (300 MHz, DMSO-d_6) δ 7.92-7.95 (m, 2H), 7.27 – 7.38 (m, 2H), 7.15 – 7.27 (m, 3H), 6.75-6.79 (d, J = 12 Hz, 1H), 6.43 (s, 1H), 5.10 (s, 2H), 2.91-2.95 (m, 1H), 2.59 – 2.79 (m, 2H), 1.27 (s, 9H), 1.17-1.19 (d, J = 6 Hz, 3H). ^{19}F NMR (282 MHz, DMSO) δ -132.02.

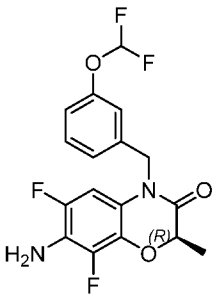
Example 335: 3-tert-butyl-1-[(2R)-4-{[3-(difluoromethoxy)phenyl]methyl}-6,8-difluoro-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]urea

Synthetic Scheme



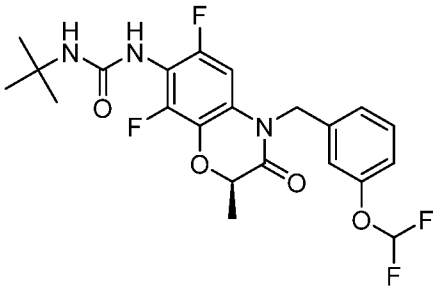
(2R)-4-{[3-(difluoromethoxy)phenyl]methyl}-6,8-difluoro-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one

To a stirred mixture of (2R)-6,8-difluoro-2-methyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (200 mg, 0.819 mmol, 1 equiv) and 1-(bromomethyl)-3-(difluoromethoxy)benzene (388.35 mg, 1.638 mmol, 2 equiv) in DMF (10 mL) was added K_2CO_3 (342.11 mg, 2.457 mmol, 3 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 4 h at 80°C under air atmosphere. After cooling down to room temperature, the reaction was quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. TLC showed the desired product was generated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to afford (2R)-4-{[3-(difluoromethoxy)phenyl]methyl}-6,8-difluoro-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (314 mg, 95.76%) as a white solid.



(2R)-7-amino-4-{[3-(difluoromethoxy)phenyl]methyl}-6,8-difluoro-2-methyl-2H-1,4-benzoxazin-3-one

To a stirred mixture of (2R)-4-{[3-(difluoromethoxy)phenyl]methyl}-6,8-difluoro-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (300 mg, 0.749 mmol, 1 equiv) and NH_4Cl (400.89 mg, 7.490 mmol, 10 equiv) in MeOH:H_2O=10:1 was added Fe (418.54 mg, 7.490 mmol, 10 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 1h at 80°C under air atmosphere. After cooling down to room temperature, the reaction was quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude product was used in the next step directly without further purification. The residue afforded (2R)-7-amino-4-{[3-(difluoromethoxy)phenyl]methyl}-6,8-difluoro-2-methyl-2H-1,4-benzoxazin-3-one (207 mg, 74.59%) as a yellow oil.



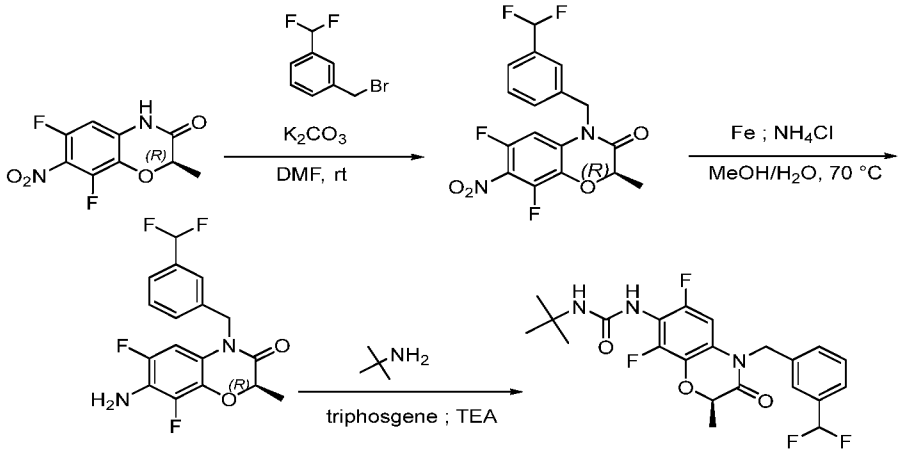
3-tert-butyl-1-[(2R)-4-{[3-(difluoromethoxy)phenyl]methyl}-6,8-difluoro-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]urea

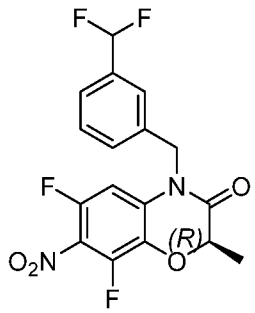
To a stirred solution of (2R)-7-amino-4-{[3-(difluoromethoxy)phenyl]methyl}-6,8-difluoro-2-methyl-2H-1,4-benzoxazin-3-one (120 mg, 0.324 mmol, 1 equiv) and triphosgene (57.69 mg, 0.194 mmol, 0.6 equiv) in DCM (5 mL) was added TEA (98.38 mg, 0.972 mmol, 3 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. To the above mixture was added 2-methylpropan-

2-amine (23.70 mg, 0.324 mmol, 1 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 30 min at room temperature. The reaction was quenched with water (20 mL) and extracted with DCM (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a YMC-Actus Triart C_{18} ExRS 150 mm x 30 mm x 5 μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford 3-tert-butyl-1-[(2R)-4-{[3-(difluoromethoxy)phenyl]methyl}-6,8-difluoro-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]urea (46.4 mg, 30.46%) as a white solid. LC/MS (ESI): mass calcd. for $C_{22}H_{23}F_4N_3O_4$:469.1 m/z, found:470.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.51 (s, 1H), 7.01-7.47 (m, 5H), 6.80-7.00 (m, 1H), 6.15 (s, 1H), 5.06-5.27 (m, 2H),4.90-5.06 (m, 1H), 1.45-1.61 (m, 3H), 1.09-1.35 (m, 9H). ^{19}F NMR (376 MHz, DMSO) δ -81.89, -126.18 -139.24.

Example 336: (R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-6,8-difluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

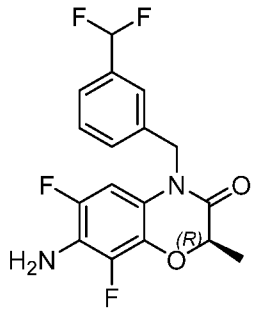
Synthetic Scheme





(2R)-4-{[3-(difluoromethyl)phenyl]methyl}-6,8-difluoro-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one

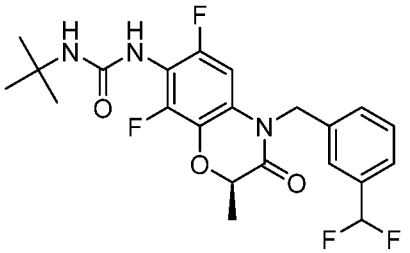
To a stirred solution of (2R)-6,8-difluoro-2-methyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (340 mg, 1.393 mmol, 1 equiv) and 1-(bromomethyl)-3-(difluoromethyl)benzene (338.60 mg, 1.532 mmol, 1.1 equiv) in DMF (10 mL) was added K_2CO_3 (581.59 mg, 4.179 mmol, 3 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 1 h at room temperature under air atmosphere. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3x20 mL), dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:3) to afford (2R)-4-{[3-(difluoromethyl)phenyl]methyl}-6,8-difluoro-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (350 mg, 65.40%) as a yellow solid. TLC showed the desired product was generated.



(2R)-7-amino-4-{[3-(difluoromethyl)phenyl]methyl}-6,8-difluoro-2-methyl-2H-1,4-benzoxazin-3-one

To a stirred mixture of (2R)-4-{[3-(difluoromethyl)phenyl]methyl}-6,8-difluoro-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (350 mg, 0.911 mmol, 1 equiv) and Fe (508.62 mg, 9.110 mmol,10 equiv) in MeOH / water(10:1, 5 mL) was added NH_4Cl (487.17 mg, 9.110 mmol, 10 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred

for 1 h at 70 °C under air atmosphere. Desired product could be detected by LCMS. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (3x10 mL), dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford (2R)-7-amino-4-{[3-(difluoromethyl)phenyl]methyl}-6,8-difluoro-2-methyl-2H-1,4-benzoxazin-3-one (280 mg, 86.77%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{17}H_{14}F_4N_2O_2$:354.10 m/z, found: 354.95 $[M+H]^+$.



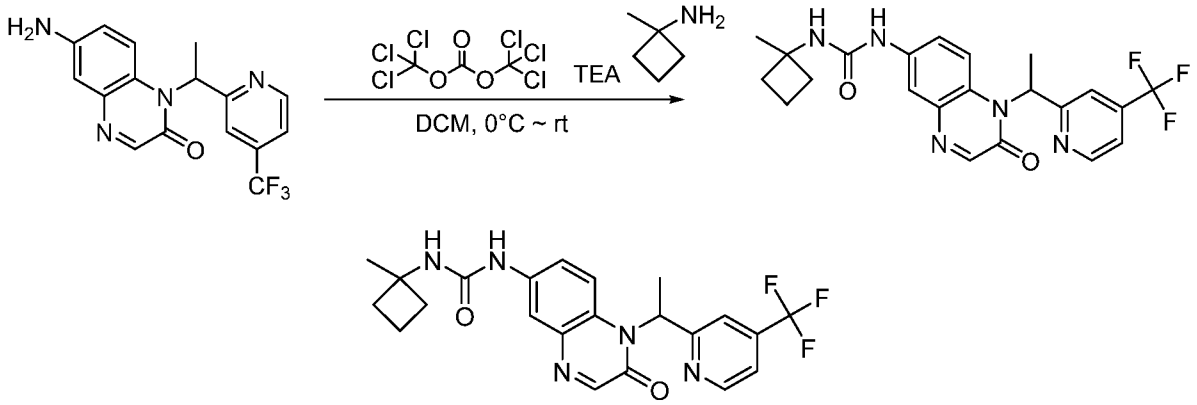
3-tert-butyl-1-[(2R)-4-{[3-(difluoromethyl)phenyl]methyl}-6,8-difluoro-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]urea

A solution of (2R)-7-amino-4-{[3-(difluoromethyl)phenyl]methyl}-6,8-difluoro-2-methyl-2H-1,4-benzoxazin-3-one (60 mg, 0.169 mmol, 1 equiv) in DCM (5 mL) was treated with triphosgene (100.50 mg, 0.338 mmol, 2 equiv) for 1 h at 0 C under nitrogen atmosphere followed by the addition of triethylamine (34.27 mg, 0.338 mmol, 2 equiv) in portions at 0 °C. To the above mixture was added erbumine (24.77 mg, 0.338 mmol, 2 equiv) and triethylamine (34.27 mg, 0.338 mmol, 2 equiv) in portions at 0 °C. The resulting mixture was stirred for additional 1 h at room temperature. Desired product could be detected by LCMS. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (3x10 mL), dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC using a XBridge Prep OBD 250 mm x 19 mm x 5 μm column (eluent: 42% to 72% (v/v) ACN and Water with 10 mmol/L NH_4HCO_3) to afford 3-tert-butyl-1-[(2R)-4-{[3-(difluoromethyl)phenyl]methyl}-6,8-difluoro-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]urea (3.6 mg, 4.55%) as a white solid. LC/MS (ESI): mass calcd. for $C_{22}H_{23}F_4N_3O_3$:453.17 m/z, found:452.00 $[M-H]^-$.^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 7.45 – 7.60 (m, 4H), 6.60 – 7.00

(m, 2H), 6.10 – 6.30 (s, 1H), 5.20 – 5.40 (s, 1H), 5.10 – 5.20 (m, 2H), 4.80 – 4.95 (m, 1H),1.55 – 1.65 (m, 3H),1.28 – 1.38 (s, 9H). ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -111.38, -128.07, -141.04.

Example 337: 1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(4-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

Synthetic Scheme



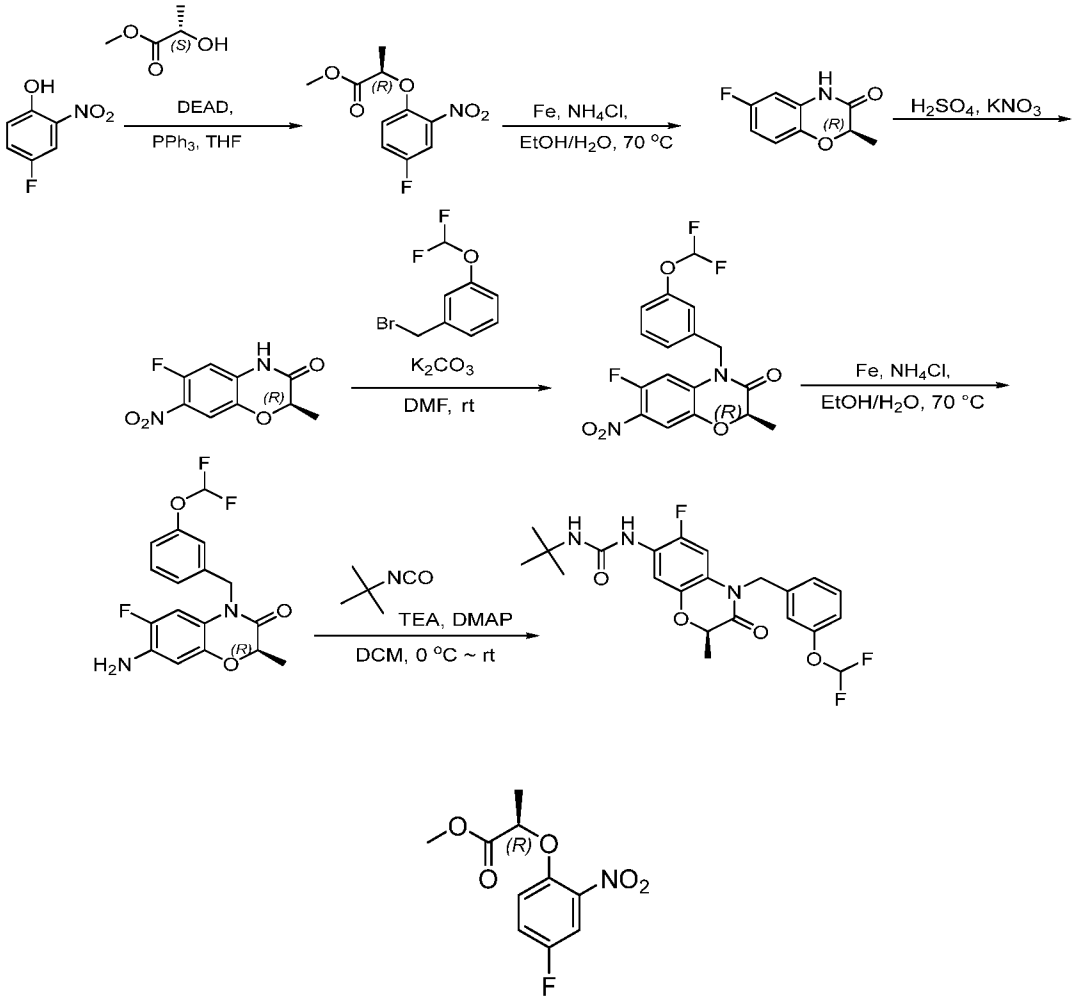
1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(4-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

To a solution of 6-amino-1-{1-[4-(trifluoromethyl)pyridin-2-yl]ethyl}quinoxalin-2-one (70 mg, 0.209 mmol, 1 equiv) in DCM (5 mL) was added triphosgene (62.13 mg, 0.209 mmol, 1 equiv) under N_2 at 0 °C. The reaction was stirred at 0 °C under N_2 for 1h. To the above mixture was added TEA (63.57 mg, 0.627 mmol, 3 equiv) at 0°C. The resulting mixture was stirred for additional 1h at rt. Then, to the above mixture was added 1-methylcyclobutan-1-amine (53.49 mg, 0.627 mmol, 3 equiv). The resulting mixture was stirred for additional 1h at rt. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column30*150 mm 5μm column (eluent: 33% to 47% (v/v) CH_3CN and Water (10mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$)) to afford the title compound 3-(1-methylcyclobutyl)-1-(2-oxo-1-{1-[4-(trifluoromethyl)pyridin-2-yl]ethyl}quinoxalin-6-yl)urea (43 mg, 46.05%) as a yellow solid. LC/MS: mass calcd. for $C_{21}H_{22}F_3N_5O_2$:445.17 m/z, found:446.05 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (d, J = 5.1 Hz, 1H), 8.46 (s, 1H), 8.20 (s, 1H), 7.96 (d, J = 2.5 Hz, 1H), 7.75 (s, 1H), 7.69 (d, J = 5.2 Hz, 1H), 7.10 – 7.56 (m, 2H),

6.54 (s, 1H), 6.33 (s, 1H), 2.29 (dt, J = 11.4, 9.1 Hz, 2H), 1.84 – 1.97 (m, 5H), 1.70 – 1.83 (m, 2H), 1.40 (s, 3H).^{19}F NMR (376 MHz, DMSO) δ(ppm): -663.0913.

Example 338: (R)-1-(tert-butyl)-3-(4-(3-(difluoromethoxy)benzyl)-6-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

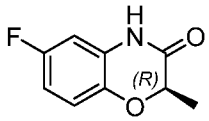
Synthetic Scheme



methyl (R)-2-(4-fluoro-2-nitrophenoxy)propanoate

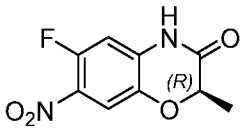
A solution of 4-fluoro-2-nitrophenol (2 g, 12.731 mmol, 1 equiv) in THF (20 mL) was treated with methyl (2S)-2-hydroxypropanoate (1.99 g, 19.096 mmol, 1.5 equiv) and PPh_3 (5.01 g, 19.096 mmol, 1.5 equiv) for 1 h at rt under nitrogen atmosphere followed by the addition of DEAD (3.33 g, 19.096 mmol, 1.5 equiv) dropwise at 0°C. The resulting mixture was stirred for 2 h at 60°C under N_2 atmosphere. The mixture was allowed to cool down to rt. Quenched with

water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give methyl (2R)-2-(4-fluoro-2-nitrophenoxy)propanoate (1 g, 32.30%) as a white solid. MS (ESI): mass calcd. for $C_{10}H_{10}FNO_5$: 243.05 m/z, found 244.15 $[M+H]^+$.



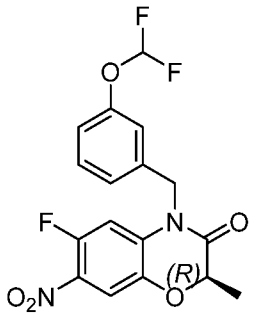
(R)-6-fluoro-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of methyl (2R)-2-(4-fluoro-2-nitrophenoxy)propanoate (1 g, 4.112 mmol, 1 equiv) in EtOH (10 mL)/H_2O (1 mL) was added Fe (2.30 g, 41.120 mmol, 10 equiv) and NH_4Cl (2.20 g, 41.120 mmol, 10 equiv). The reaction was stirred at 70°C for 3 h. The mixture was allowed to cool down to rt. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-6-fluoro-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (650 mg, 87.25%) as a white solid. MS (ESI): mass calcd. for $C_9H_8FNO_2$: 181.05 m/z, found 182.05 $[M+H]^+$.



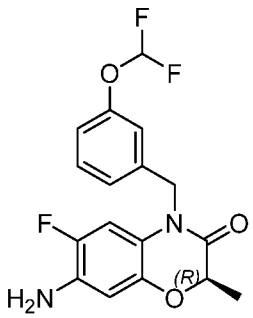
(R)-6-fluoro-2-methyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

A solution of (2R)-6-fluoro-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (1 g, 5.520 mmol, 1 equiv) and KNO_3 (558.06 mg, 5.520 mmol, 1 equiv) in H_2SO_4 (10 mL) was stirred for 1 h at 0°C. The reaction was stirred at rt for 1 h. Quenched with ice water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-6-fluoro-2-methyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (660 mg, 52.87%) as a white solid. MS (ESI): mass calcd. for $C_9H_7FN_2O_4$: 226.04 m/z, found 224.95 $[M-H]^-$.



(R)-4-(3-(difluoromethoxy)benzyl)-6-fluoro-2-methyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

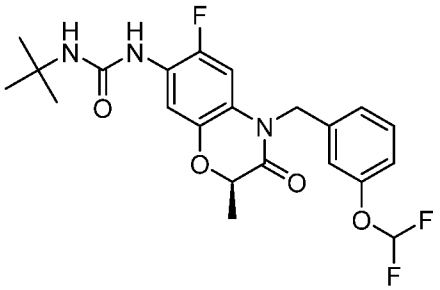
To a solution of (2R)-6-fluoro-2-methyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (300 mg, 1.326 mmol, 1 equiv) in DMF (5 mL) was added 1-(bromomethyl)-3-(difluoromethoxy)benzene (377.32 mg, 1.591 mmol, 1.2 equiv) and K_2CO_3 (553.99 mg, 3.978 mmol, 3 equiv). The reaction was stirred at rt for 3 h. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-4-{[3-(difluoromethoxy)phenyl]methyl}-6-fluoro-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (450 mg, 88.74%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{13}F_3N_2O_5$: 382.08 m/z, found 383.10 $[M+H]^+$.



(R)-7-amino-4-(3-(difluoromethoxy)benzyl)-6-fluoro-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-4-{[3-(difluoromethoxy)phenyl]methyl}-6-fluoro-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (514 mg, 1.345 mmol, 1 equiv) in EtOH (10 mL) was added Fe (750.84 mg, 13.450 mmol, 10 equiv) and NH_4Cl (719.18 mg, 13.450 mmol, 10 equiv). The reaction was stirred at 70°C for 3 h. The mixture was allowed to cool down to rt. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column

chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-4-{[3-(difluoromethoxy)phenyl]methyl}-6-fluoro-2-methyl-2H-1,4-benzoxazin-3-one (450 mg, 95.00%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{15}F_3N_2O_3$: 352.10 m/z, found 353.05 $[M+H]^+$.

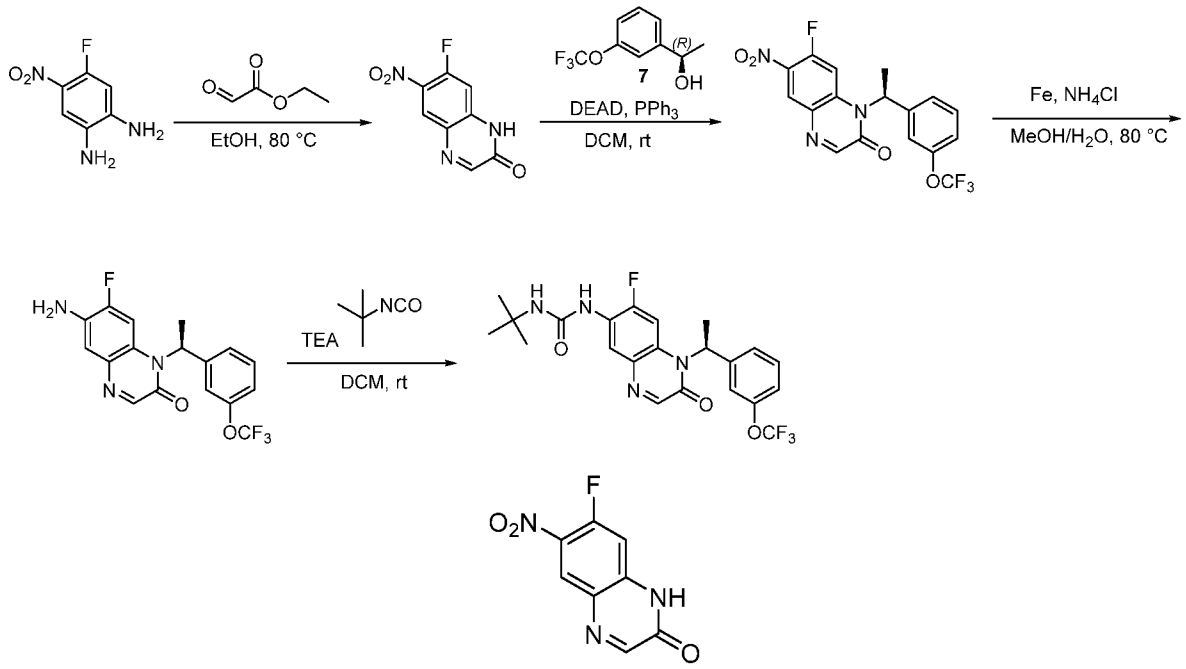


(R)-1-(tert-butyl)-3-(4-(3-(difluoromethoxy)benzyl)-6-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a solution of (2R)-7-amino-4-{[3-(difluoromethoxy)phenyl]methyl}-6-fluoro-2-methyl-2H-1,4-benzoxazin-3-one (200 mg, 0.568 mmol, 1 equiv) in DCM (5 mL) was added 2-isocyanato-2-methylpropane (168.74 mg, 2.840 mmol, 5 equiv) and TEA (287.22 mg, 2.840 mmol, 5 equiv). The reaction was stirred at rt for 24 h. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a YMC-Actus Triart C18 ExRS 150 mm x 30 mm x 5 μm column (eluent: 49% to 73% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-[(2R)-4-{[3-(difluoromethoxy)phenyl]methyl}-6-fluoro-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]urea (55.4 mg, 21.60%) as a off-white solid. LC/MS (ESI): mass calcd. for $C_{22}H_{24}F_3N_3O_4$: 451.17 m/z, found: 452.05 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.82-7.84 (d, J = 6 Hz, 1H), 6.95 – 7.46 (m, 6H), 6.51 (s, 1H), 5.12 (s, 2H), 4.78-4.85 (m, 1H), 1.46-1.48 (d, J = 6.0 Hz, 3H), 1.27 (s, 9H). ^{19}F NMR (282 MHz, DMSO) δ-81.91 -137.08.

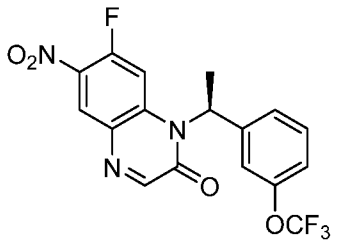
Example 339: (S)-1-(tert-butyl)-3-(7-fluoro-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

Synthetic Scheme



7-fluoro-6-nitro-1H-quinoxalin-2-one

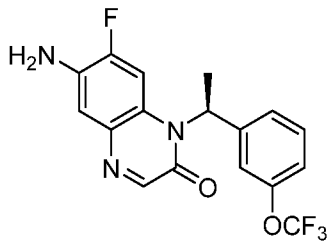
To a solution of 4-fluoro-5-nitrobenzene-1,2-diamine (2 g, 11.687 mmol, 1 equiv) in ethyl alcohol (10 mL) was added ethyl glyoxylate (1.19 g, 11.687 mmol, 1 equiv). The resulting mixture was stirred for 2 h at 80 °C. The reaction mixture was quenched by water (10 mL) and extracted with DCM (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 7-fluoro-6-nitroquinoxalin-2(1H)-one (1.7 g, 69.55%) as a white solid. MS (ESI): mass calcd. for $C_8H_4FN_3O_3$: 209.17 m/z, found: 208 $[M-H]^-$.



(S)-7-fluoro-6-nitro-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)quinoxalin-2(1H)-one

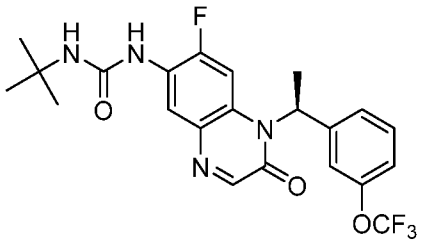
To a solution of 7-fluoro-6-nitroquinoxalin-2(1H)-one (1.6 g, 7.651 mmol, 1.2 equiv) in DCM (40 mL) was added (1R)-1-[3-(trifluoromethoxy)phenyl]ethanol (1.31 g, 6.376 mmol, 1 equiv) , PPh_3 (2.51 g, 9.564 mmol, 1.5 equiv) and DEAD (1.39 g, 7.970 mmol, 1.25 equiv). The resulting

mixture was stirred for 2 h at 25 °C under N_2 and stirred until the starting material was totally consumed by TLC. The reaction mixture was quenched by water (10 mL) and extracted with DCM (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford (S)-7-fluoro-6-nitro-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)quinoxalin-2(1H)-one (2 g, 78.96%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{11}F_4N_3O_4$: 397.17 m/z, found: 398.05 $[M+H]^+$.



(S)-6-amino-7-fluoro-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)quinoxalin-2(1H)-one

To a solution of (S)-7-fluoro-6-nitro-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)quinoxalin-2(1H)-one (2 g, 5.034 mmol, 1 equiv) in EtOH (20 mL) and H_2O (2 mL) was added Fe (2.81 g, 50.340 mmol, 10 equiv) and NH_4Cl (2.69 g, 50.340 mmol, 10 equiv). The resulting mixture was stirred for 2 h at 80 °C and stirred until the starting material was totally consumed by TLC. The reaction mixture was quenched by water and extracted with DCM (3 x 30 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford (S)-6-amino-7-fluoro-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)quinoxalin-2(1H)-one (350 mg, 87.28%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{13}F_4N_3O_2$: 367.17 m/z, found: 368.15 $[M+H]^+$.

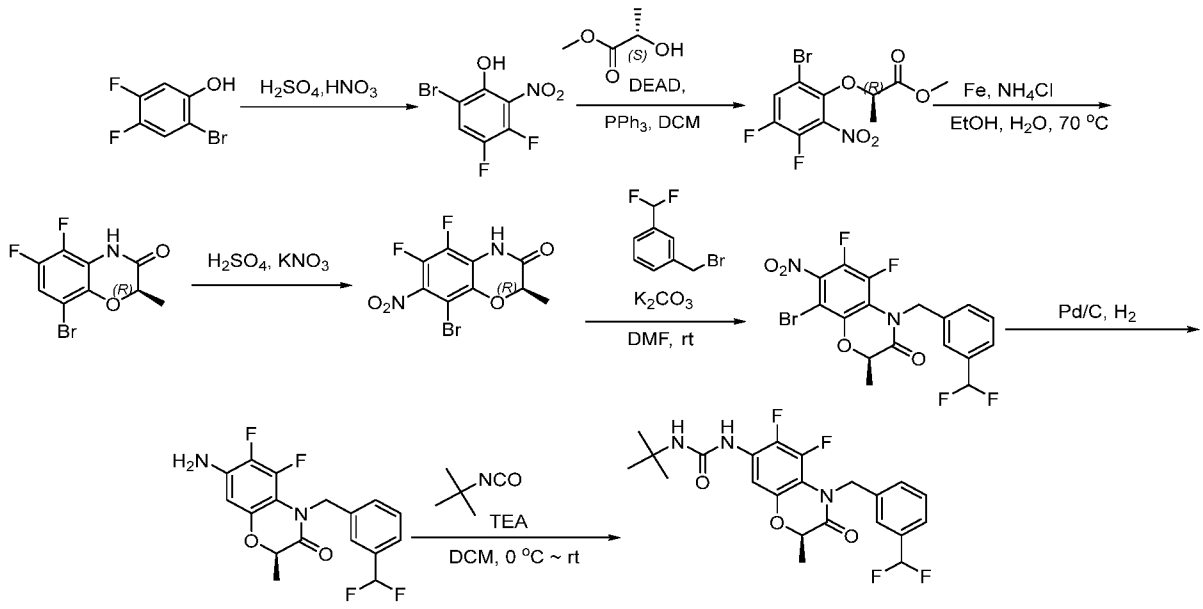


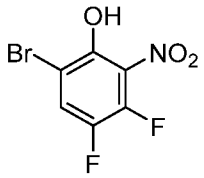
(S)-1-(tert-butyl)-3-(7-fluoro-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

To a solution of (S)-6-amino-7-fluoro-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)quinoxalin-2(1H)-one (80 mg, 0.218 mmol, 1 equiv) in DCM (20 mL) was added 2-isocyanato-2-methylpropane (64.77 mg, 0.654 mmol, 3 equiv), DMAP (2.66 mg, 0.022 mmol, 0.1 equiv)and TEA (66.12 mg, 0.654 mmol, 3 equiv). The resulting mixture was stirred for 24 h at rt. The reaction mixture was quenched by water and extracted with DCM (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 53% B in 9 min, 53% B; Wave Length: 254/220 nm; RT1(min): 8.52; Number Of Runs: 0) to afford (S)-1-(tert-butyl)-3-(7-fluoro-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea (26 mg, 25.52%)as an white solid. MS (ESI): mass calcd. For $C_{22}H_{22}F_4N_4O_3$: 466.17 m/z, found: 467.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, J = 8.7 Hz, 1H), 8.23 – 7.27 (m, 2H), 7.44 – 7.50 (m, 1H), 7.30 – 7.35 (m, 3H), 7.13 – 7.17 (m, 1H), 6.58 (s, 1H), 6.46 (br, 1H), 1.88 (d, J = 7.0 Hz, 3H), 1.30 (s, 9H).

Example 340: (R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-5,6-difluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

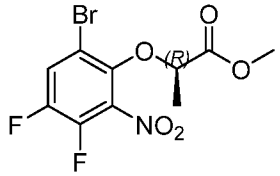
Synthetic Scheme





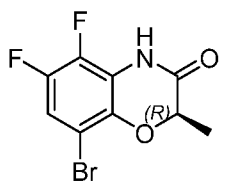
6-bromo-3,4-difluoro-2-nitrophenol

To a solution of 2-bromo-4,5-difluorophenol (1.5 g, 7.177 mmol, 1 equiv) and HNO_3 (0.45 g, 7.177 mmol, 1 equiv) in H_2SO_4 (15 mL) was stirred for 1h at 0°C. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 6-bromo-3,4-difluoro-2-nitrophenol (1.78 g, 83.00%) as a brown solid. LC/MS: mass calcd. for $C_6H_2BrF_2NO_3$: 252.92 m/z found: 253.92, 255.92 $[M+H, M+H+2]^+$.



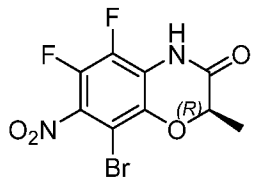
methyl (R)-2-(6-bromo-3,4-difluoro-2-nitrophenoxy)propanoate

To a solution of methyl (2S)-2-hydroxypropanoate (0.73 g, 7.008 mmol, 1 equiv) in DCM (20 mL) was added 6-bromo-3,4-difluoro-2-nitrophenol (1.78 g, 7.008 mmol, 1 equiv) and PPh_3 (2.76 g, 10.512 mmol, 1.5 equiv). The resulting mixture was stirred for 1h at rt under N_2. DEAD (1.43 g, 8.211 mmol, 1 equiv) was added the mixture at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 16 h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (1:1) to afford methyl (R)-2-(6-bromo-3,4-difluoro-2-nitrophenoxy) propanoate (2 g, 71.33%) as yellow oil. LC/MS: mass calcd. for $C_{10}H_8BrF_2NO_5$: 338.96 m/z found: 339.96, 341.96 $[M+H, M+H+2]^+$



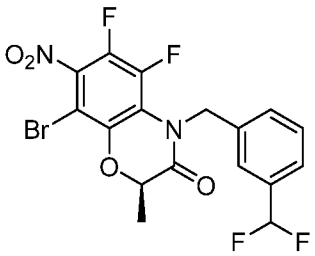
(R)-8-bromo-5,6-difluoro-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

To a mixture of methyl (2R)-2-(6-bromo-3,4-difluoro-2-nitrophenoxy) propanoate (2 g, 5.881 mmol, 1 equiv) in EtOH (10 mL) and H_2O (2.5 mL) was added Fe (3.28 g, 58.810 mmol, 10 equiv) and NH_4Cl (3.15 g, 58.810 mmol, 10 equiv). The resulting mixture was stirred for 2 h at 70 °C. The resulting mixture was filtered, the filter cake was washed with EtOH. The filtrate was concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford (2R)-8-bromo-5,6-difluoro-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (1.35 g, 82.56%) as a yellow semi-solid. LC/MS: mass calcd. for $C_9H_6BrF_2NO_2$: 276.95 m/z found: 277.95, 279.95 $[M+H, M+H+2]^+$



(R)-8-bromo-5,6-difluoro-2-methyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

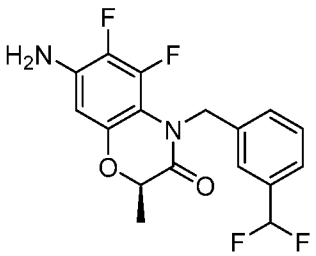
To a solution of (2R)-8-bromo-5,6-difluoro-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (1000 mg, 3.60 mmol, 1 equiv) and KNO_3 (727.23 mg, 7.20 mmol, 2 equiv) in H_2SO_4 (20 mL) was stirred for 12h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford (2R)-8-bromo-5,6-difluoro-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (1.35 g, 82.56%) as a yellow semi-solid. LC/MS: mass calcd. for $C_9H_5BrF_2N_2O_4$: 321.94 m/z found: 322.94, 324.94 $[M+H, M+H+2]^+$



(R)-8-bromo-4-(3-(difluoromethyl)benzyl)-5,6-difluoro-2-methyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

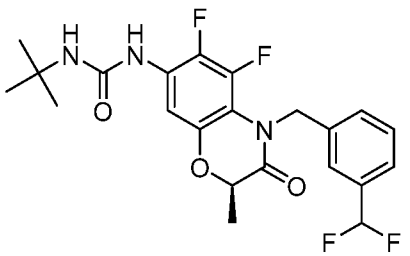
To a solution of (2R)-8-bromo-5,6-difluoro-2-methyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (390 mg, 1.207 mmol, 1 equiv) in DMF (5 mL) was added 1-(bromomethyl)-3-(difluoromethyl) benzene (266.86 mg, 1.207 mmol, 1 equiv) and K_2CO_3 (333.69 mg, 2.414 mmol, 2 equiv). The

resulting mixture was stirred for 16 h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 50 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford (2R)-8-bromo-4-{[3-(difluoromethyl)phenyl]methyl}-5,6-difluoro-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (260 mg, 39.52%) as yellow oil. LC/MS: mass calcd. for $C_{17}H_{11}BrF_4N_2O_4$: 461.98 m/z found: 462.98, 464.98 $[M+H, M+H+2]^+$.



(R)-7-amino-4-(3-(difluoromethyl)benzyl)-5,6-difluoro-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

A mixture of (2R)-8-bromo-4-{[3-(difluoromethyl)phenyl]methyl}-5,6-difluoro-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (250 mg, 0.540 mmol, 1 equiv) and Pd/C (574.40 mg, 5.400 mmol, 10 equiv) in MeOH (5 mL) was stirred for 1h at rt under H_2 atmosphere. The resulting mixture was filtered, the filter cake was washed with MeOH (20 mL). The filtrate was concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford (2R)-7-amino-4-{[3-(difluoromethyl) phenyl]methyl}-5,6-difluoro-2-methyl-2H-1,4-benzoxazin-3-one (100 mg, 44.45%) as a yellow solid. LC/MS: mass calcd. for $C_{17}H_{14}F_4N_2O_2$: 354.10 m/z found: 355.10 [M+H]+.



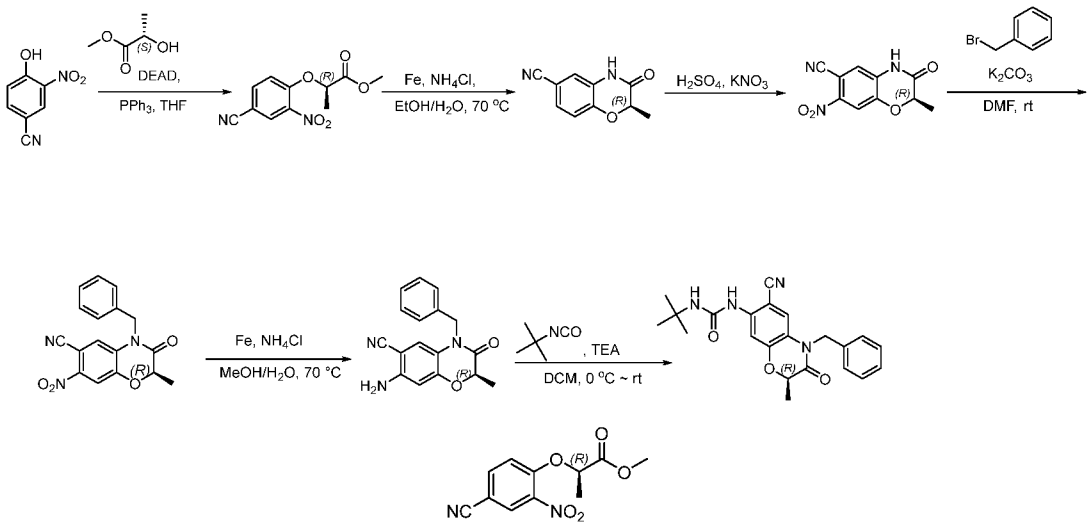
(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl) benzyl)-5,6-difluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4] oxazin-7-yl)urea

To a solution of (2R)-7-amino-4-{[3-(difluoromethyl)phenyl]methyl}-5,6-difluoro-2-methyl-2H-1,4-benzoxazin-3-one (90 mg, 0.254 mmol, 1 equiv) in DCM (5 mL) was added TEA (77.11 mg,

0.762 mmol, 3 equiv) and 2-isocyanato-2-methylpropane (76.2 mg, 0.762 mmol, 3 equiv). The resulting mixture was stirred for 16 h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column eluted with PE / EA (2:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 53% B in 9 min, 53% B; Wave Length: 254/220 nm; RT1(min): 8.52; Number Of Runs: 0) to afford 3-tert-butyl-1-[(2R)-4-{[3-(difluoromethyl)phenyl]methyl}-5,6-difluoro-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]urea (4.7 mg, 4.02%) as a white solid. LC/MS: mass calcd. for $C_{22}H_{23}F_4N_3O_3$: 453.17 m/z found: 452.10 $[M-H]^-$. ^1H NMR (300 MHz, Chloroform-d) δ 7.68 (dd, J = 7.0, 2.3 Hz, 1H), 7.34 – 7.44 (m, 2H), 7.31 (s, 1H), 6.62 (s, 1H), 6.26 (s, 1H), 5.35 (d, J = 15.6 Hz, 1H), 5.18 (d, J = 15.5 Hz, 1H), 4.65 (s, 1H), 4.60 (q, J = 6.7 Hz, 2H), 1.59 (d, J = 6.8 Hz, 3H), 1.40 (s, 9H). ^{19}F-NMR (282 MHz, $CDCl_3$) δ -110.63, -147.41, -161.57.

Example 341: 1-(4-benzyl-6-cyano-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

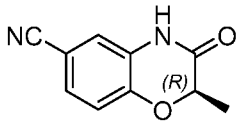
Synthetic Scheme



methyl (R)-2-(4-cyano-2-nitrophenoxy) propanoate

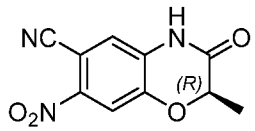
To a stirred solution of 4-hydroxy-3-nitrobenzonitrile (2.5 g, 15.233 mmol, 1 equiv) and methyl (2S)-2-hydroxypropanoate (1.59 g, 15.233 mmol, 1 equiv) in THF (20 mL) was added PPh_3 (5.99

g, 22.849 mmol, 1.5 equiv) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 0.5 h at room temperature under nitrogen atmosphere. Then, to the above solution was added DEAD (3.98 g, 22.849 mmol, 1.5 equiv) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS. The reaction was quenched with water (100 mL). The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford methyl (R)-2-(4-cyano-2-nitrophenoxy) propanoate (3 g, 74.78%) as a yellow green oil. LC/MS: mass calcd for $C_{11}H_{10}N_2O_5$:250.06, found: 251.05 $[M+H]^+$.



(R)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b] [1,4]oxazine-6-carbonitrile

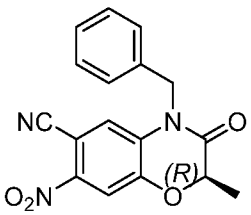
To a stirred solution of methyl (R)-2-(4-cyano-2-nitrophenoxy) propanoate (3 g, 11.990 mmol, 1 equiv) and NH_4Cl (6413.41 mg, 119.900 mmol, 10 equiv) in $EtOH/H_2O$ (4:1, 40 mL) was added Fe (6695.78 mg, 119.900 mmol, 10 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 70 °C under air atmosphere. Desired product could be detected by LCMS. After cooling down to rt, the reaction was quenched with water (100 mL). The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford (R)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b] [1,4] oxazine-6-carbonitrile (1.6 g, 49.64%) as a yellow oil. LC/MS: mass calcd for $C_{10}H_8N_2O_2$; 188.06, found: 189.05 $[M+H]^+$.



(R)-2-methyl-7-nitro-3-oxo-3,4-dihydro-2H-benzo[b] [1,4]oxazine-6-carbonitrile

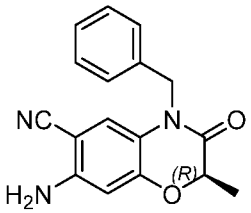
To a stirred solution of (R)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile (1.6 g, 8.502 mmol, 1 equiv) in H_2SO_4 (20 mL, 375.242 mmol, 44.13 equiv) was added KNO_3 (859.59 mg, 8.502 mmol, 1 equiv) in portions at 0 °C under air atmosphere. The resulting mixture

was stirred for 2 h at room temperature under air atmosphere. Desired product could be detected by LCMS. Pour the reaction into ice/water. The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford (R)-2-methyl-7-nitro-3-oxo-3,4-dihydro-2H-benzo[b] [1,4] oxazine-6-carbonitrile (313 mg, 15.00%) as a yellow oil. LC/MS: mass calcd for $C_{10}H_7N_3O_4$: 233.04, found: 234.05 $[M+H]^+$.



(R)-4-benzyl-2-methyl-7-nitro-3-oxo-3,4-dihydro-2H-benzo[b] [1,4]oxazine-6-carbonitrile

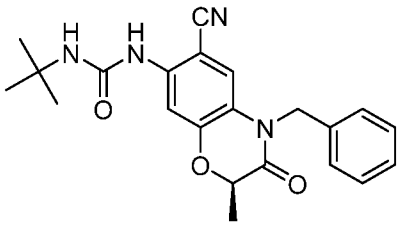
To a stirred solution of (R)-2-methyl-7-nitro-3-oxo-3,4-dihydro-2H-benzo[b] [1,4] oxazine-6-carbonitrile (150 mg, 0.643 mmol, 1 equiv) and benzyl bromide (165.03 mg, 0.965 mmol, 1.5 equiv) in DMF (5 mL) was added K_2CO_3 (268.66 mg, 1.929 mmol, 3 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 1 h at room temperature under air atmosphere. Desired product could be detected by LCMS. The reaction was quenched with water (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford (R)-4-benzyl-2-methyl-7-nitro-3-oxo-3,4-dihydro-2H-benzo[b] [1,4] oxazine-6-carbonitrile (124 mg, 56.64%) as a yellow solid. LC/MS: mass calcd for $C_{17}H_{13}N_3O_4$: 323.09, found: 324.01 $[M+H]^+$.



(R)-7-amino-4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b] [1,4]oxazine-6-carbonitrile

To a stirred solution of (R)-4-benzyl-2-methyl-7-nitro-3-oxo-3,4-dihydro-2H-benzo[b] [1,4] oxazine-6-carbonitrile (60 mg, 0.186 mmol, 1 equiv) and NH_4Cl (99.27 mg, 1.860 mmol, 10 equiv) in $MeOH/H_2O$ (10:1, 5 mL) was added Fe (103.64 mg, 1.860 mmol, 10 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 70

°C under air atmosphere. Desired product could be detected by LCMS. After cooling down to rt, the reaction was quenched with water (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford (R)-7-amino-4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b] [1,4]oxazine-6-carbonitrile (40 mg, 58.78%) as a yellow oil. LC/MS: mass calcd for $C_{17}H_{15}N_3O_2$: 293.12, found:294.05 $[M+H]^+$.

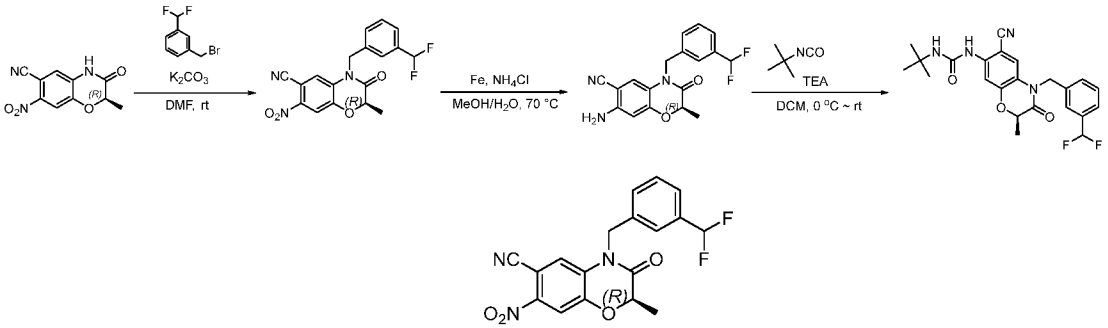


(R)-1-(4-benzyl-6-cyano-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4] oxazin-7-yl)-3-(tert-butyl)urea

To a stirred solution of (R)-7-amino-4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b] [1,4] oxazine-6-carbonitrile (35 mg, 0.119 mmol, 1 equiv) and 2-isocyanato-2-methylpropane (35.49 mg, 0.357 mmol, 3 equiv) in DCM (3 mL) was added TEA (36.22 mg, 0.357 mmol, 3 equiv) in portions at 0 °C under air atmosphere. The resulting mixture was stirred for 4 h at room temperature under air atmosphere. Desired product could be detected by LCMS. The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (30 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C_{18} OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water (10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min mL/min; Gradient: 50% B to 80% B in7min; Wave Length: 254nm nm; RT1(min): 5.9; Number Of Runs: 2) to afford (R)-1-(4-benzyl-6-cyano-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b] [1,4] oxazin-7-yl)-3-(tert-butyl)urea (23.2 mg, 49.12%) as a white solid. LC/MS: mass calcd for $C_{22}H_{24}N_4O_3$: 392.18, found: 391.00 $[M-H]^-$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 7.83 (s, 1H), 7.20 – 7.49 (m, 6H), 6.97 (s, 1H), 5.20(s, 2H), 4.10 – 5.08 (m, 1H), 1.45 – 1.61 (m, 3H), 1.28-1.38 (m, 9H).

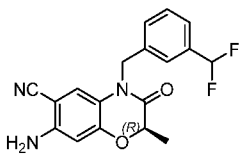
Example 342: (R)-1-(tert-butyl)-3-(6-cyano-4-(3-(difluoromethyl)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

Synthetic Scheme



(R)-4-(3-(difluoromethyl) benzyl)-2-methyl-7-nitro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile

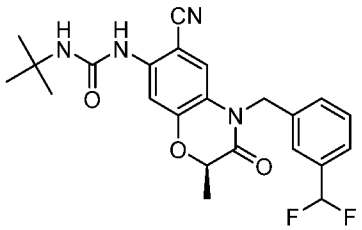
To a stirred solution of (2R)-2-methyl-7-nitro-3-oxo-2,4-dihydro-1,4-benzoxazine-6-carbonitrile (91.35 mg, 0.392 mmol, 1 equiv) and 1-(bromomethyl)-3-(difluoromethyl) benzene (129.89 mg, 0.588 mmol, 1.5 equiv) in DMF (4 mL) was added K_2CO_3 (163.61 mg, 1.176 mmol, 3 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 1 h at room temperature under air atmosphere. Desired product could be detected by LCMS. The reaction was quenched with water (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford (R)-4-(3-(difluoromethyl) benzyl) -2-methyl-7-nitro-3-oxo-3,4-dihydro-2H-benzo[b] [1,4] oxazine-6-carbonitrile (51 mg, 34.87%) as a yellow oil. LC/MS: mass calcd for $C_{18}H_{13}F_2N_3O_4$: 373.09, found 374.05 $[M+H]^+$.



(R)-7-amino-4-(3-(difluoromethyl) benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile

To a stirred mixture of (R)-4-(3-(difluoromethyl) benzyl) -2-methyl-7-nitro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile (50 mg, 0.134 mmol, 1 equiv) and Fe (74.80 mg, 1.340 mmol, 10 equiv) in MeOH/H_2O (10:1, 3 mL) was added NH_4Cl (71.64 mg, 1.340 mmol, 10 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 70 °C under air atmosphere. Desired product could be detected by LCMS. After cooling down to

rt, the reaction was quenched with water (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford (R)-7-amino-4-(3-(difluoromethyl) benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b] [1,4] oxazine-6-carbonitrile (32 mg, 69.59%) as a yellow oil. LC/MS: mass calcd. for $C_{18}H_{15}F_2N_3O_2$: 343.11, found: 344.15 $[M+H]^+$.

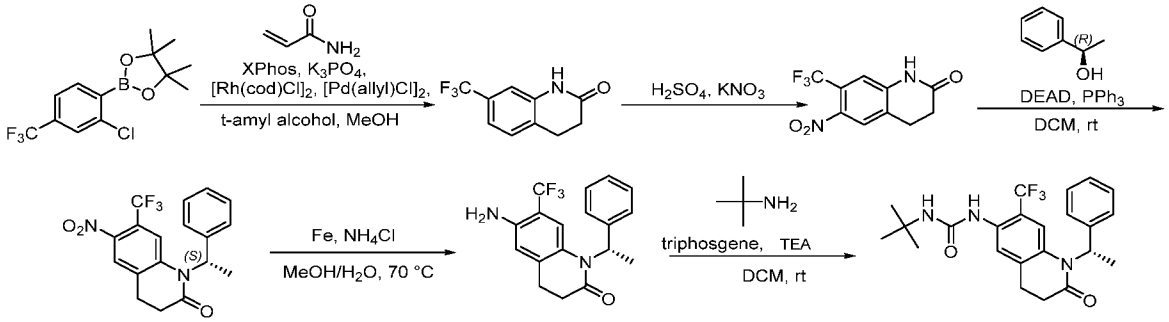


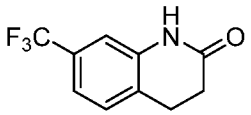
(R)-1-(tert-butyl)-3-(6-cyano-4-(3- (difluoromethyl)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4] oxazin-7-yl)urea

To a stirred solution of (R)-7-amino-4-(3-(difluoromethyl) benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b] [1,4] oxazine-6-carbonitrile (25 mg, 0.081 mmol, 1 equiv) and 2-isocyanato-2-methylpropane (24.19 mg, 0.243 mmol, 3 equiv) in DCM (2 mL) was added TEA (24.69 mg, 0.243 mmol, 3 equiv) and in portions at 0 °C under air atmosphere. The resulting mixture was stirred for 4 h at room temperature under air atmosphere. Desired product could be detected by LCMS. The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (20 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C_{18} OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water (10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min mL/min; Gradient: 50% B to 80% B in 7min ; Wave Length: 254 nm ; RT1(min): 5.9; Number of Runs: 2) to afford (R)-1-(tert-butyl)-3-(6-cyano-4-(3-(difluoromethyl) benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b] [1,4] oxazin-7-yl) urea (10 mg, 30.04%) as a white solid. LC/MS: mass calcd for $C_{23}H_{24}F_2N_4O_3$: 442.18, found: 441.05 $[M-H]^-$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 1H), 7.84 (s, 1H), 7.45 – 7.61 (m, 3H), 7.38 - 7.46(m, 2H), 6.82 - 7.20(*d*, *J* = 10.7 Hz,2H), 5.21 (s, 2H), 4.93 - 5.08 (q, *J* = 6.7 Hz, 1H), 1.48 - 1.60(d, *J* = 6.8 Hz, 3H), 1.49 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ -109.72.

Example 343: (S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-7-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl) urea

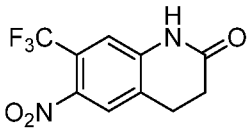
Synthetic Scheme





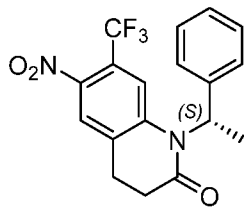
7-(trifluoromethyl)-3,4-dihydro-1H-quinolin-2-one

To a stirred solution of 2-[2-chloro-4-(trifluoromethyl) phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1 g, 3.262 mmol, 1 equiv) and polyacrylamide (0.23 g, 3.262 mmol, 1 equiv), XPhos (0.62 g, 1.305 mmol, 0.4 equiv) in t-AmOH (10 mL)/MeOH (1 mL) were added K_3PO_4 (1.52 g, 7.176 mmol, 2.2 equiv), $[Rh(COD)Cl]_2$ (0.16 g, 0.326 mmol, 0.1 equiv) and $[PdCl(allyl)]_2$ (0.12 g, 0.326 mmol, 0.1 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 110 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 7-(trifluoromethyl)-3,4-dihydro-1H-quinolin-2-one (610 mg, 86.90%) as a yellow oil. MS (ESI): mass calcd. For $C_{10}H_8F_3NO$: 215.06 m/z, found 216.20 $[M+H]^+$.



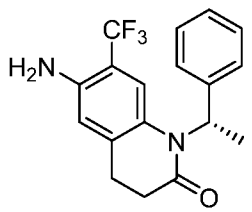
6-nitro-7-(trifluoromethyl)-3,4-dihydro-1H-quinolin-2-one

A solution of 7-(trifluoromethyl)-3,4-dihydro-1H-quinolin-2-one (580 mg, 2.695 mmol, 1 equiv) and KNO_3 (272.52 mg, 2.695 mmol, 1 equiv) in H_2SO_4 (5 mL) was stirred for 2 h at room temperature under air atmosphere. The reaction was quenched with water/ice at 0°C. The precipitated solids were collected by filtration and washed with H_2O (3x20 mL). The crude product was used in the next step directly without further purification. This resulted in 6-nitro-7-(trifluoromethyl)-3,4-dihydro-1H-quinolin-2-one (570 mg, 81.28%) as a yellow solid.



6-nitro-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)-3,4-dihydroquinolin-2-one

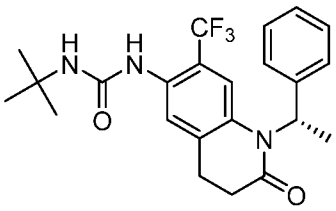
To a stirred solution of 6-nitro-7-(trifluoromethyl)-3,4-dihydro-1H-quinolin-2-one (200 mg, 0.769 mmol, 1 equiv) and 1-phenyl-ethanol (93.91 mg, 0.769 mmol, 1 equiv) in DCM (5 mL) was added PPh_3 (302.44 mg, 1.153 mmol, 1.5 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. To the above mixture was added DEAD (200.82 mg, 1.153 mmol, 1.5 equiv) dropwise over 1 min at 0 °C. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 6-nitro-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)-3,4-dihydroquinolin-2-one (190 mg, 67.84%) as a yellow oil. MS (ESI): mass calcd. for $C_{18}H_{15}F_3N_2O_3$: 364.10 m/z, found 365.05 $[M+H]^+$.



6-amino-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)-3,4-dihydroquinolin-2-one

To a stirred solution of 6-nitro-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)-3,4-dihydroquinolin-2-one (190 mg, 0.522 mmol, 1 equiv) and Fe (291.24 mg, 5.220 mmol, 10 equiv) in MeOH (5 mL)/H_2O (0.5 mL) was added NH_4Cl (278.96 mg, 5.220 mmol, 10 equiv) in portions at room

temperature under air atmosphere. The resulting mixture was stirred for 1 h at 80 °C under air atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 6-amino-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)-3,4-dihydroquinolin-2-one (50 mg, 28.68%) as a yellow oil. MS (ESI): mass calcd. for $C_{18}H_{17}F_3N_2O$: 334.13 m/z, found 335.25 $[M+H]^+$.

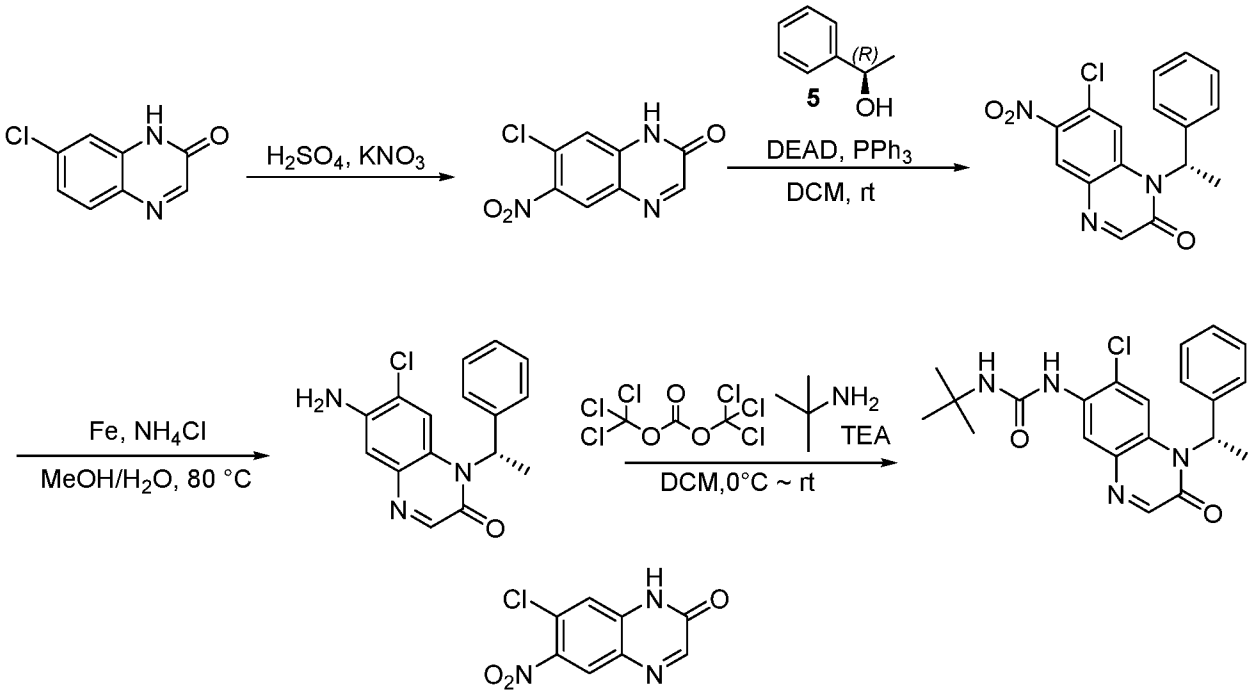


3-tert-butyl-1-{2-oxo-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)-3,4-dihydroquinolin-6-yl} urea

A solution of 6-amino-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)-3,4-dihydroquinolin-2-one (30 mg, 0.090 mmol, 1 equiv) in DCM (5 mL) was treated with triphosgene (26.89 mg, 0.090 mmol, 1 equiv) for 1 h at 0°C under nitrogen atmosphere followed by the addition of TEA (45.40 mg, 0.450 mmol, 5 equiv) dropwise at 0°C. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. To the above mixture was added erbumine (19.69 mg, 0.270 mmol, 3 equiv) dropwise over 1 min at room temperature. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column 150 mm x 30 mm x 5 μm column (eluent: 42% to 54% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$) to afford 3-tert-butyl-1-{2-oxo-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)-3,4-dihydroquinolin-6-yl} urea (18.8 mg, 48.14%) as a white solid. MS (ESI): mass calcd. for $C_{23}H_{26}F_3N_3O_2$: 433.20 m/z, found 434.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 7.76 (s, 1H), 7.49 (s, 1H), 7.21 – 7.45 (m, 5H), 7.75 – 7.89 (m, 1H), 6.62 – 7.75 (m, 1H), 6.28 (q, J = 7.0 Hz, 1H), 2.93 (d, J = 6.7 Hz, 2H), 2.62 – 2.75 (m, 2H), 1.62 – 1.85 (m, 3H), 1.15 – 1.35 (m, 9H).^{19}F NMR (282 MHz, DMSO) δ -59.825.

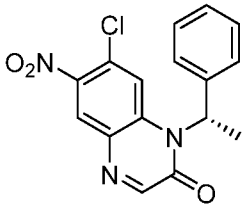
Example 344: (S)-1-(tert-butyl)-3-(7-chloro-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea

Synthetic Scheme



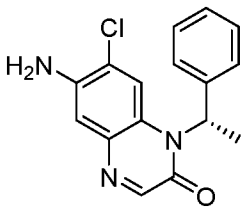
7-chloro-6-nitroquinoxalin-2(1H)-one

To a solution of 7-chloro-1H-quinoxalin-2-one (1 g, 5.537 mmol, 1 equiv) in H_2SO_4 (10 mL) was added KNO_3 (0.56 g, 5.537 mmol, 1 equiv) at 0°C. The reaction was stirred at 0 °C for 0.5h. Then, the resulting mixture was stirred for 1h at 0°C. The reaction was quenched with water/Ice at 0°C. Quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-chloro-6-nitro-1H-quinoxalin-2-one (300 mg, 24.02%) as a yellow solid. LC/MS: mass calcd. for $C_8H_4ClN_3O_3$:224.99 m/z, found:226.00 $[M+H]^+$.



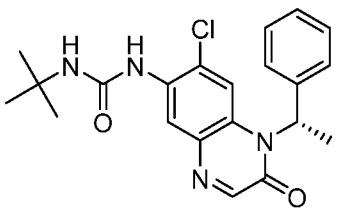
(S)-7-chloro-6-nitro-1-(1-phenylethyl)quinoxalin-2(1H)-one

To a solution of 7-chloro-6-nitro-1H-quinoxalin-2-one (300 mg, 1.330 mmol, 1 equiv) in DCM (10 mL) was added (R)-1-phenylethan-1-ol (162.46 mg, 1.330 mmol, 1 equiv) and PPh_3 (523.21 mg, 1.995 mmol, 1.5 equiv). The reaction was stirred at rt under N_2 for 0.5h. To the above mixture was added DEAD (347.40 mg, 1.995 mmol, 1.5 equiv) at 0°C under N_2. The resulting mixture was stirred for additional 1h at rt. Quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-chloro-6-nitro-1-[(1S)-1-phenylethyl]quinoxalin-2-one (70 mg, 15.96%) as a yellow solid. LC/MS: mass calcd. for $C_{16}H_{12}ClN_3O_3$:329.06 m/z, found:330.10 $[M+H]^+$.



(S)-6-amino-7-chloro-1-(1-phenylethyl)quinoxalin-2(1H)-one

To a solution of 7-chloro-6-nitro-1-[(1S)-1-phenylethyl]quinoxalin-2-one (60 mg, 0.182 mmol, 1 equiv) in MeOH (5 mL) and H_2O (0.5 mL) was added Fe (101.62 mg, 1.820 mmol, 10 equiv) and NH_4Cl (97.33 mg, 1.820 mmol, 10 equiv). The reaction was stirred at 80 °C for 1h. The mixture was allowed to cool down to rt. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 30 mL). The filtrate was concentrated under reduced pressure. Diluted with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-7-chloro-1-[(1S)-1-phenylethyl]quinoxalin-2-one (40 mg, 73.33%) as a yellow solid. LC/MS: mass calcd. for $C_{16}H_{14}ClN_3O$:299.08 m/z, found:300.00 $[M+H]^+$.



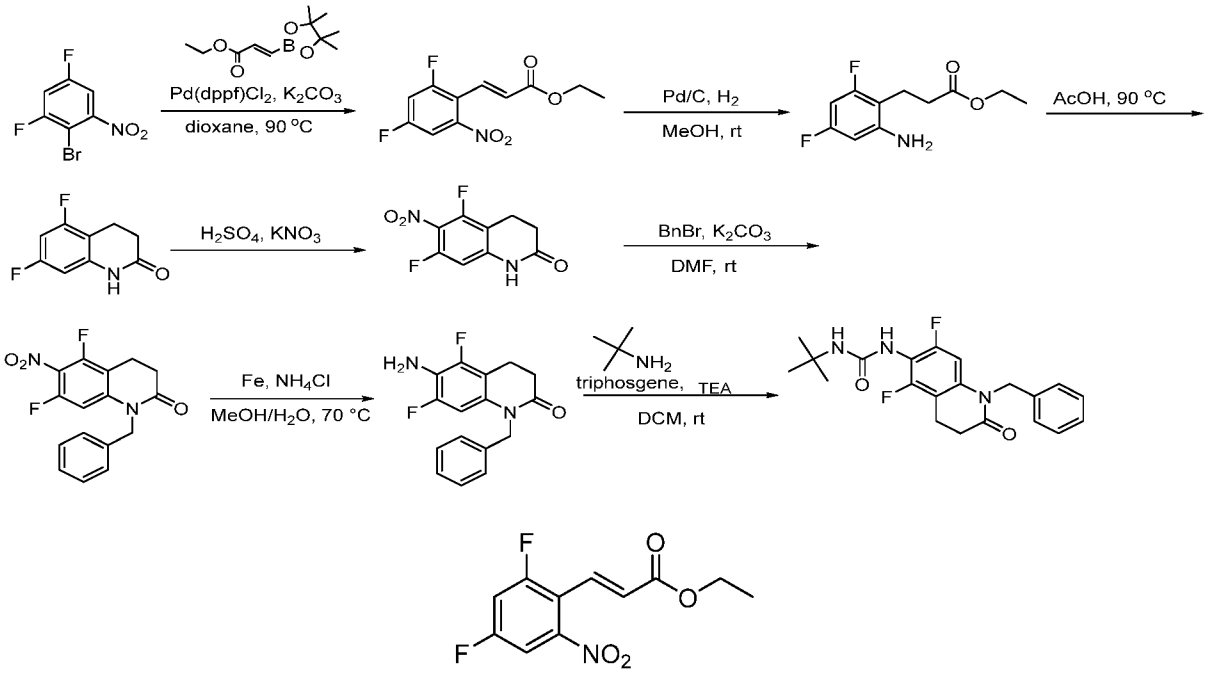
(S)-1-(tert-butyl)-3-(7-chloro-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea

To a solution of 6-amino-7-chloro-1-[(1S)-1-phenylethyl]quinoxalin-2-one (30 mg, 0.100 mmol, 1 equiv) in DCM (5 mL) was added triphosgene (29.70 mg, 0.100 mmol, 1 equiv) under N_2 at 0

°C. The reaction was stirred at 0 °C under N_2 for 1h. To the above mixture was added TEA (30.38 mg, 0.300 mmol, 3 equiv) at 0°C. The resulting mixture was stirred for additional 1h at rt. Then, to the above mixture was added erbumine (31.32 mg, 0.429 mmol, 3 equiv). The resulting mixture was stirred for additional 1h at rt. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm column (eluent: 38% to 68% (v/v) CH_3CN and Water (10mmol/L NH_4HCO_3+0.05%$NH_3.H_2O$)) to afford the title compound 3-tert-butyl-1-{7-chloro-2-oxo-1-[(1S)-1-phenylethyl]quinoxalin-6-yl}urea (15.7 mg, 38.63%) as a yellow solid. LC/MS: mass calcd. for $C_{21}H_{23}ClN_4O_2$:398.15 m/z, found:399.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.27 (s, 1H), 7.97 (s, 1H), 7.33 – 7.41 (m, 2H), 7.25 – 7.33 (m, 3H), 7.23 (s, 1H), 6.94 (s, 1H), 6.53 (d, J = 7.5 Hz, 1H), 1.87 (d, J = 7.1 Hz, 3H), 1.30 (s, 9H).

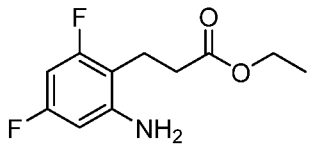
Example 345: 1-(1-benzyl-5,7-difluoro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl) urea

Synthetic Scheme



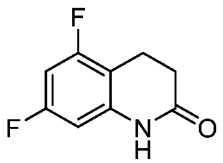
ethyl (2E)-3-(2,4-difluoro-6-nitrophenyl) prop-2-enoate

To a stirred solution of 2-bromo-1,5-difluoro-3-nitrobenzene (2 g, 8.404 mmol, 1 equiv) and ethyl (2E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) prop-2-enoate (2.28 g, 10.085 mmol, 1.2 equiv) in 1,4-dioxane (50 mL)/H_2O (5 mL) was added Pd(dppf)Cl_2 (0.68 g, 0.840 mmol, 0.1 equiv) and K_2CO_3 (2.32 g, 16.808 mmol, 2 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 90 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford ethyl (2E)-3-(2,4-difluoro-6-nitrophenyl) prop-2-enoate (1.81 g, 83.74%) as a white oil. MS (ESI): mass calcd. For $C_{11}H_9F_2NO_4$: 257.05 m/z, found 258.15$[M+H]^+$.



ethyl 3-(2-amino-4,6-difluorophenyl) propanoate

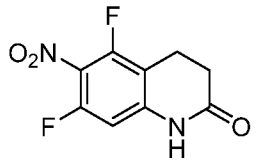
A mixture of ethyl (2E)-3-(2,4-difluoro-6-nitrophenyl) prop-2-enoate (1.81 g, 7.038 mmol, 1 equiv) and Pd/C (600 mg, 5.638 mmol, 0.80 equiv) in MeOH (10 mL) was stirred for 1 h at room temperature under hydrogen atmosphere. The resulting mixture was filtered, and the filter cake was washed with MeOH (5 x 20 mL). The filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. This resulted in ethyl 3-(2-amino-4,6-difluorophenyl) propanoate (1.5 g, 92.98%) as a black oil. MS (ESI): mass calcd. For $C_{11}H_{13}F_2NO_2$: 229.09 m/z, found 230.20$[M+H]^+$.



5,7-difluoro-3,4-dihydro-1H-quinolin-2-one

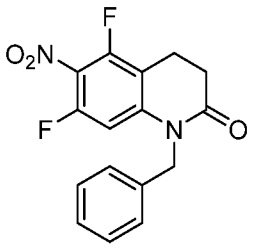
A solution of ethyl 3-(2-amino-4,6-difluorophenyl) propanoate (1.57 g, 6.849 mmol, 1 equiv) in AcOH (20 mL) was stirred for 1 h at 90 °C under air atmosphere. The resulting mixture was concentrated under reduced pressure. The mixture was neutralized to pH = 7 with saturated $NaHCO_3$ (aq.). The residue was purified by silica gel column chromatography, eluted with PE /

EA (1:1) to afford 5,7-difluoro-3,4-dihydro-1H-quinolin-2-one (1.1 g, 87.69%) as a yellow oil. MS (ESI): mass calcd. for $C_9H_7F_2NO$: 183.05 m/z, found 184.25 $[M+H]^+$.



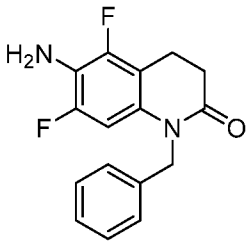
5,7-difluoro-6-nitro-3,4-dihydro-1H-quinolin-2-one

A solution of 5,7-difluoro-3,4-dihydro-1H-quinolin-2-one (800 mg, 4.368 mmol, 1 equiv) and KNO_3 (441.59 mg, 4.368 mmol, 1 equiv) in H_2SO_4 (10 mL) was stirred for 1 h at room temperature under air atmosphere. The reaction was quenched with water/ice at 0 °C. The precipitated solids were collected by filtration and washed with H_2O (3x20 mL). The crude product was used in the next step directly without further purification. This resulted in 5,7-difluoro-6-nitro-3,4-dihydro-1H-quinolin-2-one (790 mg, 79.27%) as a yellow oil. MS (ESI): mass calcd. for $C_9H_6F_2N_2O_3$: 228.03 m/z, found 229.15 $[M+H]^+$.



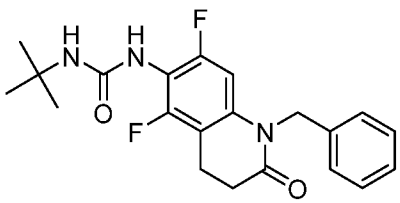
1-benzyl-5,7-difluoro-6-nitro-3,4-dihydroquinolin-2-one

To a stirred solution of 5,7-difluoro-6-nitro-3,4-dihydro-1H-quinolin-2-one (500 mg, 2.191 mmol, 1 equiv) and BnBr (374.83 mg, 2.191 mmol, 1 equiv) in DMF (5 mL) was added K_2CO_3 (605.75 mg, 4.382 mmol, 2 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 1 h at room temperature under air atmosphere. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 1-benzyl-5,7-difluoro-6-nitro-3,4-dihydroquinolin-2-one (200 mg, 28.67%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{12}F_2N_2O_3$: 318.08 m/z, found 319.20 $[M+H]^+$.



6-amino-1-benzyl-5,7-difluoro-3,4-dihydroquinolin-2-one

To a stirred solution of 1-benzyl-5,7-difluoro-6-nitro-3,4-dihydroquinolin-2-one (150 mg, 0.471 mmol, 1 equiv) and Fe (263.19 mg, 4.710 mmol, 10 equiv) in MeOH (5 mL)/H_2O (0.5 mL) was added NH_4Cl (252.09 mg, 4.710 mmol, 10 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 1 h at 80 °C under air atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 6-amino-1-benzyl-5,7-difluoro-3,4-dihydroquinolin-2-one (120 mg, 88.32%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{14}F_2N_2O$: 288.11 m/z, found 289.25 $[M+H]^+$.



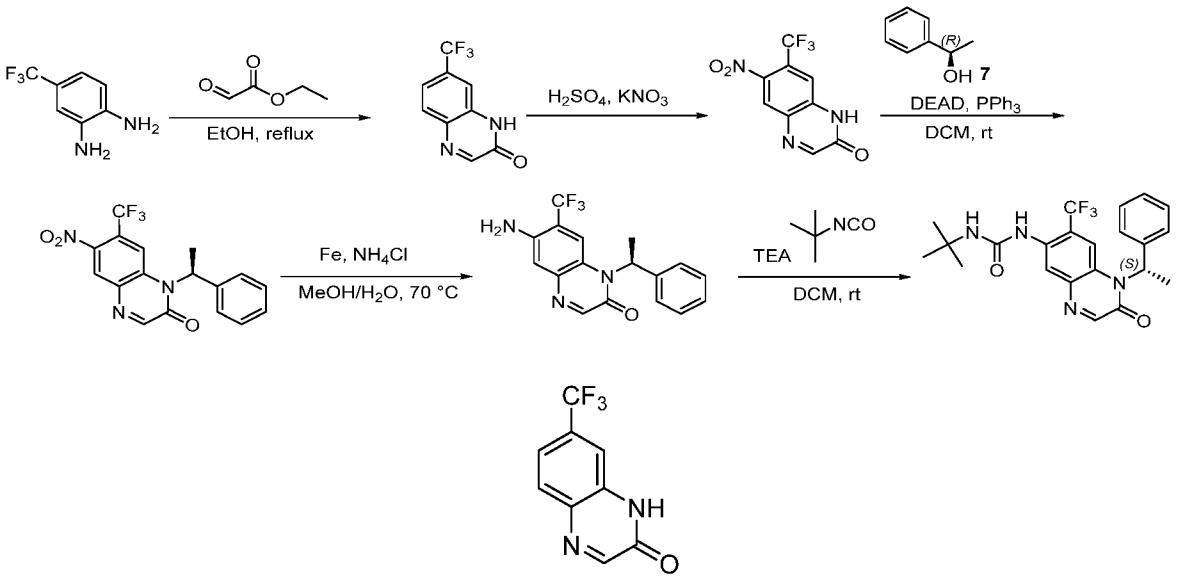
1-(1-benzyl-5,7-difluoro-2-oxo-3,4-dihydroquinolin-6-yl)-3-tert-butylurea

A solution of 6-amino-1-benzyl-5,7-difluoro-3,4-dihydroquinolin-2-one (110 mg, 0.382 mmol, 1 equiv) in DCM (5 mL) was treated with triphosgene (113.22 mg, 0.382 mmol, 1 equiv) for 1 h at 0 °C under nitrogen atmosphere followed by the addition of TEA (193.05 mg, 1.910 mmol, 5 equiv) dropwise at 0 °C. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. To the above mixture was added erbumine (67.66 mg, 1.146 mmol, 3 equiv) dropwise over 1 min at room temperature. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced

pressure. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column 150 mm x 30 mm x 5 μm column (eluent: 40% to 50% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$) to afford 1-(1-benzyl-5,7-difluoro-2-oxo-3,4-dihydroquinolin-6-yl)-3-tert-butylurea (52.7 mg, 35.36%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{23}F_2N_3O_2$: 387.18 m/z, found 388.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 7.40 (s, 1H), 7.28 – 7.38 (m, 2H), 7.24 (td, J = 4.9, 2.8 Hz, 3H), 6.72 (dd, J = 12.0, 1.8 Hz, 1H), 6.11 (s, 1H), 5.16 (s, 2H), 2.91 (t, J = 7.4 Hz, 2H), 2.73 (dd, J = 8.7, 6.1 Hz, 2H), 1.20 – 1.30 (m, 9H). ^{19}F NMR (282 MHz, DMSO) δ -120.687, -123.203.

Example 346: 3-tert-butyl-1-{2-oxo-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)quinoxalin-6-yl}urea

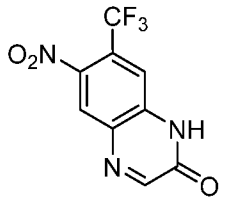
Synthetic Scheme



Synthesis of 7-(trifluoromethyl)-1H-quinoxalin-2-one

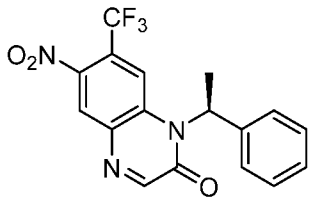
To a stirred solution of 4-(trifluoromethyl)benzene-1,2-diamine (2 g, 11.354 mmol, 1 equiv) in EtOH(20 mL) was added ethyl glyoxylate (1.16 g, 11.354 mmol, 1 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 3 h at 60 ℃ under air atmosphere.The reaction was monitored by LCMS. Quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 7-(trifluoromethyl)-1H-quinoxalin-2-

one (1 g, 41.13%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_9H_5F_3N_2O$:214.04 m/z, found:215.0 $[M+H]^+$.



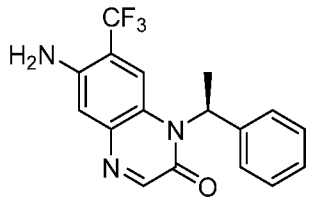
Synthesis of 6-nitro-7-(trifluoromethyl)-1H-quinoxalin-2-one

To a stirred solution of 7-(trifluoromethyl)-1H-quinoxalin-2-one (1 g, 4.670 mmol, 1 equiv) in H_2SO_4 (10 mL) was added KNO_3 (1.42 g, 14.010 mmol, 3 equiv) in portions at 0 °C under air atmosphere. The resulting mixture was stirred for 2 h at room temperature under air atmosphere. The reaction was monitored by LCMS. The reaction was quenched with water/Ice at 0 °C. The precipitated solids were collected by filtration and washed with H_2O (3x20 mL). The crude product was used in the next step directly without further purification. This resulted in 6-nitro-7-(trifluoromethyl)-1H-quinoxalin-2-one (600 mg, 49.58%) as a brown solid.LC/MS (ESI): mass calcd. for $C_9H_4F_3N_3O_3$:259.02 m/z, found:260.0 $[M+H]^+$.



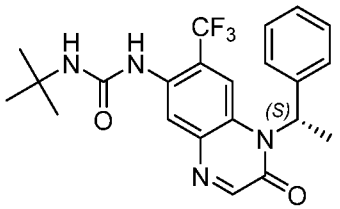
Synthesis of 6-nitro-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)quinoxalin-2-one

To a stirred solution of 6-nitro-7-(trifluoromethyl)-1H-quinoxalin-2-one (590 mg, 2.277 mmol, 1 equiv) and 1-phenyl-ethanol (278.14 mg, 2.277 mmol, 1 equiv) in DCM (6 mL) was added PPh_3 (895.75 mg, 3.416 mmol, 1.5 equiv) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 15 min at room temperature under nitrogen atmosphere. To the above mixture was added DEAD (594.76 mg, 3.416 mmol, 1.5 equiv) in portions at 0 °C. The resulting mixture was stirred for additional 2 h at room temperature. The reaction was monitored by LCMS. Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 6-nitro-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)quinoxalin-2-one (100 mg, 12.09%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{17}H_{12}F_3N_3O_3$:363.0 m/z, found:364.0 $[M+H]^+$.



Synthesis of 6-amino-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)quinoxalin-2-one

To a stirred solution of 6-nitro-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)quinoxalin-2-one (90 mg, 0.248 mmol, 1 equiv) in MeOH/H_2O(10:1,1.1 mL) was added Fe (15.37 mg, 0.280 mmol, 10 equiv) and NH_4Cl (132.51 mg, 2.480 mmol, 10 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 70 °C under air atmosphere. The reaction was monitored by LCMS. After cooling down to rt, the reaction was quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 6-amino-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)quinoxalin-2-one (30 mg, 36.33%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{17}H_{14}F_3N_3O$:333.1 m/z, found:334.1 $[M+H]^+$.



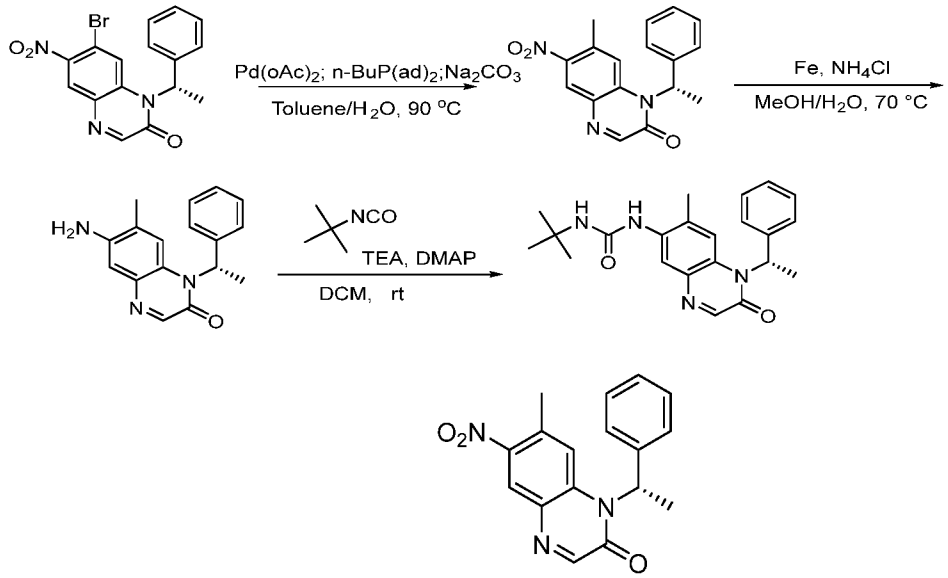
Synthesis of 3-tert-butyl-1-{2-oxo-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)quinoxalin-6-yl}urea

To a stirred solution of 6-amino-7-methyl-1-[(1S)-1-phenylethyl]quinoxalin-2-one (40 mg, 0.143 mmol, 1 equiv) in DCM(0.5 mL) was added TEA (22.77 mg, 0.225 mmol, 3 equiv) and 2-isocyanato-2-methylpropane (22.31 mg, 0.225 mmol, 3 equiv) at room temperature under air atmosphere. The resulting mixture was stirred for 1 days at room temperature under air atmosphere. The reaction was monitored by LCMS. Quenched with water (5 mL) and extracted with DCM (3 x 5 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by Prep-HPLC using a X Bridge Prep OBD C18 150 mm x 30 mm x 5 μm column (eluent: 42% to 72% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford 3-tert-butyl-1-{7-methyl-2-oxo-1-[(1S)-1-phenylethyl]quinoxalin-6-yl}urea (2.7 mg, 4.96%) as a yellow solid. LC/MS (ESI): mass

calcd. for $C_{22}H_{23}F_3N_4O_2$:432.2 m/z, found:433.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.34 (s, 1H), 7.65 (s, 1H), 7.37 – 7.31 (m, 6H), 6.90 (s, 1H), 6.62 (q, J = 7.2 Hz, 1H), 1.86 (d, J = 7.2 Hz, 3H), 1.28 (s, 9H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.29.

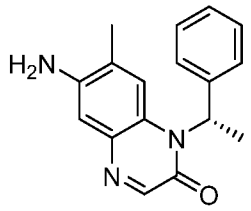
Example 347: 3-tert-butyl-1-{7-methyl-2-oxo-1-[(1S)-1-phenylethyl]quinoxalin-6-yl}urea

Synthetic Scheme



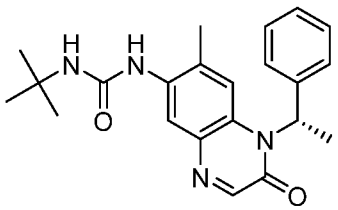
7-methyl-6-nitro-1-[(1S)-1-phenylethyl]quinoxalin-2-one

To a stirred solution of 7-bromo-6-nitro-1-[(1S)-1-phenylethyl]quinoxalin-2-one (200 mg, 0.534 mmol, 1 equiv) and methylboronic acid (63.99 mg, 1.068 mmol, 2 equiv) in toluene/H_2O(7:1, 2.4 mL) was added $Pd(OAc)_2$ (24.00 mg, 0.107 mmol, 0.2 equiv), Butyldi-1-adamantylphosphine (1.92 mg, 0.005 mmol, 0.2 equiv) and Na_2CO_3 (169.95 mg, 1.602 mmol, 3 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 90 °C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 7-methyl-6-nitro-1-[(1S)-1-phenylethyl]quinoxalin-2-one (100 mg, 60.49%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{17}H_{15}N_3O_3$:309.1 m/z, found:310.0 $[M+H]^+$.



6-amino-7-methyl-1-[(1S)-1-phenylethyl]quinoxalin-2-onee

To a stirred solution of 7-methyl-6-nitro-1-[(1S)-1-phenylethyl]quinoxalin-2-one (90 mg, 0.291 mmol, 1 equiv) in MeOH/H_2O(10:1, 1.1 mL) was added Fe (18.05 mg, 0.320 mmol, 10 equiv) and NH_4Cl (155.63 mg, 2.910 mmol, 10 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 70 °C under air atmosphere. The reaction was monitored by LCMS. After cooling down to rt, quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated.The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 6-amino-7-methyl-1-[(1S)-1-phenylethyl]quinoxalin-2-one (70 mg, 86.13%) as a yellow solid.LC/MS (ESI): mass calcd. for $C_{17}H_{17}N_3O$:279.14 m/z, found:280.1 $[M+H]^+$.



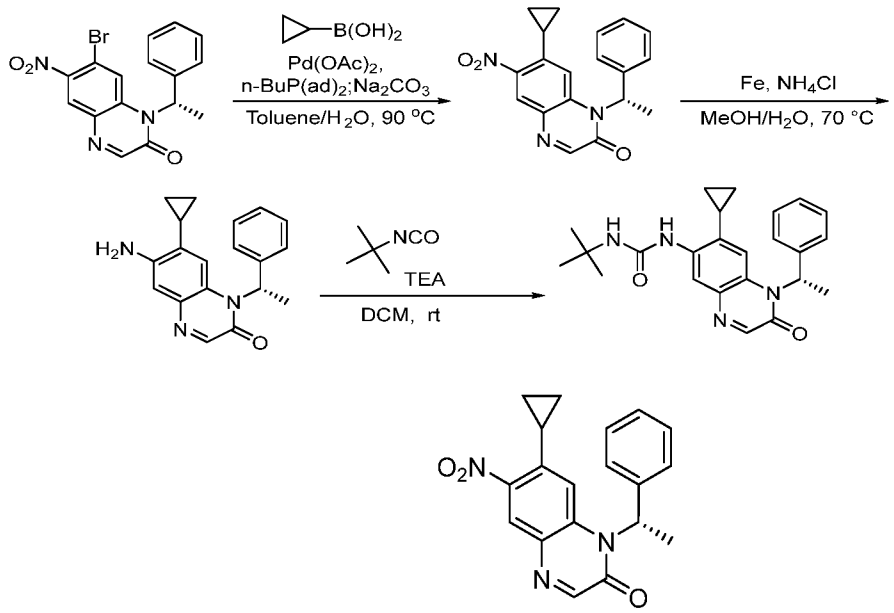
3-tert-butyl-1-{7-methyl-2-oxo-1-[(1S)-1-phenylethyl]quinoxalin-6-yl}urea

To a stirred solution of 6-amino-7-methyl-1-[(1S)-1-phenylethyl]quinoxalin-2-one (80 mg, 0.286 mmol, 1 equiv) in DCM (1 mL) was added 2-isocyanato-2-methylpropane (85.17 mg, 0.858 mmol, 3 equiv) and TEA (86.94 mg, 0.858 mmol, 3 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 1 days at room temperature under air atmosphere. The reaction was monitored by LCMS. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by Prep-HPLC using XSelect CSH Fluoro Pheny 250 mm x 19 mm x 5 μm column (eluent: 38% to 68% (v/v) CH_3CN and H_2O with 0.1% FA) to afford 3-tert-butyl-1-{7-methyl-2-oxo-1-[(1S)-1-phenylethyl]quinoxalin-6-yl}urea (4.1 mg, 3.76%) as a yellow solid.LC/MS (ESI): mass calcd. for $C_{22}H_{26}N_4O_2$:378.2 m/z, found:379.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.18 (s, 1H), 7.56 (s, 1H),

7.37 – 7.24 (m, 5H), 7.07 (s, 1H), 6.55 (d, J = 8.4 Hz, 2H), 2.12 (s, 3H), 1.89 (d, J = 6.9 Hz, 3H), 1.29 (s, 9H).

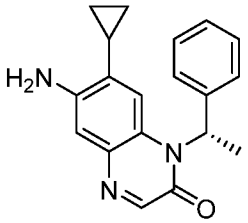
Example 348: 3-tert-butyl-1-{7-cyclopropyl-2-oxo-1-[(1S)-1-phenylethyl]quinoxalin-6-yl}urea

Synthetic Scheme



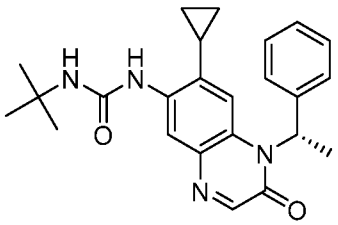
7-cyclopropyl-6-nitro-1-[(1S)-1-phenylethyl]quinoxalin-2-one

To a stirred solution of 7-bromo-6-nitro-1-[(1S)-1-phenylethyl]quinoxalin-2-one (200 mg, 0.534 mmol, 1 equiv) and cyclopropylboronic acid (229.56 mg, 2.670 mmol, 5 equiv) in toluene/H_2O (7:1, 2.4 mL) were added Na_2CO_3 (169.95 mg, 1.602 mmol, 3 equiv), $Pd(OAc)_2$ (24.00 mg, 0.107 mmol, 0.2 equiv) and Butyldi-1-adamantylphosphine (38.33 mg, 0.107 mmol, 0.2 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 90 °C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 7-cyclopropyl-6-nitro-1-[(1S)-1-phenylethyl]quinoxalin-2-one as a yellow solid. LC/MS (ESI): mass calcd. for $C_{19}H_{17}N_3O_3$:335.13 m/z, found:336.0 $[M+H]^+$.



6-amino-7-cyclopropyl-1-[(1S)-1-phenylethyl]quinoxalin-2-one

To a stirred solution of 7-cyclopropyl-6-nitro-1-[(1S)-1-phenylethyl]quinoxalin-2-one (90 mg, 0.268 mmol, 1 equiv) in MeOH/H_2O (10:1, 1.1 mL) was added Fe (16.65 mg, 0.300 mmol, 10 equiv) and NH_4Cl (143.55 mg, 2.680 mmol, 10 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 70 °C under air atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. Quenched with water (8 mL) and extracted with EA (3 x 8 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 6-amino-7-cyclopropyl-1-[(1S)-1-phenylethyl]quinoxalin-2-one (80 mg, 97.62%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{19}H_{19}N_3O$:305.15 m/z, found:306.05 $[M+H]^+$.



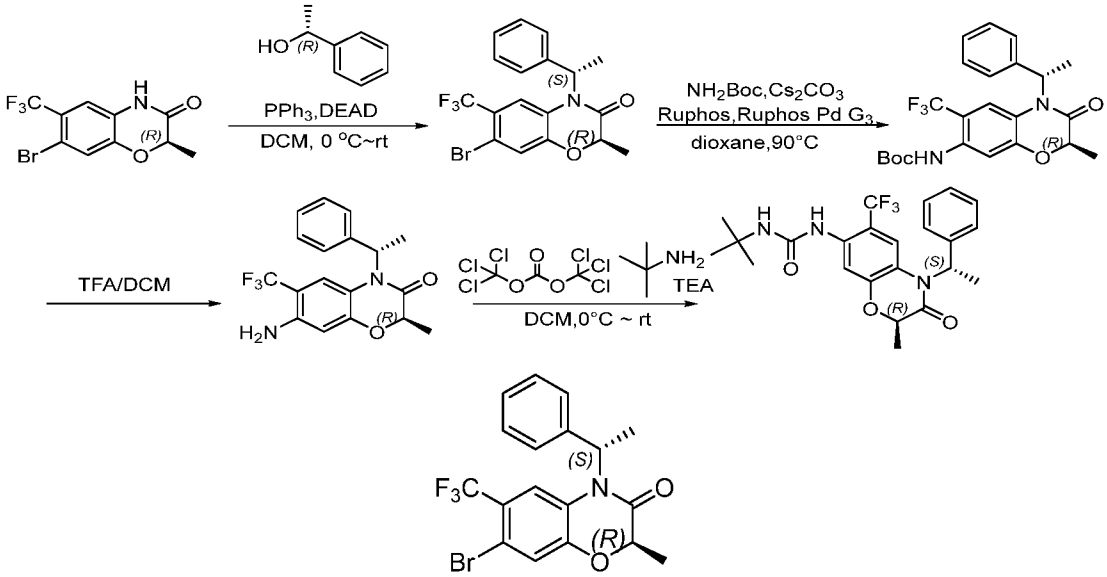
Synthesis of 3-tert-butyl-1-{7-cyclopropyl-2-oxo-1-[(1S)-1-phenylethyl]quinoxalin-6-yl}urea

To a stirred solution of 6-amino-7-cyclopropyl-1-[(1S)-1-phenylethyl]quinoxalin-2-one (80 mg, 0.262 mmol, 1 equiv) and TEA (79.53 mg, 0.786 mmol, 3 equiv) in DCM (1 mL) was added 2-isocyanato-2-methylpropane (77.91 mg, 0.786 mmol, 3 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 1 days at room temperature under air atmosphere. The reaction was monitored by LCMS. Quenched with water (8 mL) and extracted with DCM (3 x 8 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by Prep-HPLC using a X Bridge Prep OBD C18 150 mm x 30 mm x 5 μm column (eluent: 36% to 46% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford 3-tert-butyl-1-{7-cyclopropyl-2-oxo-1-[(1S)-1-phenylethyl]quinoxalin-6-yl}urea (16.7 mg, 15.65%) as a yellow solid. LC/MS (ESI):

mass calcd. for $C_{24}H_{28}N_4O_2$:404.2 m/z, found:405.2 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.21 (s, 1H), 7.71 (s, 1H), 7.40 – 7.36 (m, 2H), 7.35 – 7.26 (m, 3H), 6.64 (s, 2H), 6.52 (s, 1H), 1.84 (d, J = 7.2 Hz, 3H), 1.80 – 1.75 (m, 1H), 1.30 (s, 9H), 0.90 – 0.87 (m, 2H), 0.28 – 0.01 (m, 2H).

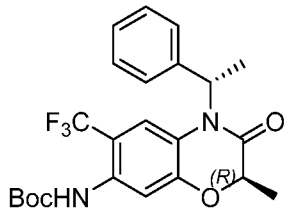
Example 349: 1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

Synthetic Scheme



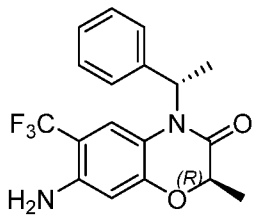
(R)-7-bromo-2-methyl-4-((S)-1-phenylethyl)-6-(trifluoromethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-7-bromo-2-methyl-6-(trifluoromethyl)-2,4-dihydro-1,4-benzoxazin-3-one (350 mg, 1.129 mmol, 1 equiv) in DCM (10 mL) was added (R)-1-phenylethan-1-ol (137.90 mg, 1.129 mmol, 1 equiv) and PPh_3 (444.10 mg, 1.694 mmol, 1.5 equiv). The reaction was stirred at rt under N_2 for 0.5h. To the above mixture was added DEAD (294.88 mg, 1.694 mmol, 1.5 equiv) at 0°C under N_2. The resulting mixture was stirred for additional 1h at rt. Quenched with water (30 mL) and extracted with DCM (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-bromo-2-methyl-4-[(1S)-1-phenylethyl]-6-(trifluoromethyl)-2H-1,4-benzoxazin-3-one (240 mg, 51.33%) as a yellow solid. LC/MS: mass calcd. for $C_{18}H_{15}BrF_3NO_2$:413.02 m/z, found:413.95, 415.95 $[M+H, M+H+2]^+$.



tert-butyl ((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)carbamate

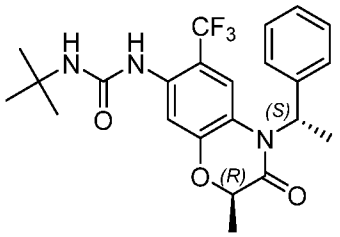
To a solution of (2R)-7-bromo-2-methyl-4-[(1S)-1-phenylethyl]-6-(trifluoromethyl)-2H-1,4-benzoxazin-3-one (260 mg, 0.628 mmol, 1 equiv) in dioxane (10 mL) was added tert-butyl carbamate (110.30 mg, 0.942 mmol, 1.5 equiv), Ruphos (29.29 mg, 0.063 mmol, 0.1 equiv), RuPhos Palladacycle Gen.3 (52.50 mg, 0.063 mmol, 0.1 equiv) and Cs_2CO_3 (613.53 mg, 1.884 mmol, 3 equiv). The reaction was stirred at 90°C under N_2 for 1h. The mixture was allowed to cool down to rt. Quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give tert-butyl N-[(2R)-2-methyl-3-oxo-4-[(1S)-1-phenylethyl]-6-(trifluoromethyl)-2H-1,4-benzoxazin-7-yl]carbamate (250 mg, 88.42%) as a yellow solid. LC/MS: mass calcd. for $C_{23}H_{25}F_3N_2O_4$:450.18 m/z, found:451.15 $[M+H]^+$.



(R)-7-amino-2-methyl-4-((S)-1-phenylethyl)-6-(trifluoromethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of tert-butyl N-[(2R)-2-methyl-3-oxo-4-[(1S)-1-phenylethyl]-6-(trifluoromethyl)-2H-1,4-benzoxazin-7-yl]carbamate (270 mg, 0.599 mmol, 1 equiv) in DCM (4 mL) was added TFA (1 mL) at 0 °C. The reaction was stirred at rt for 1h. Quenched with $NaHCO_3$ solution (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-2-methyl-4-[(1S)-1-phenylethyl]-6-

(trifluoromethyl)-2H-1,4-benzoxazin-3-one (100 mg, 47.62%) as a yellow solid. LC/MS: mass calcd. for $C_{18}H_{17}F_3N_2O_2$:350.12 m/z, found:351.05 $[M+H]^+$.

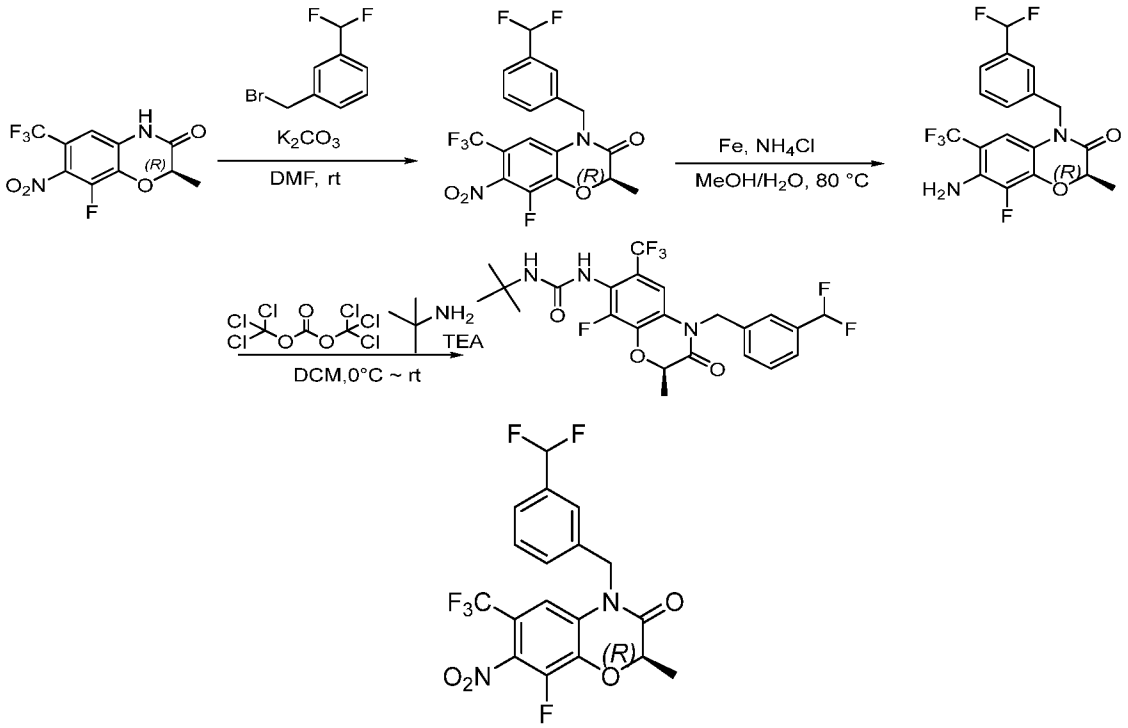


1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a solution of (2R)-7-amino-2-methyl-4-[(1S)-1-phenylethyl]-6-(trifluoromethyl)-2H-1,4-benzoxazin-3-one (50 mg, 0.143 mmol, 1 equiv) in DCM (5 mL) was added triphosgene (42.35 mg, 0.143 mmol, 1 equiv) under N_2 at 0 °C. The reaction was stirred at 0 °C under N_2 for 1h. To the above mixture was added TEA (43.33 mg, 0.429 mmol, 3 equiv) at 0°C. The resulting mixture was stirred for additional 1h at rt. Then, to the above mixture was added erbumine (31.31 mg, 0.429 mmol, 3 equiv). The resulting mixture was stirred for additional 1h at rt. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XSelect CSH C18 Column, 19*250 mm, 5μm column (eluent: 58% to 88% (v/v) CH_3CN and Water (0.1% FA)) to afford the title compound 3-tert-butyl-1-[(2R)-2-methyl-3-oxo-4-[(1S)-1-phenylethyl]-6-(trifluoromethyl)-2H-1,4-benzoxazin-7-yl]urea (26.1 mg, 40.55%) as a white solid. LC/MS: mass calcd. for $C_{23}H_{26}F_3N_3O_3$:449.19 m/z, found:450.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-*d*$_6$) δ 7.69 (s, 1H), 7.54 (s, 1H), 7.35 – 7.43 (m, 2H), 7.29 (d, *J* = 7.3 Hz, 3H), 6.93 (s, 1H), 6.82 (s, 1H), 6.19 (q, *J* = 7.1 Hz, 1H), 4.92 (q, *J* = 6.8 Hz, 1H), 1.75 (d, *J* = 7.2 Hz, 3H), 1.50 (d, *J* = 6.8 Hz, 3H), 1.27 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ(ppm): -58.9959.

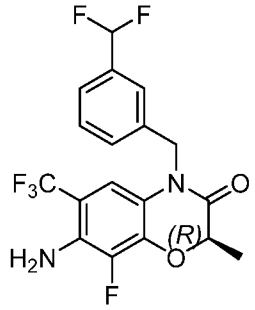
Example 350: (R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

Synthetic Scheme



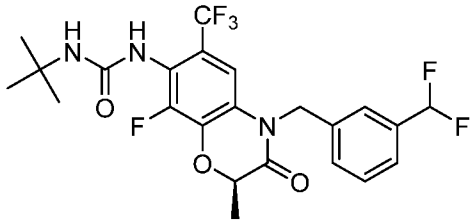
(R)-4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-7-nitro-6-(trifluoromethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-8-fluoro-2-methyl-7-nitro-6-(trifluoromethyl)-2,4-dihydro-1,4-benzoxazin-3-one (100 mg, 0.340 mmol, 1 equiv) in DMF (10 mL) was added 1-(bromomethyl)-3-(difluoromethyl)benzene (112.72 mg, 0.510 mmol, 1.5 equiv) and K_2CO_3 (141.98 mg, 1.020 mmol, 3 equiv). The reaction was stirred at rt for 1h. The reaction was monitored by TLC. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-4-{[3-(difluoromethyl)phenyl]methyl}-8-fluoro-2-methyl-7-nitro-6-(trifluoromethyl)-2H-1,4-benzoxazin-3-one (140 mg, 94.83%) as a yellow solid.



(R)-7-amino-4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-6-(trifluoromethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-4-{[3-(difluoromethyl)phenyl]methyl}-8-fluoro-2-methyl-7-nitro-6-(trifluoromethyl)-2H-1,4-benzoxazin-3-one (130 mg, 0.299 mmol, 1 equiv) in MeOH (5 mL) and H_2O (0.5 mL) was added Fe (167.16 mg, 2.990 mmol, 10 equiv) and NH_4Cl (160.12 mg, 2.990 mmol, 10 equiv). The reaction was stirred at 80 °C for 1h. The mixture was allowed to cool down to rt. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 30 mL). The filtrate was concentrated under reduced pressure. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-4-{[3-(difluoromethyl)phenyl]methyl}-8-fluoro-2-methyl-6-(trifluoromethyl)-2H-1,4-benzoxazin-3-one (100 mg, 82.63%) as a yellow solid. LC/MS: mass calcd. for $C_{18}H_{14}F_6N_2O_2$:404.10 m/z, found:405.05 $[M+H]^+$.



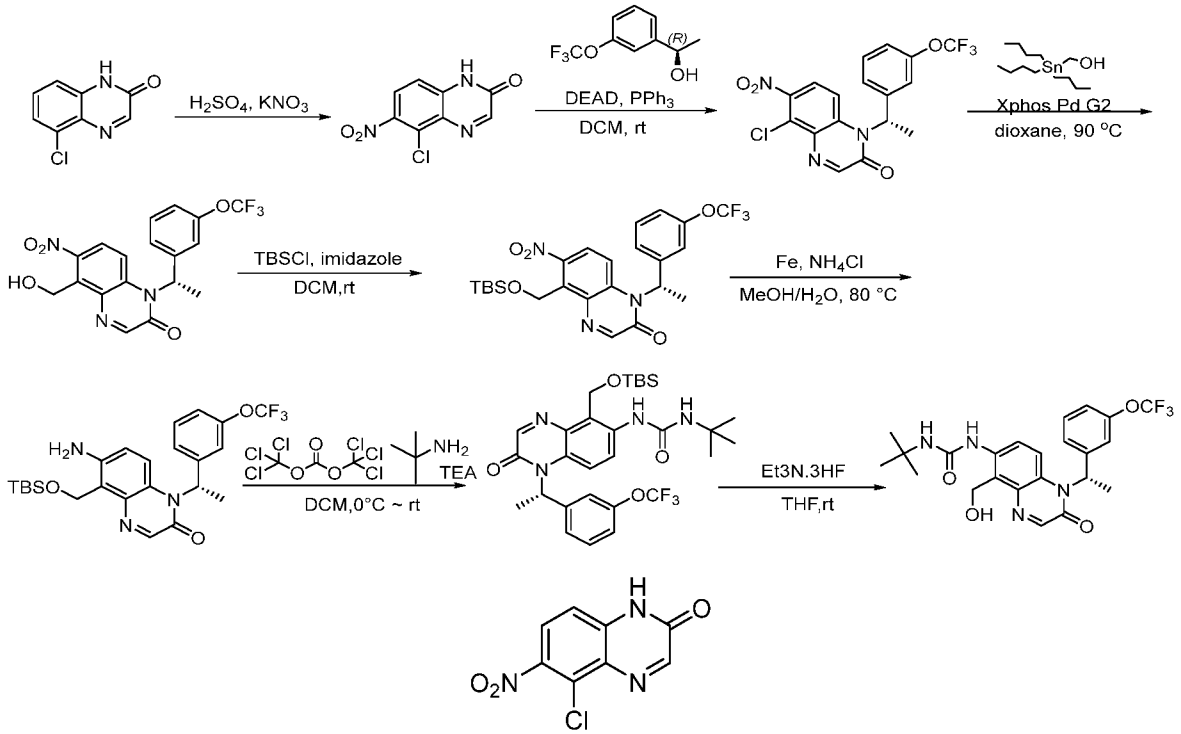
(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a solution of (2R)-7-amino-4-{[3-(difluoromethyl)phenyl]methyl}-8-fluoro-2-methyl-6-(trifluoromethyl)-2H-1,4-benzoxazin-3-one (150 mg, 0.371 mmol, 1 equiv) in DCM (5 mL) was added triphosgene (110.09 mg, 0.371 mmol, 1 equiv) under N_2 at 0 °C. The reaction was stirred at 0 °C under N_2 for 1h. To the above mixture was added TEA (112.63 mg, 1.113 mmol, 3 equiv) at 0°C. The resulting mixture was stirred for additional 1h at rt. Then, to the above mixture was added erbumine (81.40 mg, 1.113 mmol, 3 equiv). The resulting mixture was stirred for additional 1h at rt. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep C18 OBD Column, 19*250 mm, 5μm column (eluent: 49% to 79% (v/v) CH_3CN and Water (10mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$)) to afford the title compound 3-tert-butyl-1-[(2R)-4-{[3-(difluoromethyl)phenyl]methyl}-8-fluoro-2-methyl-3-oxo-6-(trifluoromethyl)-2H-1,4-benzoxazin-7-yl]urea (20.3 mg, 10.79%) as a white

solid. LC/MS: mass calcd. for $C_{23}H_{23}F_6N_3O_3$:503.16 m/z, found:504.20 $[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (s, 1H), 7.31 – 7.40 (m, 2H), 7.23 – 7.31 (m, 3H), 7.06 (d, J = 1.6 Hz, 1H), 6.27 (s, 1H), 5.28 (d, J = 16.4 Hz, 1H), 5.21 (d, J = 16.4 Hz, 1H), 5.14 (q, J = 6.7 Hz, 1H), 1.59 (d, J = 6.7 Hz, 3H), 1.25 (s, 9H).^{19}F NMR (376 MHz, DMSO) δ(ppm): -59.0147, -136.7360.

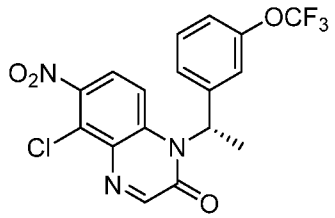
Example 351: (S)-1-(tert-butyl)-3-(5-(hydroxymethyl)-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

Synthetic Scheme



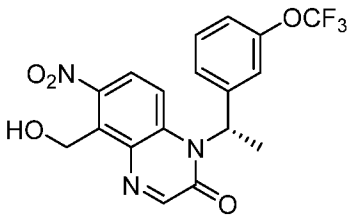
5-chloro-6-nitroquinoxalin-2(1H)-one

To a solution of 5-chloro-1H-quinoxalin-2-one (1 g, 5.537 mmol, 1 equiv) in H_2SO_4 (20 mL) was added KNO_3 (0.56 g, 5.537 mmol, 1 equiv) at 0 °C. The reaction was stirred at rt for 3h. The reaction was quenched by the addition of water/Ice at 0°C. Diluted with water (200 mL) and extracted with EA (3 x 200 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 5-chloro-6-nitro-1H-quinoxalin-2-one (610 mg, 48.83%) as a yellow solid. LC/MS: mass calcd. for $C_8H_4ClN_3O_3$:224.99 m/z, found:226.15 $[M+H]^+$.



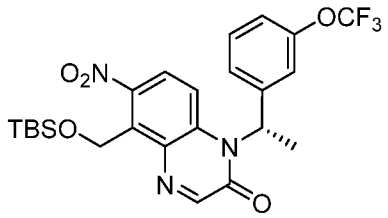
(S)-5-chloro-6-nitro-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)quinoxalin-2(1H)-one

To a solution of 5-chloro-6-nitro-1H-quinoxalin-2-one (700 mg, 3.103 mmol, 1 equiv) in DCM (10 mL) was added (1R)-1-[3-(trifluoromethoxy)phenyl]ethanol (639.72 mg, 3.103 mmol, 1 equiv) and PPh_3 (1220.83 mg, 4.655 mmol, 1.5 equiv). The reaction was stirred at rt under N_2 for 0.5h. To the above mixture was added DEAD (810.60 mg, 4.655 mmol, 1.5 equiv) at 0°C. The resulting mixture was stirred for additional 1h at rt. Quenched with water (80 mL) and extracted with DCM (3 x 80 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 5-chloro-6-nitro-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one (240 mg, 18.69%) as a yellow solid. LC/MS: mass calcd. for $C_{17}H_{11}ClF_3N_3O_4$:413.04 m/z, found:414.05 $[M+H]^+$.



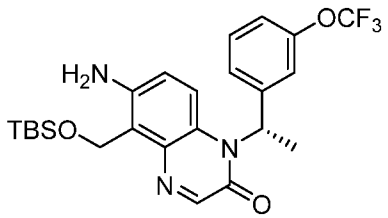
(S)-5-(hydroxymethyl)-6-nitro-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)quinoxalin-2(1H)-one

To a solution of 5-chloro-6-nitro-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one (160 mg, 0.387 mmol, 1 equiv) in dioxane (5 mL) was added X-phos Pd G2 (30.43 mg, 0.039 mmol, 0.1 equiv) and (tributylstannyl)methanol (248.34 mg, 0.774 mmol, 2 equiv). The reaction was stirred at 90°C under N_2 for 1h. After cooling down to rt, the reaction was quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 5-(hydroxymethyl)-6-nitro-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one (70 mg, 44.22%) as a yellow solid. LC/MS: mass calcd. for $C_{18}H_{14}F_3N_3O_5$:409.09 m/z, found:410.00 $[M+H]^+$.



(S)-5-(((tert-butyldimethylsilyl)oxy)methyl)-6-nitro-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)quinoxalin-2(1H)-one

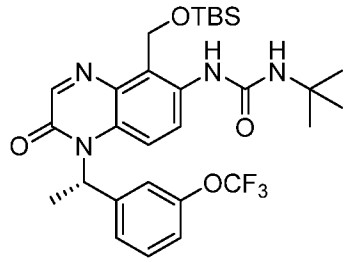
To a solution of 5-(hydroxymethyl)-6-nitro-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one (45 mg, 0.110 mmol, 1 equiv) in DCM (2 mL) was added Imidazole (22.45 mg, 0.330 mmol, 3 equiv) and TBSCl (24.85 mg, 0.165 mmol, 1.5 equiv) at 0 °C. The reaction was stirred at rt for 3h. Quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 5-{[(tert-butyldimethylsilyl)oxy]methyl}-6-nitro-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one (45 mg, 78.18%) as a yellow solid. LC/MS: mass calcd. for $C_{24}H_{28}F_3N_3O_5Si$:523.18 m/z, found:524.15 $[M+H]^+$.



(S)-6-amino-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)quinoxalin-2(1H)-one

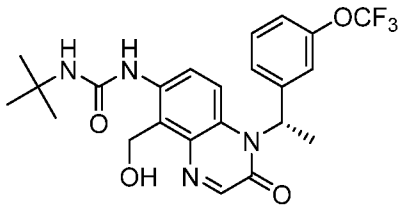
To a solution of 5-{[(tert-butyldimethylsilyl)oxy]methyl}-6-nitro-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one (30 mg, 0.057 mmol, 1 equiv) in MeOH (4 mL) and H_2O (0.4 mL) was added Fe (32.00 mg, 0.570 mmol, 10 equiv) and NH_4Cl (30.65 mg, 0.570 mmol, 10 equiv). The reaction was stirred at 80°C for 1h. The mixture was allowed to cool down to rt. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 30 mL). The filtrate was concentrated under reduced pressure. Diluted with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-5-{[(tert-butyldimethylsilyl)oxy]methyl}-1-[(1S)-1-[3-

(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one (25 mg, 88.40%) as a yellow solid. LC/MS: mass calcd. for $C_{24}H_{30}F_3N_3O_3Si$:493.20 m/z, found:494.15 $[M+H]^+$.



(S)-1-(tert-butyl)-3-(5-(((tert-butyldimethylsilyl)oxy)methyl)-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

To a solution of 6-amino-5-{[(tert-butyldimethylsilyl)oxy]methyl}-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one (20 mg, 0.041 mmol, 1 equiv) in DCM (5 mL) was added triphosgene (12.02 mg, 0.041 mmol, 1 equiv) under N_2 at 0 °C. The reaction was stirred at 0 °C under N_2 for 1h. To the above mixture was added TEA (12.30 mg, 0.123 mmol, 3 equiv) at 0°C. The resulting mixture was stirred for additional 1h at rt. Then, to the above mixture was added erbumine (8.89 mg, 0.123 mmol, 3 equiv). The resulting mixture was stirred for additional 1h at rt. Quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 3-tert-butyl-1-(5-{[(tert-butyldimethylsilyl)oxy]methyl}-2-oxo-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-6-yl)urea (20 mg, 83.28%) as a yellow solid. LC/MS: mass calcd. for $C_{29}H_{39}F_3N_4O_4Si$:592.27 m/z, found:615.10 $[M+Na]^+$.



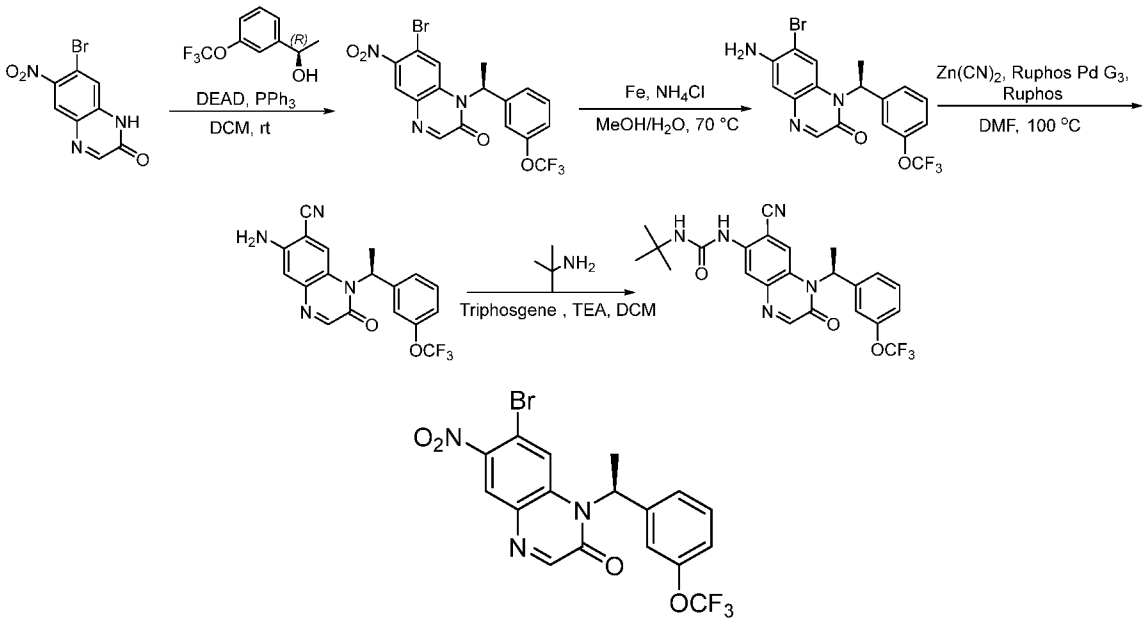
(S)-1-(tert-butyl)-3-(5-(hydroxymethyl)-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

To a solution of 3-tert-butyl-1-(5-{[(tert-butyldimethylsilyl)oxy]methyl}-2-oxo-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-6-yl)urea (20 mg, 0.034 mmol, 1 equiv) in THF (1 mL) was added $Et_3N.3HF$ (8.16 mg, 0.051 mmol, 1.5 equiv) at 0 °C. The reaction was stirred at rt for 1h. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts

were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a YMC Triart C18 ExRs Column, 20*250mm, 5μm column (eluent: 45% to 75% (v/v) CH_3CN and Water (10mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$)) to afford the title compound 3-tert-butyl-1-[5-(hydroxymethyl)-2-oxo-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-6-yl]urea (9.3 mg, 57.33%) as a white solid. LC/MS: mass calcd. for $C_{23}H_{25}F_3N_4O_4$:478.18 m/z, found:477.15 $[M-H]^-$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.90 – 8.10 (m, 2H), 7.47 (dd, J = 9.2, 7.2 Hz, 1H), 7.24 – 7.32 (m, 3H), 6.90 (s, 1H), 6.62 (s, 1H), 5.17 (s, 1H), 5.04 (dd, J = 11.7, 4.9 Hz, 1H), 4.96 (dd, J = 11.8, 5.0 Hz, 1H), 1.90 (d, J = 7.1 Hz, 3H), 1.28 (s, 9H).^{19}F NMR (376 MHz, DMSO) δ(ppm): -56.6537.

Example 352: 3-tert-butyl-1-{7-cyano-2-oxo-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-6-yl}urea

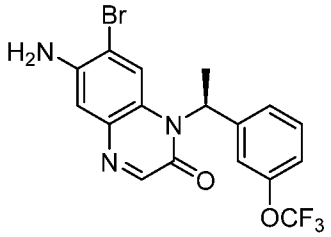
Synthetic Scheme



7-bromo-6-nitro-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one

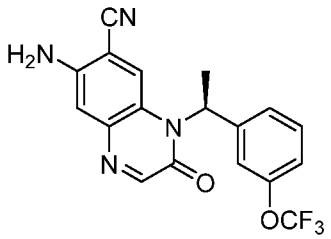
To a solution of 7-bromo-6-nitro-1H-quinoxalin-2-one (1 g, 3.703 mmol, 1 equiv) in DCM (15 mL) was added (2R,4E)-3-methylidene-5-(trifluoromethoxy)hex-4-en-2-ol (0.73 g, 3.703 mmol, 1 equiv) and PPh_3 (1.46 g, 5.554 mmol, 1.5 equiv). After the mixture was stirred at rt for 1h, to the above mixture was added DEAD (0.64 g, 3.703 mmol, 1 equiv) dropwise at 0 °C. The resulting mixture was stirred for additional for 2 h at 25 °C. Quenched with water (100 mL) and extracted with DCM (3 x 100 mL). The combined extracts were washed with water, brine, dried over

Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-bromo-6-nitro-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one (130 mg, 7.66%) as a yellow oil. MS (ESI): mass calcd. for $C_{17}H_{11}BrF_3N_3O_4$:456.99 m/z, found:457.99, 459.99 [M+H, M+H+2]$^+$.



6-amino-7-bromo-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one

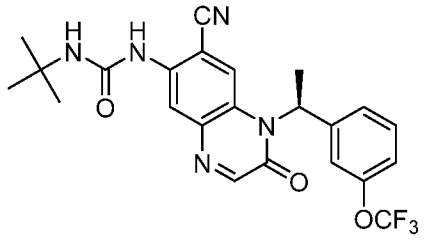
To a solution of 7-bromo-6-nitro-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one (110 mg, 0.240 mmol, 1 equiv) in MeOH (1 mL) and H_2O (10 mL) was added Fe (134.07 mg, 2.400 mmol, 10 equiv) and NH_4Cl (128.42 mg, 2.400 mmol, 10 equiv). The reaction was stirred at 70 °C for 2 h. The mixture was allowed to cool down to room temperature and quenched with water (50 mL). The resulting mixture was filtered; the filter cake was washed with EA (50 mL). The filtrate was extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-7-bromo-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one (50 mg, 48.64%) as a yellow solid. MS (ESI): mass calcd. for $C_{17}H_{13}BrF_3N_3O_2$:427.01 m/z, found:428.01, 430.01 [M+H, M+H+2]$^+$.



7-amino-3-oxo-4-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxaline-6-carbonitrile

To a solution of 6-amino-7-bromo-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one (60 mg, 0.140 mmol, 1 equiv) in dimethylformamide (4 mL) was added $Zn(CN)_2$ (19.74 mg, 0.168 mmol, 1.2 equiv) and Ruphos (6.54 mg, 0.014 mmol, 0.1 equiv) RuPhos Pd G3 (11.72 mg, 0.014 mmol, 0.1 equiv). The reaction was stirred at 100 °C for 2 h under N_2 atmosphere. The mixture was allowed to cool down to room temperature. Quenched with water (10 mL) and extracted with

EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-amino-3-oxo-4-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxaline-6-carbonitrile (15 mg, 28.60%) as a yellow oil. MS (ESI): mass calcd. for $C_{18}H_{13}F_3N_4O_2$:374.10 m/z, found:375.10 $[M+H]^+$.

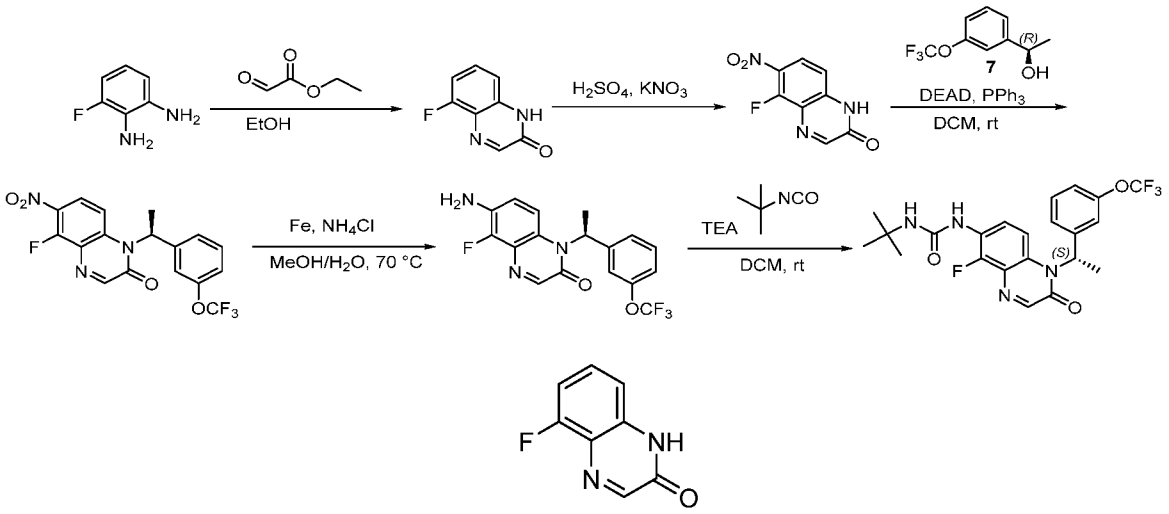


3-tert-butyl-1-{7-cyano-2-oxo-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-6-yl}urea

To a solution of 7-amino-3-oxo-4-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxaline-6-carbonitrile (15 mg, 0.040 mmol, 1 equiv) in DCM (2 mL) was added triphosgene (5.95 mg, 0.020 mmol, 0.5 equiv) at 0 °C under N_2 atmosphere. The resulting mixture was stirred 2 h at 25 °C. Then TEA (16.22 mg, 0.159 mmol, 3 equiv) was added into above system at 0 °C. The resulting mixture was stirred 1 h at 25 °C. To the above mixture were added erbumine (4.40 mg, 0.060 mmol, 1.5 equiv) dropwise at 0 °C. The reaction was stirred at 25 °C for 2 h. Quenched with water (30 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD 19*250 mm, 5μm column (eluent: 45% to 75% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-{7-cyano-2-oxo-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-6-yl}urea (4.1 mg, 21.08%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{23}H_{22}F_3N_5O_3$:473.17 m/z, found:474.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.39 (s, 1H), 8.33 (s, 1H), 7.44 – 7.72 (m, 2H), 7.27 – 7.38 (m, 3H), 6.95 (s, 1H), 6.43 (m, 1H), 1.88 (d, J = 7.0 Hz, 3H), 1.32 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ -56.71.

Example 353: 3-tert-butyl-1-{5-fluoro-2-oxo-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-6-yl}urea

Synthetic Scheme



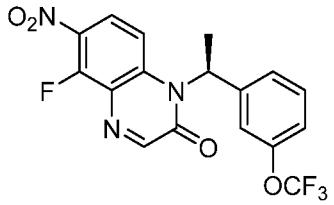
5-fluoro-1H-quinoxalin-2-one

To a stirred solution of 3-fluorobenzene-1,2-diamine (2 g, 15.856 mmol, 1 equiv) in EtOH (20 mL) was added ethyl glyoxylate (1.62 g, 15.856 mmol, 1 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 3 h at room temperature under air atmosphere. The reaction was monitored by LCMS. Quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 5-fluoro-1H-quinoxalin-2-one (1 g, 38.4%) as a brown solid. LC/MS (ESI): mass calcd. for $C_8H_5FN_2O$:164.04 m/z, found:165.0 $[M+H]^+$.

5-fluoro-6-nitro-1H-quinoxalin-2-one

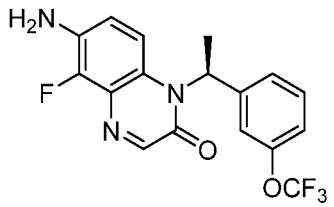
To a stirred solution of 5-fluoro-1H-quinoxalin-2-one (1 g, 6.092 mmol, 1 equiv) in H_2SO_4 (10 mL) was added KNO_3 (615.95 mg, 6.092 mmol, 1 equiv) in portions at 0 °C under air atmosphere. The resulting mixture was stirred for 2 h at room temperature under air atmosphere. The reaction was monitored by LCMS. The reaction was quenched with water/Ice (50 mL) at 0 °C, And extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 5-fluoro-6-nitro-1H-quinoxalin-2-one

(400 mg, 31.39%) as a brown solid. LC/MS (ESI): mass calcd. for $C_8H_4FN_3O_3$:209.0 m/z, found:210.0 $[M+H]^+$.



5-fluoro-6-nitro-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one

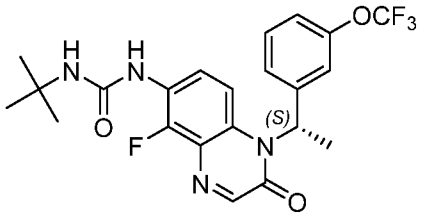
To a stirred solution of 5-fluoro-6-nitro-1H-quinoxalin-2-one (400 mg, 1.913 mmol, 1 equiv) and (1R)-1-[3-(trifluoromethoxy)phenyl]ethanol (394.32 mg, 1.913 mmol, 1 equiv) in DCM (4 mL) was added PPh_3 (752.50 mg, 2.869 mmol, 1.5 equiv) in portions at rt under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. To the above mixture was added DEAD (333.10 mg, 1.913 mmol, 1 equiv) in portions at 0 °C. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. Quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 5-fluoro-6-nitro-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one (80 mg, 10.53%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{17}H_{11}F_4N_3O_4$:397.1 m/z, found:398.0 $[M+H]^+$.



6-amino-5-fluoro-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one

To a stirred solution of 5-fluoro-6-nitro-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one (80 mg, 0.201 mmol, 1 equiv) in MeOH/H_2O(10:1, 1.1 mL) were added NH_4Cl (107.71 mg, 2.010 mmol, 10 equiv) and Fe (14.06 mg, 0.250 mmol, 10 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 70 °C under air atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated.

The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 6-amino-5-fluoro-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one (30 mg, 40.56%) as a yellow solid.LC/MS (ESI): mass calcd. for $C_{17}H_{13}F_4N_3O_2$:367.1 m/z, found:367.95 $[M+H]^+$.

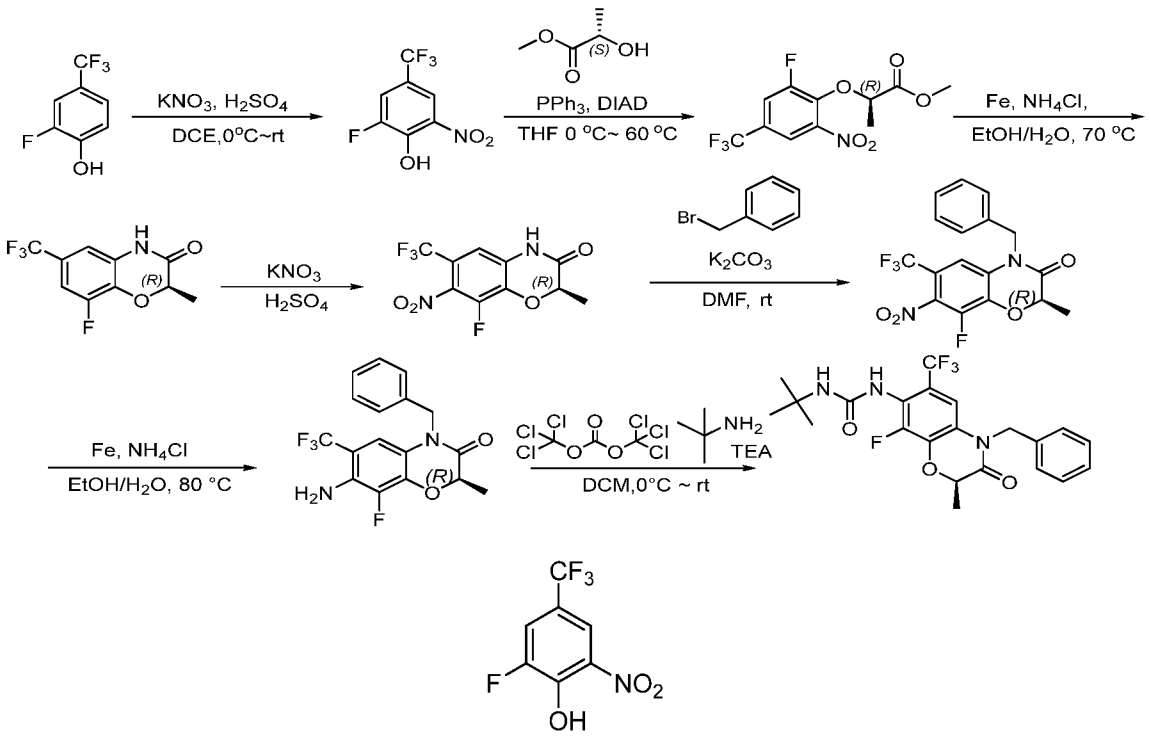


3-tert-butyl-1-{5-fluoro-2-oxo-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-6-yl}urea

To a stirred solution of 6-amino-5-fluoro-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one (20 mg, 0.054 mmol, 1 equiv) in DCM (1 mL) were added 2-isocyanato-2-methylpropane (16.19 mg, 0.162 mmol, 3 equiv) and TEA (16.53 mg, 0.162 mmol, 3 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 1 days at room temperature under air atmosphere. The reaction was monitored by LCMS. Quenched with water (5 mL) and extracted with DCM (3 x 5 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a X Bridge Prep OBD C18 250 mm x 19 mm x 5 μm column (eluent: 45% to 75% (v/v) CH_3CN and H_2O with 10mmol/L $NH_4HCO_3$0.1%$NH_3.H_2O$) to afford 3-tert-butyl-1-{5-fluoro-2-oxo-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-6-yl}urea (2.3 mg, 9.03%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{22}H_{22}F_4N_4O_3$:466.2 m/z, found:467.2 $[M+H]^+$. ^1H NMR (300 MHz, Chloroform-d) δ 8.17 (s, 1H), 7.65 (d, *J* = 15.3 Hz, 1H), 7.26 – 7.23 (m, 2H), 7.03 – 6.98 (m, 3H), 6.50 (s, 1H), 6.19 (s, 1H), 1.88 – 1.85 (m, 3H), 1.32 (s, 9H).^{19}F NMR (282 MHz, Chloroform-d) δ -57.75.

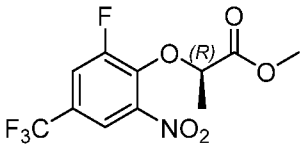
Example 354: (R)-1-(4-benzyl-8-fluoro-2-methyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

Synthetic Scheme



2-fluoro-6-nitro-4-(trifluoromethyl)phenol

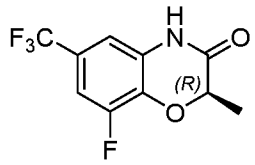
To a solution of 2-fluoro-4-(trifluoromethyl)phenol (2 g, 11.105 mmol, 1 equiv) in DCE (20 mL) was added H_2SO_4 (20 mL) at -10°C. And to the above mixture was added KNO3 (1.12 g, 11.105 mmol, 1 equiv) at -10°C. The resulting mixture was stirred for additional 30 min at -10 °C. The reaction was quenched by the addition of water/Ice at 0 °C. Quenched with water (400 mL) and extracted with EA (3 x 400 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. This resulted in 2-fluoro-6-nitro-4-(trifluoromethyl)phenol (2.14 g, 85.61%) as a yellow oil. LC/MS: mass calcd. for $C_7H_3F_4NO_3$:225.00 m/z, found:223.95 $[M-H]^-$.



methyl (R)-2-(2-fluoro-6-nitro-4-(trifluoromethyl)phenoxy)propanoate

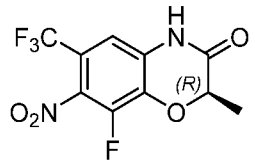
To a solution of 2-fluoro-6-nitro-4-(trifluoromethyl)phenol (1.4 g, 6.219 mmol, 1 equiv) in THF (10 mL) was added methyl (2S)-2-hydroxypropanoate (647.48 mg, 6.219 mmol, 1 equiv) and PPh_3 (2446.98 mg, 9.329 mmol, 1.5 equiv). The reaction was stirred at rt under N_2 for 0.5h. To the above mixture was added DIAD (1886.46 mg, 9.329 mmol, 1.5 equiv) at 0°C. The resulting

mixture was stirred for additional 1h at 60°C. After cooling down to rt, the reaction was quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give methyl (2R)-2-[2-fluoro-6-nitro-4-(trifluoromethyl)phenoxy]propanoate (1.14 g, 58.90%) as a yellow oil. LC/MS: mass calcd. for $C_{11}H_9F_4NO_5$:311.04 m/z, found:311.90 $[M+H]^+$.



(R)-8-fluoro-2-methyl-6-(trifluoromethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

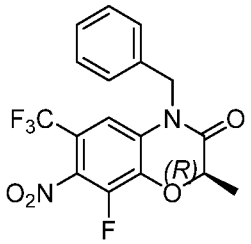
To a solution of methyl (2R)-2-[2-fluoro-6-nitro-4-(trifluoromethyl)phenoxy]propanoate (1.14 g, 3.663 mmol, 1 equiv) in EtOH (8 mL) and H_2O (2 mL) was added Fe (2.05 g, 36.630 mmol, 10 equiv) and NH_4Cl (1.96 g, 36.630 mmol, 10 equiv). The reaction was stirred at 70 °C for 1h. The mixture was allowed to cool down to rt. The filtrate was concentrated under reduced pressure. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-8-fluoro-2-methyl-6-(trifluoromethyl)-2,4-dihydro-1,4-benzoxazin-3-one (720 mg, 78.88%) as a yellow solid. LC/MS: mass calcd. for $C_{10}H_7F_4NO_2$:249.04 m/z, found:249.95 $[M+H]^+$.



(R)-8-fluoro-2-methyl-7-nitro-6-(trifluoromethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

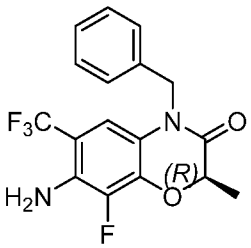
To a solution of (2R)-8-fluoro-2-methyl-6-(trifluoromethyl)-2,4-dihydro-1,4-benzoxazin-3-one (700 mg, 2.809 mmol, 1 equiv) in H_2SO_4 (10 mL) was added KNO_3 (284.03 mg, 2.809 mmol, 1 equiv) at 0 °C. The reaction was stirred at rt for 2h. The reaction was quenched with water/Ice at 0°C. Diluted with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-8-fluoro-2-

methyl-7-nitro-6-(trifluoromethyl)-2,4-dihydro-1,4-benzoxazin-3-one (400 mg, 48.40%) as a yellow solid. LC/MS: mass calcd. for $C_{10}H_8F_4N_2O_4$:294.03 m/z, found:292.95 $[M-H]^-$.



(R)-4-benzyl-8-fluoro-2-methyl-7-nitro-6-(trifluoromethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

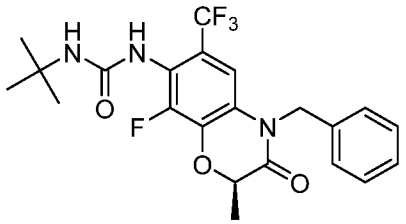
To a solution of (2R)-8-fluoro-2-methyl-7-nitro-6-(trifluoromethyl)-2,4-dihydro-1,4-benzoxazin-3-one (420 mg, 1.428 mmol, 1 equiv) in DMF (10 mL) was added benzyl bromide (366.31 mg, 2.142 mmol, 1.5 equiv) and K_2CO_3 (596.30 mg, 4.284 mmol, 3 equiv) at 0 °C. The reaction was stirred at rt for 1h. The reaction was monitored by TLC. Quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-4-benzyl-8-fluoro-2-methyl-7-nitro-6-(trifluoromethyl)-2H-1,4-benzoxazin-3-one (400 mg, 72.90%) as a yellow solid.



(R)-7-amino-4-benzyl-8-fluoro-2-methyl-6-(trifluoromethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-4-benzyl-8-fluoro-2-methyl-7-nitro-6-(trifluoromethyl)-2H-1,4-benzoxazin-3-one (400 mg, 1.041 mmol, 1 equiv) in MeOH (10 mL) and H_2O (1 mL) was added Fe (581.28 mg, 10.410 mmol, 10 equiv) and NH_4Cl (556.77 mg, 10.410 mmol, 10 equiv). The reaction was stirred at 80 °C for 1h. The mixture was allowed to cool down to rt. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 50 mL). The filtrate was concentrated under reduced pressure.Diluted with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue

was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-4-benzyl-8-fluoro-2-methyl-6-(trifluoromethyl)-2H-1,4-benzoxazin-3-one (300 mg, 81.35%) as a yellow solid. LC/MS: mass calcd. for $C_{17}H_{14}F_4N_2O_2$:354.10 m/z, found:355.10 $[M+H]^+$.

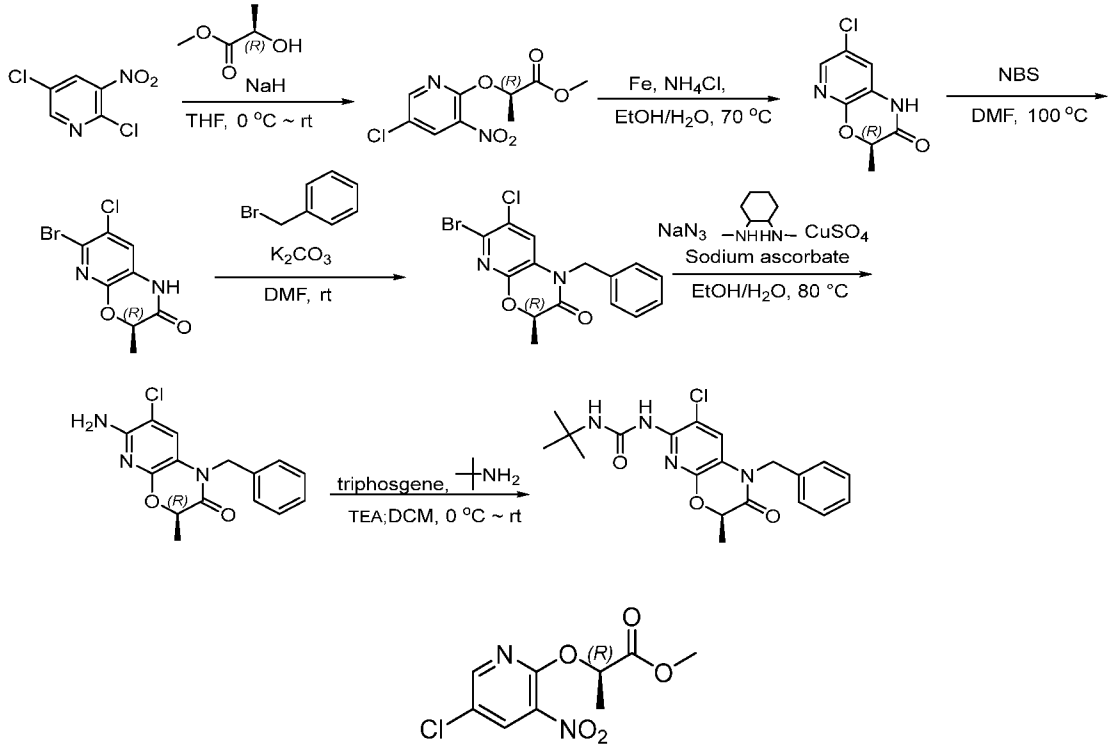


(R)-1-(4-benzyl-8-fluoro-2-methyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

To a solution of (2R)-7-amino-4-benzyl-8-fluoro-2-methyl-6-(trifluoromethyl)-2H-1,4-benzoxazin-3-one (70 mg, 0.198 mmol, 1 equiv) in DCM (5 mL) was added triphosgene (58.62 mg, 0.198 mmol, 1 equiv) under N_2 at 0 °C. The reaction was stirred at 0 °C under N_2 for 1h. To the above mixture was added TEA (19.99 mg, 0.198 mmol, 1 equiv) at 0°C. The resulting mixture was stirred for additional 1h at rt. Then, to the above mixture was added erbumine (14.45 mg, 0.198 mmol, 1 equiv). The resulting mixture was stirred for additional 1h at rt. Quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Shield RP 18 OBD Column, 19*250 mm, 5μm column (eluent: 52% to 82% (v/v) CH_3CN and Water (10mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$)) to afford the title compound 1-[(2R)-4-benzyl-8-fluoro-2-methyl-3-oxo-6-(trifluoromethyl)-2H-1,4-benzoxazin-7-yl]-3-tert-butylurea (27.2 mg, 30.36%) as a white solid. LC/MS: mass calcd. for $C_{22}H_{23}F_4N_3O_3$:453.17 m/z, found:454.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.46 (s, 1H), 7.31 – 7.40 (m, 2H), 7.23 – 7.31 (m, 3H), 7.06 (d, J = 1.6 Hz, 1H), 6.27 (s, 1H), 5.28 (d, J = 16.4 Hz, 1H), 5.21 (d, J = 16.4 Hz, 1H), 5.14 (q, J = 6.7 Hz, 1H), 1.59 (d, J = 6.7 Hz, 3H), 1.25 (s, 9H).^{19}F NMR (376 MHz, DMSO) δ(ppm): -59.0147, -136.7360.

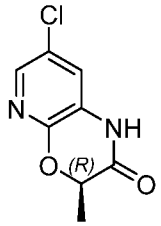
Example 355: 1-[(3R)-1-benzyl-7-chloro-3-methyl-2-oxo-3H-pyrido[2,3-b][1,4]oxazin-6-yl]-3-tert-butylurea

Synthetic Scheme



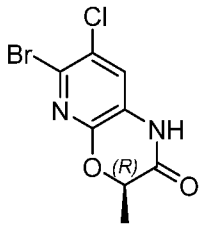
methyl (2R)-2-[(5-chloro-3-nitropyridin-2-yl)oxy]propanoate

To a stirred solution of methyl (2R)-2-hydroxypropanoate (1.08 g, 10.364 mmol, 1 equiv) in THF (30 mL) was added NaH (0.75 g, 31.092 mmol, 3 equiv) in portions at 0°C under air atmosphere. The resulting mixture was stirred for 30 min at room temperature under air atmosphere. To the above mixture was added 2,5-dichloro-3-nitropyridine (2 g, 10.364 mmol, 1 equiv) in portions at 0°C. The resulting mixture was stirred for additional 1h at room temperature. The reaction was quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%)to afford methyl (2R)-2-[(5-chloro-3-nitropyridin-2-yl)oxy]propanoate (1 g, 37.02%) as a white solid. LC/MS (ESI): mass calcd. for $C_9H_9ClN_2O_5$:260.0 m/z, found:261.10 $[M+H]^+$.



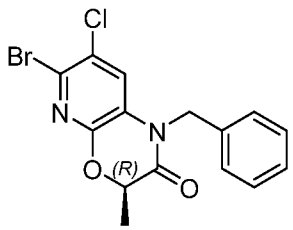
(3R)-7-chloro-3-methyl-1H,3H-pyrido[2,3-b][1,4]oxazin-2-one

To a stirred mixture of methyl (2R)-2-[(5-chloro-3-nitropyridin-2-yl)oxy]propanoate (800 mg, 3.069 mmol, 1 equiv) and NH_4Cl (1641.87 mg, 30.690 mmol, 10 equiv) in MeOH:H_2O=10:1 (15 mL) was added Fe (1714.15 mg, 30.690 mmol, 10 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 1h at 80°C under air atmosphere. After cooling down to room temperature, the reaction was quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%)to afford (3R)-7-chloro-3-methyl-1H,3H-pyrido[2,3-b][1,4]oxazin-2-one (300 mg, 49.21%) as a yellow oil. LC/MS (ESI): mass calcd. for $C_8H_7ClN_2O_2$:198.0 m/z, found:199.15 $[M+H]^+$.



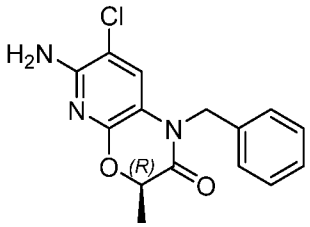
(3R)-6-bromo-7-chloro-3-methyl-1H,3H-pyrido[2,3-b][1,4]oxazin-2-one

To a stirred solution of (3R)-7-chloro-3-methyl-1H,3H-pyrido[2,3-b][1,4]oxazin-2-one (210 mg, 1.057 mmol, 1 equiv) in DMF (5 mL) were added NBS (1129.15 mg, 6.342 mmol, 6 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 4 h at 100°C under air atmosphere. After cooling down to room temperature, the reaction was quenched with water (20 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to afford (3R)-6-bromo-7-chloro-3-methyl-1H,3H-pyrido[2,3-b][1,4]oxazin-2-one (170 mg, 57.94%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_8H_6BrClN_2O_2$: 275.9 m/z, found:274.80., 272.80 $[M-H, M-H+2]^-$.



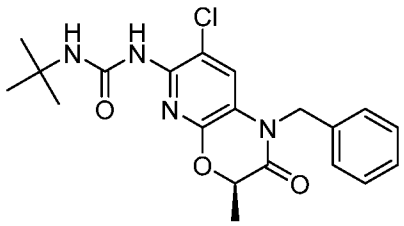
(3R)-1-benzyl-6-bromo-7-chloro-3-methyl-3H-pyrido[2,3-b][1,4]oxazin-2-one

To a stirred mixture of (3R)-6-bromo-7-chloro-3-methyl-1H,3H-pyrido[2,3-b][1,4]oxazin-2-one (160 mg, 0.577 mmol, 1 equiv) and benzyl bromide (197.23 mg, 1.154 mmol, 2 equiv) in DMF (5 mL) was added K_2CO_3 (240.80 mg, 1.731 mmol, 3 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 4h at rt under air atmosphere. After cooling down to room temperature, the reaction was quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. Desired product could be detected by LCMS. The residue was purified by column chromatography on silica gel with EA/PE (0-100%)to afford (3R)-1-benzyl-6-bromo-7-chloro-3-methyl-3H-pyrido[2,3-b][1,4]oxazin-2-one (127 mg, 59.92%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{15}H_{12}BrClN_2O_2$:366.0 m/z, found: 367.0, 369.0 [M+H, M+H+2]$^+$.



(3R)-6-amino-1-benzyl-7-chloro-3-methyl-3H-pyrido[2,3-b][1,4]oxazin-2-one

To a stirred mixture of (3R)-1-benzyl-6-bromo-7-chloro-3-methyl-3H-pyrido[2,3-b][1,4]oxazin-2-one (85 mg, 0.231 mmol, 1 equiv) and NaN_3 (45.08 mg, 0.693 mmol, 3 equiv) in EtOH:H_2O = 10:1 (5 mL) were added N1,N2-dimethylcyclohexane-1,2-diamine (19.73 mg, 0.139 mmol, 0.6 equiv) and $CuSO_4$ (36.89 mg, 0.231 mmol, 1 equiv) and sodium ascorbate (92.05 mg, 0.462 mmol, 2 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 1h at 80°C under nitrogen atmosphere. After cooling down to room temperature, the reaction quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%)to afford (3R)-6-amino-1-benzyl-7-chloro-3-methyl-3H-pyrido[2,3-b][1,4]oxazin-2-one (56 mg, 80.0%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{15}H_{14}ClN_3O_2$:303.1 m/z, found:304.25 [M+H]$^+$.

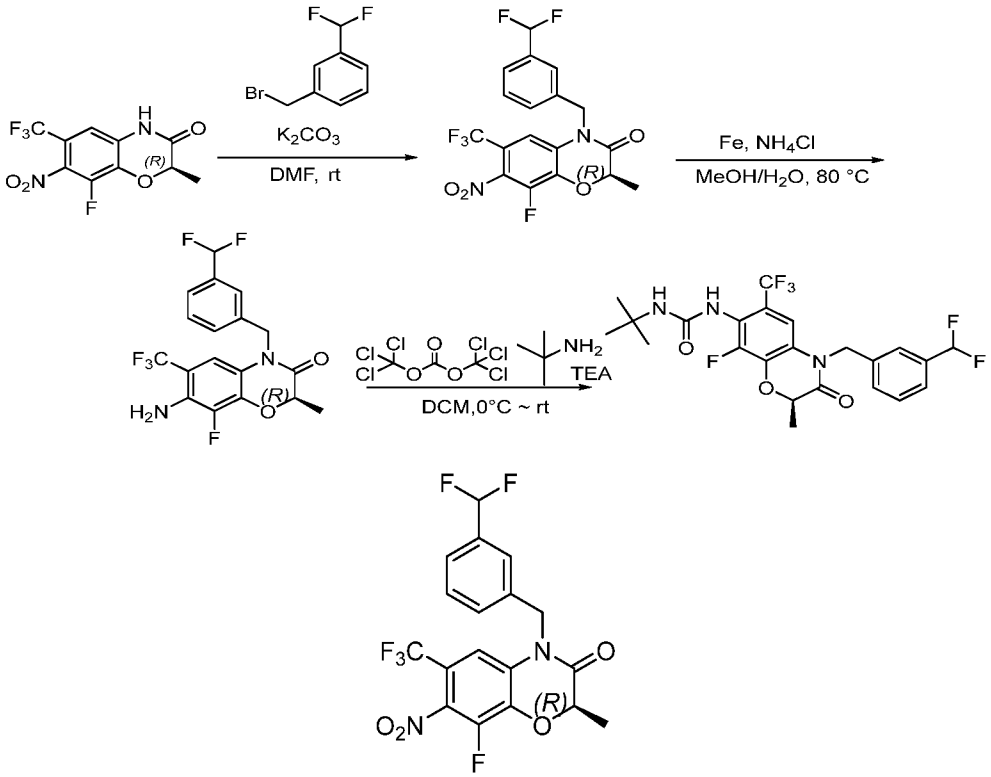


1-[(3R)-1-benzyl-7-chloro-3-methyl-2-oxo-3H-pyrido[2,3-b][1,4]oxazin-6-yl]-3-tert-butylurea

To a stirred solution of (3R)-6-amino-1-benzyl-7-chloro-3-methyl-3H-pyrido[2,3-b][1,4]oxazin-2-one (50 mg, 0.165 mmol, 1 equiv) and triphosgene (61.79 mg, 0.209 mmol, 1.2 equiv) in DCM (5 mL) was added TEA (49.97 mg, 0.495 mmol, 3 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. To the above mixture was added 2-methylpropan-2-amine (12.04 mg, 0.165 mmol, 1 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 30 min at room temperature. The reaction was quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a YMC-Actus Triart C_{18} ExRS 150 mm x 30 mm x 5 μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford 1-[(3R)-1-benzyl-7-chloro-3-methyl-2-oxo-3H-pyrido[2,3-b][1,4]oxazin-6-yl]-3-tert-butylurea (8.3 mg, 12.37%) as a white solid. LC/MS (ESI): mass calcd. for $C_{20}H_{23}ClN_4O_3$:402.1 m/z, found:403.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, J = 13.4 Hz, 2H), 7.62 (s, 1H), 7.32-7.40 (m, 2H), 7.19-7.32 (m, 3H), 5.16-5.23 (m, 3H), 1.56 (d, J = 6.8 Hz, 3H), 1.32 (s, 9H).

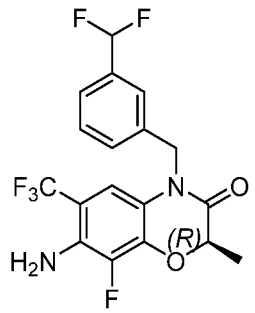
Example 356: (R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

Synthetic Scheme



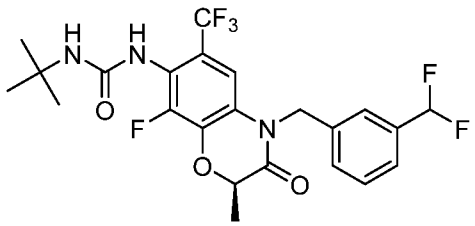
(R)-4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-7-nitro-6-(trifluoromethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-8-fluoro-2-methyl-7-nitro-6-(trifluoromethyl)-2,4-dihydro-1,4-benzoxazin-3-one (100 mg, 0.340 mmol, 1 equiv) in DMF (10 mL) was added 1-(bromomethyl)-3-(difluoromethyl)benzene (112.72 mg, 0.510 mmol, 1.5 equiv) and K_2CO_3 (141.98 mg, 1.020 mmol, 3 equiv). The reaction was stirred at rt for 1h. The reaction was monitored by TLC. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-4-{[3-(difluoromethyl)phenyl]methyl}-8-fluoro-2-methyl-7-nitro-6-(trifluoromethyl)-2H-1,4-benzoxazin-3-one (140 mg, 94.83%) as a yellow solid.



(R)-7-amino-4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-6-(trifluoromethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-4-{[3-(difluoromethyl)phenyl]methyl}-8-fluoro-2-methyl-7-nitro-6-(trifluoromethyl)-2H-1,4-benzoxazin-3-one (130 mg, 0.299 mmol, 1 equiv) in MeOH (5 mL) and H_2O (0.5 mL) was added Fe (167.16 mg, 2.990 mmol, 10 equiv) and NH_4Cl (160.12 mg, 2.990 mmol, 10 equiv). The reaction was stirred at 80 °C for 1h. The mixture was allowed to cool down to rt. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 30 mL). The filtrate was concentrated under reduced pressure. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-4-{[3-(difluoromethyl)phenyl]methyl}-8-fluoro-2-methyl-6-(trifluoromethyl)-2H-1,4-benzoxazin-3-one (100 mg, 82.63%) as a yellow solid. LC/MS: mass calcd. for $C_{18}H_{14}F_6N_2O_2$:404.10 m/z, found:405.05 $[M+H]^+$.



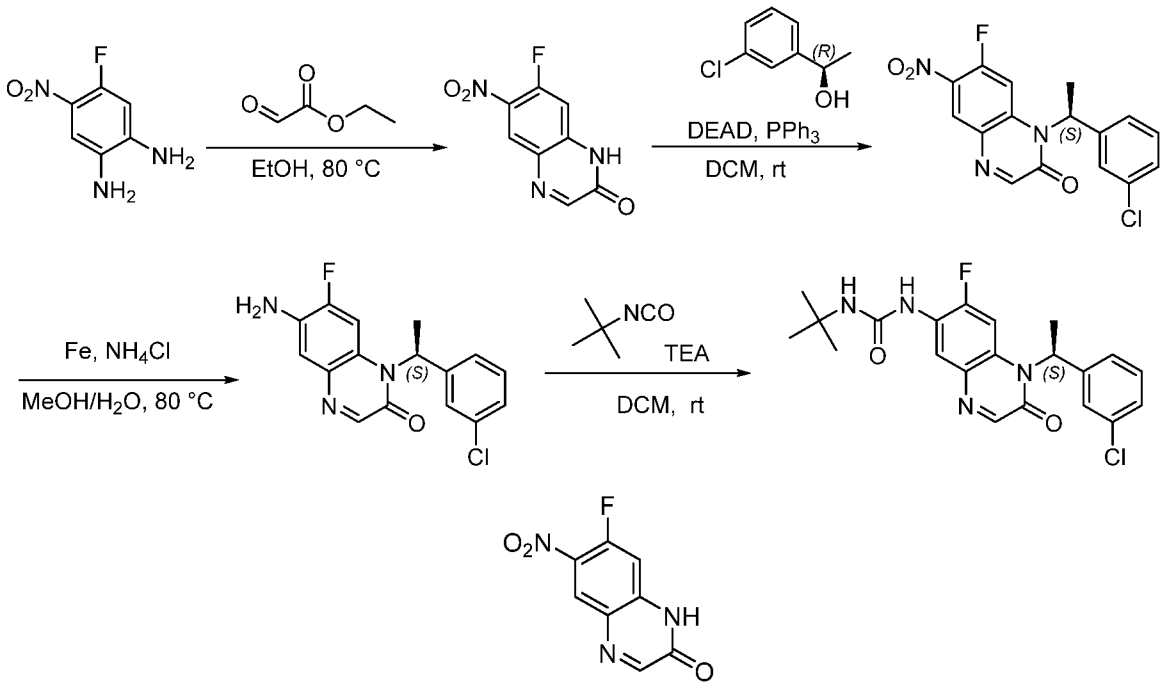
(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a solution of (2R)-7-amino-4-{[3-(difluoromethyl)phenyl]methyl}-8-fluoro-2-methyl-6-(trifluoromethyl)-2H-1,4-benzoxazin-3-one (150 mg, 0.371 mmol, 1 equiv) in DCM (5 mL) was added triphosgene (110.09 mg, 0.371 mmol, 1 equiv) under N_2 at 0 °C. The reaction was stirred at 0 °C under N_2 for 1h. To the above mixture was added TEA (112.63 mg, 1.113 mmol, 3 equiv) at 0°C. The resulting mixture was stirred for additional 1h at rt. Then, to the above mixture was added

erbumine (81.40 mg, 1.113 mmol, 3 equiv). The resulting mixture was stirred for additional 1h at rt. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep C18 OBD Column, 19*250 mm, 5μm column (eluent: 49% to 79% (v/v) CH_3CN and Water (10mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$)) to afford the title compound 3-tert-butyl-1-[(2R)-4-{[3-(difluoromethyl)phenyl]methyl}-8-fluoro-2-methyl-3-oxo-6-(trifluoromethyl)-2H-1,4-benzoxazin-7-yl]urea (20.3 mg, 10.79%) as a white solid. LC/MS: mass calcd. for $C_{23}H_{23}F_6N_3O_3$:503.16 m/z, found:504.20 $[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (s, 1H), 7.31 – 7.40 (m, 2H), 7.23 – 7.31 (m, 3H), 7.06 (d, J = 1.6 Hz, 1H), 6.27 (s, 1H), 5.28 (d, J = 16.4 Hz, 1H), 5.21 (d, J = 16.4 Hz, 1H), 5.14 (q, J = 6.7 Hz, 1H), 1.59 (d, J = 6.7 Hz, 3H), 1.25 (s, 9H).^{19}F NMR (376 MHz, DMSO) δ(ppm): -59.0147, -136.7360.

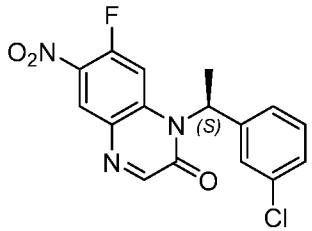
Example 357: (S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-7-fluoro-2-oxo-1,2-dihydroquinoxalin-6-yl) Urea

Synthetic Scheme



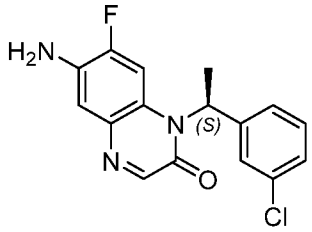
7-fluoro-6-nitroquinoxalin-2(1H)-one

To a solution of 4-fluoro-5-nitrobenzene-1,2-diamine (2 g, 11.687 mmol, 1 equiv) in ethyl alcohol (10 mL) was added ethyl glyoxylate (1.19 g, 11.687 mmol, 1 equiv). The resulting mixture was stirred for 2 h at 80 °C. The reaction mixture was quenched by water and extracted with DCM (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 7-fluoro-6-nitroquinoxalin-2(1H)-one (1.7 g, 69.55%) as a white solid. MS (ESI): mass calcd. for $C_8H_4FN_3O_3$:209.17 m/z, found:208 $[M-H]^-$.



(S)-1-(1-(3-chlorophenyl)ethyl)-7-fluoro-6-nitroquinoxalin-2(1H)-one

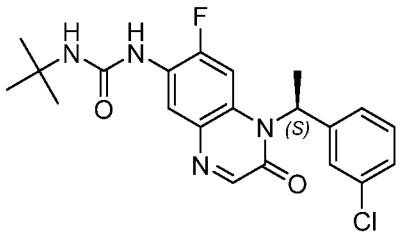
To a solution of 7-fluoro-6-nitroquinoxalin-2(1H)-one (1 g, 4.782 mmol, 1 equiv) in DCM (40 mL) was added (1R)-1-(3-chlorophenyl)ethanol (0.75 g, 4.782 mmol, 1 equiv) PPh_3 (1.88 g, 7.173 mmol, 1.5 equiv) and DEAD (1.25 g, 7.173 mmol, 1.5 equiv). The resulting mixture was stirred for 2 h at 25 °C under N_2 and stirred until the starting material was totally consumed by TLC. The reaction mixture was quenched by water and extracted with DCM (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford (S)-1-(1-(3-chlorophenyl)ethyl)-7-fluoro-6-nitroquinoxalin-2(1H)-one (400 mg, 24.06%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{11}ClFN_3O_3$: 347.17 m/z, found: 348.20 $[M+H]^+$.



(S)-6-amino-1-(1-(3-chlorophenyl)ethyl)-7-fluoroquinoxalin-2(1H)-one

To a solution of (S)-1-(1-(3-chlorophenyl)ethyl)-7-fluoro-6-nitroquinoxalin-2(1H)-one (300 mg, 0.863 mmol, 1 equiv) in EtOH (1 mL) and H_2O (0.1 mL) was added Fe (481 mg, 8.630 mmol, 10

equiv) and NH_4Cl (461 mg, 8.630 mmol, 10 equiv). The resulting mixture was stirred for 2 h at 80 °C and stirred until the starting material was totally consumed by TLC. The reaction mixture was quenched by water and extracted with DCM (3 x 30 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford (S)-6-amino-1-(1-(3-chlorophenyl)ethyl)-7-fluoroquinoxalin-2(1H)-one (120 mg, 43.77%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{13}ClFN_3O$: 317.17 m/z, found: 318.20 $[M+H]^+$.

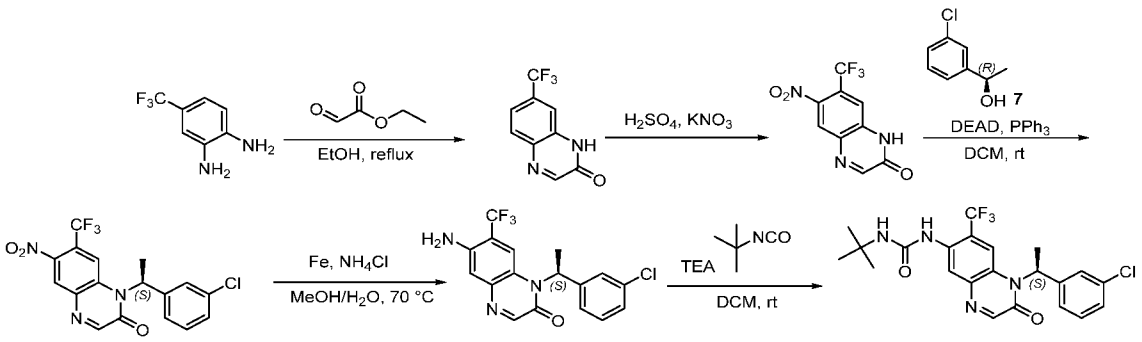


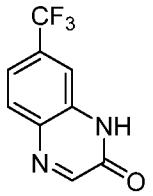
(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-7-fluoro-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

To a mixture of (S)-6-amino-1-(1-(3-chlorophenyl)ethyl)-7-fluoroquinoxalin-2(1H)-one (60 mg, 0.189 mmol, 1 equiv) and TEA (57 mg, 0.567 mmol, 3 equiv) in DCM (4 mL) was added 2-isocyanato-2-methylpropane (56 mg, 0.567 mmol, 3 equiv) at 0 °C. The reaction was stirred for overnight at rt. The reaction mixture was quenched by water (10 mL) and extracted with DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel column with PE/EA (1:1) & Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 53% B in 9 min, 53% B; Wave Length: 254/220 nm; RT1(min): 8.52; Number Of Runs: 0) to afford (S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-7-fluoro-2-oxo-1,2-dihydroquinoxalin-6-yl)urea (12.3 mg, 15.09%) as a white solid. MS (ESI): mass calcd. For $C_{21}H_{22}ClFN_4O_2$: 416.17 m/z, found: 417.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.57 (d, J = 8.7 Hz, 1H), 8.19 (s, 1H), 8.25 (s, 1H), 7.32 – 7.42 (m, 4H), 7.20 – 7.29 (m, 1H), 6.58 (s, 1H), 6.44 (s, 1H), 1.87 (d, J = 7.0 Hz, 3H), 1.30 (s, 9H).

Example 358: 3-tert-butyl-1-{1-[(1S)-1-(3-chlorophenyl)ethyl]-2-oxo-7-(trifluoromethyl)quinoxalin-6-yl}urea

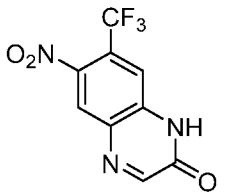
Synthetic Scheme





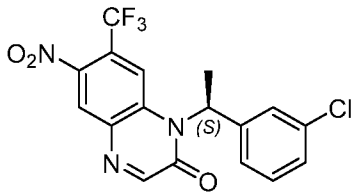
7-(trifluoromethyl)-1H-quinoxalin-2-one

To a stirred solution of 4-(trifluoromethyl)benzene-1,2-diamine (2 g, 11.354 mmol, 1 equiv) in EtOH(20 mL) was added ethyl glyoxylate (1.16 g, 11.354 mmol, 1 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 3 h at 60 ℃ under air atmosphere.The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. Quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 7-(trifluoromethyl)-1H-quinoxalin-2-one (1.2 g, 49.35%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_9H_5F_3N_2O$:214.04 m/z, found:215.0 $[M+H]^+$.



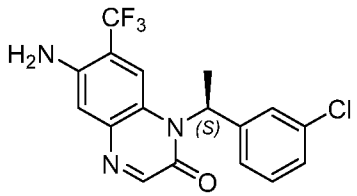
6-nitro-7-(trifluoromethyl)-1H-quinoxalin-2-one

To a stirred solution of 7-(trifluoromethyl)-1H-quinoxalin-2-one (1.1 g, 5.137 mmol, 1 equiv) in H_2SO_4 (11 mL) was added KNO_3 (1.56 g, 15.411 mmol, 3 equiv) in portions at 0 °C under air atmosphere. The resulting mixture was stirred for 2 h at room temperature under air atmosphere. The reaction was monitored by LCMS. The reaction was quenched with water/Ice (100 mL) at 0 °C, and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 6-nitro-7-(trifluoromethyl)-1H-quinoxalin-2-one (600 mg, 45.07%) as a brown solid.LC/MS (ESI): mass calcd. for $C_9H_4F_3N_3O_3$:259.02 m/z, found: 260.0 $[M+H]^+$.



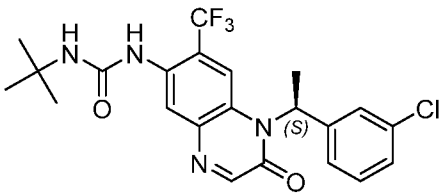
1-[(1S)-1-(3-chlorophenyl)ethyl]-6-nitro-7-(trifluoromethyl)quinoxalin-2-one

To a stirred solution of 6-nitro-7-(trifluoromethyl)-1H-quinoxalin-2-one (600 mg, 2.315 mmol, 1 equiv) and (1R)-1-(3-chlorophenyl)ethanol (362.60 mg, 2.315 mmol, 1 equiv) in DCM (10 mL) was added PPh_3 (910.93 mg, 3.473 mmol, 1.5 equiv) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 15 min at room temperature under nitrogen atmosphere. To the above mixture was added DEAD (403.23 mg, 2.315 mmol, 1 equiv) in portions at 0 °C. The resulting mixture was stirred for additional 2 h at room temperature. The reaction was monitored by LCMS. Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 1-[(1S)-1-(3-chlorophenyl)ethyl]-6-nitro-7-(trifluoromethyl)quinoxalin-2-one (110 mg, 11.94%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{17}H_{11}ClF_3N_3O_3$:397.04 m/z, found:398.0 $[M+H]^+$.



6-amino-1-[(1S)-1-(3-chlorophenyl)ethyl]-7-(trifluoromethyl)quinoxalin-2-one

To a stirred solution of 1-[(1S)-1-(3-chlorophenyl)ethyl]-6-nitro-7-(trifluoromethyl)quinoxalin-2-one (100 mg, 0.251 mmol, 1 equiv) in MeOH/H_2O(10:1, 5 mL) was added Fe (14.04 mg, 0.250 mmol, 10 equiv) and NH_4Cl (134.48 mg, 2.510 mmol, 10 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 70 °C under air atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (0-100%) to afford 6-amino-1-[(1S)-1-(3-chlorophenyl)ethyl]-7-(trifluoromethyl)quinoxalin-2-one (55 mg, 59.48%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{17}H_{14}F_3N_3O$:367.1 m/z, found:368.05 $[M+H]^+$.

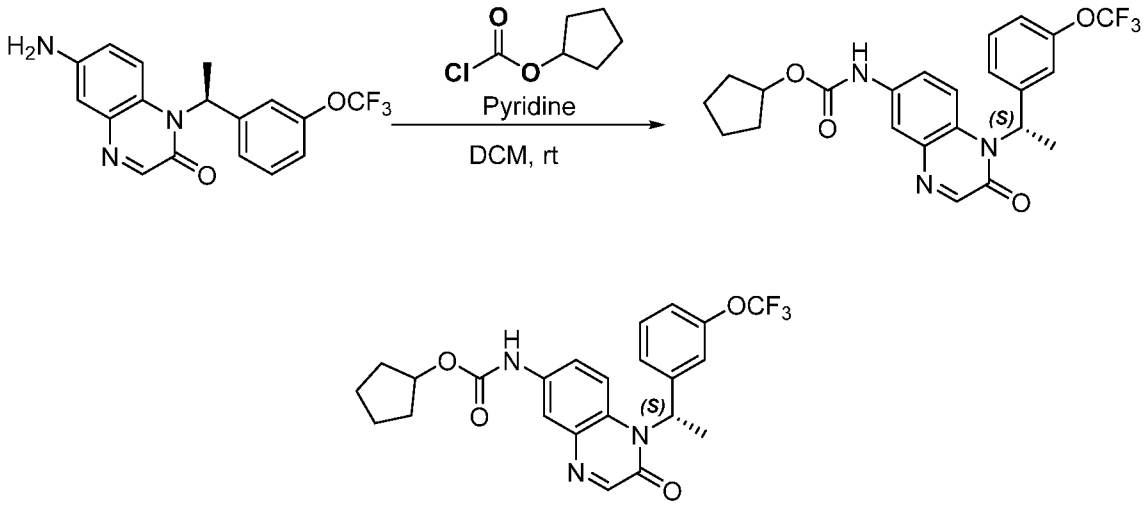


3-tert-butyl-1-{1-[(1S)-1-(3-chlorophenyl)ethyl]-2-oxo-7-(trifluoromethyl)quinoxalin-6-yl}urea

To a stirred solution of 6-amino-1-[(1S)-1-(3-chlorophenyl)ethyl]-7-(trifluoromethyl)quinoxalin-2-one (50 mg, 0.136 mmol, 1 equiv) in DCM (4 mL) was added TEA (41.27 mg, 0.408 mmol, 3 equiv) and 2-isocyanato-2-methylpropane (40.43 mg, 0.408 mmol, 3 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 1 days at room temperature under air atmosphere. The reaction was monitored by LCMS. Quenched with water (5 mL) and extracted with DCM (3 x 5 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by Prep-HPLC using a X Bridge Prep OBD C18 150 mm x 30 mm x 5 μm column (eluent: 43% to 59% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford 3-tert-butyl-1-{1-[(1S)-1-(3-chlorophenyl)ethyl]-2-oxo-7-(trifluoromethyl)quinoxalin-6-yl}urea (2.7 mg, 4.23%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{22}H_{22}ClF_3N_4O_2$:466.1 m/z, found:467.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.37 (d, J = 3.0 Hz, 2H), 7.68 (s, 1H), 7.44 – 7.37(m, 3H), 7.29 (s, 2H), 6.92 (s, 1H), 6.55 (d, J = 7.2 Hz, 1H), 1.85 (d, J = 7.2 Hz, 3H), 1.29 (s, 9H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.17.

Example 359: cyclopentyl (S)-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)carbamate

Synthetic Scheme

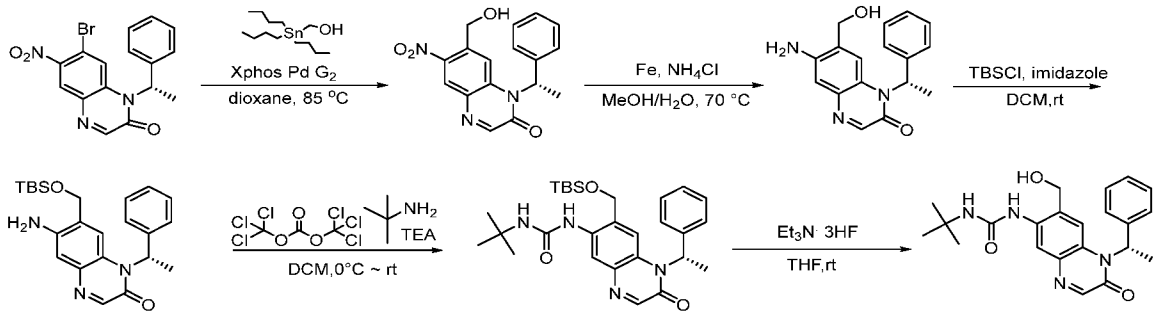


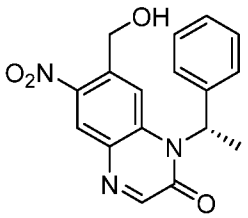
cyclopentyl (S)-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)carbamate

To a solution of 6-amino-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-2-one (80 mg, 0.229 mmol, 1 equiv) in DCM (5 mL) was added cyclopentyl carbonochloridate (51.05 mg, 0.344 mmol, 1.5 equiv) and pyridine (54.35 mg, 0.687 mmol, 3 equiv) at 0°C. The reaction was stirred at rt for 1h. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm column (eluent: 49% to 63% (v/v) CH_3CN and Water (10mmol/L NH_4HCO_3+0.05%$NH_3.H_2O$)) to afford the title compound cyclopentyl N-{2-oxo-1-[(1S)-1-[3-(trifluoromethoxy)phenyl]ethyl]quinoxalin-6-yl}carbamate (32.2 mg, 30.22%) as a yellow solid.LC/MS: mass calcd. for $C_{23}H_{22}F_3N_3O_4$:461.16 m/z, found:462.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.26 (s, 1H), 8.00 (s, 1H), 7.43 – 7.51 (m, 1H), 7.46 (s, 1H), 7.29 (q, J = 5.7 Hz, 3H), 7.17 (s, 1H), 6.57 (s, 1H), 5.00 – 5.15 (m, 1H), 1.85 – 1.91 (m, 5H), 1.65 – 1.72 (m, 4H), 1.60 (d, J = 9.4 Hz, 2H).^{19}F NMR (376 MHz, DMSO) δ(ppm): -56.6795.

Example 360: (S)-1-(tert-butyl)-3-(7-(hydroxymethyl)-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea

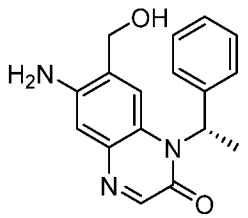
Synthetic Scheme





(S)-7-(hydroxymethyl)-6-nitro-1-(1-phenylethyl)quinoxalin-2(1H)-one

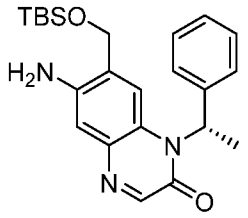
To a solution of 7-bromo-6-nitro-1-[(1S)-1-phenylethyl]quinoxalin-2-one (300 mg, 0.802 mmol, 1 equiv) in dioxane (3 mL) was added (tributylstannyl)methanol (386.14 mg, 1.203 mmol, 1.5 equiv) and XPhos Pd G_2 (63.08 mg, 0.080 mmol, 0.1 equiv). The reaction was stirred at 90°C for 12 h under N_2. The mixture was allowed to cool down to rt. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-(hydroxymethyl)-6-nitro-1-[(1S)-1-phenylethyl]quinoxalin-2-one (40 mg, 15.34%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{15}N_3O_4$: 325.11 m/z, found 323.95 $[M-H]^-$.



(S)-6-amino-7-(hydroxymethyl)-1-(1-phenylethyl)quinoxalin-2(1H)-one

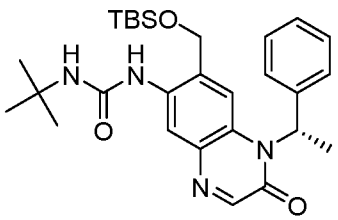
To a solution of 7-(hydroxymethyl)-6-nitro-1-[(1S)-1-phenylethyl]quinoxalin-2-one (40 mg, 0.123 mmol, 1 equiv) in MeOH (2 mL)/H_2O (0.2 mL) was added Fe (68.66 mg, 1.230 mmol, 10 equiv) and NH_4Cl (65.77 mg, 1.230 mmol, 10 equiv). The reaction was stirred at 70°C for 3 h.

Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to 6-amino-7-(hydroxymethyl)-1-[(1S)-1-phenylethyl]quinoxalin-2-one (25 mg, 68.84%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{17}N_3O_2$: 295.13 m/z, found 296.10 $[M+H]^+$.



(S)-6-amino-7-(((tert-butyldimethylsilyl)oxy)methyl)-1-(1-phenylethyl)quinoxalin-2(1H)-one

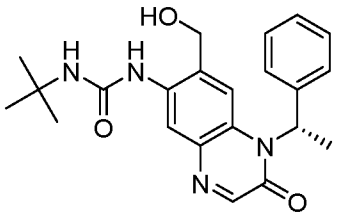
To a solution of 6-amino-7-(hydroxymethyl)-1-[(1S)-1-phenylethyl]quinoxalin-2-one (70 mg, 0.237 mmol, 1 equiv) in DCM (3 mL) was added TBSCl (53.58 mg, 0.355 mmol, 1.5 equiv) and imidazole (48.41 mg, 0.711 mmol, 3 equiv). The reaction was stirred at rt for 3 h. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-7-{[(tert-butyldimethylsilyl)oxy]methyl}-1-[(1S)-1-phenylethyl]quinoxalin-2-one (75 mg, 77.25%) as a white solid. MS (ESI): mass calcd. for $C_{23}H_{31}N_3O_2Si$: 409.22 m/z, found 410.25 $[M+H]^+$.



(S)-1-(tert-butyl)-3-(7-(((tert-butyldimethylsilyl)oxy)methyl)-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea

To a solution of 6-amino-7-{[(tert-butyldimethylsilyl)oxy]methyl}-1-[(1S)-1-phenylethyl]quinoxalin-2-one (50 mg, 0.122 mmol, 1 equiv) in DCM (1 mL) was added triphosgene (36.22 mg, 0.122 mmol, 1 equiv). The reaction was stirred at 0°C under N_2 for 1 h. The reaction was added TEA (74.12 mg, 0.732 mmol, 6 equiv) and stirred at rt under N_2 for 1 h. The reaction was added 2-methylpropan-2-amine (26.78 mg, 0.366 mmol, 3 equiv) and stirred at

rt under N_2 for 1 h. Quenched with water (5 mL) and extracted with DCM (3 x 5 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 3-tert-butyl-1-(7-{[(tert-butyldimethylsilyl)oxy]methyl}-2-oxo-1-[(1S)-1-phenylethyl]quinoxalin-6-yl)urea (20 mg, 32.21%) as a white solid. LC/MS (ESI): mass calcd. for $C_{28}H_{40}N_4O_3Si$: 508.29 m/z, found: 509.35 $[M+H]^+$.

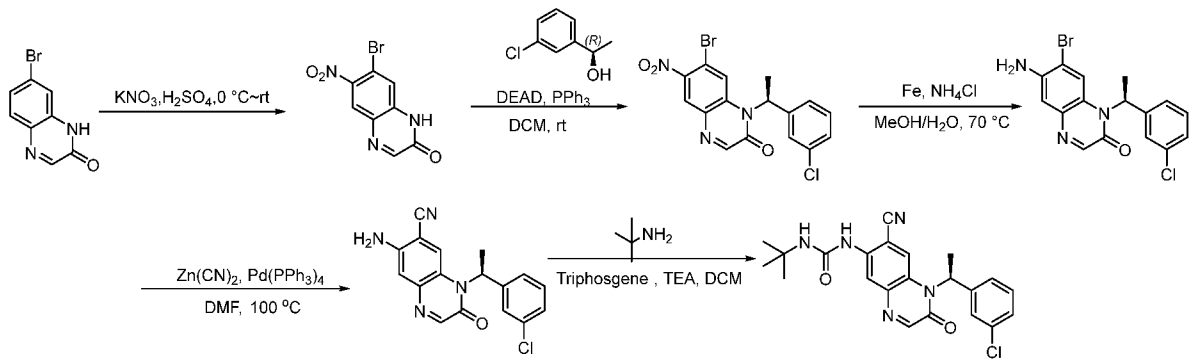


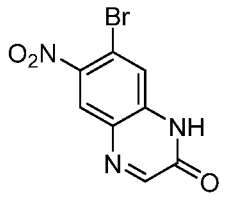
1-(1-benzyl-5-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

To a solution of 3-tert-butyl-1-(7-{[(tert-butyldimethylsilyl)oxy]methyl}-2-oxo-1-[(1S)-1-phenylethyl]quinoxalin-6-yl)urea (20 mg, 0.039 mmol, 1 equiv) in THF (1 mL) was added Triethylamine trihydrofluoride (9.51 mg, 0.058 mmol, 1.5 equiv). The reaction was stirred at rt for 1 h. Quenched with water (5 mL) and extracted with EA (3 x 5 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm (eluent: 22% to 38% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-[7-(hydroxymethyl)-2-oxo-1-[(1S)-1-phenylethyl]quinoxalin-6-yl]urea (6.2 mg, 39.70%) as a white solid. LC/MS (ESI): mass calcd. for $C_{22}H_{26}N_4O_3$: 394.20 m/z, found: 395.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.21-8.27 (d, J = 18 Hz, 2H), 7.58 (s, 1H), 7.21 – 7.38 (m, 6H), 6.60 (s, 2H), 5.29-5.33 (t, J = 12 Hz, 1H), 4.26-4.42 (m, 2H), 1.87-1.89 (d, J = 6 Hz, 3H), 1.27 (s, 9H).

Example 361: 3-tert-butyl-1-{1-[(1S)-1-(3-chlorophenyl)ethyl]-7-cyano-2-oxoquinoxalin-6-yl}urea

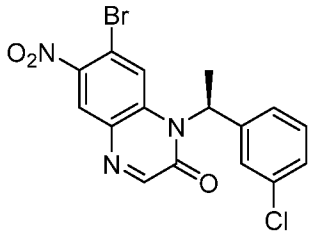
Synthetic Scheme





7-bromo-6-nitro-1H-quinoxalin-2-one

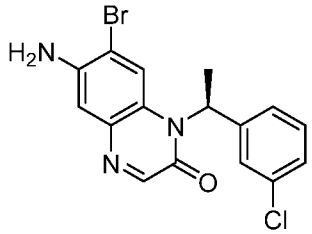
To a solution of 7-bromo-1H-quinoxalin-2-one (5 g, 22.218 mmol, 1 equiv) in H_2SO_4 (50 mL) was added KNO_3 (2.92 g, 28.883 mmol, 1.3 equiv) at 0 °C. The reaction was stirred at 0 °C for 1 h. Quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-bromo-6-nitro-1H-quinoxalin-2-one (4.5 g, 75.00%) as a yellow solid. MS (ESI): mass calcd. for $C_8H_4BrN_3O_3$:268.94 m/z, found:269.94, 271.96 $[M+H, M+H+2]^+$.



7-bromo-1-[(1S)-1-(3-chlorophenyl)ethyl]-6-nitroquinoxalin-2-one

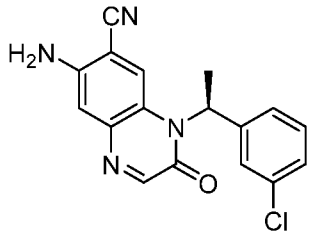
To a solution of 7-bromo-6-nitro-1H-quinoxalin-2-one (1.5 g, 5.555 mmol, 1 equiv) in DCM (20 mL) was added (1R)-1-(3-chlorophenyl)ethanol (0.87 g, 5.555 mmol, 1 equiv) and PPh_3 (2.19 g, 8.332 mmol, 1.5 equiv). After the mixture was stirred at rt for 1h, to the above mixture was added DEAD (0.97 g, 5.555 mmol, 1 equiv) dropwise at 0 °C. The resulting mixture was stirred for 2 h at 25 °C. Quenched with water (100 mL) and extracted with DCM (3 x 100 mL). The

combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-bromo-1-[(1S)-1-(3-chlorophenyl)ethyl]-6-nitroquinoxalin-2-one (210 mg, 9.25%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{11}BrClN_3O_3$:406.97 m/z, found:407.97, 409.97 [M+H, M+H+2]$^+$.



6-amino-7-bromo-1-[(1S)-1-(3-chlorophenyl)ethyl]quinoxalin-2-one

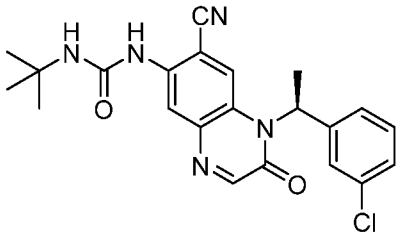
To a solution of 7-bromo-1-[(1S)-1-(3-chlorophenyl)ethyl]-6-nitroquinoxalin-2-one (280 mg, 0.685 mmol, 1 equiv) in MeOH (10 mL) and H_2O (1 mL) was added Fe (382.65 mg, 6.850 mmol, 10 equiv) and NH_4Cl (366.51 mg, 6.850 mmol, 10 equiv). The reaction was stirred at 70 °C for 2 h. The mixture was allowed to cool down to room temperature and quenched with water (50 mL). The resulting mixture was filtered; the filter cake was washed with EA (50 mL). The filtrate was extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-7-bromo-1-[(1S)-1-(3-chlorophenyl)ethyl]quinoxalin-2-one) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{13}BrClN_3O$:376.99 m/z, found:377.99, 379.99 [M+H, M+H+2]$^+$.



7-amino-4-[(1S)-1-(3-chlorophenyl)ethyl]-3-oxoquinoxaline-6-carbonitrile

To a solution of 6-amino-7-bromo-1-[(1S)-1-(3-chlorophenyl)ethyl]quinoxalin-2-one (140 mg, 0.370 mmol, 1 equiv) in dimethylformamide (8 mL) was added $Zn(CN)_2$ (52.10 mg, 0.444 mmol, 1.2 equiv) and $Pd(PPh_3)_4$ (42.73 mg, 0.037 mmol, 0.1 equiv). The reaction was stirred at 100 °C for 2 h under N_2 atmosphere. The mixture was allowed to cool down to room temperature. Quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were

washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-amino-4-[(1S)-1-(3-chlorophenyl)ethyl]-3-oxoquinoxaline-6-carbonitrile (60 mg, 49.97%) as a red solid. MS (ESI): mass calcd. for $C_{17}H_{13}ClN_4O$:324.08 m/z, found:325.08 $[M+H]^+$.

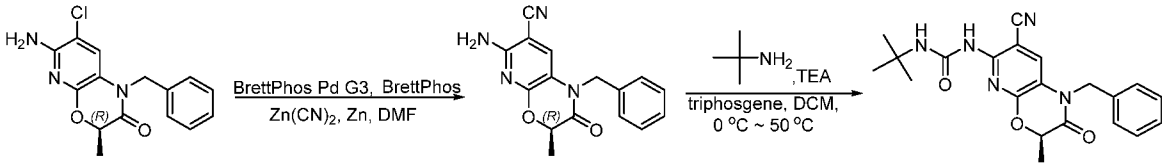


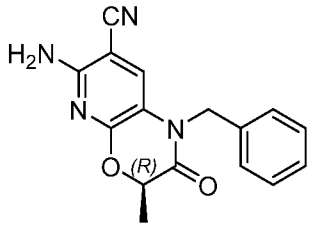
3-tert-butyl-1-{1-[(1S)-1-(3-chlorophenyl)ethyl]-7-cyano-2-oxoquinoxalin-6-yl}urea

To a solution of 7-amino-4-[(1S)-1-(3-chlorophenyl)ethyl]-3-oxoquinoxaline-6-carbonitrile (50 mg, 0.154 mmol, 1 equiv) in DCM (8 mL) was added triphosgene (22.84 mg, 0.077 mmol, 0.5 equiv) at 0 °C under N_2 atmosphere. The resulting mixture was stirred for 2 h at 25 °C. Then TEA (46.74 mg, 0.462 mmol, 3 equiv) was added into above system at 0 °C. The resulting mixture was stirred for 1 h at 25 °C. To the above mixture was added erbumine (16.89 mg, 0.231 mmol, 1.5 equiv) dropwise at 0 °C. The reaction was stirred at 25 °C for 2 h. Quenched with water (30 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using aXselect CSH C18 OBD 30*150 mm, 5μm column (eluent: 42% to 82% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-{1-[(1S)-1-(3-chlorophenyl)ethyl]-7-cyano-2-oxoquinoxalin-6-yl}urea (14.7 mg, 21.84%) as a yellow solid. LC/MS (ESI): mass calcd. for $C_{22}H_{22}ClN_5O_2$:423.15 m/z, found:424.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.40 (s, 1H), 8.32 (s, 1H), 7.53 – 7.90 (m, 1H), 7.40 – 7.45 (m, 1H), 7.32 – 7.40 (m, 2H), 7.23 – 7.40 (m, 1H), 6.96 (s, 1H), 6.38 (s, 1H), 1.87 (d, J = 7.0 Hz, 3H), 1.31 (s, 9H).

Example 362: 1-[(3R)-1-benzyl-7-cyano-3-methyl-2-oxo-3H-pyrido[2,3-b][1,4]oxazin-6-yl]-3-tert-butylurea

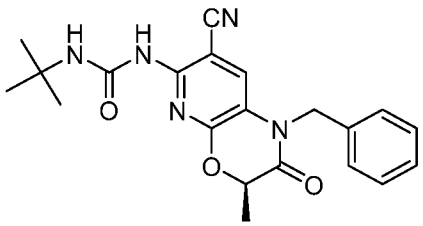
Synthetic Scheme





(3R)-6-amino-1-benzyl-3-methyl-2-oxo-3H-pyrido[2,3-b][1,4]oxazine-7-carbonitrile

To a stirred mixture of (3R)-6-amino-1-benzyl-7-chloro-3-methyl-3H-pyrido[2,3-b][1,4]oxazin-2-one (50 mg, 0.165 mmol, 1 equiv) and $Zn(CN)_2$ (38.66 mg, 0.330 mmol, 2 equiv) in DMF (5 mL) was added BrettPhos Pd G_3 (298.44 mg, 0.330 mmol, 02 equiv) and BrettPhos (17.67 mg, 0.033 mmol, 0.2 equiv) and Zn (3.23 mg, 0.050 mmol, 0.3 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 1h at 120°C under nitrogen atmosphere. After cooling down to room temperature, the reaction was quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%)to afford (3R)-6-amino-1-benzyl-3-methyl-2-oxo-3H-pyrido[2,3-b][1,4]oxazine-7-carbonitrile (44 mg, 90.7%) as a white solid. LC/MS (ESI): mass calcd. for $C_{16}H_{14}N_4O_2$:294.1 m/z, found:295.2 $[M+H]^+$.



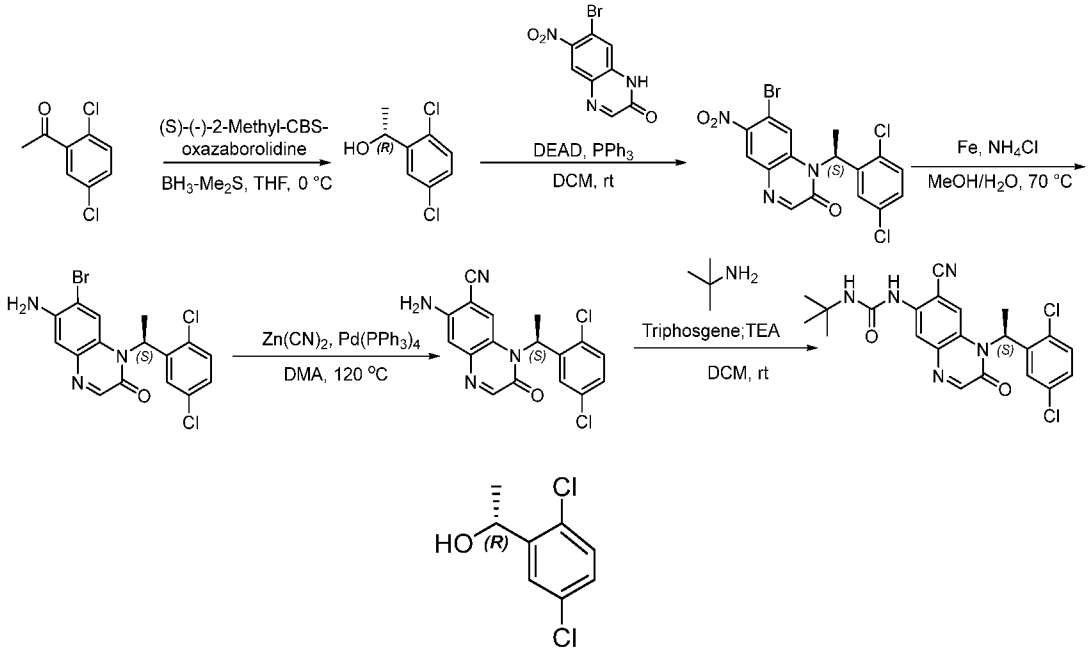
1-[(3R)-1-benzyl-7-cyano-3-methyl-2-oxo-3H-pyrido[2,3-b][1,4]oxazin-6-yl]-3-tert-butylurea

To a stirred solution of (3R)-6-amino-1-benzyl-3-methyl-2-oxo-3H-pyrido[2,3-b][1,4]oxazine-7-carbonitrile (50 mg, 0.170 mmol, 1 equiv) and triphosgene (60.49 mg, 0.204 mmol, 1.2 equiv) in DCM (5 mL) was added TEA (51.57 mg, 0.510 mmol, 3 equiv) dropwise at 0°C under nitrogen

atmosphere. The resulting mixture was stirred for 30 min at 50 °C under nitrogen atmosphere. To the above mixture was added 2-methylpropan-2-amine (24.85 mg, 0.340 mmol, 2 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 30 min at room temperature. The reaction was quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a YMC-Actus Triart C_{18} ExRS 150 mm x 30 mm x 5 μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford 1-[(3R)-1-benzyl-7-cyano-3-methyl-2-oxo-3H-pyrido[2,3-b][1,4]oxazin-6-yl]-3-tert-butylurea (2.4 mg, 3.55%) as a white solid. LC/MS (ESI): mass calcd. for $C_{21}H_{23}N_5O_3$:393.2 m/z, found:394.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 7.82 (s, 1H), 7.32-7.46 (m, 2H), 7.23-7.32 (m, 3H), 6.89 (s, 1H), 5.22-5.35 (m, 1H), 5.15 (s, 2H), 1.58 (d, J = 6.8 Hz, 3H), 1.29 (s, 9H).

Example 363: (S)-1-(tert-butyl)-3-(7-cyano-1-(1-(2,5-dichlorophenyl) ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl) urea

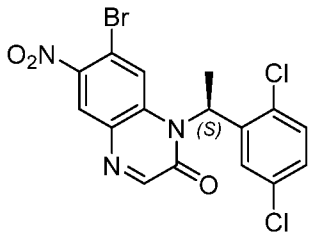
Synthetic Scheme



(1R)-1-(2,5-dichlorophenyl) ethanol

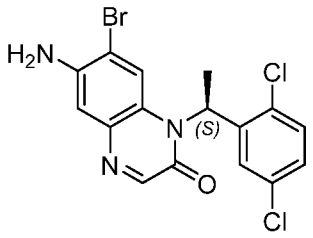
To a stirred solution of CBS (0.56 g, 2.116 mmol, 0.2 equiv) in THF (10 mL) was added BH_3-Me_2S (0.53 g, 6.983 mmol, 0.66 equiv) and 1-(2,5-dichlorophenyl) ethanone (2 g, 10.580 mmol,

1 equiv) in portions at 0 °C under air atmosphere. The resulting mixture was stirred for 1 h at 0 °C under air atmosphere. The reaction was quenched with water at 0 °C. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford (1R)-1-(2,5-dichlorophenyl) ethanol (1.83 g, 90.54%) as a yellow oil. MS (ESI): mass calcd. For $C_8H_8Cl_2O$: 190.00 m/z, found 191.15$[M+H]^+$.



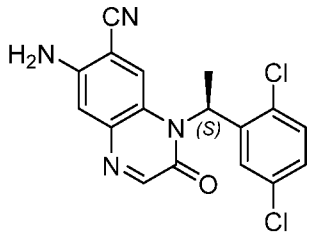
7-bromo-1-[(1S)-1-(2,5-dichlorophenyl) ethyl]-6-nitroquinoxalin-2-one

To a stirred solution of (1R)-1-(2,5-dichlorophenyl) ethanol (300 mg, 1.570 mmol, 1 equiv) and 7-bromo-6-nitro-1H-quinoxalin-2-one (508.85 mg, 1.884 mmol, 1.2 equiv) in DCM (5 mL) was added PPh_3 (617.80 mg, 2.355 mmol, 1.5 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. To the above mixture was added DEAD (410.21 mg, 2.355 mmol, 1.5 equiv) dropwise over 1 min at 0 °C. The resulting mixture was stirred for additional 1 h at room temperature. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The reaction was quenched with water at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 7-bromo-1-[(1S)-1-(2,5-dichlorophenyl) ethyl]-6-nitroquinoxalin-2-one (50 mg, 7.19%) as a yellow oil. MS (ESI): mass calcd. For $C_{16}H_{10}BrCl_2N_3O_3$: 440.93 m/z, found 443.85 $[M+H, M+H+2]^+$.



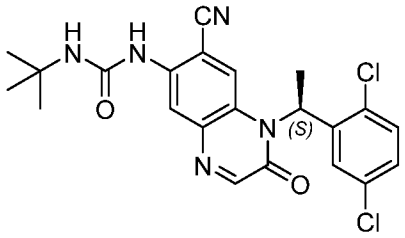
6-amino-7-bromo-1-[(1S)-1-(2,5-dichlorophenyl) ethyl] quinoxalin-2-one

A mixture of 7-bromo-1-[(1S)-1-(2,5-dichlorophenyl) ethyl]-6-nitroquinoxalin-2-one (220 mg, 0.497 mmol, 1 equiv), Fe (277.28 mg, 4.970 mmol, 10 equiv) and NH_4Cl (265.59 mg, 4.970 mmol, 10 equiv) was added EtOH (10 mL) and H_2O (1 mL) and stirred at 70 °C for 1 h. The mixture was allowed to cool down to room temperature. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-7-bromo-1-[(1S)-1-(2,5-dichlorophenyl) ethyl] quinoxalin-2-one (200 mg, 97.51%) as a yellow solid. MS (ESI): mass calcd. for $C_{16}H_{12}BrCl_2N_3O$: 410.95 m/z, found 413.95 $[M+H, M+H+2]^+$.



7-amino-4-[(1S)-1-(2,5-dichlorophenyl) ethyl]-3-oxoquinoxaline-6-carbonitrile

A mixture of 6-amino-7-bromo-1-[(1S)-1-(2,5-dichlorophenyl) ethyl] quinoxalin-2-one (200 mg, 0.484 mmol, 1 equiv), $Zn(CN)_2$ (68.22 mg, 0.581 mmol, 1.2 equiv) and $Pd(PPh_3)_4$ (55.95 mg, 0.048 mmol, 0.1 equiv) was treated with dimethylformamide (10 mL) and stirred at 110 °C under N_2 for 1 h. The mixture was allowed to cool down to room temperature. Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-amino-4-[(1S)-1-(2,5-dichlorophenyl) ethyl]-3-oxoquinoxaline-6-carbonitrile (120 mg, 69.00%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{12}Cl_2N_4O$: 358.04 m/z, found 359.10 $[M+H]^+$.



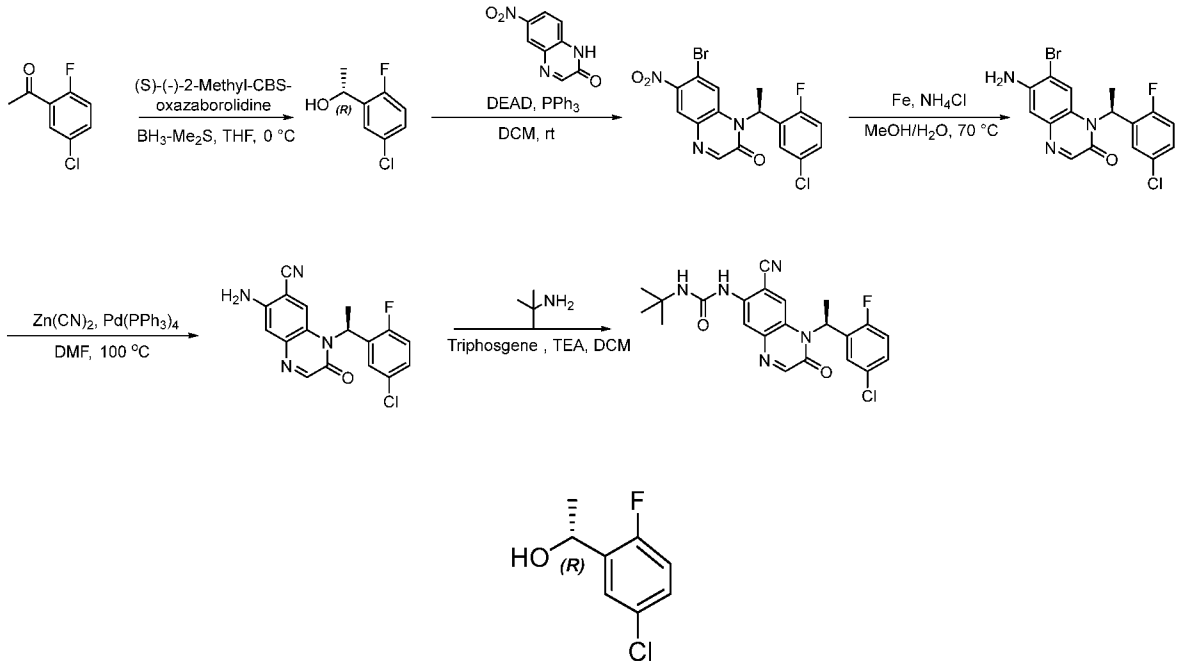
3-tert-butyl-1-{7-cyano-1-[(1S)-1-(2,5-dichlorophenyl) ethyl]-2-oxoquinoxalin-6-yl} urea

A solution of 7-amino-4-[(1S)-1-(2,5-dichlorophenyl) ethyl]-3-oxoquinoxaline-6-carbonitrile (20 mg, 0.056 mmol, 1 equiv) in DCM (5 mL) was treated with Triphosgene (16.52 mg, 0.056

mmol, 1 equiv) for 1 h at 0 °C under nitrogen atmosphere followed by the addition of TEA (28.17 mg, 0.280 mmol, 5 equiv) dropwise at 0 °C. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. To the above mixture was added erbumine (12.22 mg, 0.168 mmol, 3 equiv) dropwise over 1 min at room temperature. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column 150 mm x 30 mm x 5 μm column (eluent: 44% to 74% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3+0.05%NH_3H_2O) to afford 3-tert-butyl-1-{7-cyano-1-[(1S)-1-(2,5-dichlorophenyl) ethyl]-2-oxoquinoxalin-6-yl} urea (1 mg, 3.89%) as a yellow solid. MS (ESI): mass calcd. for $C_{22}H_{21}Cl_2N_5O_2$: 457.11 m/z, found 458.15 $[M+H]^+$. ^1H NMR (300 MHz, Acetonitrile-d_3) δ 8.45 (s, 1H), 8.12 (s, 1H), 7.83 – 7.98 (m, 2H), 7. 28 – 7.45 (m, 2H), 7.15 (s, 1H), 5.92 – 6.20 (m, 1H), 5.75 (s, 1H), 1.90 – 1.95 (m, 3H), 1.38 – 1.41 (m, 9H).

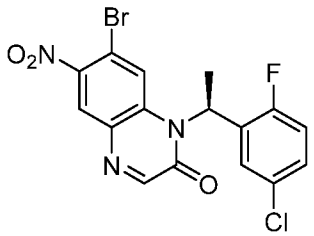
Example 364: 3-tert-butyl-1-{1-[(1S)-1-(5-chloro-2-fluorophenyl)ethyl]-7-cyano-2-oxoquinoxalin-6-yl}urea

Synthetic Schemes



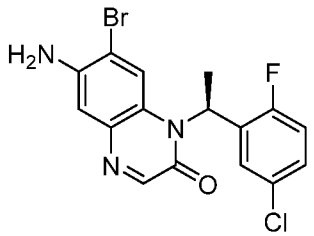
(1R)-1-(5-chloro-2-fluorophenyl)ethanol

To a solution of (S)-(-)-2-Methyl-CBS-oxazaborolidine (1.22 g, 4.636 mmol, 0.4 equiv) in THF (24 mL) was added BH_3-Me_2S (1.16 g, 15.297 mmol, 1.32 equiv) and 1-(5-chloro-2-fluorophenyl)ethanone (2 g, 11.589 mmol, 1 equiv) at 0°C. The reaction was stirred at 0°C for 2 h. TLC showed the desired product was generated. Quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (1R)-1-(5-chloro-2-fluorophenyl)ethanol (1.4 g, 69.19%) as a white solid.



7-bromo-1-[(1S)-1-(5-chloro-2-fluorophenyl)ethyl]-6-nitroquinoxalin-2-one

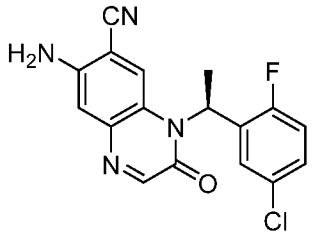
To a solution of (1R)-1-(5-chloro-2-fluorophenyl)ethanol (970 mg, 5.556 mmol, 1 equiv) in DCM (12 mL) was added 7-bromo-6-nitro-1H-quinoxalin-2-one (1.50 g, 5.556 mmol, 1 equiv) and PPh_3 (2.19 g, 8.334 mmol, 1.5 equiv). After the mixture was stirred at rt for 1 h, to the above mixture was added DEAD (0.97 g, 5.556 mmol, 1 equiv) dropwise at 0 °C. The resulting mixture was stirred for 2 h at 25 °C. Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-bromo-1-[(1S)-1-(5-chloro-2-fluorophenyl)ethyl]-6-nitroquinoxalin-2-one (140 mg, 5.91%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{10}BrClFN_3O_3$:424.96 m/z, found:425.96, 427.96 [M+H, M+H+2]$^+$.



6-amino-7-bromo-1-[(1S)-1-(5-chloro-2-fluorophenyl)ethyl]quinoxalin-2-one

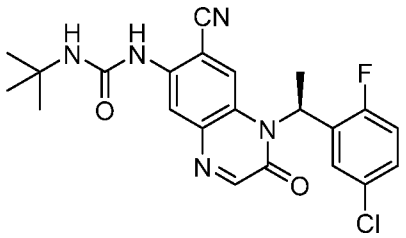
To a solution of 7-bromo-1-[(1S)-1-(5-chloro-2-fluorophenyl)ethyl]-6-nitroquinoxalin-2-one (190 mg, 0.445 mmol, 1 equiv) in MeOH (4 mL) and H_2O (0.4 mL) was added Fe (248.71 mg, 4.450

mmol, 10 equiv) and NH_4Cl (238.22 mg, 4.450 mmol, 10 equiv). The reaction was stirred at 70 °C for 2 h. The mixture was allowed to cool down to room temperature and quenched with water (50 mL). The resulting mixture was filtered, the filter cake was washed with EA (50 mL). The filtrate was extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-7-bromo-1-[(1S)-1-(5-chloro-2-fluorophenyl)ethyl]quinoxalin-2-one (50 mg, 28.31%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{12}BrClFN_3O$:394.98 m/z, found:395.98, 397.98 $[M+H, M+H+2]^+$.



7-amino-4-[(1S)-1-(5-chloro-2-fluorophenyl)ethyl]-3-oxoquinoxaline-6-carbonitrile

To a solution of 6-amino-7-bromo-1-[(1S)-1-(5-chloro-2-fluorophenyl)ethyl]quinoxalin-2-one (60 mg, 0.151 mmol, 1 equiv) in dimethylformamide (3 mL) was added $Zn(CN)_2$ (21.31 mg, 0.181 mmol, 1.2 equiv) and $Pd(PPh_3)_4$ (17.48 mg, 0.015 mmol, 0.1 equiv). The reaction was stirred at 100 °C for 2 h under N_2 atmosphere. The mixture was allowed to cool down to room temperature. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-amino-4-[(1S)-1-(5-chloro-2-fluorophenyl)ethyl]-3-oxoquinoxaline-6-carbonitrile (30 mg, 57.86%) as a red solid. MS (ESI): mass calcd. for $C_{17}H_{12}ClFN_4O$:342.07 m/z, found:343.07 $[M+H]^+$.

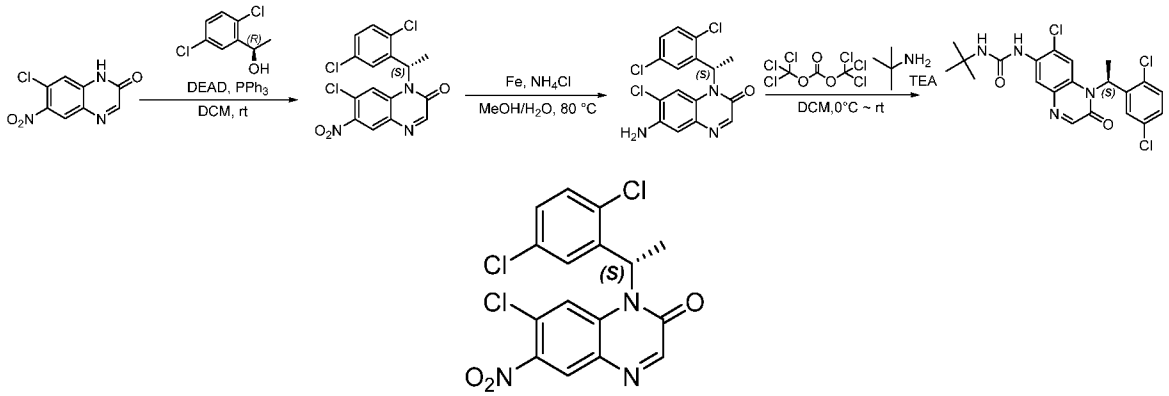


3-tert-butyl-1-{1-[(1S)-1-(5-chloro-2-fluorophenyl)ethyl]-7-cyano-2-oxoquinoxalin-6-yl}urea

To a solution of 7-amino-4-[(1S)-1-(5-chloro-2-fluorophenyl)ethyl]-3-oxoquinoxaline-6-carbonitrile (30 mg, 0.088 mmol, 1 equiv) in DCM (5 mL) was added triphosgene (12.99 mg, 0.044 mmol, 0.5 equiv) at 0 °C under N_2 atmosphere. The resulting mixture was stirred for 1 h at 25 °C. Then TEA (26.57 mg, 0.264 mmol, 3 equiv) was added into above system at 0 °C. The resulting mixture was stirred 1 h at 25 °C. To the above mixture was added erbumine (9.60 mg, 0.132 mmol, 1.5 equiv) dropwise at 0 °C. The reaction was stirred at 25 °C for 2 h. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using XBridge Prep OBD C18 30*150 mm, 5μm column (eluent: 40% to 62% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-{1-[(1S)-1-(5-chloro-2-fluorophenyl)ethyl]-7-cyano-2-oxoquinoxalin-6-yl}urea (12.6 mg, 30.13%) as a yellow solid. MS (ESI): mass calcd. for $C_{22}H_{21}ClFN_5O_2$:441.14 m/z, found: 440.10 $[M-H]^-$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.47 – 8.38 (m, 2H), 8.25 – 8.38 (s, 2H), 7.67 – 7.76 (m, 1H), 7.35 – 7.46 (m, 1H), 7.07 – 7.19 (m, 1H), 6.95 (s, 1H), 6.29 – 6.37 (m, 1H), 1.83 (d, J = 6.9 Hz, 3H), 1.36 (s, 9H). ^{19}F NMR (282 MHz, DMSO) δ -118.07.

Example 365: (S)-1-(tert-butyl)-3-(7-chloro-1-(1-(2,5-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

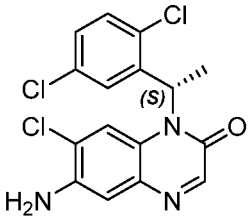
Synthetic Scheme



(S)-7-chloro-1-(1-(2,5-dichlorophenyl)ethyl)-6-nitroquinoxalin-2(1H)-one

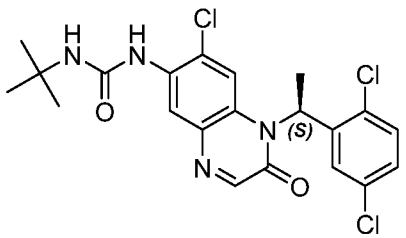
To a solution of 7-chloro-6-nitro-1H-quinoxalin-2-one (800 mg, 3.546 mmol, 1 equiv) in DCM (10 mL) was added (1R)-1-(2,5-dichlorophenyl)ethanol (1016.27 mg, 5.319 mmol, 1.5 equiv) and PPh_3 (1395.23 mg, 5.319 mmol, 1.5 equiv). The reaction was stirred at rt under N_2 for 0.5h. To the above mixture was added DEAD (926.40 mg, 5.319 mmol, 1.5 equiv) under N_2 at 0°C. The

resulting mixture was stirred for additional 1h at 0°C. The reaction was monitored by TLC. Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-chloro-1-[(1S)-1-(2,5-dichlorophenyl)ethyl]-6-nitroquinoxalin-2-one) as a yellow solid.



(S)-6-amino-7-chloro-1-(1-(2,5-dichlorophenyl)ethyl)quinoxalin-2(1H)-one

To a solution of 7-chloro-1-[(1S)-1-(2,5-dichlorophenyl)ethyl]-6-nitroquinoxalin-2-one (60 mg, 0.151 mmol, 1 equiv) in MeOH (5 mL) and H_2O (0.5 mL) was added Fe (84.06 mg, 1.510 mmol, 10 equiv) and NH_4Cl (80.51 mg, 1.510 mmol, 10 equiv). The reaction was stirred at 80 °C for 1h. The mixture was allowed to cool down to rt. The resulting mixture was filtered, the filter cake was washed with MeOH (3x50 mL). The filtrate was concentrated under reduced pressure. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-7-chloro-1-[(1S)-1-(2,5-dichlorophenyl)ethyl]quinoxalin-2-one (30 mg, 54.07%) as a yellow solid. LC/MS: mass calcd. for $C_{16}H_{12}Cl_3N_3O$:367.00 m/z, found:367.95 $[M+H]^+$.



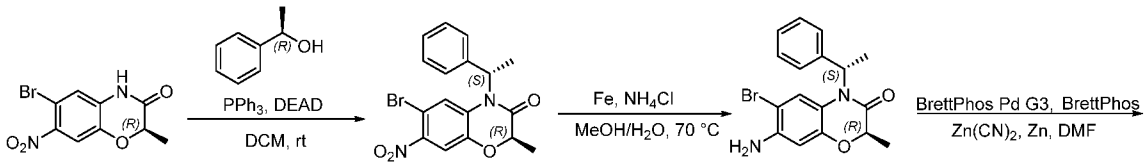
(S)-1-(tert-butyl)-3-(7-chloro-1-(1-(2,5-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

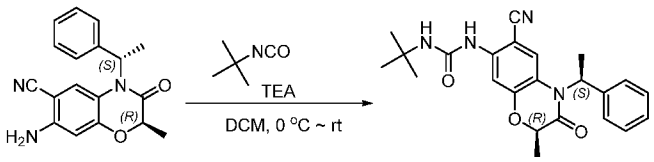
To a solution of 6-amino-7-chloro-1-[(1S)-1-(2,5-dichlorophenyl)ethyl]quinoxalin-2-one (30 mg, 0.081 mmol, 1 equiv) in DCM (3 mL) was added triphosgene (24.15 mg, 0.081 mmol, 1 equiv) under N_2 at 0 °C. The reaction was stirred at 0 °C under N_2 for 1h. To the above mixture was added TEA (24.71 mg, 0.243 mmol, 3 equiv) at 0°C. The resulting mixture was stirred for additional 1h

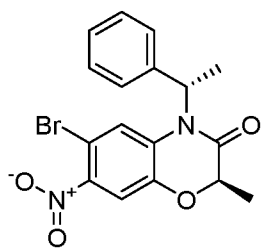
at rt. Then, to the above mixture was added erbumine (17.86 mg, 0.243 mmol, 3 equiv). The resulting mixture was stirred for additional 1h at rt. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Shield RP18 OBD Column30*150 mm column (eluent: 51% to 67% (v/v) CH_3CN and Water(10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$)) to afford the title compound 3-tert-butyl-1-{7-chloro-1-[(1S)-1-(2,5-dichlorophenyl)ethyl]-2-oxoquinoxalin-6-yl}urea (22 mg, 57.79%) as a yellow solid. LC/MS: mass calcd. for $C_{21}H_{21}Cl_3N_4O_2$:466.07 m/z, found:467.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.06 (d, J = 9.7 Hz, 2H), 7.92 (s, 1H), 7.84 (d, J = 2.2 Hz, 1H), 7.35 – 7.48 (m, 2H), 6.98 (s, 1H), 6.09 (d, J = 7.0 Hz, 1H), 1.84 (d, J = 6.8 Hz, 3H), 1.32 (s, 9H).

Example 366: 1-(tert-butyl)-3-((R)-6-cyano-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

Synthetic Scheme

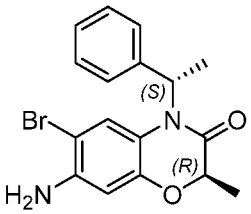






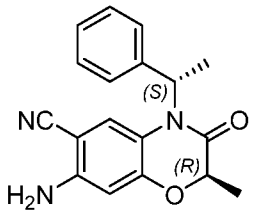
(R)-6-bromo-2-methyl-7-nitro-4-((S)-1-phenylethyl)-2H-benzo[b][1,4] oxazin-3(4H)-one

To a stirred solution of (2R)-6-bromo-2-methyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (300 mg, 1.045 mmol, 1 equiv) and (R)-1-phenylethan-1-ol (127.67 mg, 1.045 mmol, 1 equiv) in DCM (4 mL) were added PPh_3 (411.16 mg, 1.567 mmol, 1.5 equiv) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 0.5 h at room temperature under nitrogen atmosphere. Then, to the above solution was added DEAD (546.00 mg, 3.135 mmol, 3 equiv) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS. The reaction was quenched with water (15 mL). The resulting mixture was extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford (R)-6-bromo-2-methyl-7-nitro-4-((S)-1-phenylethyl)-2H-benzo[b][1,4] oxazin-3(4H)-one (225 mg, 55%) as a yellow oil. LC/MS: mass calcd for $C_{17}H_{15}BrN_2O_4$: 390.02, found: 391.05, 393.05 $[M+H, M+H+2]^+$.



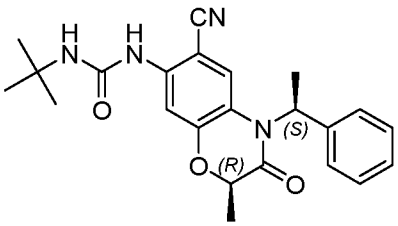
(R)-7-amino-6-bromo-2-methyl-4-((S)-1-phenylethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

To a stirred solution of (R)-6-bromo-2-methyl-7-nitro-4-((S)-1-phenylethyl)-2H-benzo[b][1,4] oxazin-3(4H)-one (220 mg, 0.562 mmol, 1 equiv) and NH_4Cl (300.80 mg, 5.620 mmol, 10 equiv) in $MeOH/H_2O$ (10:1, 4 mL) was added Fe (314.04 mg, 5.620 mmol, 10 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 70 °C under air atmosphere. Desired product could be detected by LCMS. After cooling down to rt, the reaction was quenched with water (15 mL). The resulting mixture was extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford (R)-7-amino-6-bromo-2-methyl-4-((S)-1-phenylethyl)-2H-benzo[b][1,4] oxazin-3(4H)-one (190 mg, 70.15%) as a yellow solid. LC/MS: mass calcd for $C_{17}H_{17}BrN_2O_2$: 360.05, found: 361.02, 363.02 $[M+H, M+H+2]^+$.



(R)-7-amino-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile

To a stirred solution of (R)-7-amino-6-bromo-2-methyl-4-((S)-1-phenylethyl)-2H-benzo[b] [1,4] oxazin-3(4H)-one (190 mg, 0.526 mmol, 1 equiv) and BrettPhos Pd G3 (95.36 mg, 0.105 mmol, 0.2 equiv) in DMF (5 mL) were added BrettPhos (56.47 mg, 0.105 mmol, 0.2 equiv), $Zn(CN)_2$ (12.35 mg, 0.105 mmol, 0.2 equiv), and Zn (68.78 mg, 1.052 mmol, 2 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere. Desired product could be detected by LCMS. After cooling down to rt, the reaction was quenched with water (15 mL). The resulting mixture was extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford (R)-7-amino-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b] [1,4] oxazine-6-carbonitrile (118 mg, 51.10%) as a yellow oil. LC/MS: mass for $C_{18}H_{17}N_3O_2$:307.13, found: 308.02 $[M+H]^+$.



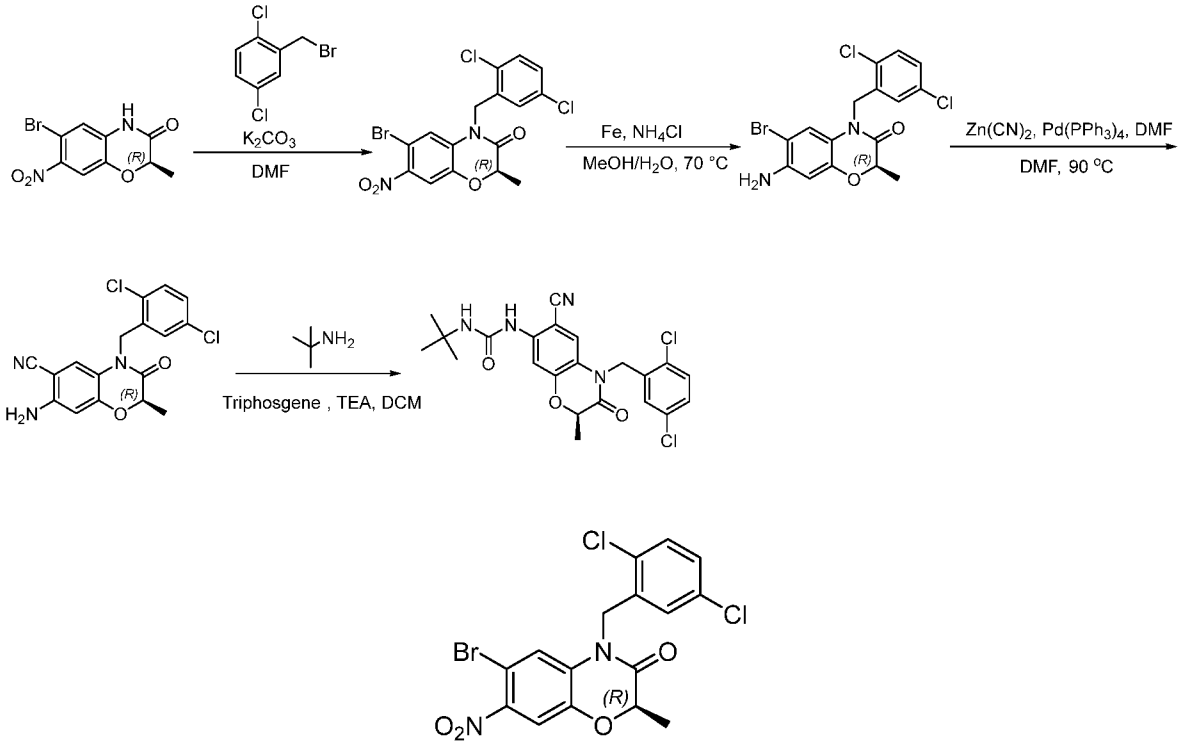
1-(tert-butyl)-3-((R)-6-cyano-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4] oxazin-7-yl)urea

To a stirred solution of (R)-7-amino-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b] [1,4] oxazine-6-carbonitrile (108 mg, 0.351 mmol, 1 equiv) and 2-isocyanato-2-methylpropane (34.83 mg, 0.351 mmol, 1 equiv) in DCM (4 mL) was added TEA (106.67 mg, 1.053 mmol, 3 equiv) in portions at 0 °C under air atmosphere. The resulting mixture was stirred for 2 h at room temperature under air atmosphere. Desired product could be detected by LCMS. The reaction was quenched with water (15 mL). The resulting mixture was extracted with ethyl

acetate (3 x 15 mL). The crude product (60mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C_{18} OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water (10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min mL/min; Gradient: 50% B to 80% B in 7 min; Wave Length: 254 nm; RT1(min): 5.9 ; Number Of Runs: 2) to afford 1-(tert-butyl)-3-((R)-6-cyano-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4] oxazin-7-yl)urea(37.7 mg, 26.39%) as a white solid. LC/MS: mass calcd for $C_{23}H_{26}N_4O_3$:406.20, found: 407.25 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 1H), 7.84 (s, 1H), 7.43 – 7.33 (m, 3H), 7.20-7.33 (m, 3H), 6.97 (d, J = 9.2 Hz,2H), 5.95-6.14 (m, 1H),1.78(d, J = 7.1 Hz,3H),1.48(d, J = 6.8 Hz,3H), 1.28 (s, 9H).

Example 367: 3-tert-butyl-1-[(2R)-6-cyano-4-[(2,5-dichlorophenyl)methyl]-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]urea

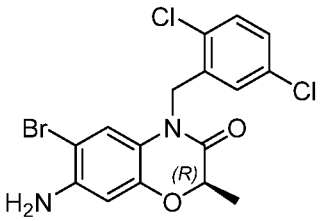
Synthetic Scheme



(2R)-6-bromo-4-[(2,5-dichlorophenyl)methyl]-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one

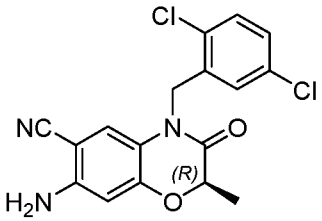
To a solution of (2R)-6-bromo-2-methyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (300 mg, 1.045 mmol, 1 equiv) in DMF (5 mL) was added 2-(bromomethyl)-1,4-dichlorobenzene (300.87 mg, 1.254 mmol, 1.2 equiv) and K_2CO_3 (436.45 mg, 3.135 mmol, 3 equiv). The reaction was

stirred at 80 °C for 1 h. The mixture was allowed to cool down to room temperature. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-6-bromo-4-[(2,5-dichlorophenyl)methyl]-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (370 mg, 79.37%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{11}BrCl_2N_2O_4$:443.93 m/z, found: 444.92, 446.92 [M+H, M+H+2]$^+$.



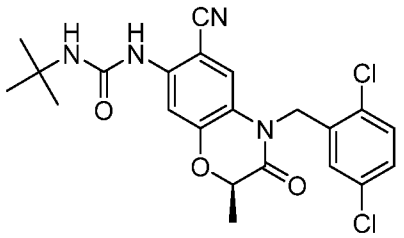
(2R)-7-amino-6-bromo-4-[(2,5-dichlorophenyl)methyl]-2-methyl-2H-1,4-benzoxazin-3-one

To a solution of (2R)-6-bromo-4-[(2,5-dichlorophenyl)methyl]-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (370 mg, 0.829 mmol, 1 equiv) in MeOH (0.5 mL) and H_2O (5 mL) was added Fe (463.21 mg, 8.290 mmol, 10 equiv) and NH_4Cl (443.67 mg, 8.290 mmol, 10 equiv). The reaction was stirred at 70 °C for 2 h. The mixture was allowed to cool down to room temperature and quenched with water (50 mL). The resulting mixture was filtered, the filter cake was washed with EA (50 mL). The filtrate was extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-6-bromo-4-[(2,5-dichlorophenyl)methyl]-2-methyl-2H-1,4-benzoxazin-3-one (270 mg, 78.23%) as a yellow oil. MS (ESI): mass calcd. for $C_{16}H_{13}BrCl_2N_2O_2$:413.95 m/z, found:414.95, 416.95 [M+H, M+H+2]$^+$.



(2R)-7-amino-4-[(2,5-dichlorophenyl)methyl]-2-methyl-3-oxo-2H-1,4-benzoxazine-6-carbonitrile

To a solution of (2R)-7-amino-6-bromo-4-[(2,5-dichlorophenyl)methyl]-2-methyl-2H-1,4-benzoxazin-3-one (260 mg, 0.625 mmol, 1 equiv) in DMF (5 mL) was added $Zn(CN)_2$ (88.04 mg, 0.750 mmol, 1.2 equiv) and $Pd(PPh_3)_4$ (72.21 mg, 0.063 mmol, 0.1 equiv). The reaction was stirred at 90 °C for 2 h under N_2 atmosphere. The mixture was allowed to cool down to room temperature. Quenched with water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-4-[(2,5-dichlorophenyl)methyl]-2-methyl-3-oxo-2H-1,4-benzoxazine-6-carbonitrile (120 mg, 53.02%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{13}Cl_2N_3O_2$:361.04 m/z, found:362.04 $[M+H]^+$.



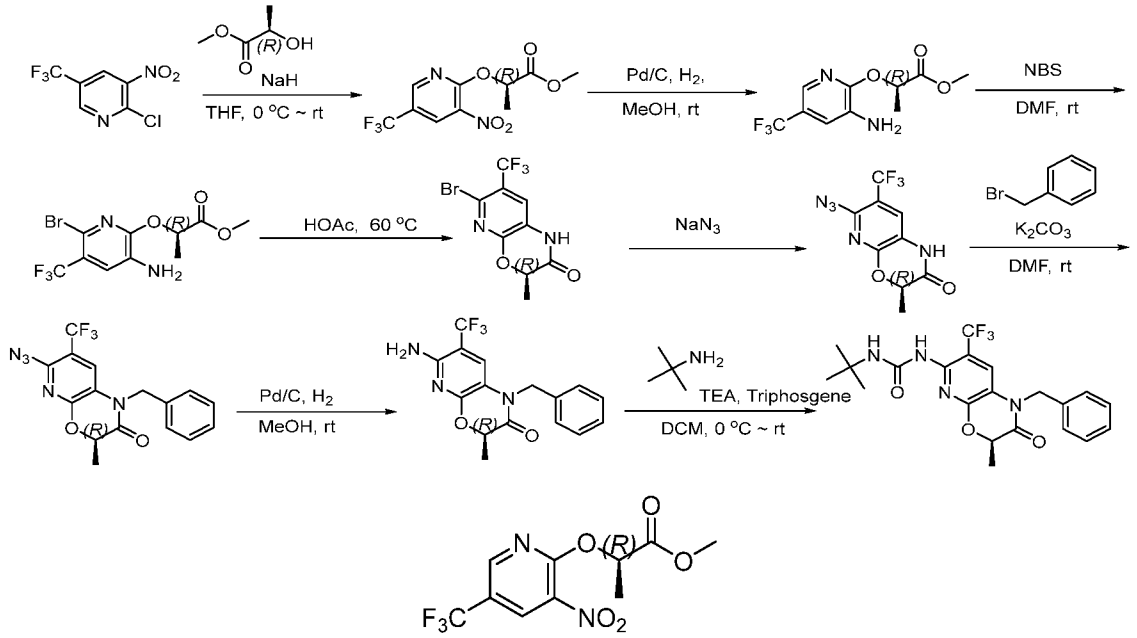
3-tert-butyl-1-[(2R)-6-cyano-4-[(2,5-dichlorophenyl)methyl]-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]urea

To a solution of (2R)-7-amino-4-[(2,5-dichlorophenyl)methyl]-2-methyl-3-oxo-2H-1,4-benzoxazine-6-carbonitrile (110 mg, 0.304 mmol, 1 equiv) in DCM (10 mL) was added triphosgene (45.06 mg, 0.152 mmol, 0.5 equiv) at 0°C under N_2 atmosphere. The resulting mixture was stirred for 1 h at 25 °C. Then, TEA (92.19 mg, 0.912 mmol, 3 equiv) was added into above system at 0 °C. The resulting mixture was stirred for 1 h at 25 °C. To the above mixture was added erbumine (33.32 mg, 0.456 mmol, 1.5 equiv) dropwise at 0 °C. The reaction was stirred at 25 °C for 2 h. Quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using XBridge Prep OBD C18 30*150 mm, 5μm column (eluent: 53% to 67% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-[(2R)-6-cyano-4-[(2,5-dichlorophenyl)methyl]-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]urea (68.4 mg, 48.33%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{22}Cl_2N_4O_3$:460.11 m/z, found:461.05 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.31 (s, 1H),

7.88 (s, 1H), 7.53 – 7.62 (m, 1H), 7.37 – 7.47 (m, 1H), 7.32 (s, 1H), 7.03 – 7.11 (m, 1H), 6.98 (s, 1H), 4.96 – 5.25 (m, 3H), 1.52 (d, J = 6.8 Hz, 3H), 1.30 (s, 9H).

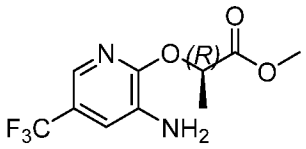
Example 368: (R)-1-(1-benzyl-3-methyl-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea

Synthetic Scheme



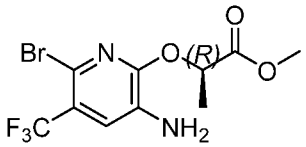
methyl (R)-2-((3-nitro-5-(trifluoromethyl)pyridin-2-yl)oxy)propanoate

To a solution of methyl (R)-2-hydroxypropanoate (2.30 g, 22.071 mmol, 1 equiv) in THF (60 mL) was added NaH (794.50 mg, 33.107 mmol, 1.5 equiv) at 0°C under air atmosphere. After 30 min, the 2-chloro-3-nitro-5-(trifluoromethyl)pyridine (5 g, 22.071 mmol, 1 equiv) was added to the mixture at 0°C. The resulting mixture was stirred for 2h at room temperature. Desired product could be detected by LCMS. The mixture was diluted with water (150 mL). The resulting mixture was extracted with EA (3 x 150 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue obtained was purified by silica gel chromatography (0-20% ethyl acetate/petroleum ether) to afford the methyl (R)-2-((3-nitro-5-(trifluoromethyl)pyridin-2-yl)oxy)propanoate (3.5 g, 53.90%) as a white solid. MS (ESI): mass calcd. for $C_{10}H_9F_3N_2O_5$: 294.05 m/z, found 295.05 $[M+H]^+$.



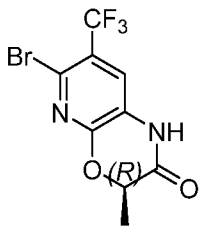
(R)-2-((3-amino-5-(trifluoromethyl)pyridin-2-yl)oxy)propanoate

To a solution of methyl (R)-2-((3-nitro-5-(trifluoromethyl)pyridin-2-yl)oxy)propanoate (3.5 g, 11.897 mmol, 1 equiv) in MeOH (40 mL, 24.699 mmol) was added Pd/C (3.49 g) at 0°C under N_2 atmosphere. The resulting mixture was maintained under hydrogen and stirred at 25 °C for 3 h. The resulting mixture was filtered, and the filter cake was washed with MeOH (4 x 40 mL). The filtrate was concentrated under reduced pressure. The residue obtained was purified by silica gel chromatography (0 - 50% ethyl acetate/petroleum ether) to afford the methyl (R)-2-((3-amino-5-(trifluoromethyl)pyridin-2-yl)oxy)propanoate (2.8 g, 89.08%) as a yellow oil. LC/MS: mass calcd. for $C_{10}H_{11}F_3N_2O_3$: 264.07, found: 265.05, 267.05 $[M+H, M+H+2]^+$.



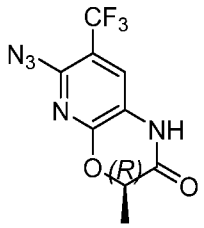
methyl (R)-2-((3-amino-6-bromo-5-(trifluoromethyl)pyridin-2-yl)oxy)propanoate

To a stirred mixture of methyl (R)-2-((3-amino-5-(trifluoromethyl)pyridin-2-yl)oxy)propanoate (1.5 g, 5.677 mmol, 1 equiv) in DMF (15 mL) was added NBS (1.5 g, 8.515 mmol, 1.5 equiv) at -40°C under air atmosphere. The resulting mixture was maintained under air and stirred at -40 °C for 3 h. The reaction was quenched with water (50 mL). The resulting mixture was extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-30% ethyl acetate/petroleum ether) to afford the methyl (R)-2-((3-amino-6-bromo-5-(trifluoromethyl)pyridin-2-yl)oxy)propanoate (530 mg, 27.21%) as a yellow oil. LC/MS: mass calcd. for $C_{10}H_{10}BrF_3N_2O_3$: 341.98, found: 342.90, 344.90 $[M+H, M+H+2]^+$.



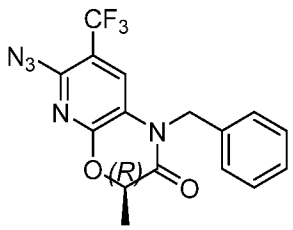
(R)-6-bromo-3-methyl-7-(trifluoromethyl)-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one

A stirred mixture of methyl (R)-2-((3-amino-6-bromo-5-(trifluoromethyl)pyridin-2-yl)oxy)propanoate (700 mg, 2.040 mmol, 1 equiv) in HOAc (10 mL) was stirred at 80 °C for 3 h. After cooling down to room temperature, the reaction was quenched with $NaHCO_3$ solution (30 mL). The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% ethyl acetate/petroleum ether) to afford the (R)-6-bromo-3-methyl-7-(trifluoromethyl)-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (370 mg, 58.30%) as a yellow oil. LC/MS: mass calcd. for $C_9H_6BrF_3N_2O_2$: 309.96, found: 310.85, 312.85 [M+H, M+H+2] $^+$.



(R)-6-azido-3-methyl-7-(trifluoromethyl)-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one

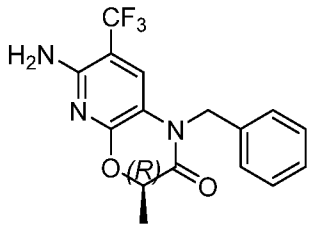
To a stirred mixture of (R)-6-bromo-3-methyl-7-(trifluoromethyl)-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (300 mg, 0.964 mmol, 1 equiv) in DMF (5 mL) was added NaN_3 (94.05 mg, 1.446 mmol, 1.5 equiv) at 25°C under air atmosphere. The resulting mixture was maintained under nitrogen and stirred at 110 °C for 3 h. After cooling down to room temperature, the reaction was quenched with water (20 mL). The resulting mixture was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% ethyl acetate/petroleum ether) to afford the (R)-6-azido-3-methyl-7-(trifluoromethyl)-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one as a yellow oil. LC/MS: mass calcd. for $C_9H_6F_3N_5O_2$: 273.05, found: 274.10 [M+H] $^+$.



(R)-6-azido-1-benzyl-3-methyl-7-(trifluoromethyl)-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one

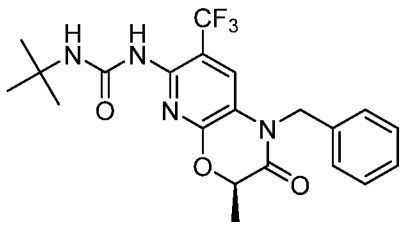
To a stirred mixture of (R)-6-azido-3-methyl-7-(trifluoromethyl)-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (147 mg, 0.538 mmol, 1 equiv) in DMF (5 mL) was added (bromomethyl)benzene

(138.06 mg, 0.807 mmol, 1.5 equiv) , K_2CO_3 (224.74 mg, 1.614 mmol, 3 equiv) at 25°C under air atmosphere. The resulting mixture was maintained under air and stirred at 25 °C for 3 h. The reaction was quenched with water (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% ethyl acetate/petroleum ether) to afford the (R)-6-azido-1-benzyl-3-methyl-7-(trifluoromethyl)-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (140 mg, 71.61%) as a yellow oil. LC/MS: mass calcd. for $C_{16}H_{12}F_3N_5O_2$: 363.09, found: 364.20 $[M+H]^+$.



(R)-6-amino-1-benzyl-3-methyl-7-(trifluoromethyl)-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one

To a stirred mixture of (R)-6-azido-1-benzyl-3-methyl-7-(trifluoromethyl)-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (130 mg, 0.358 mmol, 1 equiv) in MeOH (3 mL) was added Pd/C (129.85 mg) at 0°C under air atmosphere. The resulting mixture was maintained under hydrogen and stirred at 25 °C for 3 h. The resulting mixture was filtered, and the filter cake was washed with MeOH (4 x 40 mL). The filtrate was concentrated under reduced pressure. This afforded the (R)-6-amino-1-benzyl-3-methyl-7-(trifluoromethyl)-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (110 mg, 91.14%) as a yellow oil. LC/MS: mass calcd. for $C_{16}H_{14}F_3N_3O_2$: 337.10, found: 338.15 $[M+H]^+$.



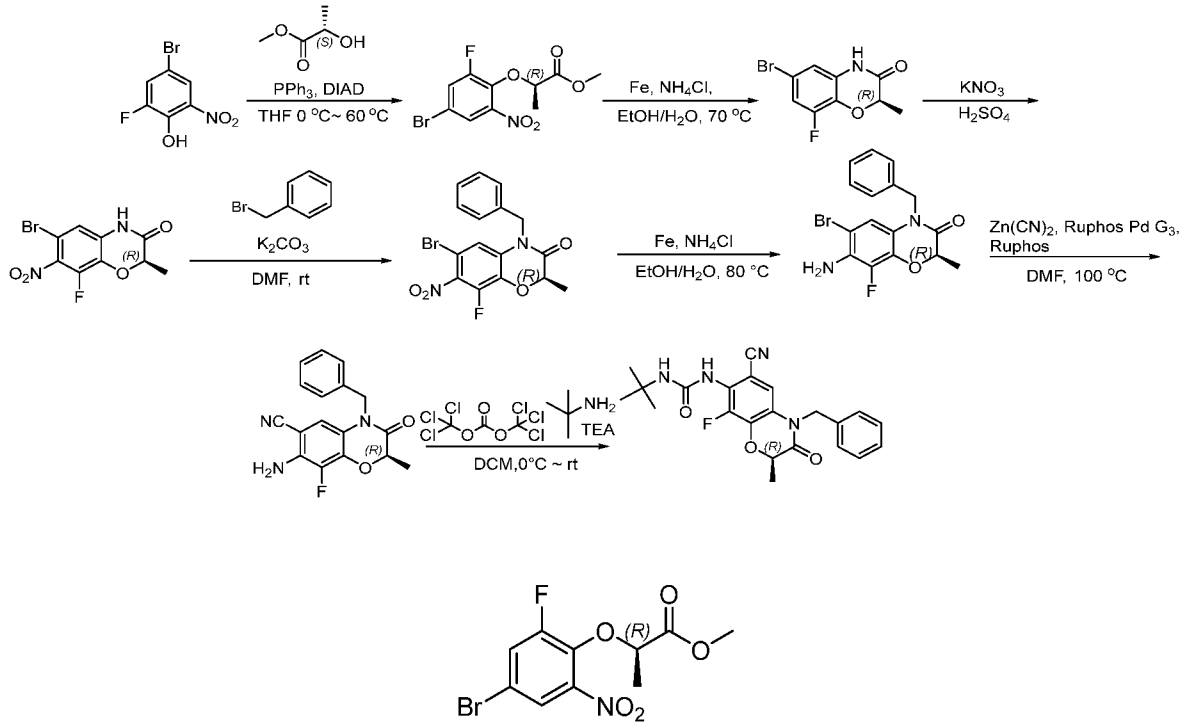
(R)-1-(1-benzyl-3-methyl-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea

To a stirred mixture of (R)-6-amino-1-benzyl-3-methyl-7-(trifluoromethyl)-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one (100 mg, 0.296 mmol, 1 equiv) in DCM (3 mL) was added triphosgene (87.97 mg, 0.296 mmol, 1 equiv) at 0 degrees C under nitrogen atmosphere. After stirring at 0

degrees C for 1h, the TEA (150.00 mg, 1.480 mmol, 5 equiv) was added to the mixture at room temperature. After 30 min, erbumine (65.05 mg, 0.888 mmol, 3 equiv) and TEA (150.00 mg, 1.480 mmol, 5 equiv) was added to the reaction system. The resulting mixture was stirred for 1h at 25 degrees C. Desired product could be detected by LCMS. The mixture was diluted with water (10 mL). The resulting mixture was extracted with EA (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a X Bridge Prep OBD C18 150 mm x 30 mm x 5μm column (eluent: 49% to 71% (v/v) CH_3CN and H_2O with 10 mmol /L NH_4HCO_3) to afford the (R)-1-(1-benzyl-3-methyl-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea (12.8 mg, 9.52%) as a white solid. MS (ESI): mass calcd. for $C_{21}H_{23}F_3N_4O_3$: 436.17 m/z, found 437.15 [M +H] $^+$.^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.72 (s, 1H), 7.57 (s, 1H), 7.31 – 7.39 (m, 2H), 7.23 – 7.31 (m, 4H), 5.24 – 5.33 (m, 1H), 5.21 (d, J = 7.5 Hz, 2H), 1.60 (d, J = 6.8 Hz, 3H), 1.29 (s, 9H).^{19}F-NMR (376 MHz, DMSO) δ -58.98.

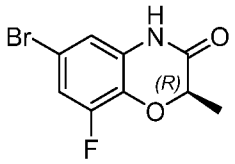
Example 369: (R)-1-(4-benzyl-6-cyano-8-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

Synthetic Scheme



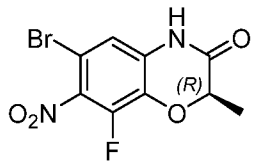
methyl (R)-2-(4-bromo-2-fluoro-6-nitrophenoxy)propanoate

A solution of 4-bromo-2-fluoro-6-nitrophenol (5 g, 21.187 mmol, 1 equiv) in tetrahydrofuran (50 mL) was treated with methyl (2S)-2-hydroxypropanoate (2.21 g, 21.187 mmol, 1 equiv) and PPh_3 (8.34 g, 31.781 mmol, 1.5 equiv) for 1 h at rt under nitrogen atmosphere followed by the addition of DIAD (6.43 g, 31.781 mmol, 1.5 equiv) dropwise at 0°C. The resulting mixture was stirred for 2 h at rt under N_2 atmosphere. Quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give methyl (2R)-2-(4-bromo-2-fluoro-6-nitrophenoxy)propanoate (5.8 g, 84.99%) as a white solid. Desired product could be detected by TLC.



(R)-6-bromo-8-fluoro-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

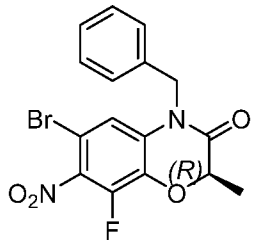
To a solution of methyl (2R)-2-(4-bromo-2-fluoro-6-nitrophenoxy)propanoate (5.8 g, 18.008 mmol, 1 equiv) in EtOH (60 mL)/H_2O (6 mL) was added Fe (10.06 g, 180.080 mmol, 10 equiv) and NH_4Cl (9.63 g, 180.080 mmol, 10 equiv). The reaction was stirred at 70°C for 3 h. The mixture was allowed to cool down to rt. Quenched with water (100 mL) and extracted with EA (3 x 100 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-6-bromo-8-fluoro-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (4.5 g, 96.09%) as a white solid. MS (ESI): mass calcd. for$C_9H_7BrFNO_2$: 258.96 m/z, found 259.95, 261.95 $[M+H, M+H+2]^+$.



(R)-6-bromo-8-fluoro-2-methyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

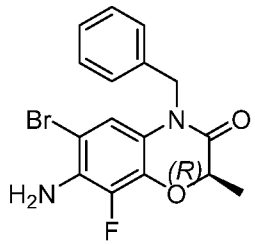
To a solution of (2R)-6-bromo-8-fluoro-2-methyl-2,4-dihydro-1,4-benzoxazin-3-one (1.5 g, 5.768 mmol, 1 equiv) in sulfuric acid (10 mL) was added KNO_3 (0.58 g, 5.768 mmol, 1 equiv) at 0°C. The reaction was stirred at 0°C for 1 h. Quenched with ice water (50 mL) and extracted with EA (3 x 50 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4,

filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-6-bromo-8-fluoro-2-methyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (1.46 g, 82.98%) as a white solid. MS (ESI): mass calcd. for $C_9H_6BrFN_2O_4$: 303.95 m/z, found: 302.95, 304.95 [M-H, M-H+2]$^-$.



(R)-4-benzyl-6-bromo-8-fluoro-2-methyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

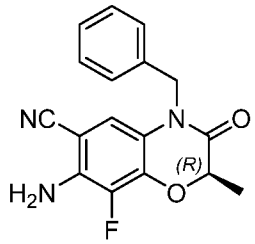
To a solution of (2R)-6-bromo-8-fluoro-2-methyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (350 mg, 1.147 mmol, 1 equiv) in DMF (3 mL) was added benzyl bromide (294.35 mg, 1.720 mmol, 1.5 equiv) and K_2CO_3 (479.17 mg, 3.441 mmol, 3 equiv). The reaction was stirred at rt for 1 h. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-4-benzyl-6-bromo-8-fluoro-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (416 mg, 91.75%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{12}BrFN_2O_4$: 394.00 m/z, found: 395.18, 397.18 [M+H, M+H+2]$^+$.



(R)-7-amino-4-benzyl-6-bromo-8-fluoro-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

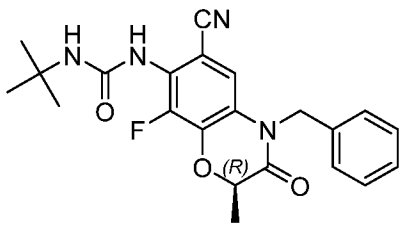
To a solution of (2R)-4-benzyl-6-bromo-8-fluoro-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (400 mg, 1.012 mmol, 1 equiv) in EtOH (8 mL)/H_2O (1 mL) was added Fe (565.26 mg, 10.120 mmol, 10 equiv) and NH_4Cl (541.42 mg, 10.120 mmol, 10 equiv). The reaction was stirred at 70°C for 3 h. The mixture was allowed to cool down to rt. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-4-benzyl-6-bromo-8-fluoro-2-methyl-2H-

1,4-benzoxazin-3-one (250 mg, 67.63%) as a white solid. MS (ESI): mass calcd. for $C_{16}H_{14}BrFN_2O_2$: 364.02 m/z, found 365.05, 367.05 $[M+H, M+H+2]^+$.



(R)-7-amino-4-benzyl-8-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile

To a solution of (2R)-7-amino-4-benzyl-6-bromo-8-fluoro-2-methyl-2H-1,4-benzoxazin-3-one (240 mg, 0.657 mmol, 1 equiv) in DMF (5 mL) was added $Zn(CN)_2$ (154.33 mg, 1.314 mmol, 2 equiv), Zn (12.89 mg, 0.197 mmol, 0.3 equiv), BrettPhos (70.55 mg, 0.131 mmol, 0.2 equiv) and BrettPhos Pd G_3 (119.15 mg, 0.131 mmol, 0.2 equiv). The reaction was stirred at 120°C for 3 h under N_2 atmosphere. The mixture was allowed to cool down to rt. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-4-benzyl-8-fluoro-2-methyl-3-oxo-2H-1,4-benzoxazine-6-carbonitrile (160 mg, 78.21%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{14}FN_3O_2$: 311.11 m/z, found: 312.20 $[M+H]^+$.



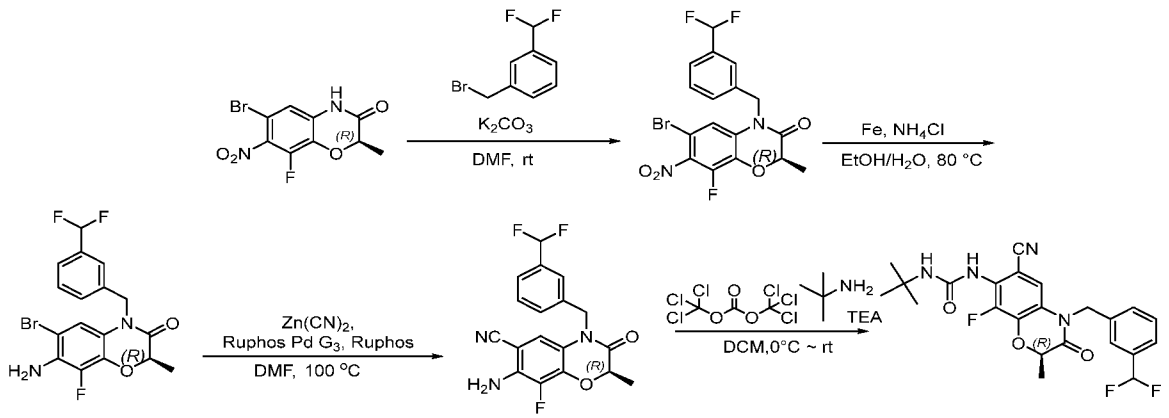
(R)-1-(4-benzyl-6-cyano-8-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

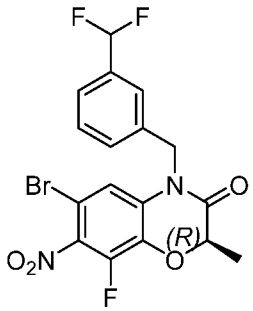
To a solution of (2R)-7-amino-4-benzyl-8-fluoro-2-methyl-3-oxo-2H-1,4-benzoxazine-6-carbonitrile (100 mg, 0.321 mmol, 1 equiv) in DCM (5 mL) was added triphosgene (95.31 mg, 0.321 mmol, 1 equiv). The reaction was stirred at 0 °C under N_2 for 1 h. The reaction was added TEA (162.52 mg, 1.605 mmol, 5 equiv) and stirred at 0 °C under N_2 for 1 h. The reaction was added erbumine (70.48 mg, 0.963 mmol, 3 equiv) and stirred at rt under N_2 for 1 h. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed

with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a Aeris PEPTIDE 5um XB-C18 Axia 21.2 mm X 250 mm, 5 μm column (eluent: 43% to 57% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford the title compound 1-[(2R)-4-benzyl-6-cyano-8-fluoro-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]-3-tert-butylurea (42.1 mg, 31.66%) as a white solid. LC/MS (ESI): mass calcd. for $C_{22}H_{23}FN_4O_3$: 410.18 m/z, found: 411.15 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.31 – 7.42 (m, 3H), 7.21 – 7.31 (m, 3H), 6.32 (s, 1H), 5.21 (s, 2H), 5.10-5.17 (m, 1H), 1.55-1.58 (d, J = 9 Hz, 3H), 1.27 (s, 9H).^{19}F NMR (282 MHz, DMSO) δ -140.79.

Example 370: (R)-1-(tert-butyl)-3-(6-cyano-4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

Synthetic Scheme

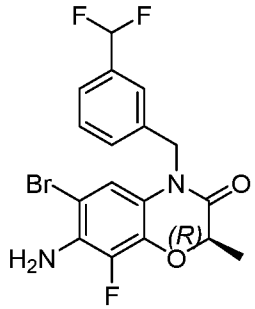




(R)-6-bromo-4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one

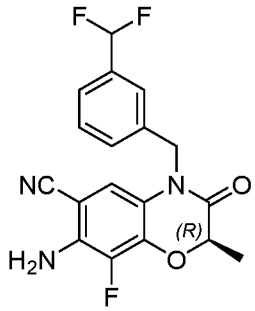
To a solution of (2R)-6-bromo-8-fluoro-2-methyl-7-nitro-2,4-dihydro-1,4-benzoxazin-3-one (300 mg, 0.983 mmol, 1 equiv) in DMF (5 mL) was added 1-(bromomethyl)-3-

(difluoromethyl)benzene (326.07 mg, 1.474 mmol, 1.5 equiv) and K_2CO_3 (410.71 mg, 2.949 mmol, 3 equiv). The reaction was stirred at rt for 3 h. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-6-bromo-4-{[3-(difluoromethyl)phenyl]methyl}-8-fluoro-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (400 mg, 91.36%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{12}BrF_3N_2O_4$: 443.99 m/z, found: 443.00, 445.00 $[M-H, M-H+2]^-$.



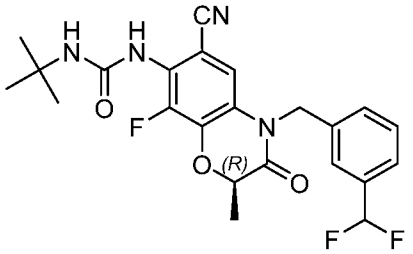
(R)-7-amino-6-bromo-4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

To a solution of (2R)-6-bromo-4-{[3-(difluoromethyl)phenyl]methyl}-8-fluoro-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (600 mg, 1.348 mmol, 1 equiv) in EtOH (6 mL)/H_2O (0.6 mL) was added Fe (752.64 mg, 13.480 mmol, 10 equiv) and NH_4Cl (720.90 mg, 13.480 mmol, 10 equiv) . The reaction was stirred at 70°C for 3 h. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-6-bromo-4-{[3-(difluoromethyl)phenyl]methyl}-8-fluoro-2-methyl-2H-1,4-benzoxazin-3-one (376 mg, 67.19%) as a white solid. MS (ESI): mass calcd. for$C_{17}H_{14}BrF_3N_2O_2$: 414.02 m/z, found 415.05, 417.05 $[M+H, M+H+2]^+$.



(R)-7-amino-4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile

To a solution of (2R)-7-amino-6-bromo-4-{[3-(difluoromethyl)phenyl]methyl}-8-fluoro-2-methyl-2H-1,4-benzoxazin-3-one (370 mg, 0.891 mmol, 1 equiv) in DMF (5 mL) was added $Zn(CN)_2$ (313.90 mg, 2.673 mmol, 3 equiv), Brettphos (95.67 mg, 0.178 mmol, 0.2 equiv), BrettPhos Pd G_3 (140.23 mg, 0.178 mmol, 0.2 equiv), Zn (17.48 mg, 0.267 mmol, 0.3 equiv). The reaction was stirred at 120°C for 3 h under N_2. The mixture was allowed to cool down to rt. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (2R)-7-amino-4-{[3-(difluoromethyl)phenyl]methyl}-8-fluoro-2-methyl-3-oxo-2H-1,4-benzoxazine-6-carbonitrile (190 mg, 59.01%) as a white solid. MS (ESI): mass calcd. for $C_{18}H_{14}F_3N_3O_2$: 361.10 m/z, found: 360.00 $[M-H]^-$.



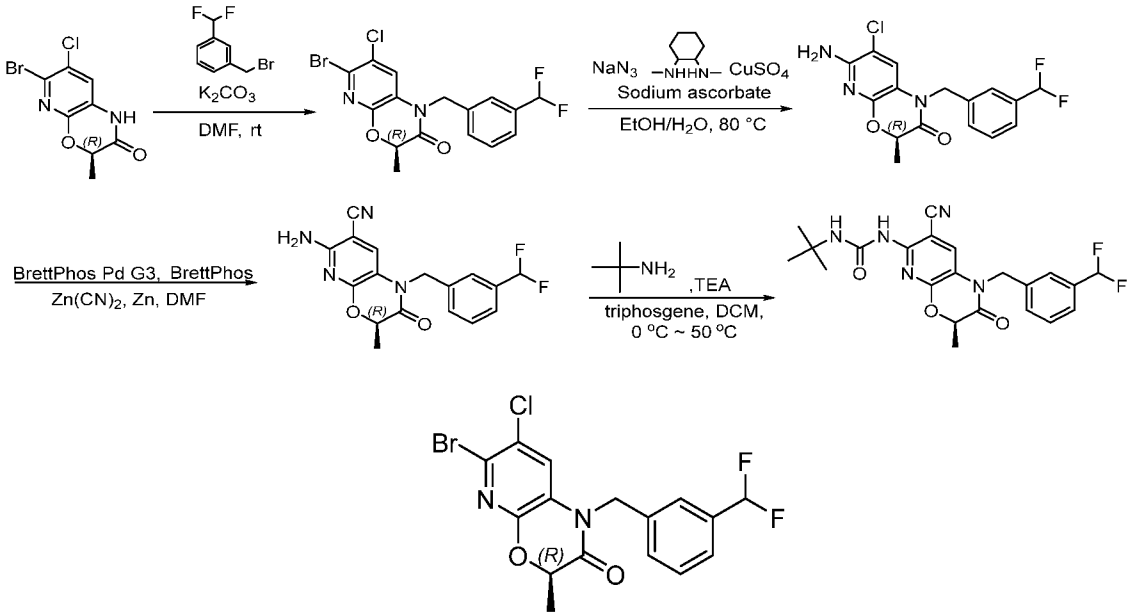
(R)-1-(tert-butyl)-3-(6-cyano-4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

To a solution of (2R)-7-amino-4-{[3-(difluoromethyl)phenyl]methyl}-8-fluoro-2-methyl-3-oxo-2H-1,4-benzoxazine-6-carbonitrile (100 mg, 0.277 mmol, 1 equiv) in DCM (5 mL) was added triphosgene (82.12 mg, 0.277 mmol, 1 equiv). The reaction was stirred at 0 °C under N_2 for 1 h. The reaction was added TEA (140.03 mg, 1.385 mmol, 5 equiv) and stirred at 0 °C under N_2 for 1 h. The reaction was added erbumine (60.73 mg, 0.831 mmol, 3 equiv) and stirred at rt under N_2 for 1 h. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a Aeris PEPTIDE 5um XB-C18 Axia 21.2 mm X 250 mm, 5 μm column (eluent: 43% to 57% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-[(2R)-6-cyano-4-{[3-(difluoromethyl)phenyl]methyl}-8-fluoro-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]urea (32.8

mg, 25.64%) as a white solid. LC/MS (ESI): mass calcd. for $C_{23}H_{23}F_3N_4O_3$: 460.17 m/z, found: 461.10 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.35 – 7.57 (m, 5H), 7.03 (s, 1H), 6.32 (s, 1H), 5.27 (s, 2H), 5.12-5.18 (m, 1H), 1.56-1.58 (d, J = 6 Hz, 3H), 1.27 (s, 9H). ^{19}F NMR (282 MHz, DMSO) δ -109.47, -109.77, -140.68.

Example 371: 3-tert-butyl-1-[(3R)-7-cyano-1-{[3-(difluoromethyl)phenyl]methyl}-3-methyl-2-oxo-3H-pyrido[2,3-b][1,4]oxazin-6-yl]urea

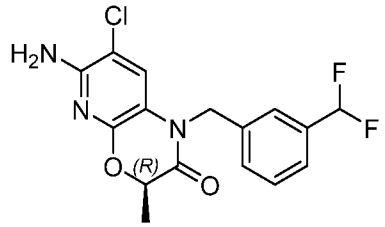
Synthetic Scheme



(3R)-6-bromo-7-chloro-1-{[3-(difluoromethyl)phenyl**]methyl}-3-methyl-3H-pyrido[2,3-b][1,4]oxazin-2-one**

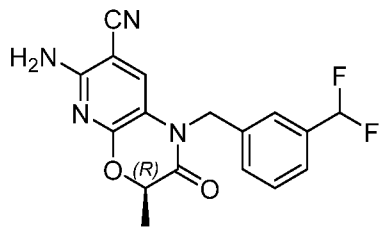
To a stirred mixture of (3R)-6-bromo-7-chloro-3-methyl-1H,3H-pyrido[2,3-b][1,4]oxazin-2-one (150 mg, 0.541 mmol, 1 equiv) and 1-(bromomethyl)-3-(difluoromethyl)benzene (238.97 mg, 1.082 mmol, 2 equiv) in DMF (10 mL) was added K_2CO_3 (225.75 mg, 1.623 mmol, 3 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 4 h at 80°C under air atmosphere. After cooling down to room temperature, the reaction was quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%)to afford (3R)-6-bromo-7-chloro-1-{[3-(difluoromethyl)phenyl]methyl}-3-methyl-3H-pyrido[2,3-b][1,4]oxazin-2-one (150 mg,

66.45%) as a white solid. LC/MS (ESI): mass calcd. for $C_{16}H_{12}BrClF_2N_2O_2$:416.0 m/z., found:417.0, 419.0 $[M+H, M+H+2]^+$.



(3R)-6-amino-7-chloro-1-{[3-(difluoromethyl)phenyl]methyl}-3-methyl-3H-pyrido[2,3-b][1,4]oxazin-2-one

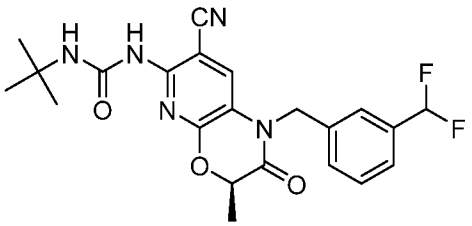
To a stirred mixture of (3R)-6-bromo-7-chloro-1-{[3-(difluoromethyl)phenyl]methyl}-3-methyl-3H-pyrido[2,3-b][1,4]oxazin-2-one (150 mg, 0.359 mmol, 1 equiv) and NaN_3 (30.65 mg, 0.471 mmol, 3 equiv) in EtOH:H_2O=10:1 (5 mL) was added N1,N2-dimethylcyclohexane-1,2-diamine (30.65 mg, 0.215 mmol, 0.6 equiv) and $CuSO_4$ (25.09 mg, 0.157 mmol, 1 equiv) and sodium ascorbate (143.03 mg, 0.718 mmol, 2 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 1h at 80°C under nitrogen atmosphere. After cooling down to room temperature, the reaction was quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a YMC-Actus Triart C_{18} ExRS 150 mm x 30 mm x 5 μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3)to afford (3R)-6-amino-7-chloro-1-{[3-(difluoromethyl)phenyl]methyl}-3-methyl-3H-pyrido[2,3-b][1,4]oxazin-2-one (100 mg, 78.71%) as a white solid. LC/MS (ESI): mass calcd. for $C_{16}H_{14}ClF_2N_3O_2$:353.1 m/z, found:354.1 $[M+H]^+$.



(3R)-6-amino-1-{[3-(difluoromethyl)phenyl]methyl}-3-methyl-2-oxo-3H-pyrido[2,3-b][1,4]oxazine-7-carbonitrile

To a stirred mixture of (3R)-6-amino-7-chloro-1-{[3-(difluoromethyl)phenyl]methyl}-3-methyl-3H-pyrido[2,3-b][1,4]oxazin-2-one (100 mg, 0.283 mmol, 1 equiv) and $Zn(CN)_2$ (66.39 mg, 0.566 mmol, 2 equiv) in DMF (5 mL) was added BrettPhos Pd G_3 (51.25 mg, 0.057 mmol, 0.2

equiv) and BrettPhos (17.67 mg, 0.033 mmol, 0.2 equiv) and Zn (5.54 mg, 0.085 mmol, 0.3 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 1h at 120°C under nitrogen atmosphere. After cooling down to room temperature, the reaction was quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to afford (3R)-6-amino-1-{[3-(difluoromethyl)phenyl]methyl}-3-methyl-2-oxo-3H-pyrido[2,3-b][1,4]oxazine-7-carbonitrile (60 mg, 61.5%) as a white solid. LC/MS (ESI): mass calcd. for $C_{17}H_{14}F_2N_4O_2$:344.1 m/z, found: 345.1 $[M+H]^+$.

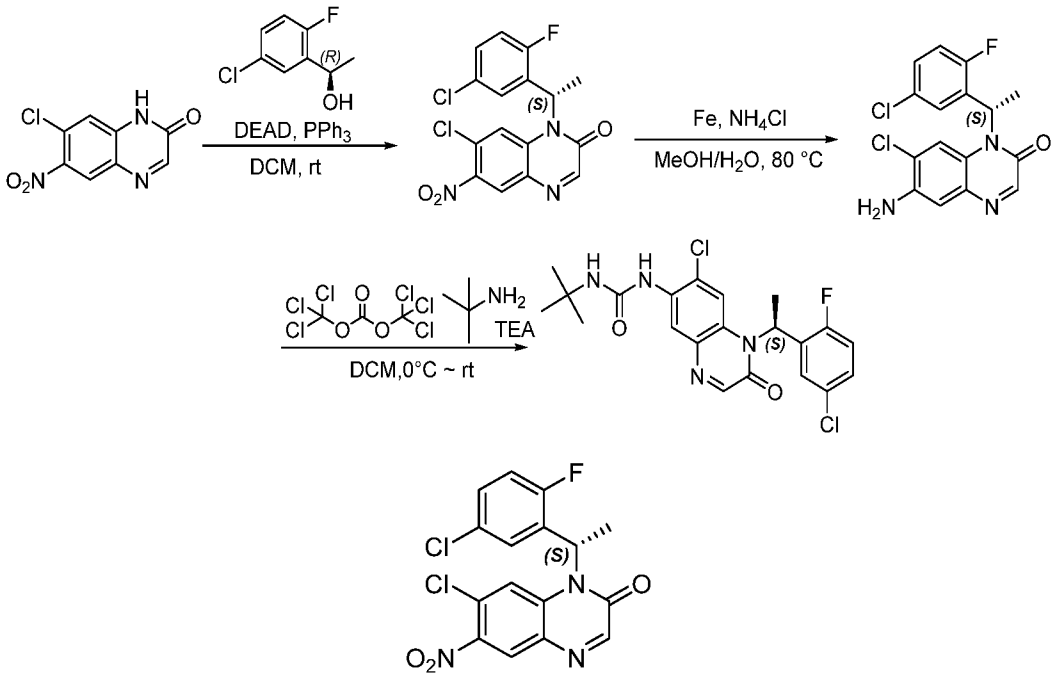


3-tert-butyl-1-[(3R)-7-cyano-1-{[3-(difluoromethyl)phenyl]methyl}-3-methyl-2-oxo-3H-pyrido[2,3-b][1,4]oxazin-6-yl]urea

To a stirred solution of (3R)-6-amino-1-{[3-(difluoromethyl)phenyl]methyl}-3-methyl-2-oxo-3H-pyrido[2,3-b][1,4]oxazine-7-carbonitrile (60 mg, 0.174 mmol, 1 equiv) and triphosgene (62.05 mg, 0.209 mmol, 1.2 equiv) in DCM (5 mL) was added TEA (52.90 mg, 0.522 mmol, 3 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. To the above mixture was added 2-methylpropan-2-amine (25.49 mg, 0.348 mmol, 2 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 30 min at room temperature. The reaction was quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%)to afford 3-tert-butyl-1-[(3R)-7-cyano-1-{[3-(difluoromethyl)phenyl]methyl}-3-methyl-2-oxo-3H-pyrido[2,3-b][1,4]oxazin-6-yl]urea (2.8 mg, 3.51%) as a white solid. LC/MS (ESI): mass calcd. for $C_{22}H_{23}F_2N_5O_3$:443.2 m/z, found:444.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 7.85 (s, 1H), 7.32-7.45 (m, 4H), 6.85-7.20 (m, 2H), 5.25-5.34 (m, 1H), 5.20 (s, 2H), 1.58 (d, J = 6.9 Hz, 3H), 1.29 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ -109.69.

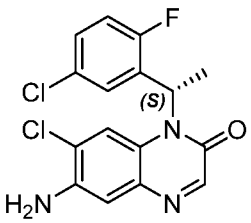
Example 372: (S)-1-(tert-butyl)-3-(7-chloro-1-(1-(5-chloro-2-fluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

Synthetic Scheme



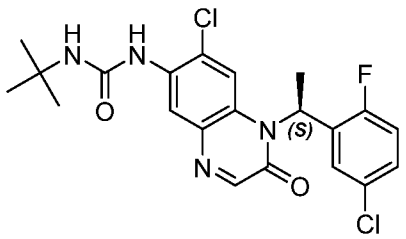
(S)-7-chloro-1-(1-(5-chloro-2-fluorophenyl)ethyl)-6-nitroquinoxalin-2(1H)-one

To a solution of 7-chloro-6-nitro-1H-quinoxalin-2-one (500 mg, 2.216 mmol, 1 equiv) in DCM (10 mL) was added (1R)-1-(5-chloro-2-fluorophenyl)ethanol (386.99 mg, 2.216 mmol, 1 equiv) and PPh_3 (872.02 mg, 3.324 mmol, 1.5 equiv). The reaction was stirred at rt under N_2 for 0.5h. To the above mixture was added DEAD (579.00 mg, 3.324 mmol, 1.5 equiv) at 0°C. The resulting mixture was stirred for additional 1h at 0°C. Quenched with water (30 mL) and extracted with DCM (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 7-chloro-1-[(1S)-1-(5-chloro-2-fluorophenyl)ethyl]-6-nitroquinoxalin-2-one (120 mg, 14.17%) as a yellow solid. LC/MS: mass calcd. for $C_{16}H_{10}Cl_2FN_3O_3$:381.01 m/z, found:382.10 $[M+H]^+$.



(S)-6-amino-7-chloro-1-(1-(5-chloro-2-fluorophenyl)ethyl)quinoxalin-2(1H)-one

To a solution of 7-chloro-1-[(1S)-1-(5-chloro-2-fluorophenyl)ethyl]-6-nitroquinoxalin-2-one (140 mg, 0.366 mmol, 1 equiv) in MeOH (10 mL) and H_2O (1 mL) was added Fe (204.58 mg, 3.660 mmol, 10 equiv) and NH_4Cl (195.95 mg, 3.660 mmol, 10 equiv). The reaction was stirred at 80 °C for 1h. The mixture was allowed to cool down to rt. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 50 mL). The filtrate was concentrated under reduced pressure. Quenched with water (20 mL) and extracted with EA (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-7-chloro-1-[(1S)-1-(5-chloro-2-fluorophenyl)ethyl]quinoxalin-2-one (120 mg, 93.01%) as a yellow solid. LC/MS: mass calcd. for $C_{16}H_{12}Cl_2FN_3O$:351.03 m/z, found:352.00 $[M+H]^+$.



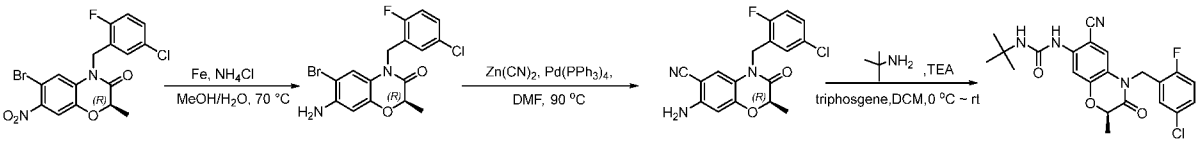
(S)-1-(tert-butyl)-3-(7-chloro-1-(1-(5-chloro-2-fluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

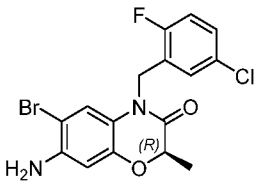
To a solution of 6-amino-7-chloro-1-[(1S)-1-(5-chloro-2-fluorophenyl)ethyl]quinoxalin-2-one (100 mg, 0.284 mmol, 1 equiv) in DCM (5 mL) was added triphosgene (84.25 mg, 0.284 mmol, 1 equiv) under N_2 at 0 °C. The reaction was stirred at 0 °C under N_2 for 1h. To the above mixture was added TEA (86.20 mg, 0.852 mmol, 3 equiv) at 0°C. The resulting mixture was stirred for additional 1h at rt. Then, to the above mixture was added erbumine (62.30 mg, 0.852 mmol, 3 equiv). The resulting mixture was stirred for additional 1h at rt. Quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Prep OBD C18 Column, 30*150 mm, 5μm column (eluent: 43% to 73% (v/v) CH3CN and Water (10mmol/L NH_4HCO_3+0.05%NH_3H_2O)) to afford the title compound 3-tert-butyl-1-{7-chloro-1-[(1S)-1-(5-chloro-2-fluorophenyl)ethyl]-2-oxoquinoxalin-6-yl}urea (48.8 mg, 37.94%) as a yellow solid. LC/MS: mass calcd. for $C_{21}H_{21}Cl_2FN_4O_2$:450.10 m/z, found:451.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.11 (s, 1H), 8.05 (s, 1H), 7.90 (s, 1H),

7.73 (dd, J = 6.8, 2.7 Hz, 1H), 7.43 (ddd, J = 8.7, 4.2, 2.6 Hz, 1H), 7.15 (dd, J = 10.5, 8.8 Hz, 1H), 6.99 (s, 1H), 6.36 (s, 1H), 1.84 (d, J = 6.8 Hz, 3H), 1.32 (s, 9H).^{19}F NMR (376 MHz, DMSO) δ(ppm): -118.1424.

Example 373: 3-tert-butyl-1-[(2R)-4-[(5-chloro-2-fluorophenyl)methyl]-6-cyano-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]urea

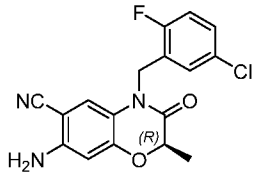
Synthetic Scheme





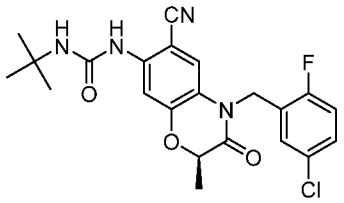
(2R)-7-amino-6-bromo-4-[(5-chloro-2-fluorophenyl)methyl]-2-methyl-2H-1,4-benzoxazin-3-one

To a stirred mixture of (2R)-6-bromo-4-[(5-chloro-2-fluorophenyl)methyl]-2-methyl-7-nitro-2H-1,4-benzoxazin-3-one (300 mg, 0.698 mmol, 1 equiv) and NH_4Cl (373.51 mg, 6.980 mmol, 10 equiv) in MeOH:H_2O=10:1 (10 mL) was added Fe (389.95 mg, 6.980 mmol, 10 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 70°C under air atmosphere. After cooling down to room temperature, the reaction was quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%)to afford (2R)-7-amino-6-bromo-4-[(5-chloro-2-fluorophenyl)methyl]-2-methyl-2H-1,4-benzoxazin-3-one (236 mg, 84.57%) as a white solid. LC/MS (ESI): mass calcd. for $C_{16}H_{13}BrClFN_2O_2$:398.0 m/z, found: 399.0, 401.0 $[M+H, M+H+2]^+$.



(2R)-7-amino-4-[(5-chloro-2-fluorophenyl)methyl]-2-methyl-3-oxo-2H-1,4-benzoxazine-6-carbonitrile

To a stirred mixture of (2R)-7-amino-6-bromo-4-[(5-chloro-2-fluorophenyl)methyl]-2-methyl-2H-1,4-benzoxazin-3-one (230 mg, 0.576 mmol, 1 equiv) and $Zn(CN)_2$ (81.09 mg, 0.691 mmol, 1.2 equiv) in DMF (10 mL) was added $Pd(PPh_3)_4$ (66.51 mg, 0.058 mmol, 0.1 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2h at 90°C under nitrogen atmosphere. After cooling down to room temperature, the reaction was quenched with water (30 mL) and extracted with EA (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. TLC showed the desired product was generated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to afford (2R)-7-amino-4-[(5-chloro-2-fluorophenyl)methyl]-2-methyl-3-oxo-2H-1,4-benzoxazine-6-carbonitrile (111 mg, 55.78%) as a white solid.



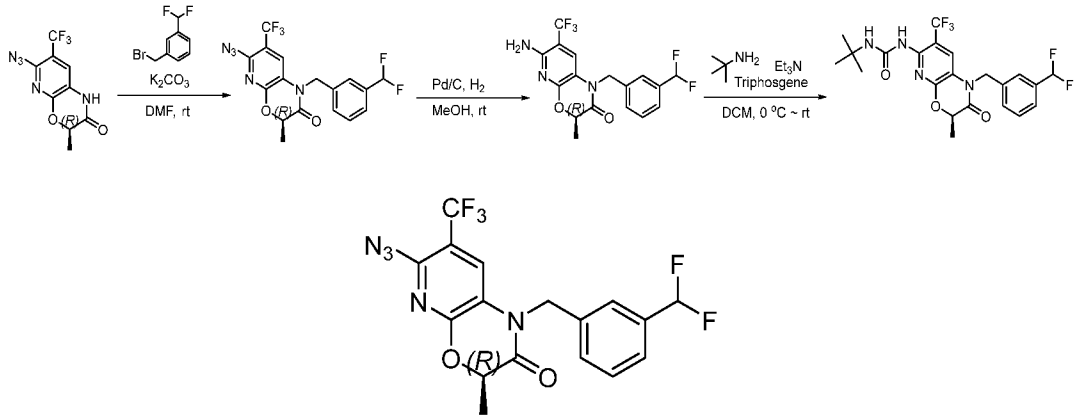
3-tert-butyl-1-[(2R)-4-[(5-chloro-2-fluorophenyl)methyl]-6-cyano-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]urea

To a stirred solution of (2R)-7-amino-4-[(5-chloro-2-fluorophenyl)methyl]-2-methyl-3-oxo-2H-1,4-benzoxazine-6-carbonitrile (60 mg, 0.174 mmol, 1 equiv) and triphosgene (61.79 mg, 0.209 mmol, 1.2 equiv) in DCM (5 mL) was added TEA (52.68 mg, 0.522 mmol, 3 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. To the above mixture was added 2-methylpropan-2-amine (25.38 mg, 0.348 mmol, 2 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 30 min at room temperature. The reaction was quenched with water (30 mL) and extracted with DCM (3 x 30 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a YMC-Actus Triart C_{18} ExRS 150 mm x 30 mm x 5 μm column (eluent: 17% to 42% (v/v) CH_3CN and H_2O with 10mmol/L NH_4HCO_3) to afford 3-tert-butyl-1-[(2R)-4-[(5-chloro-2-fluorophenyl)methyl]-6-cyano-2-methyl-3-oxo-2H-1,4-benzoxazin-7-yl]urea (26.1 mg, 33.81%) as a white solid. LC/MS (ESI): mass calcd. for $C_{22}H_{22}ClFN_4O_3$:444.1 m/z,

found:445.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1H), 7.86 (s, 1H), 7.38-7.50 (m, 2H), 7.26-7.38 (m, 1H), 7.10-7.26 (m, 1H), 6.99 (s, 1H), 5.09-5.41 (m, 2H), 4.89-5.08 (m, 1H), 1.49 (d, J = 6.8 Hz, 3H), 1.29 (s, 9H). ^{19}F NMR (376 MHz, DMSO) δ -119.29.

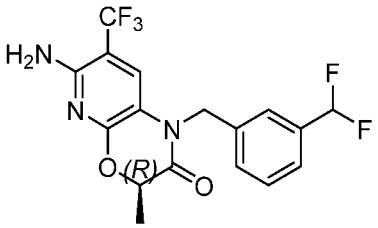
Example 374: (R)-1-(tert-butyl)-3-(1-(3-(difluoromethyl) benzyl)-3-methyl-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b] [1,4] oxazin-6-yl) urea

Synthetic Scheme



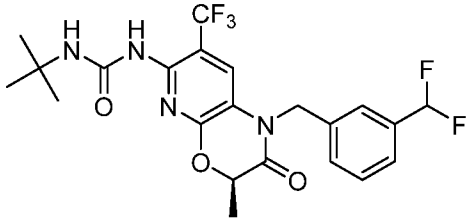
(3R)-6-azido-1-{[3-(difluoromethyl) phenyl] methyl}-3-methyl-7-(trifluoromethyl)-3H-pyrido[2,3-b] [1,4] oxazin-2-one

To a stirred solution of (3R)-6-azido-3-methyl-7-(trifluoromethyl)-1H,3H-pyrido[2,3-b] [1,4] oxazin-2-one (80 mg, 0.293 mmol, 1 equiv) and 1-(bromomethyl)-3-(difluoromethyl) benzene (77.68 mg, 0.352 mmol, 1.2 equiv) in DMF (5 mL) was added K_2CO_3 (122.31 mg, 0.879 mmol, 3 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at room temperature under air atmosphere. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford (3R)-6-azido-1-{[3-(difluoromethyl) phenyl] methyl}-3-methyl-7-(trifluoromethyl)-3H-pyrido[2,3-b] [1,4] oxazin-2-one (100 mg, 82.62%) as a yellow oil. MS (ESI): mass calcd. for $C_{17}H_{12}F_5N_5O_2$: 413.09 m/z, found 414.05 $[M+H]^+$.



(3R)-6-amino-1-{[3-(difluoromethyl) phenyl] methyl}-3-methyl-7-(trifluoromethyl)-3H-pyrido[2,3-b] [1,4] oxazin-2-one

A mixture of (3R)-6-azido-1-{[3-(difluoromethyl) phenyl] methyl}-3-methyl-7-(trifluoromethyl)-3H-pyrido[2,3-b] [1,4] oxazin-2-one (100 mg, 0.242 mmol, 1 equiv) and Pd/C (30 mg, 0.282 mmol, 1.17 equiv) in MeOH (5 mL) was stirred for 1 h at room temperature under hydrogen atmosphere. The resulting mixture was filtered, and the filter cake was washed with MeOH (4 x 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford (3R)-6-amino-1-{[3-(difluoromethyl) phenyl] methyl}-3-methyl-7-(trifluoromethyl)-3H-pyrido[2,3-b] [1,4] oxazin-2-one (80 mg, 85.37%) as a yellow oil. MS (ESI): mass calcd. for $C_{17}H_{14}F_5N_3O_2$: 387.10 m/z, found 388.05 $[M+H]^+$.



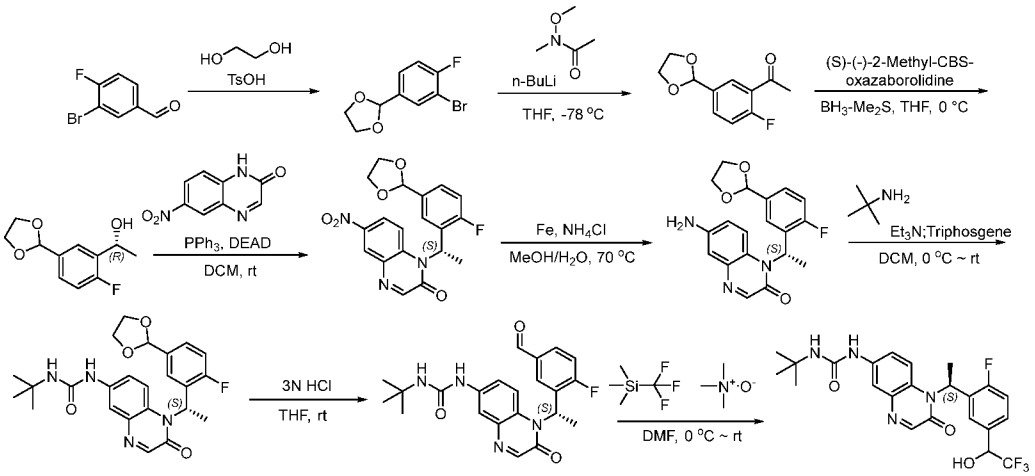
(R)-1-(tert-butyl)-3-(1-(3-(difluoromethyl) benzyl)-3-methyl-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b] [1,4] oxazin-6-yl) urea

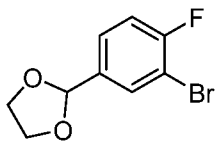
A solution of (3R)-6-amino-1-{[3-(difluoromethyl) phenyl] methyl}-3-methyl-7-(trifluoromethyl)-3H-pyrido[2,3-b] [1,4] oxazin-2-one (80 mg, 0.207 mmol, 1 equiv) in toluene (5 mL) was treated with Triphosgene (122.58 mg, 0.414 mmol, 2 equiv) for 30 min at room temperature under nitrogen atmosphere followed by the addition of triethylamine (104.51 mg, 1.035 mmol, 5 equiv) in portions at 0 °C. The resulting mixture was stirred for 2 h at 90 °C under nitrogen atmosphere. To the above mixture was added erbumine (45.32 mg, 0.621 mmol, 3 equiv) dropwise over 1 min at room temperature. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were

dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC using a XSelect CSH Fluoro Pheny 250 mm x 19 mm x 5 μm column (eluent: 45% to 75% (v/v) CH_3CN and H_2O with 10 mmol/L 0.05% TFA) to afford 3-tert-butyl-1-[(3R)-1-{[3-(difluoromethyl) phenyl] methyl}-3-methyl-2-oxo-7-(trifluoromethyl)-3H-pyrido[2,3-b] [1,4] oxazin-6-yl] urea (30 mg, 29.38%) as a yellow solid. MS (ESI): mass calcd. for $C_{22}H_{23}F_5N_4O_3$: 486.17 m/z, found 487.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 7.72 (s, 1H), 7.61 (s, 1H), 7.38 – 7.58 (m, 4H), 7.30 (s, 1H), 7.02 (s, 1H), 5.18 – 5.40 (m, 3H), 1.60 (d, J = 6.8 Hz, 3H), 1.15 – 1.42 (m, 9H). ^{19}F NMR (282 MHz, DMSO) δ -59.022, -109.803

Example 375: 3-tert-butyl-1-{1-[(1S)-1-[2-fluoro-5-(2,2,2-trifluoro-1-hydroxyethyl)phenyl]ethyl]-2-oxoquinoxalin-6-yl}urea

Synthetic Scheme

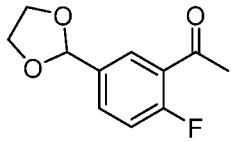




2-(3-bromo-4-fluorophenyl)-1,3-dioxolane

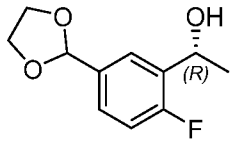
To a solution of 3-bromo-4-fluorobenzaldehyde (10 g, 49.259 mmol, 1 equiv) in Toluene (50 mL) was added ethylene glycol (9477.90 mg, 152.703 mmol, 3.1 equiv) and para-toluene sulfonate (1696.47 mg, 9.852 mmol, 0.2 equiv). The resulting mixture was stirred for 3 h at 120°C. The mixture was diluted with EtOAc (100 mL), washed with water (3 x 50 mL), brine (2 x 50 mL) and

concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 2-(3-bromo-4-fluorophenyl)-1,3-dioxolane (10 g, 82.17%) as a white solid. MS (ESI): mass calcd. for $C_9H_8BrFO_2$: 245.97 m/z, found 247.00 [M+H, M+H+2]$^+$.



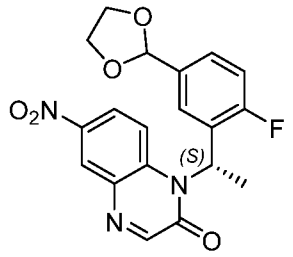
1-[5-(1,3-dioxolan-2-yl)-2-fluorophenyl]ethanone

To a solution of 2-(3-bromo-4-fluorophenyl)-1,3-dioxolane (2 g, 8.095 mmol, 1 equiv) in THF (20 mL) was added butyllithium (601.54 mg, 9.390 mmol, 1.16 equiv) dropwise at -78°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at -78 °C. N-methoxy-N-methylacetamide (868.17 mg, 8.419 mmol, 1.04 equiv) was added to the reaction at -78 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 1-[5-(1,3-dioxolan-2-yl)-2-fluorophenyl]ethanone (1.2 g, 70.52%) as a yellow solid. MS (ESI): mass calcd. for $C_{11}H_{11}FO_3$: 210.07 m/z, found 211.00 [M+H]$^+$.



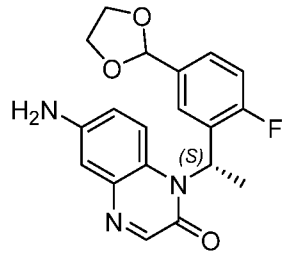
(1R)-1-[5-(1,3-dioxolan-2-yl)-2-fluorophenyl]ethanol

To a solution of CBS (1001.50 mg, 3.806 mmol, 0.4 equiv) in THF (20 mL) was added BH_3-Me_2S (1084.09 mg, 14.273 mmol, 1.5 equiv) and 1-[5-(1,3-dioxolan-2-yl)-2-fluorophenyl]ethanone (2 g, 9.515 mmol, 1 equiv) dropwise at 0°C. The resulting mixture was stirred for 1 h at 0°C. The mixture was diluted with EtOAc (100 mL), washed with water (3 x 50 mL), brine (2 x 50 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford (1R)-1-[5-(1,3-dioxolan-2-yl)-2-fluorophenyl]ethanol (1.5 g, 74.29%) as a white solid. MS (ESI): mass calcd. for $C_{11}H_{13}FO_3$: 212.08 m/z, found 213.30 [M+H]$^+$.



1-[(1S)-1-[5-(1,3-dioxolan-2-yl)-2-fluorophenyl]ethyl]-6-nitroquinoxalin-2-one

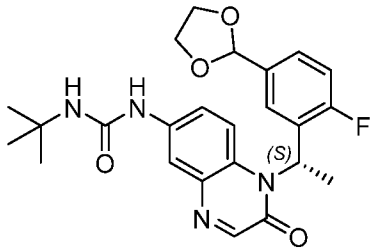
To a solution of (1R)-1-[5-(1,3-dioxolan-2-yl)-2-fluorophenyl]ethanol (1.6 g, 7.539 mmol, 1 equiv) in DCM (20 mL) was added 6-nitro-1H-quinoxalin-2-one (1.44 g, 7.539 mmol, 1 equiv) and PPh_3 (2.97 g, 11.308 mmol, 1.5 equiv) dropwise under nitrogen atmosphere. The resulting mixture was stirred for 0.5 h at rt. DEAD (1.97 g, 11.308 mmol, 1.5 equiv) was added to the reaction under nitrogen atmosphere. The resulting mixture was stirred for 1 h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 30 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 1-[(1S)-1-[5-(1,3-dioxolan-2-yl)-2-fluorophenyl]ethyl]-6-nitroquinoxalin-2-one (1.2 g, 41.30%) as a yellow solid. MS (ESI): mass calcd. for $C_{19}H_{16}FN_3O_5$: 385.10 m/z, found 386.00 $[M+H]^+$.



6-amino-1-[(1S)-1-[5-(1,3-dioxolan-2-yl)-2-fluorophenyl]ethyl]quinoxalin-2-one

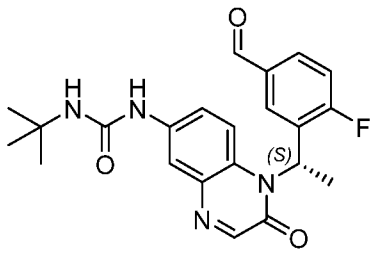
To a solution of 1-[(1S)-1-[5-(1,3-dioxolan-2-yl)-2-fluorophenyl]ethyl]-6-nitroquinoxalin-2-one (1.2 g, 3.114 mmol, 1 equiv) in MeOH (15 mL) and H_2O (1.5 mL) was added Fe (1.74 g, 31.140 mmol, 10 equiv) and NH_4Cl (1.67 g, 31.140 mmol, 10 equiv). The resulting mixture was stirred for 3 h at 70°C. After cooling down to rt, the mixture was diluted with EtOAc (100 mL), washed with water (3 x 50 mL), brine (2 x 50 mL) and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (3:1) to afford 6-amino-1-

[(1S)-1-[5-(1,3-dioxolan-2-yl)-2-fluorophenyl]ethyl]quinoxalin-2-one (200 mg, 18.07%) as a white solid. MS (ESI): mass calcd. For $C_{19}H_{18}FN_3O_3$: 355.13 m/z, found 356.20 $[M+H]^+$.



3-tert-butyl-1-{1-[(1S)-1-[5-(1,3-dioxolan-2-yl)-2-fluorophenyl]ethyl]-2-oxoquinoxalin-6-yl}urea

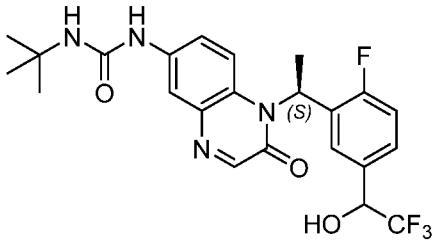
To a solution of 6-amino-1-[(1S)-1-[5-(1,3-dioxolan-2-yl)-2-fluorophenyl]ethyl]quinoxalin-2-one (200 mg, 0.563 mmol, 1 equiv) in DCM (10 mL) was added triphosgene (167.01 mg, 0.563 mmol, 1 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 10 min at rt. TEA (113.90 mg, 1.126 mmol, 2 equiv) was added to the reaction under nitrogen atmosphere. The resulting mixture was stirred for 15 min at rt. Then erbumine (82.32 mg, 1.126 mmol, 2 equiv) and TEA (113.90 mg, 1.126 mmol, 2 equiv) was added to the reaction under nitrogen atmosphere. The resulting mixture was stirred for 1h at rt. The reaction mixture was quenched by water and extracted with DCM (3 x 30 mL).The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column, eluted with PE / EA (2:1) to afford 3-tert-butyl-1-{1-[(1S)-1-[5-(1,3-dioxolan-2-yl)-2-fluorophenyl]ethyl]-2-oxoquinoxalin-6-yl}urea (150 mg, 58.64%) as a yellow solid. MS (ESI): mass calcd. for $C_{24}H_{27}FN_4O_4$: 454.20 m/z, found 455.30 $[M+H]^+$.



3-tert-butyl-1-{1-[(1S)-1-(2-fluoro-5-formylphenyl)ethyl]-2-oxoquinoxalin-6-yl}urea

To a solution of 3-tert-butyl-1-{1-[(1S)-1-[5-(1,3-dioxolan-2-yl)-2-fluorophenyl]ethyl]-2-oxoquinoxalin-6-yl}urea (130 mg, 0.286 mmol, 1 equiv) in THF (7 mL) was added 3N HCl (3.5 mL) dropwise at 0°C. The resulting mixture was stirred for 1 h at rt. The mixture was diluted with EtOAc (20 mL), washed with water (3 x 10 mL), brine (2 x 10 mL) and concentrated under vacuum

to afford 3-tert-butyl-1-{1-[(1S)-1-(2-fluoro-5-formylphenyl)ethyl]-2-oxoquinoxalin-6-yl}urea (85 mg, 72.4%) as a white solid. MS (ESI): mass calcd. for $C_{22}H_{23}FN_4O_3$: 410.17 m/z, found 411.30 $[M+H]^+$.

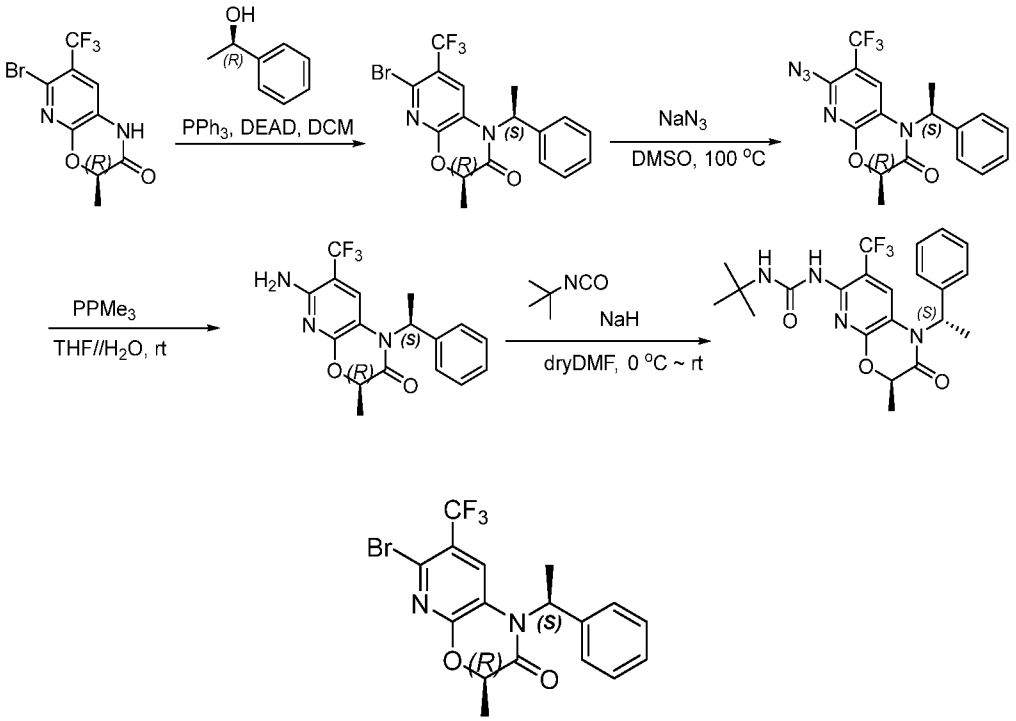


3-tert-butyl-1-{1-[(1S)-1-[2-fluoro-5-(2,2,2-trifluoro-1-hydroxyethyl)phenyl]ethyl]-2-oxoquinoxalin-6-yl}urea

To a solution of 3-tert-butyl-1-{1-[(1S)-1-(2-fluoro-5-formylphenyl)ethyl]-2-oxoquinoxalin-6-yl}urea (150 mg, 0.365 mmol, 1 equiv) in dimethylformamide (10 mL) was added trimethyl(trifluoromethyl)silane (207.86 mg, 1.460 mmol, 4 equiv) and N,N-dimethylmethanamine oxide (109.80 mg, 1.460 mmol, 4 equiv) dropwise at 0°C. The resulting mixture was stirred for 8 h at rt. The reaction mixture was quenched by water and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield a crude product which was directly purified by silica gel column eluted with PE / EA (2:1) & Prep-HPLC (Column: YMC Triart C18 ExRs Column, 20*250mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min mL/min; Gradient: 41%B to 71%B in 7 min; Wave Length: 254nm/220nm nm; RT1(min): 6.42 Column: YMC Triart C18 ExRs Column, 20*250mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min mL/min; Gradient: 41%B to 71%B in 7 min; Wave Length: 254nm/220nm nm; RT1(min): 6.42) to afford 3-tert-butyl-1-{1-[(1S)-1-[2-fluoro-5-(2,2,2-trifluoro-1-hydroxyethyl)phenyl]ethyl]-2-oxoquinoxalin-6-yl}urea (2.8 mg, 1.57%) as an light yellow. MS (ESI): mass calcd. For $C_{23}H_{24}F_4N_4O_3$, 480.18 m/z, found 481.25 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.17 (s, 1H), 7.79 – 8.00 (m, 2H), 7.29 – 7.55 (m, 3H), 7.13 (dd, J = 10.8, 8.5 Hz, 1H), 6.97 (s, 1H), 6.57 (s, 1H), 6.01 (s, 1H), 5.28 (d, J = 7.3 Hz, 1H), 1.88 (d, J = 7.0 Hz, 3H), 1.29 (s, 9H). ^{19}F NMR (282 MHz, DMSO) δ -76.88, -116.10.

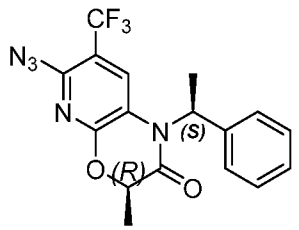
Example 376: 1-(tert-butyl)-3-((R)-3-methyl-2-oxo-1-((S)-1-phenylethyl)-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b] [1,4] oxazin-6-yl)urea

Synthetic Scheme



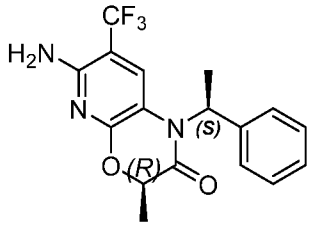
(R)-6-bromo-3-methyl-1-((S)-1-phenylethyl)-7-(trifluoromethyl)-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one

A solution of (3R)-6-bromo-3-methyl-7-(trifluoromethyl)-1H,3H-pyrido[2,3-b][1,4]oxazin-2-one (50 mg, 0.161 mmol, 1 equiv) in DCM (5 mL) was treated with (R)-1-phenylethan-1-ol (29.46 mg, 0.241 mmol, 1.5 equiv) and PPh_3 (63.24 mg, 0.241 mmol, 1.5 equiv) for 1 h at rt under nitrogen atmosphere followed by the addition of DEAD (41.99 mg, 0.241 mmol, 1.5 equiv) dropwise at 0°C. The resulting mixture was stirred for 2 h at rt under N_2 atmosphere. Quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (3R)-6-bromo-3-methyl-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)-3H-pyrido[2,3-b][1,4]oxazin-2-one (40 mg, 59.93%) as a yellow solid. LC/MS: mass calcd. for $C_{17}H_{14}BrF_3N_2O_2$: 414.02 m/z, found: 415.10, 417.10 $[M+H, M+H+2]^+$.



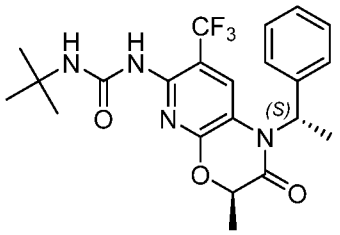
(R)-6-azido-3-methyl-1-((S)-1-phenylethyl)-7-(trifluoromethyl)-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one

To a solution of (3R)-6-bromo-3-methyl-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)-3H-pyrido[2,3-b][1,4]oxazin-2-one (100 mg, 0.241 mmol, 1 equiv) in DMSO (3 mL) was added NaN_3 (31.31 mg, 0.482 mmol, 2 equiv). The reaction was stirred at 100 °C under N_2 for 0.5 h. After cooling down to rt, the reaction was quenched with water (10 mL) and extracted with EA (3 x 10 mL). The mixture was allowed to cool down to rt. The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give (3R)-6-azido-3-methyl-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)-3H-pyrido[2,3-b][1,4]oxazin-2-one (31 mg, 30.70%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{14}F_3N_5O_2$: 377.11 m/z, found: 378.05 $[M+H]^+$.



(R)-6-amino-3-methyl-1-((S)-1-phenylethyl)-7-(trifluoromethyl)-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one

To a solution of 6-azido-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)-3H-pyrido[2,3-b][1,4]oxazin-2-one (60 mg, 0.165 mmol, 1 equiv) in THF (2.5 mL)/H_2O (0.5 mL) was added trimethylphosphine (125.65 mg, 1.650 mmol, 10 equiv). The reaction was stirred at rt for 1 h. Quenched with water (5 mL) and extracted with EA (3 x 5 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel with EA/PE (0-100%) to give 6-amino-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)-3H-pyrido[2,3-b][1,4]oxazin-2-one (50 mg, 80.78%) as a white solid. MS (ESI): mass calcd. for $C_{17}H_{16}F_3N_3O_2$: 351.12 m/z, found: 352.05 $[M+H]^+$.

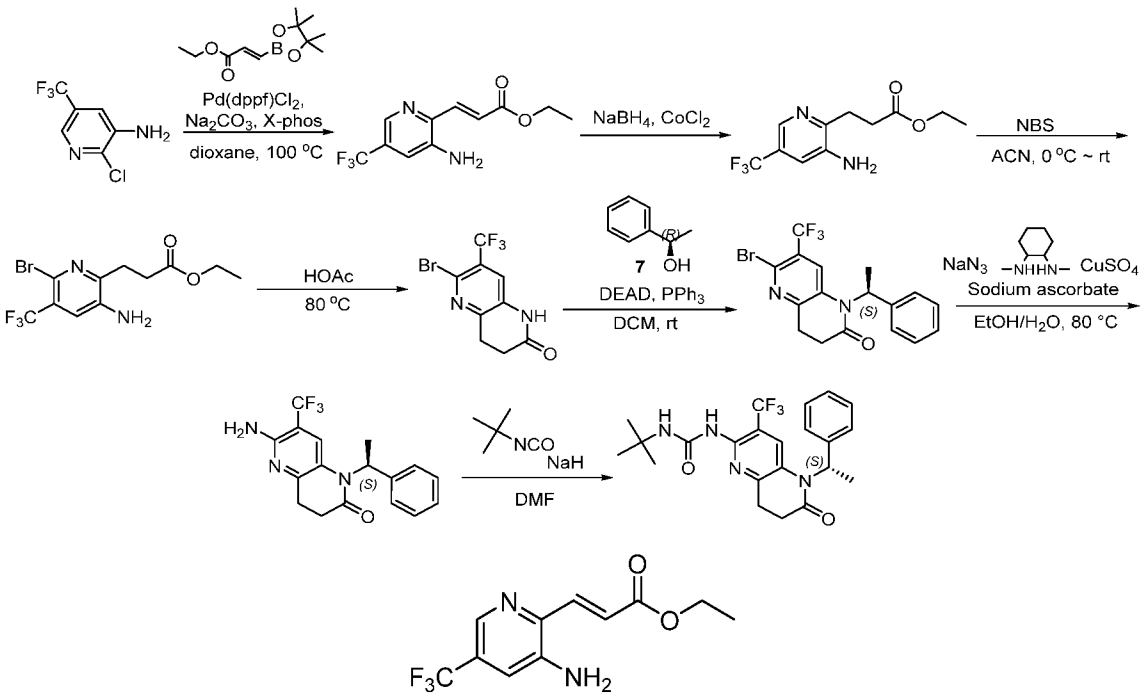


1-(tert-butyl)-3-((R)-3-methyl-2-oxo-1-((S)-1-phenylethyl)-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea

To a solution of (3R)-6-amino-3-methyl-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)-3H-pyrido[2,3-b][1,4]oxazin-2-one (100 mg, 0.285 mmol, 1 equiv) in dry-DMF(3 mL) was added NaH (6.83 mg, 0.285 mmol, 1 equiv). The reaction was stirred at rt for 0.5 h. The reaction was added 2-isocyanato-2-methylpropane (84.65 mg, 0.855 mmol, 3 equiv) and stirred at rt for 1 h. Quenched with water (10 mL) and extracted with EA (3 x 10 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a YMC-Actus Triart C18 ExRS 150 mm x 30 mm x 5 μm column (eluent: 49% to 73% (v/v) CH_3CN and H_2O with 10 mmol/L NH_4HCO_3) to afford the title compound 3-tert-butyl-1-[(3R)-3-methyl-2-oxo-1-[(1S)-1-phenylethyl]-7-(trifluoromethyl)-3H-pyrido[2,3-b][1,4]oxazin-6-yl]urea (38.2 mg, 29.42%) as a white solid. LC/MS (ESI): mass calcd. for $C_{22}H_{25}F_3N_4O_3$: 450.19 m/z, found: 451.20 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 7.69 (s, 1H), 7.19 – 7.47 (m, 7H), 6.07 – 6.26 (m, 1H), 5.13-5.24 (m, 1H), 1.74-1.76 (m, 3H), 1.55-1.57 (m, 3H), 1.28 (s, 9H). ^{19}F NMR (282 MHz, DMSO) δ -59.29, -59.33, -59.41.

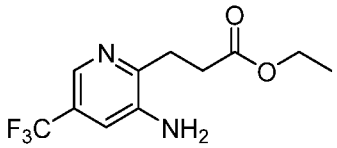
Example 377: (S)-1-(tert-butyl)-3-(6-oxo-5-(1-phenylethyl)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea

Synthetic Scheme



ethyl (E)-3-(3-amino-5-(trifluoromethyl)pyridin-2-yl)acrylate

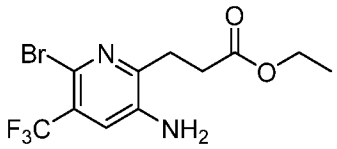
To a stirred mixture of 2-chloro-5-(trifluoromethyl) pyridin-3-amine (3 g, 15.263 mmol, 1 equiv) in dioxane (40 mL) and H_2O (10 mL) was added ethyl (E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (5.18 g, 22.895 mmol, 1.5 equiv) , $Pd(dppf)Cl_2$ (1.12 g, 1.526 mmol, 0.1 equiv) , Na_2CO_3 (4.85 g, 45.789 mmol, 3 equiv) and X-phos (727.61 mg, 1.526 mmol, 0.1 equiv) at room temperature under air atmosphere. The resulting mixture was maintained under nitrogen and stirred at 90 °C for 3 h. After cooling down to room temperature, the reaction was quenched with water (60 mL). The resulting mixture was extracted with ethyl acetate (3 x 60 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% ethyl acetate/petroleum ether) to afford the ethyl (E)-3-(3-amino-5-(trifluoromethyl) pyridin-2-yl)acrylate (2.5 g, 62.95%) as a yellow oil. LC/MS: mass calcd. for $C_{11}H_{11}F_3N_2O_2$: 260.08, found: 261.15 $[M+H]^+$.



ethyl 3-(3-amino-5-(trifluoromethyl)pyridin-2-yl)propanoate

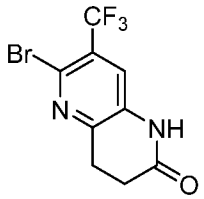
To a stirred mixture of ethyl (E)-3-(3-amino-5-(trifluoromethyl) pyridin-2-yl)acrylate (1 g, 3.843 mmol, 1 equiv) in THF (15 mL) was added $NaBH_4$ (726.90 mg, 19.215 mmol, 5 equiv) and $CoCl_2$

(249.47 mg, 1.921 mmol, 0.5 equiv) at 0 degrees C under air atmosphere. The resulting mixture was maintained under air and stirred at 25 °C for 3 h. The reaction was quenched with water (30 mL). The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% ethyl acetate/petroleum ether) to afford the ethyl 3-(3-amino-5-(trifluoromethyl) pyridin-2-yl)propanoate (750 mg, 74.42%) as a yellow oil. LC/MS: mass calcd. for $C_{11}H_{13}F_3N_2O_2$: 262.09, found: 263.15 $[M+H]^+$.



ethyl 3-(3-amino-6-bromo-5-(trifluoromethyl)pyridin-2-yl)propanoate

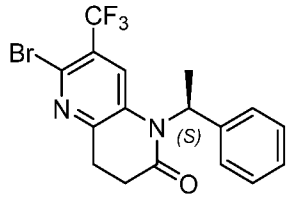
To a stirred mixture of ethyl 3-(3-amino-5-(trifluoromethyl)pyridin-2-yl)propanoate (700 mg, 2.669 mmol, 1 equiv) in ACN (5 mL) was added NBS (570.13 mg, 3.203 mmol, 1.2 equiv) at 0 degrees C under air atmosphere. The resulting mixture was maintained under air and stirred at 0 °C for 3 h. The reaction was quenched with water (20 mL). The resulting mixture was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-50% ethyl acetate/petroleum ether) to afford the ethyl 3-(3-amino-6-bromo-5-(trifluoromethyl)pyridin-2-yl)propanoate (350 mg, 38.44%) as a yellow oil. LC/MS: mass calcd. for $C_{11}H_{12}BrF_3N_2O_2$: 340.00, found: 341.05, 343.05 $[M+H, M+H+2]^+$.



6-bromo-7-(trifluoromethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one

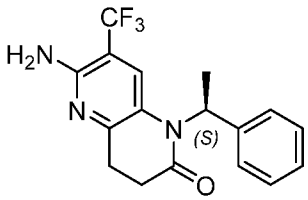
The ethyl 3-(3-amino-6-bromo-5-(trifluoromethyl)pyridin-2-yl)propanoate (300 mg, 0.879 mmol, 1 equiv) was dissolved in HOAc (3 mL) at 0 degrees C under air atmosphere. The resulting mixture was maintained under air and stirred at 80 °C for 3 h. After cooling down to room temperature, the reaction was quenched with $NaHCO_3$ solution (20 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-60%

ethyl acetate/petroleum ether) to afford the 6-bromo-7-(trifluoromethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (250 mg, 96.34%) as a yellow oil. LC/MS: mass calcd. for $C_9H_6BrF_3N_2O$: 293.96, found: 295. 05, 297.05 $[M+H, M+H+2]^+$.



(S)-6-bromo-1-(1-phenylethyl)-7-(trifluoromethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one

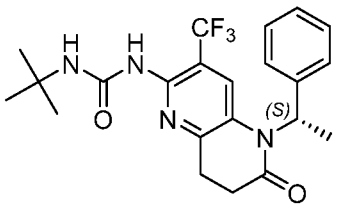
To a stirred mixture of 6-bromo-7-(trifluoromethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (240 mg, 0.813 mmol, 1 equiv) in DCM (5 mL) was added (R)-1-phenylethan-1-ol (149.06 mg, 1.220 mmol, 1.5 equiv) and PPh_3 (320.02 mg, 1.220 mmol, 1.5 equiv) at 0 degrees C under air atmosphere. After stirring at 25 °C for 30 min under nitrogen, DEAD (212.49 mg, 1.220 mmol, 1.5 equiv) was added to the reaction system at 0 degrees C. The resulting mixture was maintained under nitrogen and stirred at 25 °C for 3 h. The reaction was quenched with water (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% ethyl acetate/petroleum ether) to afford the (S)-6-bromo-1-(1-phenylethyl)-7-(trifluoromethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (140 mg, 43.11%) as a yellow oil. LC/MS: mass calcd. for $C_{17}H_{14}BrF_3N_2O$: 398.02, found: 399.10, 401.10 $[M+H, M+H+2]^+$.



(S)-6-amino-1-(1-phenylethyl)-7-(trifluoromethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one

To a stirred mixture of (S)-6-bromo-1-(1-phenylethyl)-7-(trifluoromethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (130 mg, 0.326 mmol, 1 equiv) in EtOH (2 mL) and H_2O (1 mL) was added NaN_3 (63.51 mg, 0.978 mmol, 3 equiv), N1, N2-dimethylcyclohexane-1,2-diamine (27.79 mg, 0.196 mmol, 0.6 equiv), $CuSO_4$ (51.97 mg, 0.326 mmol, 1 equiv) and sodium ascorbate (129.68 mg, 0.652 mmol, 2 equiv) at room temperature under air atmosphere. The resulting mixture was maintained under nitrogen and stirred at 80 °C for 3 h. After cooling down to room

temperature, the reaction was quenched with water (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-100% ethyl acetate/petroleum ether) to afford the (S)-6-amino-1-(1-phenylethyl)-7-(trifluoromethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (50 mg, 45.79%) as a yellow oil. LC/MS: mass calcd. for $C_{17}H_{16}F_3N_3O$: 335.12, found: 336.00 $[M+H]^+$.

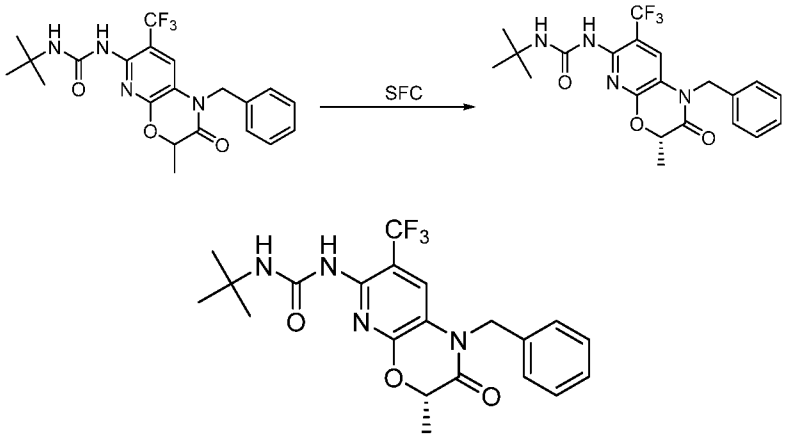


(R)-6-amino-1-benzyl-3-methyl-7-(trifluoromethyl)-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one

To a stirred mixture of (S)-6-amino-1-(1-phenylethyl)-7-(trifluoromethyl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one (45 mg, 0.134 mmol, 1 equiv) in DMF (2 mL) was added NaH (4.83 mg, 0.201 mmol, 1.5 equiv) at 0 degrees C under air atmosphere. After stirring at 0 degrees C for 30 min, 2-isocyanato-2-methylpropane (39.91 mg, 0.402 mmol, 3 equiv) was added to the reaction system. The resulting mixture was stirred at 25 °C for 3h. Quenched with water (5 mL) and extracted with EA (3 x 5 mL). The combined extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC using a XBridge Shield RP18 OBD Column 150 mm x 30 mm x 5 μm column (eluent: 70% to 85% (v/v) Me and Water with 0.1%FA) to afford the title compound (S)-1-(tert-butyl)-3-(6-oxo-5-(1-phenylethyl)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea (12.9 mg, 21.43%) as a white solid.LC/MS (ESI): mass calcd. for $C_{22}H_{25}F_3N_4O_2$:434.19 m/z, found:435.25 $[M+H]^+$.^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.00 (s, 1H), 7.51 (s, 1H), 7.23 – 7.44 (m, 5H), 7.06 (s, 1H), 6.16 – 6.32 (m, 1H), 2.95 – 3.15 (m, 2H), 2.87 – 2.96(m, 1H), 2.76 – 2.82(m, 1H), 1.68 (d, J = 7.2 Hz, 3H), 1.31 (s, 9H). ^{19}F-NMR (282 MHz, DMSO) δ -60.51.

Example 378: 1-[(3S)-1-benzyl-3-methyl-2-oxo-7-(trifluoromethyl)-3H-pyrido[2,3-b][1,4]oxazin-6-yl]-3-tert-butylurea

Synthetic Scheme



1-[(3S)-1-benzyl-3-methyl-2-oxo-7-(trifluoromethyl)-3H-pyrido[2,3-b][1,4]oxazin-6-yl]-3-tert-butylurea

The crude product (130 mg) was separated by chiral-HPLC using a CHIRALPAK IA, 5*25 cm, 5 μm (eluent: 35% to 35%(v/v) : EtOH--HPLC and Hex(0.5% 2M NH_3-MeOH) to yield second enantiomer example 1-[(3S)-1-benzyl-3-methyl-2-oxo-7-(trifluoromethyl)-3H-pyrido[2,3-b][1,4]oxazin-6-yl]-3-tert-butylurea (20 mg, 15.09%) as a white solid. LC/MS: mass calcd. for $C_{21}H_{23}F_3N_4O_3$: 436.2, found: 437.20 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.72 (s, 1H), 7.58 (s, 1H), 7.30 – 7.40 (m, 2H), 7.21 – 7.30 (m, 4H), 5.13 – 5.34 (m, 3H), 1.60 (d, J = 6.8 Hz, 3H), 1.29 (s, 6H). ^{19}F NMR (376 MHz, DMSO) δ -58.74.

hTSHR TR-FRET cAMP Assay

Assays were performed using Expi293F Inducible cells (Invitrogen) stably expressing hTSHR via a pcZeo TetO DNA plasmid. Cell lines were maintained in suspension in Expi293 Expression Medium (ThermoFisher Scientific) supplemented with 10 μg/mL Blasticidin and 10 μg/mL Zeocin and incubated at 37°C, 8% CO_2, with shaking. hTSHR cells were incubated overnight at 32°C, 5% CO_2, with shaking, but without Doxycycline. Assay-ready aliquots were prepared by harvesting each cell type separately 24-hours post-induction. Cells were pelleted at 4°C, resuspended in Expi293 Expression media + 10% DMSO, aliquoted, and kept frozen at -80°C until ready for use.

For the assay, concentration-response curves of test and reference compounds were added to 384-well plates using an Echo 650 liquid handler (Beckman Coulter) and backfilled with DMSO to a final concentration of 0.5%. cAMP was measured using the cisbio cAMP Gs

dynamic HTRF kit (PerkinElmer) according to manufacturer instructions. Aliquots of frozen hTSHR cells were quickly thawed and washed with phosphate-buffered saline (Sigma-Aldrich) to remove media and DMSO. The cells were resuspended in kit-supplied Stimulation Buffer at 0.8 x 10^6 cells/mL. 7.5 µL of the hTSHR cell dilution were added to each well of the assay plate and incubated with the compounds for 15 minutes in a 37°C, 0% CO_2 incubator. 2.5 µL of Vehicle control or an EC_{80} concentration of recombinant human anti-TSHR antibody (M22, Creative Biolabs) was added to stimulate cAMP production. Cells were incubated with for 30 minutes at 37°C, 0% CO_2. Following this incubation, the cells were lysed and accumulated cAMP was detected through the addition of kit-supplied lysis buffer containing d2-reagent and Eu-cryptate antibody. The HTRF signal was quantified using a BMG Clariostar plate reader optimized for HTRF assays. The HTRF ratio was determined by dividing the signal output at 655 nm by that at 620 nm. Data were normalized to the signal produced by the EC_{80} concentration of either M22 or FSH (0% inhibition) and vehicle (no agonist, 100% inhibition). Results of the assay are provided in Table 17.

Table 17.

Example	IUPAC Name	Activity*
1	1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	+++
2	1-(tert-butyl)-3-(2-oxo-1-(pyridin-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea	+
3	1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++
4	1-(tert-butyl)-3-(1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+
5	1-(1-benzyl-3-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	+++
6	1-(tert-butyl)-3-(1-(3-chlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++
7	1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea	+++
8	1-(tert-butyl)-3-(1-(2-chlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	++
9	tert-butyl (1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)carbamate	+++
10	1-(1-benzyl-4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	+

11	1-(1-benzyl-3-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	++
12	1-(1-benzyl-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-3-(tert-butyl)urea	++
13	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++
14	(R)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea	+
15	1-(1-benzyl-4-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	+
16	1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-hydroxy-2-methylbutan-2-yl)urea	++
17	1-(tert-butyl)-3-(1-(4-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+
18	1-(tert-butyl)-3-(1-(3-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+
19	1-(tert-butyl)-3-(1-(2-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++
20	1-(tert-butyl)-3-(1-(2-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++
21	1-(tert-butyl)-3-(1-(3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++
22	1-(tert-butyl)-3-(1-(3-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++
23	1-(tert-butyl)-3-(2-oxo-1-(3-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++
24	1-(tert-butyl)-3-(1-(2,5-dichlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++
25	1-(tert-butyl)-3-(1-(3,5-dichlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++
26	1-(tert-butyl)-3-(1-(3-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++
27	1-(tert-butyl)-3-(1-(4-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	++
28	1-(tert-butyl)-3-(2-oxo-1-(1-phenylpropyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea	+
29	1-(1-benzyl-3,3-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	+
30	1-(tert-butyl)-3-(1-(2-hydroxy-1-phenylethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+
31	1-(1-benzyl-2-oxoindolin-5-yl)-3-(tert-butyl)urea	+
32	1-(1-benzyl-3-isopropyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	+
33	1-(tert-butyl)-3-(4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++

34	(R)-1-(tert-butyl)-3-(3-oxo-4-(1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
35	(S)-1-(tert-butyl)-3-(3-oxo-4-(1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
36	(R)-1-(tert-butyl)-3-(4-(1-(3-chlorophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+
37	(S)-1-(tert-butyl)-3-(4-(1-(3-chlorophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
38	1-(3-benzyl-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-(tert-butyl)urea	+
39	1-(tert-butyl)-3-(1-(2-fluoro-5-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++
40	1-(tert-butyl)-3-(4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
41	(R)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea	+++
42	(S)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea	+++
43	(R)-1-(tert-butyl)-3-(4-(3-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
44	(S)-1-(tert-butyl)-3-(4-(3-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
45	(S)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea	+++
45A	(R)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea	+
46	(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea	+++
47	1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea	+++
48	1-(tert-butyl)-3-(1-(2-fluoro-3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++
49	1-(tert-butyl)-3-(1-(2-fluoro-5-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++
50	1-(tert-butyl)-3-(3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
51	1-(1-benzyl-3-(hydroxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	+
52	(R)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea	+
53	1-(tert-butyl)-3-(1-(2-cyano-3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	++
54	1-(tert-butyl)-3-(1-(2-fluoro-3-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++

55	1-(tert-butyl)-3-(1-(2-cyano-5-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++
56	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(m-tolyl)ethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++
57	(S)-1-(tert-butyl)-3-(3-oxo-4-(1-(m-tolyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
58	(S)-1-(tert-butyl)-3-(1-(1-(2-fluorophenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++
59	1-(tert-butyl)-3-(1-(2-cyano-3-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	++
60	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++
61	(S)-1-(tert-butyl)-3-(1-(1-(2-cyanophenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	++
62	(S)-1-(tert-butyl)-3-(3-oxo-4-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
63	1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl tert-butylcarbamate	+
64	1-(tert-butyl)-3-(1-(cyclohexylmethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+
65	1-(1-benzyl-7-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	++
66	1-(1-benzyl-7-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	++
67	1-(5-benzyl-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)-3-(tert-butyl)urea	++
68	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea	+++
69	1-(1-benzyl-8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	++
70	1-(tert-butyl)-3-(3-methyl-2-oxo-1-(3-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea	+++
71	1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
72	1-(tert-butyl)-3-(4-(3-(hydroxymethyl)benzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+
73	1-(tert-butyl)-3-(4-(3-cyclopropylbenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
74	1-(tert-butyl)-3-(3-oxo-4-(3-(trifluoromethoxy)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
75	1-(tert-butyl)-3-(4-(3-isopropoxybenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
76	1-(4-((1H-indazol-7-yl)methyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea	+
77	1-(tert-butyl)-3-(3-oxo-4-(3-(2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++

78	(R)-1-(tert-butyl)-3-(3-oxo-4-(3-(2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
79	(S)-1-(tert-butyl)-3-(3-oxo-4-(3-(2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
80	1-(tert-butyl)-3-(3-oxo-4-(3-(3,3,3-trifluoro-1-hydroxypropyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
81	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
82	(S)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
83	(R)-1-(tert-butyl)-3-(4-(2-cyano-5-(trifluoromethyl)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+
84	(S)-1-(tert-butyl)-3-(4-(2-cyano-5-(trifluoromethyl)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
85	(R)-1-(tert-butyl)-3-(4-(5-chloro-2-cyanobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
86	(S)-1-(tert-butyl)-3-(4-(5-chloro-2-cyanobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+
87	(R)-1-(tert-butyl)-3-(4-(2-cyano-5-methylbenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+
88	(S)-1-(tert-butyl)-3-(4-(2-cyano-5-methylbenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+
89	1-(tert-butyl)-3-(1-(3-chlorobenzyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
90	1-(tert-butyl)-3-(2-oxo-1-(3-(trifluoromethyl)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	++
91	1-(tert-butyl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	++
92	1-(tert-butyl)-3-(2-oxo-1-(3-(3,3,3-trifluoropropyl)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	++
93	1-(tert-butyl)-3-(2-oxo-1-(3-(4,4,4-trifluorobutyl)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	+++
94	1-(tert-butyl)-3-(2-oxo-1-(3-(2,2,2-trifluoroethyl)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	++
95	1-(tert-butyl)-3-(2-oxo-1-((6-(4,4,4-trifluorobutyl)pyridin-2-yl)methyl)-1,2-dihydroquinoxalin-6-yl)urea	++
96	1-(tert-butyl)-3-(1-(chroman-8-ylmethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
97	1-(tert-butyl)-3-(1-(chroman-5-ylmethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
98	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea	++

99	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
100	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	+++
101	(S)-1-(tert-butyl)-3-(1-(1-(3,5-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
102	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2,2,2-trifluoroethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
103	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
104	(S)-1-(tert-butyl)-3-(1-(1-(2-fluoro-5-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
105	(S)-1-(tert-butyl)-3-(1-(1-(4-fluoro-3-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	+++
106	(S)-1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(6-(trifluoromethoxy)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
107	(S)-1-(tert-butyl)-3-(1-(1-(3-isopentylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
108	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(4,4,4-trifluorobutyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
109	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(3,3,3-trifluoropropoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
110	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2-(trifluoromethoxy)ethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
111	(S)-1-(tert-butyl)-3-(1-(1-(3-(cyclopentyloxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	+
112	(S)-1-(1-(1-([1,1'-biphenyl]-3-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea	++
113	(S)-1-(tert-butyl)-3-(1-(1-(3-(3-hydroxy-3-methylbut-1-yn-1-yl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	+
114	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-phenoxyphenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
115	(S)-1-(tert-butyl)-3-(1-(1-(3-(cyclohexyloxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
116	(S)-1-(tert-butyl)-3-(1-(1-(3-(3-hydroxy-3-methylbutyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	+
117	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	+
118	(S)-1-(tert-butyl)-3-(1-(1-(3-(4-hydroxy-4-methylpentyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	+

119	(S)-1-(1-(1-(3-(2-((1H-pyrazol-4-yl)oxy)ethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea	+
120	(S)-N-(3-(1-(6-(3-(tert-butyl)ureido)-2-oxoquinoxalin-1(2H)-yl)ethyl)phenethyl)-2-hydroxy-N,2-dimethylpropanamide	+
121	(S)-1-(tert-butyl)-3-(1-(1-(3-(2-(2-hydroxy-2-methylpropoxy)ethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	+
122	(S)-1-(tert-butyl)-3-(1-(1-(3-(difluoromethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
123	(S)-1-(tert-butyl)-3-(1-(1-(isochroman-8-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
124	(S)-1-(tert-butyl)-3-(1-(1-(isochroman-5-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	+
125	(S)-1-(tert-butyl)-3-(1-(1-(2,3-dihydro-1H-inden-4-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
126	(S)-1-(tert-butyl)-3-(1-(1-(isoquinolin-8-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	+
127	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(piperidin-1-yl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
128	(S)-1-(tert-butyl)-3-(1-(1-(3-(difluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
129	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(4-(trifluoromethoxy)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	+
130	(S)-1-(tert-butyl)-3-(1-(1-(2,5-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
131	(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	+++
132	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(m-tolyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
133	(S)-1-(tert-butyl)-3-(1-(1-(3,4-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
134	(S)-1-(tert-butyl)-3-(1-(1-(3-cyclopropylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
135	(S)-1-(tert-butyl)-3-(1-(1-(3-cyclobutylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
136	(S)-1-(tert-butyl)-3-(1-(1-(3-isopropylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
137	(S)-1-(tert-butyl)-3-(1-(1-(3-isopropoxyphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
138	(S)-1-(tert-butyl)-3-(1-(1-(3-(tert-butyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
139	(S)-1-(tert-butyl)-3-(1-(1-(5-chloro-2-fluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
140	(S)-1-(tert-butyl)-3-(1-(1-(2,6-difluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++

141	(S)-1-(tert-butyl)-3-(1-(1-(5-chloro-2-methylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
142	(S)-1-(tert-butyl)-3-(1-(1-(2,3-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
143	(S)-1-(tert-butyl)-3-(1-(1-(6-cyclopropylpyridin-2-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
144	(S)-1-(tert-butyl)-3-(1-(1-(6-methoxypyridin-2-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
145	(S)-1-(tert-butyl)-3-(1-(1-(6-(dimethylamino)pyridin-2-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
146	1-(tert-butyl)-3-(1-((1S)-1-(3-(1-hydroxyethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	+
147	(S)-1-(tert-butyl)-3-(1-(1-(2-chloro-5-fluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
148	(S)-1-(tert-butyl)-3-(1-(1-(2,5-difluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
149	(S)-1-(tert-butyl)-3-(1-(1-(5-chloro-2,4-difluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
150	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(6-(2,2,2-trifluoroethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
151	(S)-1-(tert-butyl)-3-(1-(1-(2,4-difluoro-5-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
152	(S)-1-(tert-butyl)-3-(1-(1-(chroman-7-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	+
153	1-(tert-butyl)-3-(2-oxo-1-((S)-1-(6-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
154	1-(tert-butyl)-3-(2-oxo-1-((S)-1-(6-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
155	1-(tert-butyl)-3-(2-oxo-1-((S)-1-(3-((R)-2,2,2-trifluoro-1-hydroxyethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
156	1-(tert-butyl)-3-(2-oxo-1-((S)-1-(3-((S)-2,2,2-trifluoro-1-hydroxyethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
157	(R)-1-(tert-butyl)-3-(2-methyl-4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
158	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
159	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-(3-(trifluoromethoxy)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
160	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethoxy)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
161	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++

162	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((4-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
163	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((2-(trifluoromethyl)pyridin-4-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
164	(R)-1-(tert-butyl)-3-(4-(3-methoxybenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
165	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((2-(trifluoromethyl)thiazol-4-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
166	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethoxy)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
167	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((2-(trifluoromethyl)pyrimidin-4-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
168	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((4-(trifluoromethyl)thiazol-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
169	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyrazin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
170	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((4-(trifluoromethyl)pyrimidin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
171	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((5-(trifluoromethyl)pyridin-3-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
172	1-(tert-butyl)-3-((2R)-2-methyl-3-oxo-4-(3-(2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
173	1-(tert-butyl)-3-((2R)-2-methyl-3-oxo-4-((6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
174	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-(3-((R)-2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
175	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-(3-((S)-2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
176	(R)-1-(tert-butyl)-3-(4-(2,5-dichlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
177	(R)-1-(tert-butyl)-3-(4-(2,5-difluorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
178	(R)-1-(tert-butyl)-3-(4-(2-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
179	(S)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
180	(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++

181	(S)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
182	(S)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
183	1-(tert-butyl)-3-((R)-4-((S)-1-(3-chlorophenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
184	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
185	1-(tert-butyl)-3-((R)-4-((S)-1-(3-(difluoromethyl)phenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
186	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
187	1-(tert-butyl)-3-((R)-4-((S)-1-(3-methoxyphenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
188	1-(tert-butyl)-3-((R)-4-((S)-1-(2,5-difluorophenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
189	1-(tert-butyl)-3-((R)-4-((S)-1-(2-chlorophenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
190	1-(tert-butyl)-3-((R)-4-((S)-1-(2,5-dichlorophenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
191	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1-methylcyclobutyl)urea	++
192	N-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3,3-dimethylazetidine-1-carboxamide	+
193	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1-methylcyclopentyl)urea	++
194	N-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3,3-dimethylpyrrolidine-1-carboxamide	+
195	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1-fluoro-2-methylpropan-2-yl)urea	+
196	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-cyclopentylurea	+
197	N-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)cyclopentanecarboxamide	+
198	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1,1,1-trifluoro-2-methylpropan-2-yl)urea	++
199	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1,1-difluoro-2-methylpropan-2-yl)urea	++
200	(S)-1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	+++
201	(S)-1-neopentyl-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
202	(S)-N-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)phenyl)propanamide	+++

203	(S)-1-(1-methylcyclopentyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
204	(S)-1-(3,3-difluorocyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
205	(S)-1-cyclobutyl-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
206	(S)-1-(bicyclo[1.1.1]pentan-1-yl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
207	(S)-1-isopentyl-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
208	(S)-1-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(1,1,1-trifluoro-2-methylpropan-2-yl)urea	++
209	(S)-1-(tert-butyl)-3-(5-methyl-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
210	(S)-1-(1-methylcyclohexyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	+++
211	(S)-1-(bicyclo[2.2.1]heptan-1-yl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	+++
212	(S)-1-(3-methyloxetan-3-yl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	+
213	(S)-1-(bicyclo[2.1.1]hexan-1-yl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	+++
214	(S)-1-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(1-(trifluoromethyl)cyclobutyl)urea	++
215	(S)-1-(1-(methoxymethyl)cyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
216	(S)-1-(4,4-difluorocyclohexyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
217	(S)-1-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(1-(trifluoromethyl)cyclopentyl)urea	++
218	(S)-1-(tert-butyl)-3-(5-chloro-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
219	(R)-2,2-dimethyl-N-(2-oxo-1-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)cyclobutane-1-carboxamide	+++
220	(S)-2,2-dimethyl-N-(2-oxo-1-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)cyclobutane-1-carboxamide	++
221	(S)-1-(3,3-difluoro-1-methylcyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
222	(S)-1-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)oxetan-3-yl)urea	++

223	1-(2-oxo-1-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-((1r,3S)-3-(trifluoromethyl)cyclobutyl)urea	++
224	1-(2-oxo-1-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-((1s,3R)-3-(trifluoromethyl)cyclobutyl)urea	++
225	(S)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
226	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclobutyl)urea	+++
227	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea	+++
228	(R)-1-cyclohexyl-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
229	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclohexyl)urea	+++
230	1-(bicyclo[3.1.0]hexan-3-yl)-3-((R)-2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
231	(R)-1-(3,3-difluoro-1-methylcyclobutyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
232	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-(trifluoromethyl)cyclobutyl)urea	++
233	(R)-1-(1-(methoxymethyl)cyclobutyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
234	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-(trifluoromethyl)cyclopentyl)urea	+++
235	(R)-1-(4,4-difluorocyclohexyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
236	(R)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(4-hydroxy-2-methylbutan-2-yl)urea	++
237	(R)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-cyclopentylurea	+++
238	1-((R)-4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(2-((1s,3S)-3-hydroxycyclobutyl)propan-2-yl)urea	+

239	1-(2-hydroxy-2-methylpropyl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	+
240	1-neopentyl-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	++
241	1-(2-cyano-2-methylpropyl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	+
242	1-(3-hydroxy-2,2-dimethylpropyl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	+
243	1-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)-3-(4,4,4-trifluoro-2-methylbutan-2-yl)urea	++
244	1-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)-3-(3,3,3-trifluoro-2,2-dimethylpropyl)urea	++
245	1-(1-cyano-2-methylpropan-2-yl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	+
246	1-(tert-butyl)-3-(1-(1-(3-cyclobutylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
247	1-(tert-butyl)-3-(1-(1-(3-fluoro-5-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
248	1-(tert-butyl)-3-(1-(1-(3-(2-(oxetan-3-yl)ethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	+
249	1-(tert-butyl)-3-(2-oxo-1-(1-(1-(3,3,3-trifluoropropyl)-1H-indazol-6-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	+
250	1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2-(pyridin-4-ylmethoxy)ethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	+
251	1-(tert-butyl)-3-(2-oxo-1-(1-(1-(3,3,3-trifluoropropyl)-1H-indazol-4-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	+
252	1-(tert-butyl)-3-(2-oxo-1-(1-(quinolin-5-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	+
253	1-(tert-butyl)-3-(2-oxo-1-(1-(4-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	+
254	1-(tert-butyl)-3-(1-(1-(3,6-dichloropyridin-2-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
255	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclobutyl)urea	+++
256	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea	+++
257	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-(trifluoromethyl)cyclopentyl)urea	+++
258	1-(4,4-difluorocyclohexyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
259	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-(trifluoromethyl)cyclobutyl)urea	+++
260	1-(3,3-difluoro-1-methylcyclobutyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++

261	1-(1-(methoxymethyl)cyclobutyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
262	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(3-methyloxetan-3-yl)urea	+
263	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(3-(trifluoromethyl)oxetan-3-yl)urea	++
264	1-(3,3-difluoro-1-(trifluoromethyl)cyclobutyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
265	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(4-methyltetrahydro-2H-pyran-4-yl)urea	++
266	1-(tert-butyl)-3-(1-(2-cyano-5-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+
267	1-(1-benzyl-5-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	++
268	1-(tert-butyl)-3-((S)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
269	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
270	1-(1-benzyl-7-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	+
271	1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea	+
272	1-(1-benzyl-3-methyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea	+
273	1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
274	1-(tert-butyl)-3-(6-oxo-5-(3-(trifluoromethyl)benzyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea	++
275	(R)-1-(1-benzyl-3-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	+
276	(S)-1-(1-benzyl-3-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	+
277	(R)-1-(4-benzyl-2-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea	+
278	(S)-1-(4-benzyl-2-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea	+
279	1-(1-benzyl-5-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	+
280	(R)-1-(1-benzyl-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea	++
281	1-(tert-butyl)-3-(5-(3-chlorobenzyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea	++

282	(S)-1-(tert-butyl)-3-(6-oxo-5-(1-(3-(trifluoromethyl)phenyl)ethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea	++
283	(R)-1-(tert-butyl)-3-(6-oxo-5-(1-(3-(trifluoromethyl)phenyl)ethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea	+
284	1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-phenylurea	+
285	N-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3,3-dimethylbutanamide	+
286	(S)-1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea	+
287	(R)-1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea	++
288	(S)-1-(4-benzyl-2-(methoxymethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea	+
289	(R)-1-(4-benzyl-2-(methoxymethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea	+
290	(S)-1-(tert-butyl)-3-(5-(1-(3-chlorophenyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea	+
291	(R)-1-(tert-butyl)-3-(5-(1-(3-chlorophenyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea	++
292	1-(4-benzyl-2,2-dimethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea	+
293	1-(tert-butyl)-3-(4-(1-(5-chloro-2-cyanophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+
294	1-(3-amino-1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea	+
295	1-(tert-butyl)-3-(3-ethyl-2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea	+
296	1-(tert-butyl)-3-(3-oxo-4-(2,2,2-trifluoro-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
297	(S)-1-(tert-butyl)-3-(1-(1-(3-methoxyphenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	++
298	1-(tert-butyl)-3-(1-(chroman-4-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	+
299	(S)-N-(2-oxo-1-(1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)phenyl)propanamide	++
300	(S)-4,4-dimethyl-N-(2-oxo-1-(1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)pentanamide	++
301	1-(1-benzyl-2-oxo-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	+
302	1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-3-(tert-butyl)urea	+
303	cyclopentyl ((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)carbamate	+++
304	cyclopentyl (R)-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)carbamate	+++

305	1-(4-benzyl-2-(fluoromethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea	++
306	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethyl)pyrazin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+
307	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-(6-(trifluoromethyl)pyrazin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
308	N-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-2,2-dimethylcyclopentane-1-carboxamide	++
309	1-(tert-butyl)-3-(1-(2,3-dihydro-1H-inden-1-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea	++
310	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(2-(trifluoromethyl)pyrimidin-4-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
311	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-(2-(trifluoromethyl)pyrimidin-4-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+
312	1-(tert-butyl)-3-(1-(1-(2-fluoro-3-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
313	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	+
314	(R)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
315	(S)-N-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)cyclopentanecarboxamide	++
316	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(4-(trifluoromethyl)pyrimidin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+
317	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-(4-(trifluoromethyl)pyrimidin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
318	(S)-N-(2-oxo-1-(1-(6-(trifluoromethoxy)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)phenyl)propanamide	++
319	(S)-1-(1-(1-(3-chlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1-methylcyclobutyl)urea	++
320	(S)-1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
321	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethoxy)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea	+++
322	1-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea	+++

323	1-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethoxy)pyridin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea	+++
324	1-((R)-2-methyl-3-oxo-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-((1r,3R)-3-(trifluoromethyl)cyclobutyl)urea	++
325	1-((R)-2-methyl-3-oxo-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-((1s,3S)-3-(trifluoromethyl)cyclobutyl)urea	++
326	(R)-1-(4-benzyl-6-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea	++
327	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-6-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
328	1-(tert-butyl)-3-((R)-6-fluoro-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
329	(R)-1-(4-benzyl-6,8-difluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea	++
330	(R)-1-(4-benzyl-2-methyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea	+++
331	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+
332	(R)-1-(4-benzyl-2,6-dimethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea	++
333	(S)-1-(1-benzyl-7-fluoro-3-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	+
334	(R)-1-(1-benzyl-7-fluoro-3-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	+
335	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethoxy)benzyl)-6,8-difluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
336	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-6,8-difluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
337	1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(4-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
338	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethoxy)benzyl)-6-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
339	(S)-1-(tert-butyl)-3-(7-fluoro-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
340	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-5,6-difluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
341	(R)-1-(4-benzyl-6-cyano-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea	++
342	(R)-1-(tert-butyl)-3-(6-cyano-4-(3-(difluoromethyl)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
343	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-7-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea	+++

344	(S)-1-(tert-butyl)-3-(7-chloro-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
345	1-(1-benzyl-5,7-difluoro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	++
346	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-7-(trifluoromethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
347	(S)-1-(tert-butyl)-3-(7-methyl-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
348	(S)-1-(tert-butyl)-3-(7-cyclopropyl-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
349	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
350	1-(1-benzyl-2-oxo-7-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea	++
351	(S)-1-(tert-butyl)-3-(5-(hydroxymethyl)-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	+
352	(S)-1-(tert-butyl)-3-(7-cyano-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
353	(S)-1-(tert-butyl)-3-(5-fluoro-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
354	(R)-1-(4-benzyl-8-fluoro-2-methyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea	++
355	(R)-1-(1-benzyl-7-chloro-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea	++
356	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
357	(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-7-fluoro-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
358	(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-2-oxo-7-(trifluoromethyl)-1,2-dihydroquinoxalin-6-yl)urea	++
359	cyclopentyl (S)-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)carbamate	+++
360	(S)-1-(tert-butyl)-3-(7-(hydroxymethyl)-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea	+
361	(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-7-cyano-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
362	(R)-1-(1-benzyl-7-cyano-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea	++
363	(S)-1-(tert-butyl)-3-(7-cyano-1-(1-(2,5-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
364	(S)-1-(tert-butyl)-3-(1-(1-(5-chloro-2-fluorophenyl)ethyl)-7-cyano-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	++
365	(S)-1-(tert-butyl)-3-(7-chloro-1-(1-(2,5-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	+++

366	1-(tert-butyl)-3-((R)-6-cyano-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
367	(R)-1-(tert-butyl)-3-(6-cyano-4-(2,5-dichlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
368	(R)-1-(1-benzyl-3-methyl-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea	+++
369	(R)-1-(4-benzyl-6-cyano-8-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea	+++
370	(R)-1-(tert-butyl)-3-(6-cyano-4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	+++
371	(R)-1-(tert-butyl)-3-(7-cyano-1-(3-(difluoromethyl)benzyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea	+++
372	(S)-1-(tert-butyl)-3-(7-chloro-1-(1-(5-chloro-2-fluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	+++
373	(R)-1-(tert-butyl)-3-(4-(5-chloro-2-fluorobenzyl)-6-cyano-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea	++
374	(R)-1-(tert-butyl)-3-(1-(3-(difluoromethyl)benzyl)-3-methyl-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea	+++
375	1-(tert-butyl)-3-(1-(1-(2-fluoro-5-(2,2,2-trifluoro-1-hydroxyethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea	+
376	1-(tert-butyl)-3-((R)-3-methyl-2-oxo-1-((S)-1-phenylethyl)-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea	+++
377	(S)-1-(tert-butyl)-3-(6-oxo-5-(1-phenylethyl)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea	+++
378	(R)-1-(1-benzyl-3-methyl-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea	++

* IC_{50} bins: + >1 μM; ++ = 1 μM-100 nM; and +++ <100 nM

INCORPORATION BY REFERENCE

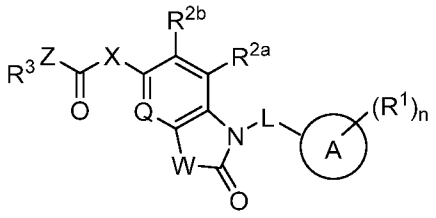
All of the U.S. patents and U.S. and PCT patent application publications cited herein are hereby incorporated by reference.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

We claim:

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

A is (C_6-C_{10})aryl, 5- to 10-membered heteroaryl, (C_3-C_8)cycloalkyl, or 4- to 7-membered heterocycloalkyl;

n is 0, 1, 2, 3, 4, or 5;

R^1 is independently for each occurrence (C_1-C_6)alkyl, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy, (C_6-C_{10})aryl(C_1-C_6)alkyl, 4- to 7-membered heterocycloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo, cyano, amino, formyl, carboxy, or alkoxycarbonyl,

wherein (C_1-C_6)alkyl, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_3-C_8)cycloalkyl, C_3-C_8)cycloalkoxy, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and 4- to 7-membered heterocycloalkyl are each optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, 4- to 7-membered heterocycloalkyl, 5- to 6-membered heteroaryl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)fluoroalkoxy, 5- to 6-membered heteroaryloxy, or

two vicinal occurrences of R^1 taken together with the atoms to which they are attached form a fused 5- to 7-membered cycloalkyl, 5- to 7-membered heterocycloalkyl ring, 5- to 6-membered heteroaryl ring or phenyl ring, any of which is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

Q is N or CR^{2c};

R^{2a}, R^{2b}, and R^{2c}, are each independently hydrogen, halo, cyano, (C_1-C_6)alkyl, or (C_3-C_8)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

R^3 is (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl), (C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkyl), or 4- to 7-membered heterocycloalkyl; each of which is optionally substituted with one or more substituents independently selected from halo, cyano, (C_1-C_6)haloalkyl, hydroxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and (C_1-C_6)alkoxy;

X and Z are independently NR^4, $C(R^5)_2$, or O;

R^4 and R^5 independently for each occurrence hydrogen or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy, or when Z is NR^4, R^3 and R^4 taken together with the nitrogen to which they are attached form a 4- to 7-member heterocycloalkyl optionally substituted with one or more (C_1-C_6)alkyl or halo;

L is (C_1-C_6)alkylene optionally substituted with one or more substituents independently selected from halo, hydroxy, C_1-C_6)alkoxy, and cyano;

W represents:

$–C(R^6)_2–C(R^7)_2–$,

$–C(R^7)_2–$,

$–O–C(R^8)_2–$,

$–C(R^8)_2–O–$,

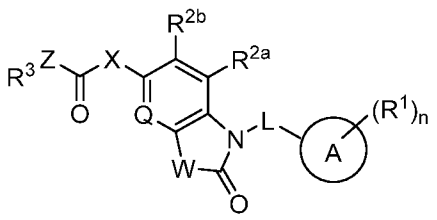
$–C(R^8)_2–NR^9–$,

$–N=C(R^{10})$ –, or

–O–; and

R^6, R^7, R^8, R^9 and R^{10} are independently for each occurrence hydrogen, (C_1-C_6)alkyl,or NH_2, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, cyano, hydroxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and (C_1-C_6)alkoxy.

2. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

A is (C_6-C_{10})aryl or 5- to 10-membered heteroaryl;

n is 0, 1, 2, 3, 4, or 5;

R^1 is independently for each occurrence (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, 4- to 7-membered heterocycloalkyl, (C_1-C_6)alkoxy, halo, cyano, formyl, carboxy, or alkoxycarbonyl, wherein (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_1-C_6)alkoxy, and 4- to 7-membered heterocycloalkyl are each optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy, or

two vicinal occurrences of R^1 taken together with the atoms to which they are attached form a fused 5- to 7-membered cycloalkyl or 5- to 7-membered heterocycloalkyl ring, either of which is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

Q is N or CR^{2c};

R^{2a}, R^{2b}, and R^{2c}, are each independently hydrogen, halo, cyano, or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

R^3 is (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

X and Z are independently NR^4, $C(R^5)_2$, or O;

R^4 and R^5 independently for each occurrence hydrogen or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

L is (C_1-C_6)alkylene optionally substituted with one or more substituents independently selected from halo, hydroxy, C_1-C_6)alkoxy, and cyano;

W represents:

$–C(R^6)_2–C(R^7)_2–$,

$–C(R^7)_2–$,

$–O–C(R^8)_2–$,

$–C(R^8)_2–O–$,

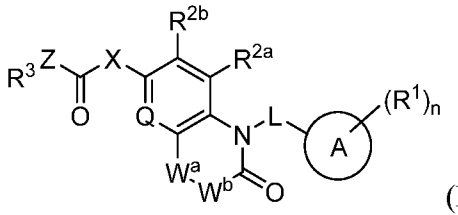
$–C(R^8)_2–NR^9–$,

–N=C(R^{10}) –, or

–O–; and

R^6, R^7, R^8, R^9 and R^{10} are independently for each occurrence hydrogen or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy.

3. A compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof,

wherein

A is (C_6-C_{10})aryl, 5- to 10-membered heteroaryl, (C_3-C_8)cycloalkyl, or 4- to 7-membered heterocycloalkyl;

n is 0, 1, 2, 3, 4, or 5;

R^1 is independently for each occurrence (C_1-C_6)alkyl, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy, (C_6-C_{10})aryl(C_1-C_6)alkyl, 4- to 7-membered heterocycloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo, cyano, amino, formyl, carboxy, or alkoxycarbonyl,

wherein (C_1-C_6)alkyl, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and 4- to 7-membered heterocycloalkyl are each optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, 4- to 7-membered heterocycloalkyl, 5- to 6-membered heteroaryl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)fluoroalkoxy, 5- to 6-membered heteroaryloxy, or

two vicinal occurrences of R^1 taken together with the atoms to which they are attached form a fused 5- to 7-membered cycloalkyl, 5- to 7-membered heterocycloalkyl ring, 5- to 6-membered heteroaryl ring or phenyl ring, any of which is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

Q is N or CR^{2c};

R^{2a}, R^{2b}, and R^{2c}, are each independently hydrogen, halo, cyano, $(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_8)$cycloalkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and $(C_1\text{-}C_6)$alkoxy;

R^3 is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_3\text{-}C_8)$cycloalkyl$(C_1\text{-}C_6)$alkyl), $(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl), or 4- to 7-membered heterocycloalkyl; each of which is optionally substituted with one or more substituents independently selected from halo, cyano, $(C_1\text{-}C_6)$haloalkyl, hydroxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, and $(C_1\text{-}C_6)$alkoxy;

X and Z are independently NR^4, $C(R^5)_2$, or O;

R^4 and R^5 independently for each occurrence hydrogen or $(C_1\text{-}C_6)$alkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and $(C_1\text{-}C_6)$alkoxy, or when Z is NR^4, R^3 and R^4 taken together with the nitrogen to which they are attached form a 4- to 7-member heterocycloalkyl optionally substituted with one or more $(C_1\text{-}C_6)$alkyl or halo;

L is $(C_1\text{-}C_6)$alkylene optionally substituted with one or more substituents independently selected from halo, hydroxy, $C_1\text{-}C_6)$alkoxy, and cyano;

W represents:

$–C(R^6)_2–C(R^7)_2–$,

$–C(R^7)_2–$,

$–O–C(R^8)_2–$,

$–C(R^8)_2–O–$,

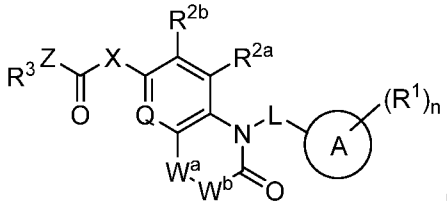
$–C(R^8)_2–NR^9–$,

$–N=C(R^{10})$ –, or

–O–; and

R^6, R^7, R^8, R^9 and R^{10} are independently for each occurrence hydrogen, $(C_1\text{-}C_6)$alkyl,or NH_2, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one or more substituents independently selected from halo, cyano, hydroxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, and $(C_1\text{-}C_6)$alkoxy.

4. A compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof,

wherein

A is (C_6-C_{10})aryl or 5- to 10-membered heteroaryl;

n is 0, 1, 2, 3, 4 or 5;

R^1 is independently for each occurrence (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, , 4- to 7-membered heterocycloalkyl, (C_1-C_6)alkoxy, halo, cyano, formyl, carboxy, or alkoxycarbonyl, wherein (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, 4- to 7-membered heterocycloalkyl, and (C_1-C_6)alkoxy are each optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy; or

two vicinal occurrences of R^1 taken together with the atoms to which they are attached form a fused 5- to 7-membered cycloalkyl or 5- to 7-membered heterocycloalkyl ring, either of which is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

Q is N or CR^{2c};

R^{2a}, R^{2b}, and R^{2c}, are each independently hydrogen, halo, cyano, or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

R^3 is (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

X and Z are independently NR^4, $C(R^5)_2$, or O;

R^4 and R^5 are independently for each occurrence hydrogen or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

L is (C_1-C_6)alkylene optionally substituted with one or more substituents independently selected from halo, hydroxy, C_1-C_6)alkoxy, and cyano;

W^a–W^b represents:

–$C(R^6)_2$–$C(R^7)_2$–,

–O–C(R^8)$_2$–,

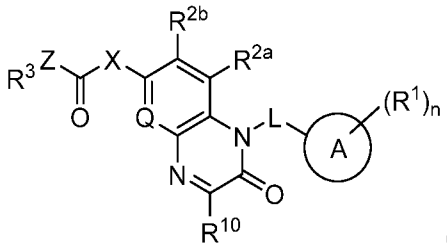
–C(R^8)$_2$–O–,

–C(R^8)$_2$–NR^9–, or

–N=C(R^{10}) –; and

R^6, R^7, R^8, R^9 and R^{10} are independently for each occurrence hydrogen or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy.

5. A compound of Formula (III):



(III),

or a pharmaceutically acceptable salt thereof,

wherein:

A is (C_6-C_{10})aryl, 5- to 10-membered heteroaryl, (C_3-C_8)cycloalkyl, or 4- to 7-membered heterocycloalkyl;

n is 0, 1, 2, 3, 4, or 5;

R^1 is independently for each occurrence (C_1-C_6)alkyl, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkoxy, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy, (C_6-C_{10})aryl(C_1-C_6)alkyl, 4- to 7-membered heterocycloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo, cyano, amino, formyl, carboxy, or alkoxycarbonyl,

wherein (C_1-C_6)alkyl, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_3-C_8)cycloalkyl, C_3-C_8)cycloalkoxy, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and 4- to 7-membered heterocycloalkyl are each optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, 4- to 7-membered heterocycloalkyl, 5- to 6-membered heteroaryl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy, (C_1-C_6)fluoroalkoxy, 5- to 6-membered heteroaryloxy, or

two vicinal occurrences of R^1 taken together with the atoms to which they are attached form a fused 5- to 7-membered cycloalkyl, 5- to 7-membered heterocycloalkyl ring, 5- to 6-membered heteroaryl ring or phenyl ring, any of which is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

Q is N or CR^{2c};

R^{2a}, R^{2b}, and R^{2c}, are each independently hydrogen, halo, cyano, (C_1-C_6)alkyl, or (C_3-C_8)cycloalkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

R^3 is (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl), (C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkyl), or 4- to 7-membered heterocycloalkyl; each of which is optionally substituted with one or more substituents independently selected from halo, cyano, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, hydroxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and (C_1-C_6)alkoxy;

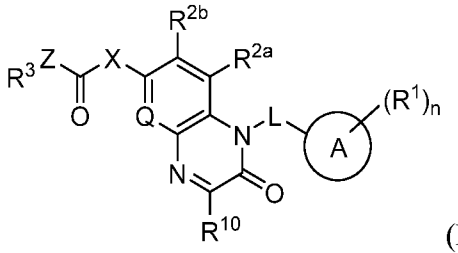
X and Z are independently NR^4, $C(R^5)_2$, or O;

R^4 and R^5 independently for each occurrence hydrogen or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy, or when Z is NR^4, R^3 and R^4 taken together with the nitrogen to which they are attached form a 4- to 7-member heterocycloalkyl optionally substituted with one or more (C_1-C_6)alkyl or halo, or when Z is $C(R^5)_2$, R^3 and one R^5 taken together with the carbon to which they are attached form a 4, (C_3-C_8)cycloalkyl optionally substituted with one or more (C_1-C_6)alkyl or halo;

L is (C_1-C_6)alkylene optionally substituted with one or more substituents independently selected from halo, hydroxy, C_1-C_6)alkoxy, and cyano;

R^{10} is hydrogen, (C_1-C_6)alkyl,or NH_2, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, cyano, hydroxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, and (C_1-C_6)alkoxy.

6. A compound of Formula (III):



(III),

or a pharmaceutically acceptable salt thereof,

wherein

A is (C_6-C_{10})aryl or 5- to 10-membered heteroaryl;

n is 0, 1, 2, 3, 4 or 5;

R^1 is independently for each occurrence (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, 4- to 7-membered heterocycloalkyl, (C_1-C_6)alkoxy, halo, cyano, formyl, carboxy, or alkoxycarbonyl, wherein (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, 4- to 7-membered heterocycloalkyl, and (C_1-C_6)alkoxy are each optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy; or

two vicinal occurrences of R^1 taken together with the atoms to which they are attached form a fused 5- to 7-membered cycloalkyl or 5- to 7-membered heterocycloalkyl ring, either of which is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy;

Q is N or CR^{2c};

R^{2a}, R^{2b}, and R^{2c}, are each independently hydrogen, halo, cyano, (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

R^3 is (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

X and Z are independently NR^4, $C(R^5)_2$, or O;

R^4 and R^5 are independently for each occurrence hydrogen or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy;

L is (C_1-C_6)alkylene optionally substituted with one or more substituents independently selected from halo, hydroxy, C_1-C_6)alkoxy, and cyano; and

R^{10} is hydrogen or (C_1-C_6)alkyl, wherein (C_1-C_6)alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and (C_1-C_6)alkoxy.

7. The compound of any one of claims 1 to 6, wherein A is phenyl.

8. The compound of any one of claims 1 to 6, wherein A is a 5- to 7-membered heteroaryl comprising 1 or 2 nitrogen atoms.

9. The compound of claim 8, wherein A is pyridyl or diazolyl. thiazolyl, pyrazinyl, pyrimidinyl,

10. The compound of claim 9, wherein A is pyridyl or diazolyl.

11. The compound of any one of claims 1 to 6, wherein A is isoquinolinyl or indazolyl.

12. The compound of any one of calims 1 to 6, wherein A is cyclopentyl, cyclohexyl, or tetrahydropyranyl.

13. The compound of any one of claims 1 to 12, wherein R^1 is independently for each occurrence (C_1-C_6)alkyl, (C_1-C_6)alkoxy, fluoro, chloro, or cyano, wherein (C_1-C_6)alkyl and (C_1-C_6)alkoxy are optionally substituted with one or more substituents independently selected from fluoro and hydroxyl.

14. The compound of any one of claims 1 to 12, wherein at least one R^1 is fluoro, chloro, or cyano.

15. The compound of any one of claims 1 to 14, wherein at least one R^1 is (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from hydroxyl and fluoro,

16. The compound claim 15, wherein at least one R^1 is 2,2,2-trifluoroethyl-1-hydroxyethyl.

17. The compound claim 15, wherein at least one R^1 wherein at least one R^1 is difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluropropyl, or 4,4,4-trifluorobutyl.

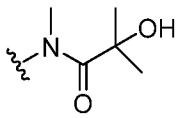
18. The compound of any one of claims 1 to 14, wherein at least one R^1 is (C_1-C_6)alkoxy optionally substituted with at least one fluoro.

19. The compound of claim 18, wherein at least one R^1 is difluoromethoxy or trifluoromethoxy.

20. The compound of claim 18, wherein at least one R^1 is methoxy or isopropoxy.

21. The compound of any one of claims 1 to 14, wherein at least one R^1 is methyl optionally substituted with hydroxy or one or more fluoro.

22. The compound of any one of claims 1 to 14, wherein at least R^1 is (C_1-C_6)alkyl substituted with an amido having the structure:



.

23. The compound of any one of claims 1 to 14, wherein at least one R^1 is (C_3-C_8)cycloalkyl.

24. The compound of claim 23, wherein the (C_3-C_8)cycloalkyl is cyclopropyl or cyclobutyl.

25. The compound of any one of claims 1 to 14, wherein at least R^1 is (C_3-C_8)cycloalkoxy.

26. The compound of claim 25, wherein the (C_3-C_8)cycloalkoxy is cyclopentyloxy or cyclohexyloxy.

27. The compound of any one of claims 1 to 14, wherein R^1 is (C_2-C_6)alkynyl optionally substituted with hydroxy.

28. The compound of any one of claims 1 to 12, wherein two vicinal occurrences of R^1 taken together with the atoms to which they are attached form a fused 5- to 7-membered cycloalkyl or 5- to 7-membered heterocycloalkyl ring, either of which is optionally substituted with one or more substituents independently selected from halo, hydroxy, cyano, amido, sulfonamido, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and (C_1-C_6)alkoxy.

29. The compound of claim 28, wherein A is phenyl comprising two vicinal occurrences of R^1, wherein the two vicinal occurrences of R^1, taken together with the atoms to which they are attached, form a fused 5- to 7-membered cycloalkyl or 5- to 7-membered heterocycloalkyl ring.

30. The compound of any one of claims 1 to 27, wherein n is 2.

31. The compound of any one of claims 1 to 27, wherein n is 1.

32. The compound of any one of claims 1 to 12, wherein n is 0.

33. The compound of any one of claims 1 to 32, wherein Q is CR^{2c}.

34. The compound of any one of claims 1 to 32, wherein Q is N.

35. The compound of any one of claims 1 to 33, wherein R^{2a}, R^{2b}, and R^{2c} are each hydrogen.

36. The compound of any one of claims 1 to 33, wherein at least one of R^{2a}, R^{2b}, and R^{2c} is fluoro, chloro, or cyano.

37. The compound of any one of claims 1 to 36, wherein R^3 is (C_1-C_6)alkyl optionally substituted with hydroxy.

38. The compound of claim 37, wherein R^3 is t-butyl.

39. The compound of any one of claims 1 to 36, wherein R^3 is (C_3-C_8)cycloalkyl optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)fluoroalkyl, fluoro, or (C_1-C_6)alkoxy(C_1-C_6)alkyl.

40. The compound of claim 39, wherein the (C_3-C_8)cycloalkyl is cyclobutyl, cyclopentyl, cylohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl,bicycle[2.1.1]hexanyl, or bicyclo[3.1.0]hexanyl.

41. The compound of claim 40 or 41, wherein the (C_3-C_8)cycloalkyl is optionally substituted with one or more substituents selected from fluoro, trifluoromethyl, methoxymethyl, methyl, and hydroxyl.

42. The compound of any one of claims 1 to 36, wherein R^3 is 4- to 7-membered heterocycloalkyl optionally substituted with one or more substituents selected from (C_1-C_6)alkyl, (C_1-C_6)fluoroalkyl, or fluoro.

43. The compound of claim 42, wherein the 4- to 7-membered heterocycloalkyl is etrahydropyranyl or oxetanyl.

44. The compound of any one of claims 1 to 36, wherein Z is NR^4, R^3 and R^4 taken together with the nitrogen to which they are attached form a 4- to 7-member heterocycloalkyl optionally substituted with one or more (C_1-C_6)alkyl or halo.

45. The compound of claim 44, wherein the 4- to 7 membered heterocycloalkyl is azetidine or pyrrolidine,

46. The compound of any one of claims 1 to 45, wherein X is NR^4 or O.

47. The compound of any one of claims 1 to 45 wherein X is NH.

48. The compound of any one of claims 1 to 43 and 46 to 47, wherein Z is NR^4, or O.

49. The compound of any one of claims 1 to 43 and 46 to 47, wherein Z is NH.

50. The compound of any one of claims 1 to 49, wherein one and only one of X and Z is CH_2.

51. The compound of any one of claims 1 to 43 and 46 to 47, wherein X and Z are each NH.

52. The compound of any one of claims 1 to 51, wherein L is unsubstituted (C_1-C_6)alkylene.

53. The compound of any one of claims 1 to 51, wherein L is (C_1-C_6)alkylene substituted with hydroxy.

54. The compound of any one of claims 1 to 51, wherein L is (C_1-C_6)alkylene substituted with 1 to 3 halo atoms.

55. The compound of any one of claims 1 to 51, wherein L is $–CH_2–$, $–CH(CH_3)–$, $–CH(CH_2CH_3)–$, or $–CH(CH_2OH)–$.

56. The compound of any one of claims 2 to 55, wherein

$W^a–W^b$ represents:

$–C(R^6)_2–C(R^7)_2–$.

57. The compound of claim 56, wherein at least one R^6 is $(C_1\text{-}C_6)$alkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, and $(C_1\text{-}C_6)$alkoxy.

58. The compound of claim 56 or 57, wherein at least one R^7 is $(C_1\text{-}C_6)$alkyl, wherein $(C_1\text{-}C_6)$alkyl is optionally substituted with one or more substituents independently selected from halo, hydroxy, $(C_1\text{-}C_6)$alkoxy and cyano.

59. The compound of claim 56, wherein each R^6 and each R^7 is hydrogen.

60. The compound of any one of claims 2 to 55, wherein:

$W^a–W^b$ represents:

$–O–C(R^8)_2–$.

61. The compound of claim 60, wherein each R^8 is hydrogen.

62. The compound of claim 60, wherein one R^8 is $(C_1\text{-}C_6)$alkyl; and one R^8 is hydrogen.

63. The compound of claim 62, wherein one R^8 is methyl.

64. The compound of any one of claims 2 to 55, wherein:

$W^a–W^b$ represents:

$–C(R^8)_2–O–$.

65. The compound of claim 64, wherein each R^8 is hydrogen.

66. The compound of any one of claims 2 to 30, wherein:

$W^a–W^b$ represents:

$–C(R^8)_2–NR^9–$.

67. The compound of claim 66, wherein each R^8 is hydrogen.

68. The compound of claim 66 or 67, wherein R^9 is $(C_1\text{-}C_6)$alkyl.

69. The compound of claim 68, wherein R^9 is methyl.

70. The compound of any one of claims 2 to 55, wherein:

$W^a–W^b$ represents:

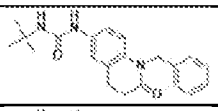
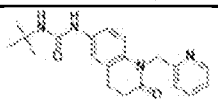
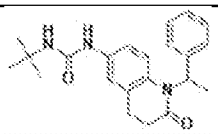
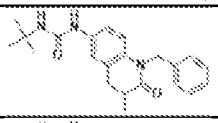
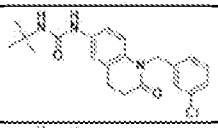
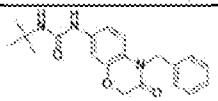
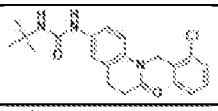
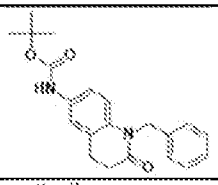
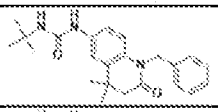
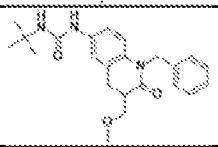
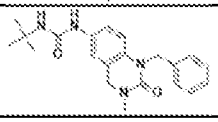
$–N=C(R^{10})–$.

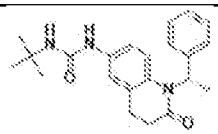
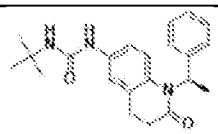
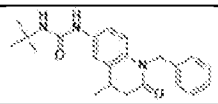
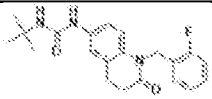
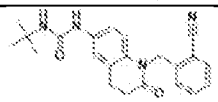
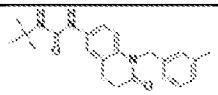
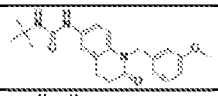
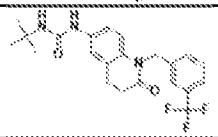
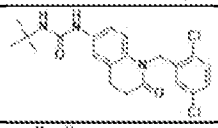
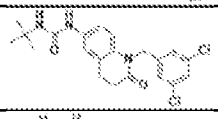
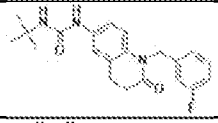
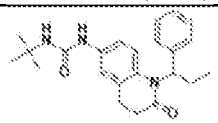
71. The compound of claim 70, wherein R^{10} is hydrogen.

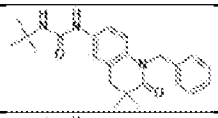
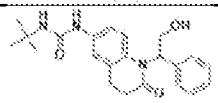
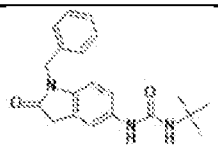
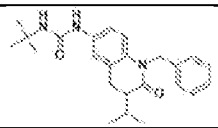
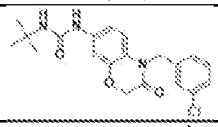
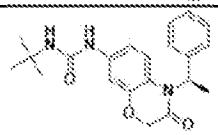
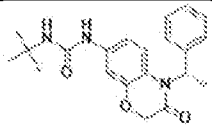
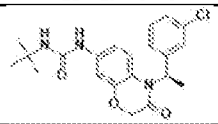
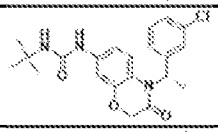
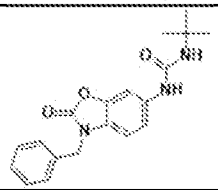
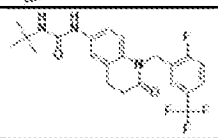
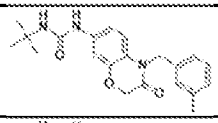
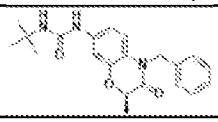
72. The compound of claim 70, wherein R^{10} is $(C_1\text{-}C_6)$alkyl.

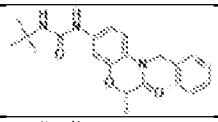
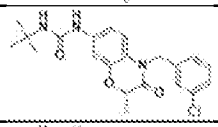
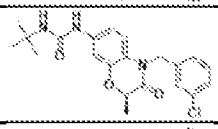
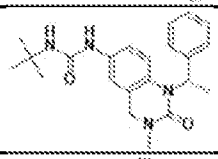
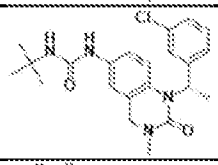
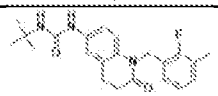
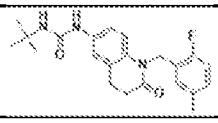
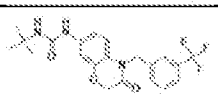
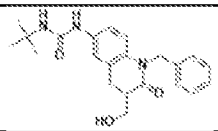
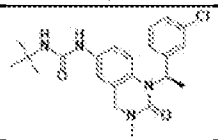
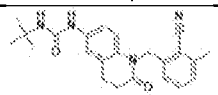
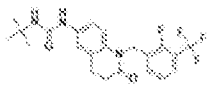
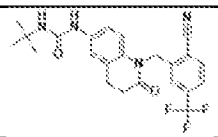
73. The compound of claim 70, wherein R^{10} is methyl.

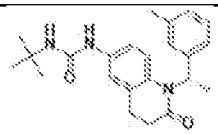
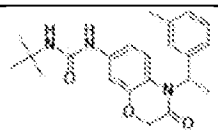
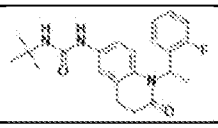
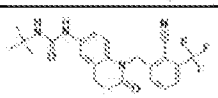
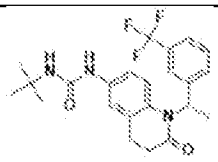
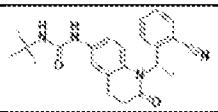
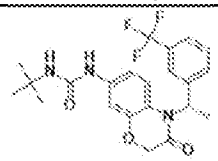
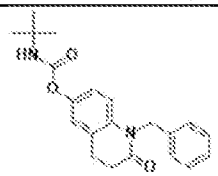
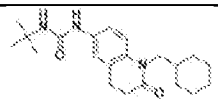
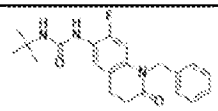
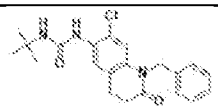
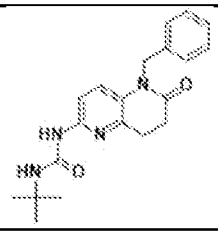
74. A compound selected from the following table:

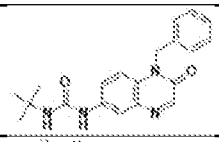
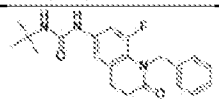
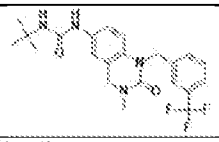
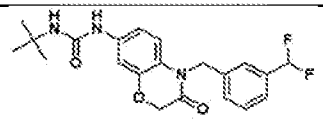
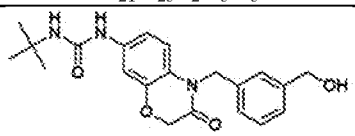
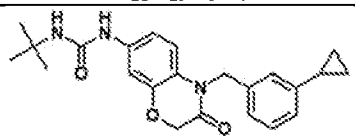
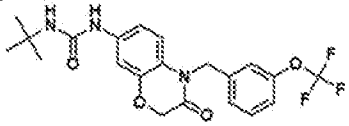
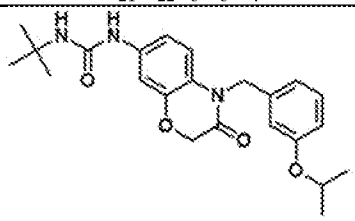
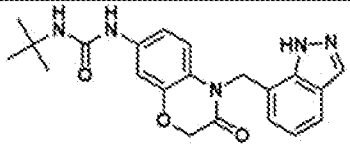
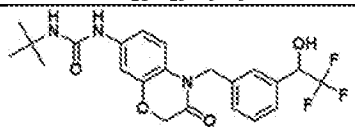
1		1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
2		1-(tert-butyl)-3-(2-oxo-1-(pyridin-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
3		1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
4		1-(tert-butyl)-3-(1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
5		1-(1-benzyl-3-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
6		1-(tert-butyl)-3-(1-(3-chlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
7		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
8		1-(tert-butyl)-3-(1-(2-chlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
9		tert-butyl (1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)carbamate
10		1-(1-benzyl-4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
11		1-(1-benzyl-3-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
12		1-(1-benzyl-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-3-(tert-butyl)urea

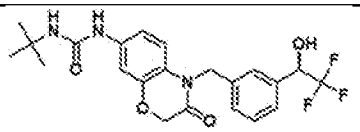
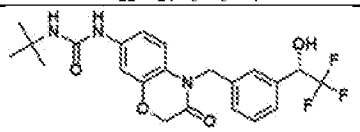
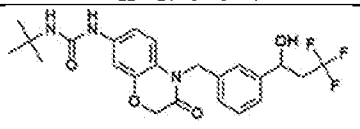
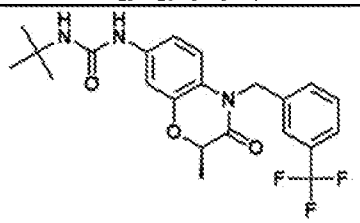
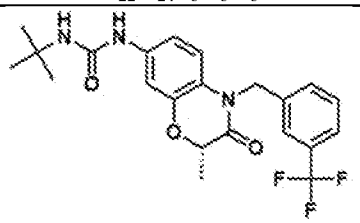
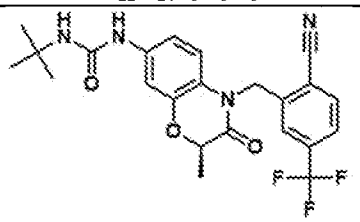
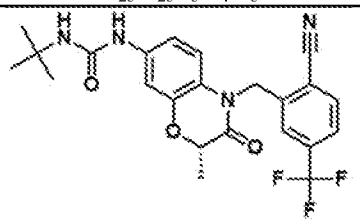
13		(S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
14		(R)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
15		1-(1-benzyl-4-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
16		1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-hydroxy-2-methylbutan-2-yl)urea
17		1-(tert-butyl)-3-(1-(4-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
18		1-(tert-butyl)-3-(1-(3-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
19		1-(tert-butyl)-3-(1-(2-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
20		1-(tert-butyl)-3-(1-(2-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
21		1-(tert-butyl)-3-(1-(3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
22		1-(tert-butyl)-3-(1-(3-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
23		1-(tert-butyl)-3-(2-oxo-1-(3-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
24		1-(tert-butyl)-3-(1-(2,5-dichlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
25		1-(tert-butyl)-3-(1-(3,5-dichlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
26		1-(tert-butyl)-3-(1-(3-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
27		1-(tert-butyl)-3-(1-(4-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
28		1-(tert-butyl)-3-(2-oxo-1-(1-phenylpropyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea

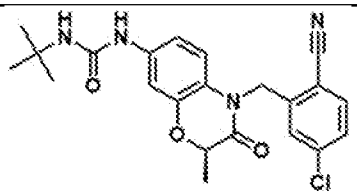
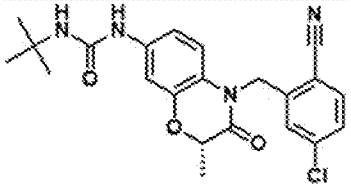
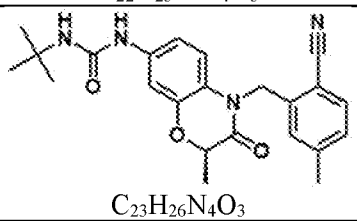
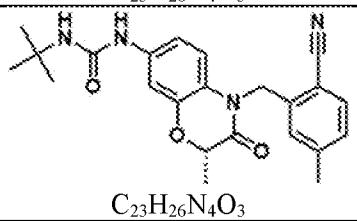
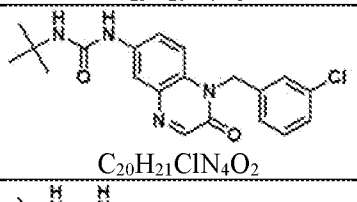
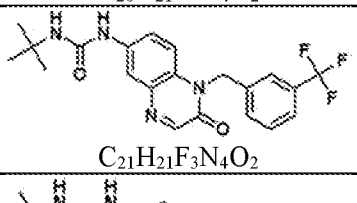
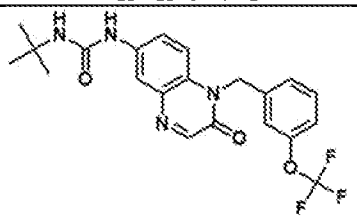
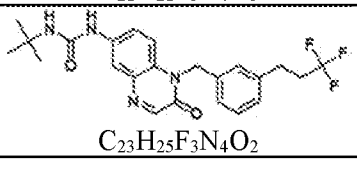
29		1-(1-benzyl-3,3-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
30		1-(tert-butyl)-3-(1-(2-hydroxy-1-phenylethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
31		1-(1-benzyl-2-oxoindolin-5-yl)-3-(tert-butyl)urea
32		1-(1-benzyl-3-isopropyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
33		1-(tert-butyl)-3-(4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
34		(R)-1-(tert-butyl)-3-(3-oxo-4-(1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
35	 $C_{21}H_{25}N_3O_3$	(S)-1-(tert-butyl)-3-(3-oxo-4-(1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
36		(R)-1-(tert-butyl)-3-(4-(1-(3-chlorophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
37		(S)-1-(tert-butyl)-3-(4-(1-(3-chlorophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
38		1-(3-benzyl-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-(tert-butyl)urea
39		1-(tert-butyl)-3-(1-(2-fluoro-5-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
40		1-(tert-butyl)-3-(4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
41		(R)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

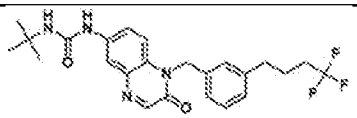
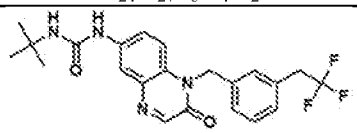
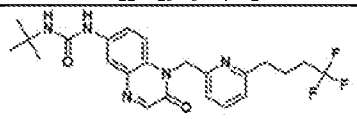
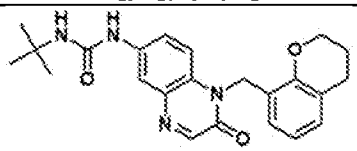
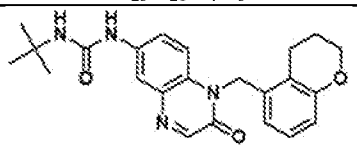
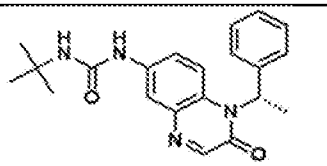
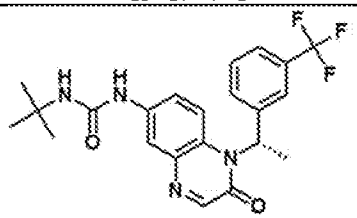
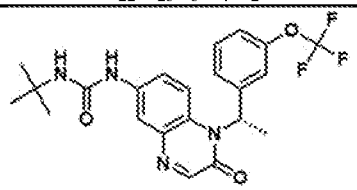
42		(S)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
43		(S)-1-(tert-butyl)-3-(4-(3-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
44		(R)-1-(tert-butyl)-3-(4-(3-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
45		(S)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea
46		(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea
47		1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea
48		1-(tert-butyl)-3-(1-(2-fluoro-3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
49		1-(tert-butyl)-3-(1-(2-fluoro-5-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
50		1-(tert-butyl)-3-(3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
51		1-(1-benzyl-3-(hydroxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
52		(R)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea
53		1-(tert-butyl)-3-(1-(2-cyano-3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
54		1-(tert-butyl)-3-(1-(2-fluoro-3-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
55		1-(tert-butyl)-3-(1-(2-cyano-5-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

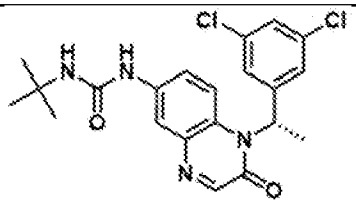
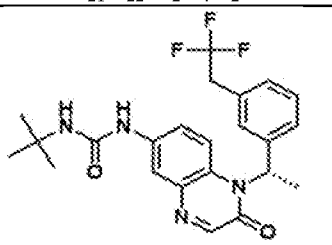
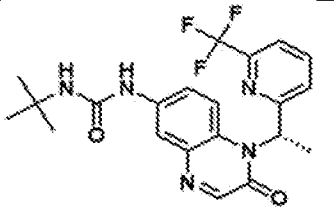
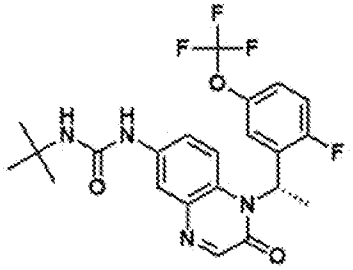
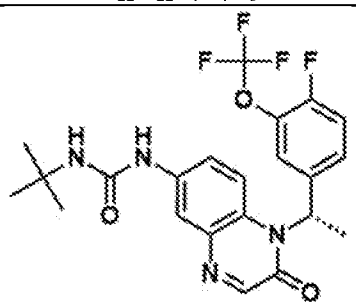
56		(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(m-tolyl)ethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
57		(S)-1-(tert-butyl)-3-(3-oxo-4-(1-(m-tolyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
58		(S)-1-(tert-butyl)-3-(1-(1-(2-fluorophenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
59		1-(tert-butyl)-3-(1-(2-cyano-3-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
60		(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
61		(S)-1-(tert-butyl)-3-(1-(1-(2-cyanophenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
62		(S)-1-(tert-butyl)-3-(3-oxo-4-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
63		1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl tert-butylcarbamate
64		1-(tert-butyl)-3-(1-(cyclohexylmethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
65		1-(1-benzyl-7-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
66		1-(1-benzyl-7-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
67		1-(5-benzyl-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)-3-(tert-butyl)urea

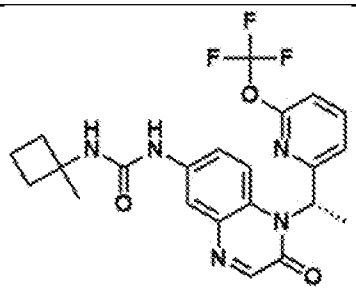
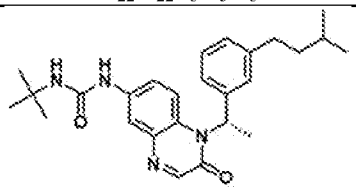
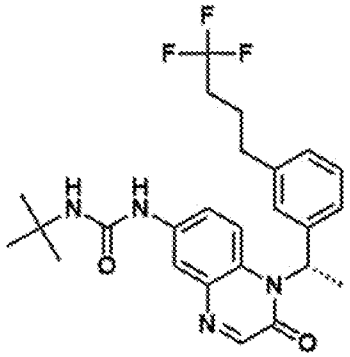
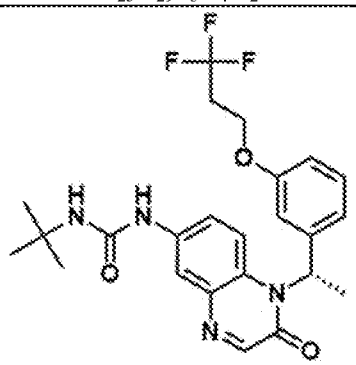
68		1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea
69		1-(1-benzyl-8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea; and
70		1-(tert-butyl)-3-(3-methyl-2-oxo-1-(3-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea
71	 $C_{21}H_{23}F_2N_3O_3$	1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
72	 $C_{21}H_{25}N_3O_4$	1-(tert-butyl)-3-(4-(3-(hydroxymethyl)benzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
73	 $C_{23}H_{27}N_3O_3$	1-(tert-butyl)-3-(4-(3-cyclopropylbenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
74	 $C_{21}H_{22}F_3N_3O_4$	1-(tert-butyl)-3-(3-oxo-4-(3-(trifluoromethoxy)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
75	 $C_{23}H_{29}N_3O_4$	1-(tert-butyl)-3-(4-(3-isopropoxybenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
76	 $C_{21}H_{23}N_5O_3$	1-(4-((1H-indazol-7-yl)methyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
77	 $C_{22}H_{24}F_3N_3O_4$	1-(tert-butyl)-3-(3-oxo-4-(3-(2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

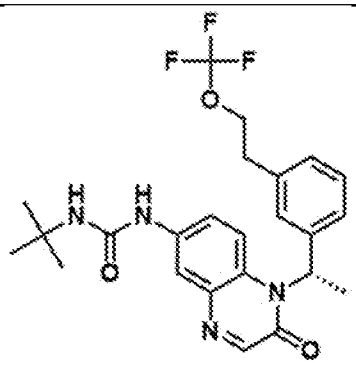
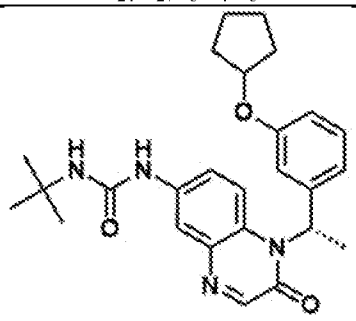
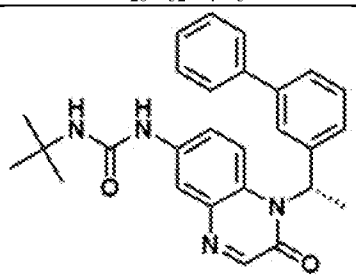
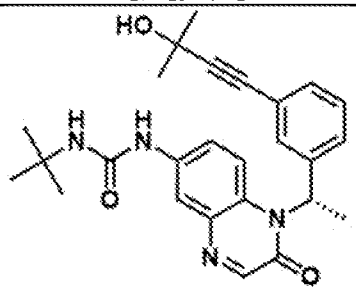
78	 $C_{22}H_{24}F_3N_3O_4$	(R)-1-(tert-butyl)-3-(3-oxo-4-(3-(2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
79	 $C_{22}H_{24}F_3N_3O_4$	(S)-1-(tert-butyl)-3-(3-oxo-4-(3-(2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
80	 $C_{23}H_{26}F_3N_3O_4$	1-(tert-butyl)-3-(3-oxo-4-(3-(3,3,3-trifluoro-1-hydroxypropyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
81	 $C_{22}H_{24}F_3N_3O_3$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
82	 $C_{22}H_{24}F_3N_3O_3$	(S)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
83	 $C_{23}H_{23}F_3N_4O_3$	(R)-1-(tert-butyl)-3-(4-(2-cyano-5-(trifluoromethyl)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
84	 $C_{23}H_{23}F_3N_4O_3$	(S)-1-(tert-butyl)-3-(4-(2-cyano-5-(trifluoromethyl)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

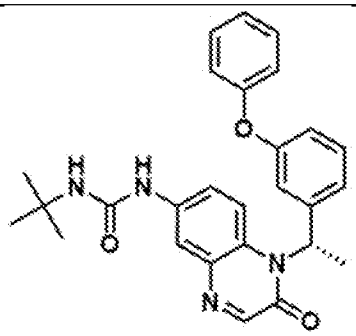
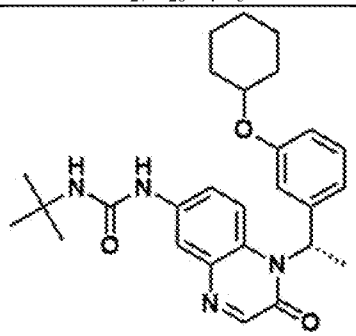
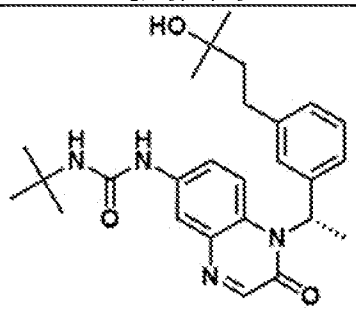
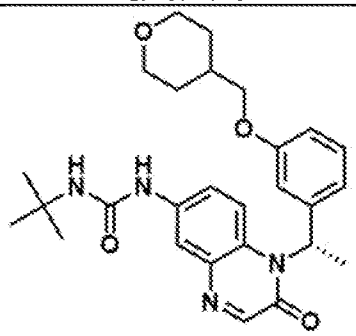
85	 $C_{22}H_{23}ClN_4O_3$	(R)-1-(tert-butyl)-3-(4-(5-chloro-2-cyanobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
86	 $C_{22}H_{23}ClN_4O_3$	(S)-1-(tert-butyl)-3-(4-(5-chloro-2-cyanobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
87	 $C_{23}H_{26}N_4O_3$	(R)-1-(tert-butyl)-3-(4-(2-cyano-5-methylbenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
88	 $C_{23}H_{26}N_4O_3$	(S)-1-(tert-butyl)-3-(4-(2-cyano-5-methylbenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
89	 $C_{20}H_{21}ClN_4O_2$	1-(tert-butyl)-3-(1-(3-chlorobenzyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
90	 $C_{21}H_{21}F_3N_4O_2$	1-(tert-butyl)-3-(2-oxo-1-(3-(trifluoromethyl)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
91	 $C_{21}H_{21}F_3N_4O_3$	1-(tert-butyl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
92	 $C_{23}H_{25}F_3N_4O_2$	1-(tert-butyl)-3-(2-oxo-1-(3-(3,3,3-trifluoropropyl)benzyl)-1,2-dihydroquinoxalin-6-yl)urea

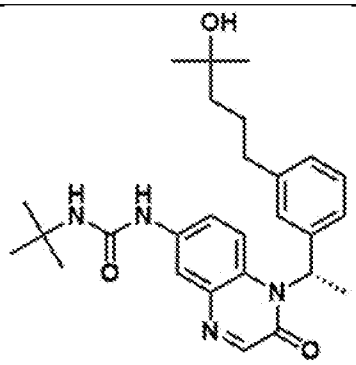
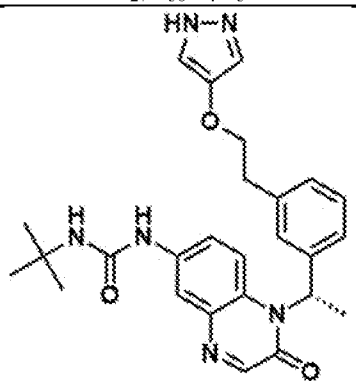
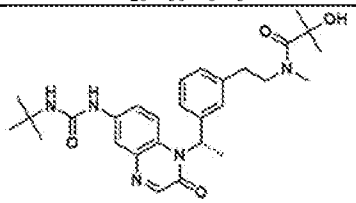
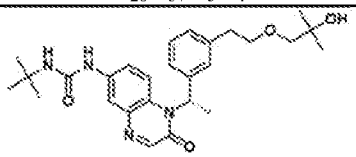
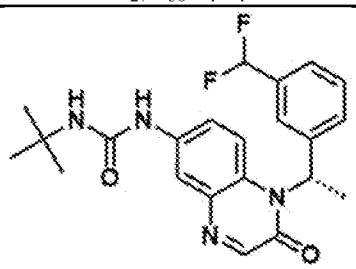
93	 $C_{24}H_{27}F_3N_4O_2$	1-(tert-butyl)-3-(2-oxo-1-(3-(4,4,4-trifluorobutyl)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
94	 $C_{22}H_{23}F_3N_4O_2$	1-(tert-butyl)-3-(2-oxo-1-(3-(2,2,2-trifluoroethyl)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
95	 $C_{23}H_{26}F_3N_5O_2$	1-(tert-butyl)-3-(2-oxo-1-((6-(4,4,4-trifluorobutyl)pyridin-2-yl)methyl)-1,2-dihydroquinoxalin-6-yl)urea
96	 $C_{23}H_{26}N_4O_3$	1-(tert-butyl)-3-(1-(chroman-8-ylmethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
97	 $C_{23}H_{26}N_4O_3$	1-(tert-butyl)-3-(1-(chroman-5-ylmethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
98	 $C_{21}H_{24}N_4O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea
99	 $C_{22}H_{23}F_3N_4O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
100	 $C_{22}H_{23}F_3N_4O_3$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

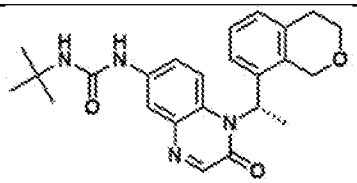
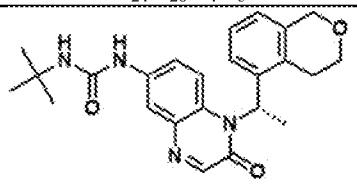
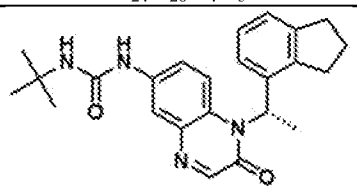
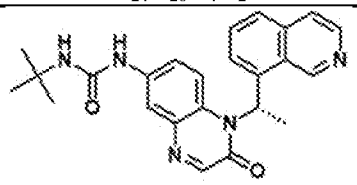
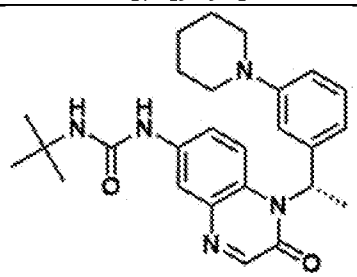
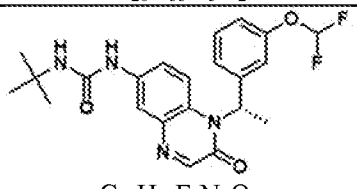
101	 $C_{21}H_{22}Cl_2N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3,5-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
102	 $C_{23}H_{25}F_3N_4O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2,2,2-trifluoroethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
103	 $C_{21}H_{22}F_3N_5O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
104	 $C_{22}H_{22}F_4N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(2-fluoro-5-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
105	 $C_{22}H_{22}F_4N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(4-fluoro-3-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

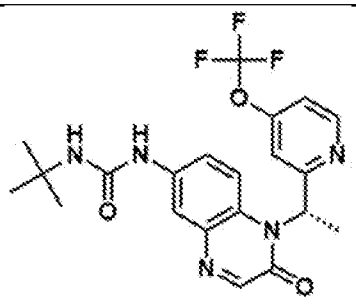
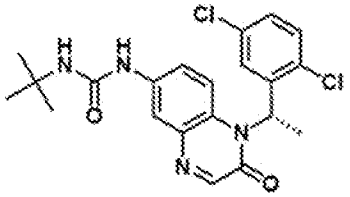
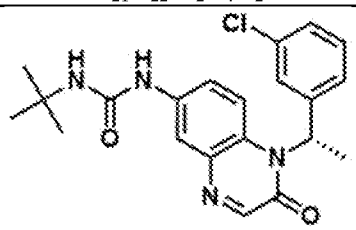
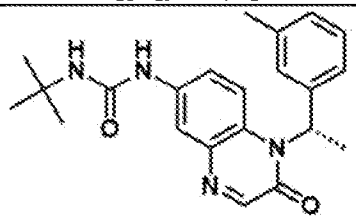
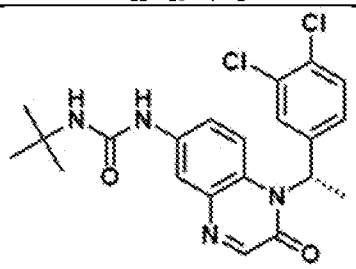
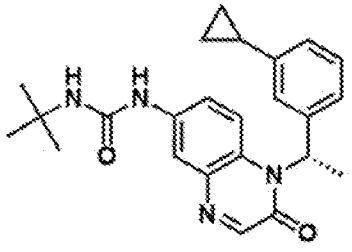
106	 $C_{22}H_{22}F_3N_5O_3$	(S)-1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(6-(trifluoromethoxy)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
107	 $C_{26}H_{34}N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-isopentylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
108	 $C_{25}H_{29}F_3N_4O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(4,4,4-trifluorobutyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
109	 $C_{24}H_{27}F_3N_4O_3$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(3,3,3-trifluoropropoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

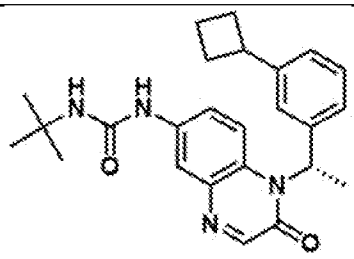
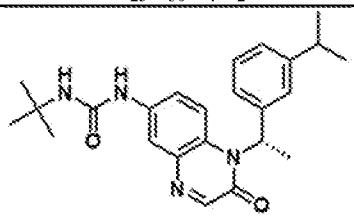
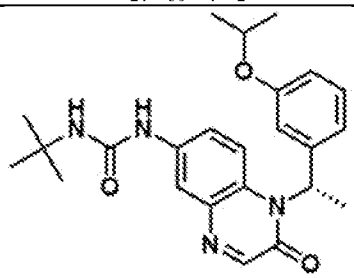
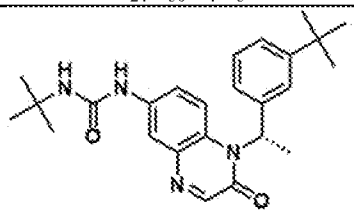
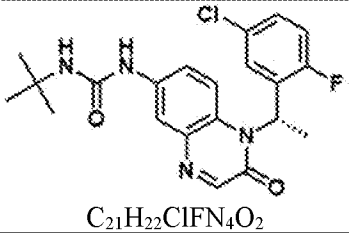
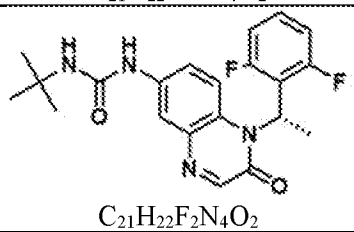
110	 $C_{24}H_{27}F_3N_4O_3$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2-(trifluoromethoxy)ethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
111	 $C_{26}H_{32}N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(3-(cyclopentyloxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
112	 $C_{27}H_{28}N_4O_2$	(S)-1-(1-(1-([1,1'-biphenyl]-3-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea
113	 $C_{26}H_{30}N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(3-(3-hydroxy-3-methylbut-1-yn-1-yl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

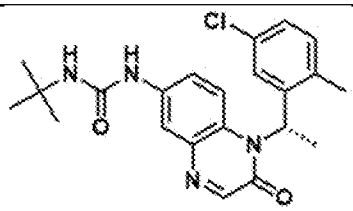
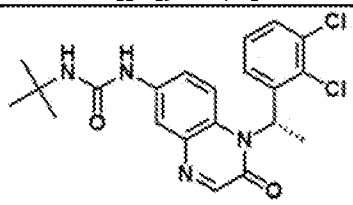
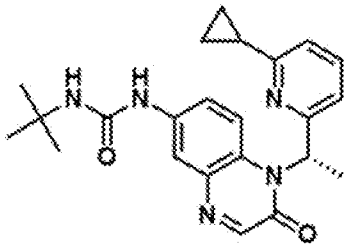
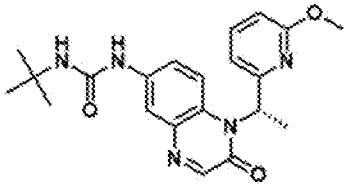
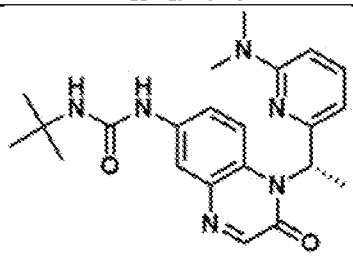
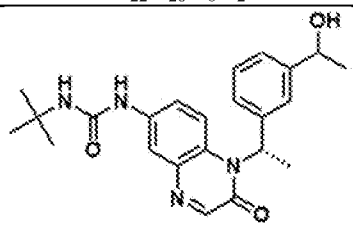
114	 $C_{27}H_{28}N_4O_3$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-phenoxyphenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
115	 $C_{27}H_{34}N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(3-(cyclohexyloxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
116	 $C_{26}H_{34}N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(3-(3-hydroxy-3-methylbutyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
117	 $C_{27}H_{34}N_4O_4$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

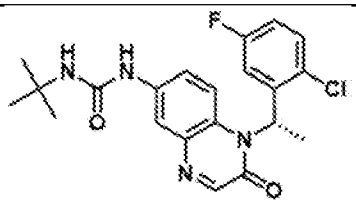
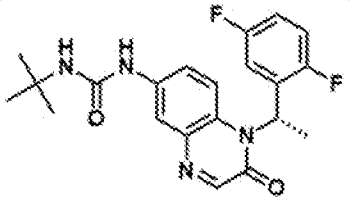
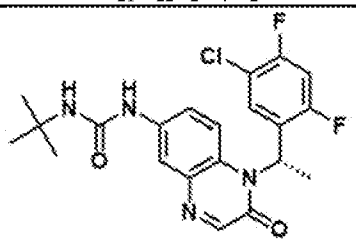
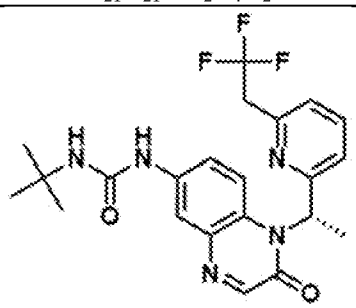
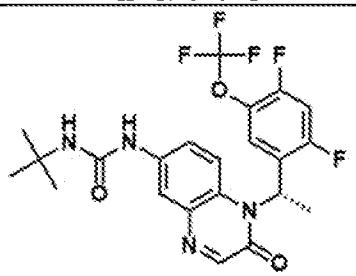
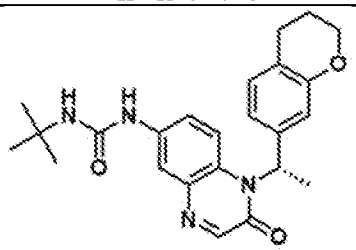
118	 $C_{27}H_{36}N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(3-(4-hydroxy-4-methylpentyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
119	 $C_{26}H_{30}N_6O_3$	(S)-1-(1-(1-(3-(2-((1H-pyrazol-4-yl)oxy)ethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea
120	 $C_{28}H_{37}N_5O_4$	(S)-N-(3-(1-(6-(3-(tert-butyl)ureido)-2-oxoquinoxalin-1(2H)-yl)ethyl)phenethyl)-2-hydroxy-N,2-dimethylpropanamide
121	 $C_{27}H_{36}N_4O_4$	(S)-1-(tert-butyl)-3-(1-(1-(3-(2-(2-hydroxy-2-methylpropoxy)ethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
122	 $C_{22}H_{24}F_2N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-(difluoromethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

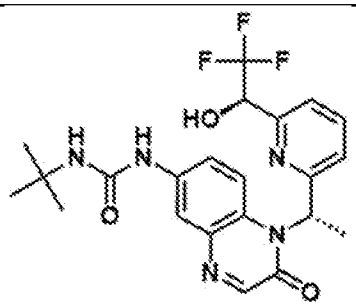
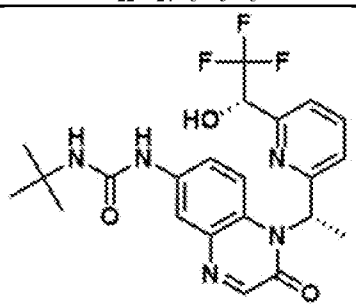
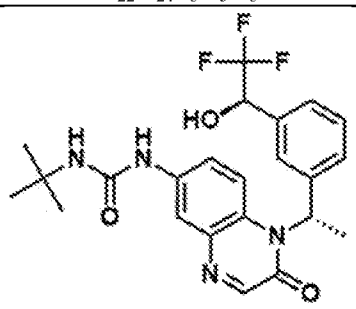
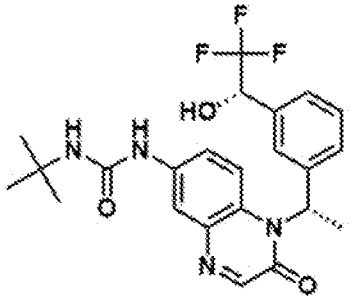
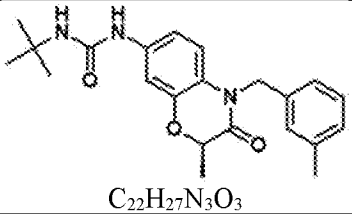
123	 $C_{24}H_{28}N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(isochroman-8-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
124	 $C_{24}H_{28}N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(isochroman-5-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
125	 $C_{24}H_{28}N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(2,3-dihydro-1H-inden-4-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
126	 $C_{24}H_{25}N_5O_2$	(S)-1-(tert-butyl)-3-(1-(1-(isoquinolin-8-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
127	 $C_{26}H_{33}N_5O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(piperidin-1-yl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
128	 $C_{22}H_{24}F_2N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(3-(difluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

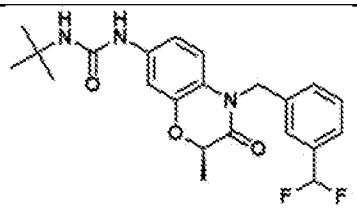
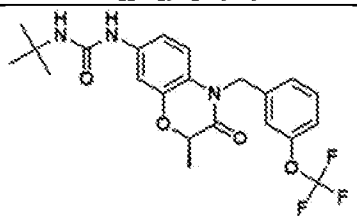
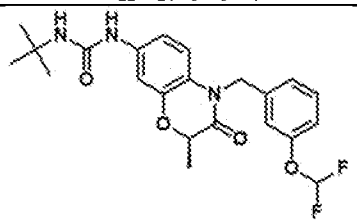
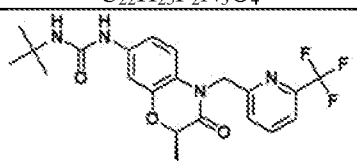
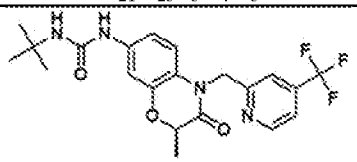
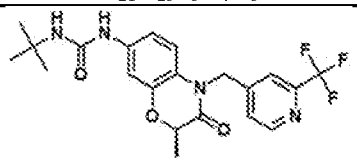
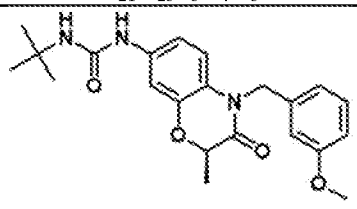
129	 $C_{21}H_{22}F_3N_5O_3$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(4-(trifluoromethoxy)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
130	 $C_{21}H_{22}Cl_2N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(2,5-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
131	 $C_{21}H_{23}ClN_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
132	 $C_{22}H_{26}N_4O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(m-tolyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
133	 $C_{21}H_{22}Cl_2N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3,4-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
134	 $C_{24}H_{28}N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-cyclopropylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

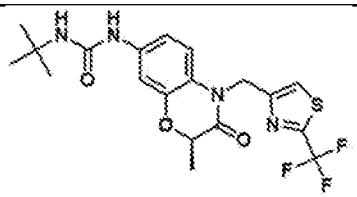
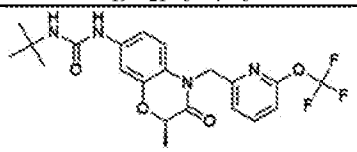
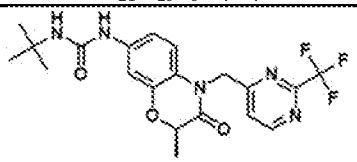
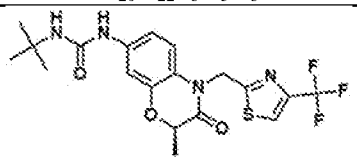
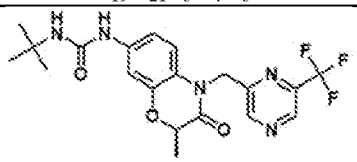
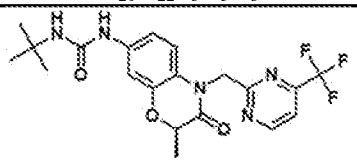
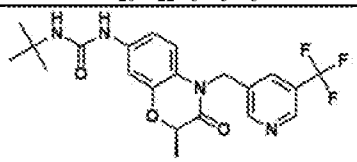
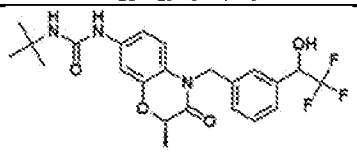
135	 $C_{25}H_{30}N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-cyclobutylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
136	 $C_{24}H_{30}N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-isopropylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
137	 $C_{24}H_{30}N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(3-isopropoxyphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
138	 $C_{25}H_{32}N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-(tert-butyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
139	 $C_{21}H_{22}ClFN_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(5-chloro-2-fluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
140	 $C_{21}H_{22}F_2N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(2,6-difluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

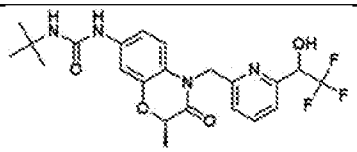
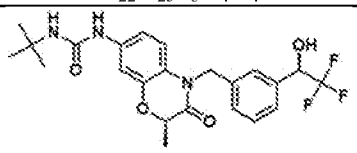
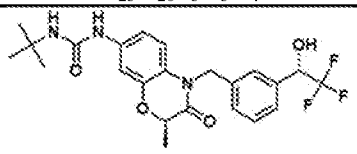
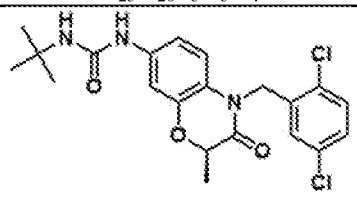
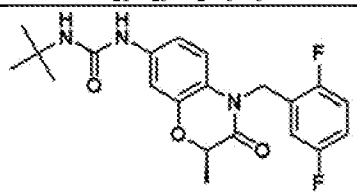
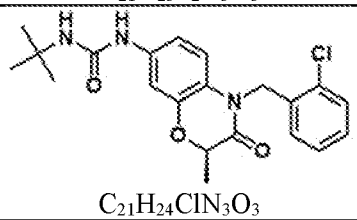
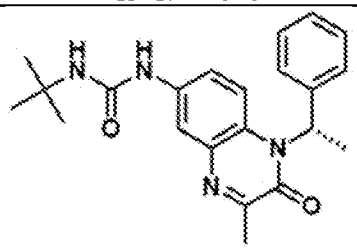
141	 $C_{22}H_{25}ClN_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(5-chloro-2-methylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
142	 $C_{21}H_{22}Cl_2N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(2,3-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
143	 $C_{23}H_{27}N_5O_2$	(S)-1-(tert-butyl)-3-(1-(1-(6-cyclopropylpyridin-2-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
144	 $C_{21}H_{25}N_5O_3$	(S)-1-(tert-butyl)-3-(1-(1-(6-methoxypyridin-2-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
145	 $C_{22}H_{28}N_6O_2$	(S)-1-(tert-butyl)-3-(1-(1-(6-(dimethylamino)pyridin-2-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
146	 $C_{23}H_{28}N_4O_3$	1-(tert-butyl)-3-(1-((1S)-1-(3-(1-hydroxyethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

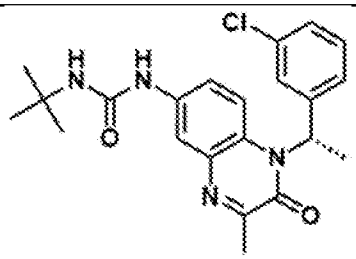
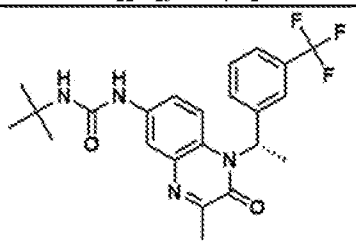
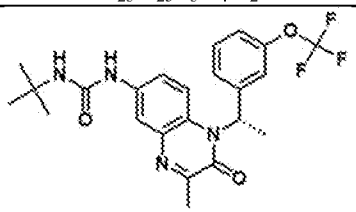
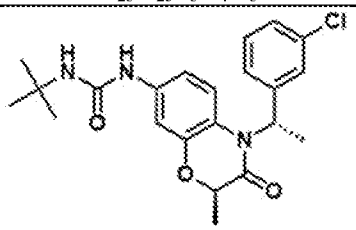
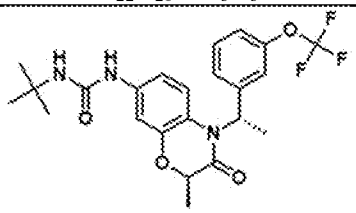
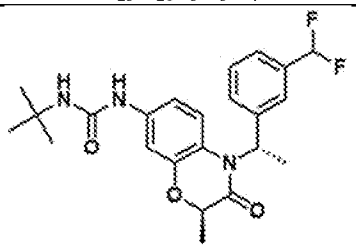
147	 $C_{21}H_{22}ClFN_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(2-chloro-5-fluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
148	 $C_{21}H_{22}F_2N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(2,5-difluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
149	 $C_{21}H_{21}ClF_2N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(5-chloro-2,4-difluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
150	 $C_{22}H_{24}F_3N_5O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(6-(2,2,2-trifluoroethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
151	 $C_{22}H_{21}F_5N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(2,4-difluoro-5-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
152	 $C_{24}H_{28}N_4O_3$	(S)-1-(tert-butyl)-3-(1-(1-(chroman-7-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

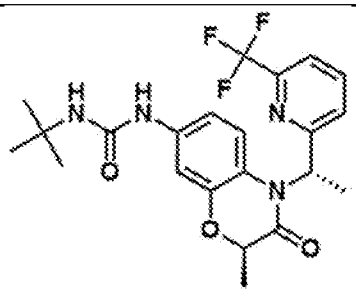
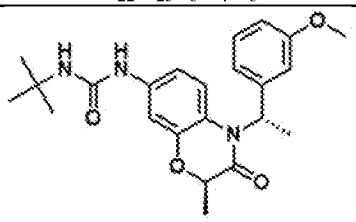
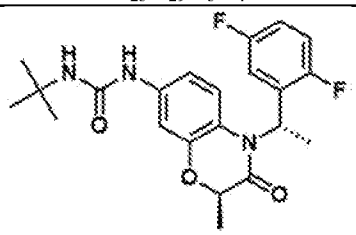
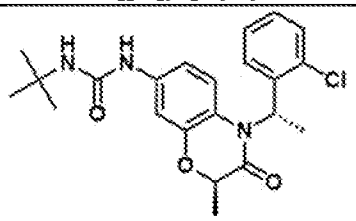
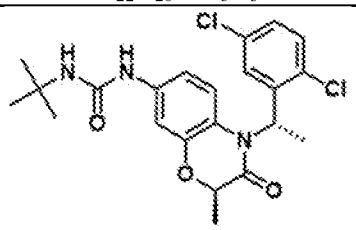
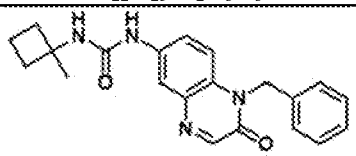
153	 $C_{22}H_{24}F_3N_5O_3$	1-(tert-butyl)-3-(2-oxo-1-((S)-1-(6-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
154	 $C_{22}H_{24}F_3N_5O_3$	1-(tert-butyl)-3-(2-oxo-1-((S)-1-(6-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
155	 $C_{23}H_{25}F_3N_4O_3$	1-(tert-butyl)-3-(2-oxo-1-((S)-1-(3-((R)-2,2,2-trifluoro-1-hydroxyethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
156	 $C_{23}H_{25}F_3N_4O_3$	1-(tert-butyl)-3-(2-oxo-1-((S)-1-(3-((S)-2,2,2-trifluoro-1-hydroxyethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
157	 $C_{22}H_{27}N_3O_3$	(R)-1-(tert-butyl)-3-(2-methyl-4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

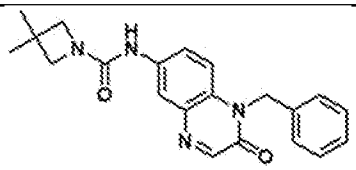
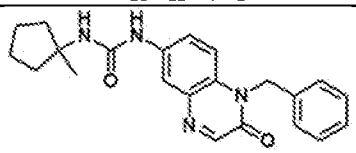
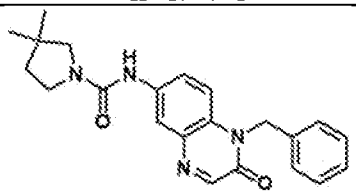
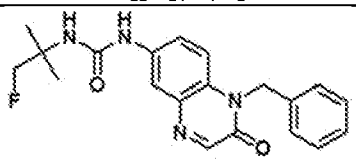
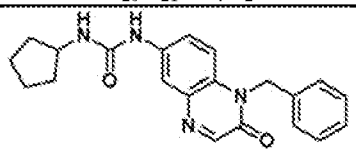
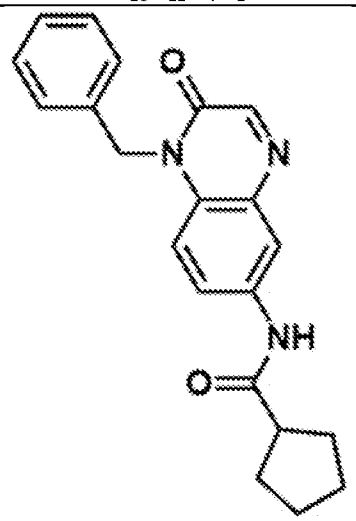
158	 $C_{22}H_{25}F_2N_3O_3$	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
159	 $C_{22}H_{24}F_3N_3O_4$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-(3-(trifluoromethoxy)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
160	 $C_{22}H_{25}F_2N_3O_4$	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethoxy)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
161	 $C_{21}H_{23}F_3N_4O_3$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
162	 $C_{21}H_{23}F_3N_4O_3$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((4-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
163	 $C_{21}H_{23}F_3N_4O_3$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((2-(trifluoromethyl)pyridin-4-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
164	 $C_{22}H_{27}N_3O_4$	(R)-1-(tert-butyl)-3-(4-(3-methoxybenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

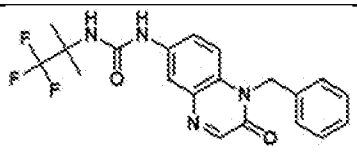
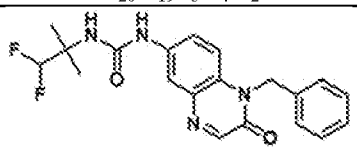
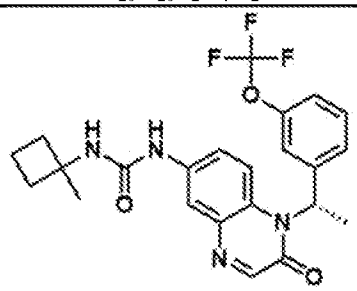
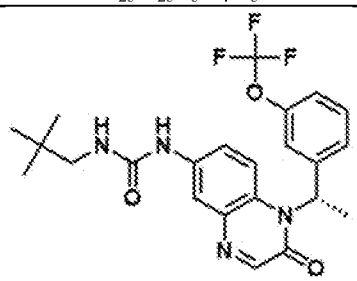
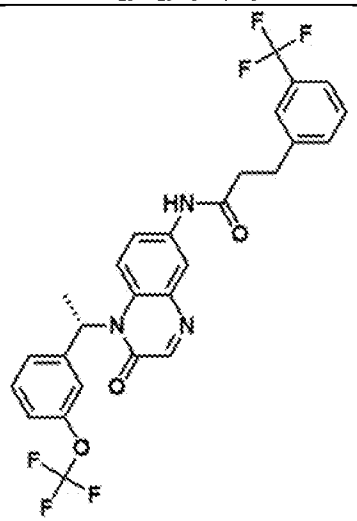
165	 $C_{19}H_{21}F_3N_4O_3S$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((2-(trifluoromethyl)thiazol-4-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
166	 $C_{21}H_{23}F_3N_4O_4$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethoxy)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
167	 $C_{20}H_{22}F_3N_5O_3$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((2-(trifluoromethyl)pyrimidin-4-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
168	 $C_{19}H_{21}F_3N_4O_3S$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((4-(trifluoromethyl)thiazol-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
169	 $C_{20}H_{22}F_3N_5O_3$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyrazin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
170	 $C_{20}H_{22}F_3N_5O_3$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((4-(trifluoromethyl)pyrimidin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
171	 $C_{21}H_{23}F_3N_4O_3$	(R)-1-(tert-butyl)-3-(2-methyl-3-oxo-4-((5-(trifluoromethyl)pyridin-3-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
172	 $C_{23}H_{26}F_3N_3O_4$	1-(tert-butyl)-3-((2R)-2-methyl-3-oxo-4-(3-(2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

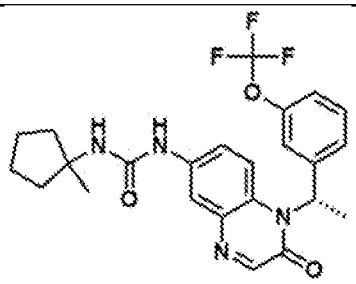
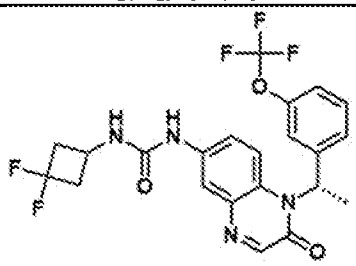
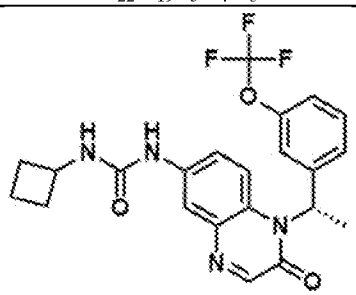
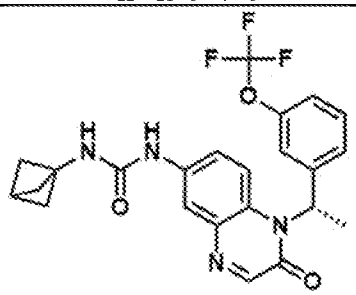
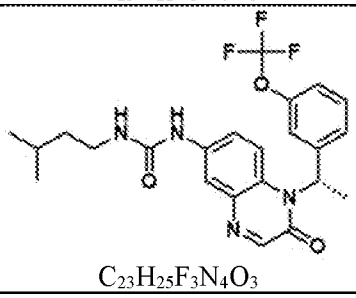
173	 $C_{22}H_{25}F_3N_4O_4$	1-(tert-butyl)-3-((2R)-2-methyl-3-oxo-4-((6-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
174	 $C_{23}H_{26}F_3N_3O_4$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-(3-((R)-2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
175	 $C_{23}H_{26}F_3N_3O_4$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-(3-((S)-2,2,2-trifluoro-1-hydroxyethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
176	 $C_{21}H_{23}Cl_2N_3O_3$	(R)-1-(tert-butyl)-3-(4-(2,5-dichlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
177	 $C_{21}H_{23}F_2N_3O_3$	(R)-1-(tert-butyl)-3-(4-(2,5-difluorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
178	 $C_{21}H_{24}ClN_3O_3$	(R)-1-(tert-butyl)-3-(4-(2-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
179	 $C_{22}H_{26}N_4O_2$	(S)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea

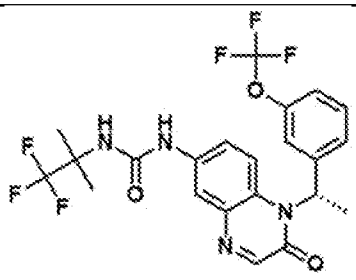
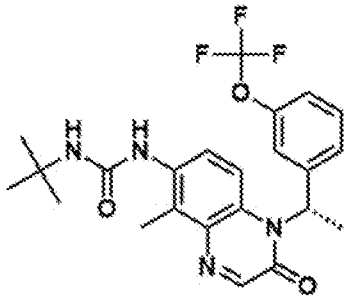
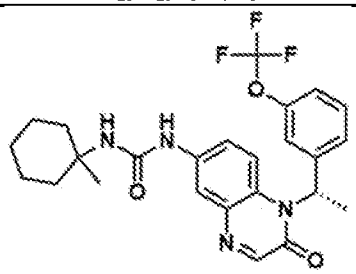
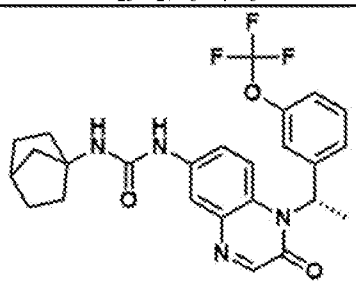
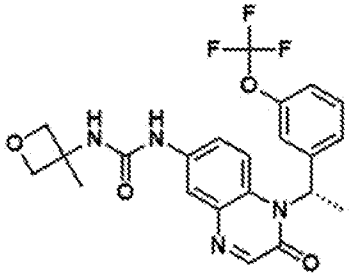
180	 $C_{22}H_{25}ClN_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
181	 $C_{23}H_{25}F_3N_4O_2$	(S)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
182	 $C_{23}H_{25}F_3N_4O_3$	(S)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
183	 $C_{22}H_{26}ClN_3O_3$	1-(tert-butyl)-3-((R)-4-((S)-1-(3-chlorophenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
184	 $C_{23}H_{26}F_3N_3O_4$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
185	 $C_{23}H_{27}F_2N_3O_3$	1-(tert-butyl)-3-((R)-4-((S)-1-(3-(difluoromethyl)phenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

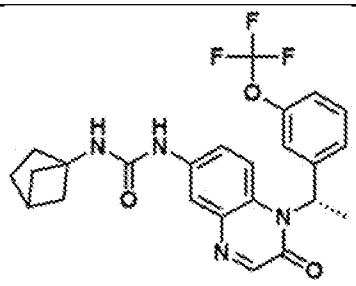
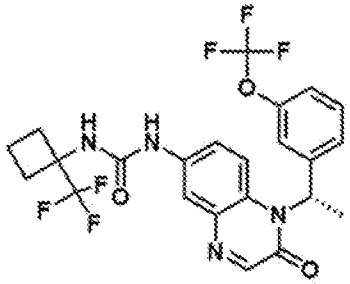
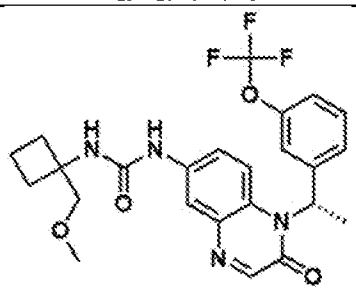
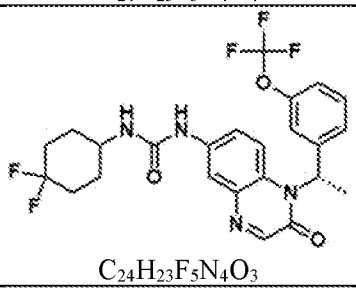
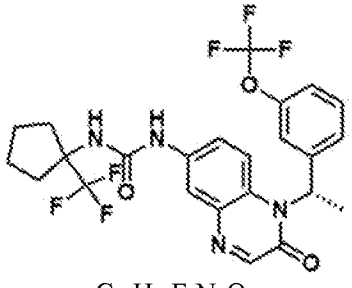
186	 $C_{22}H_{25}F_3N_4O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
187	 $C_{23}H_{29}N_3O_4$	1-(tert-butyl)-3-((R)-4-((S)-1-(3-methoxyphenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
188	 $C_{22}H_{25}F_2N_3O_3$	1-(tert-butyl)-3-((R)-4-((S)-1-(2,5-difluorophenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
189	 $C_{22}H_{26}ClN_3O_3$	1-(tert-butyl)-3-((R)-4-((S)-1-(2-chlorophenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
190	 $C_{22}H_{25}Cl_2N_3O_3$	1-(tert-butyl)-3-((R)-4-((S)-1-(2,5-dichlorophenyl)ethyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
191	 $C_{21}H_{22}N_4O_2$	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1-methylcyclobutyl)urea

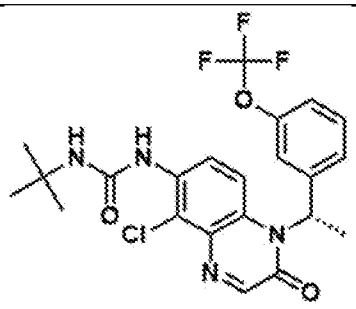
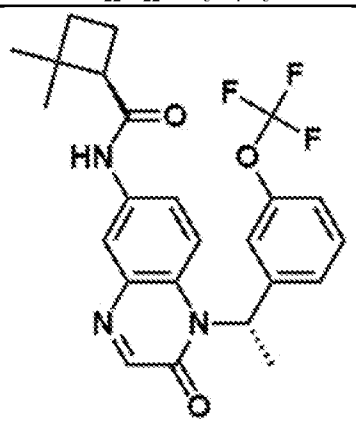
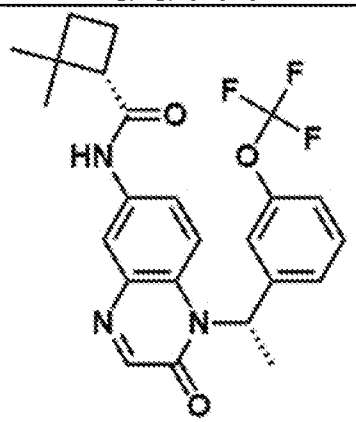
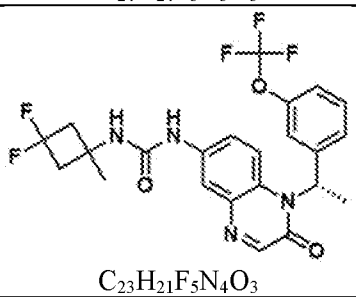
192	 $C_{21}H_{22}N_4O_2$	N-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3,3-dimethylazetidine-1-carboxamide
193	 $C_{22}H_{24}N_4O_2$	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1-methylcyclopentyl)urea
194	 $C_{22}H_{24}N_4O_2$	N-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3,3-dimethylpyrrolidine-1-carboxamide
195	 $C_{20}H_{21}FN_4O_2$	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1-fluoro-2-methylpropan-2-yl)urea
196	 $C_{21}H_{22}N_4O_2$	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-cyclopentylurea
197	 $C_{21}H_{21}N_3O_2$	N-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)cyclopentanecarboxamide

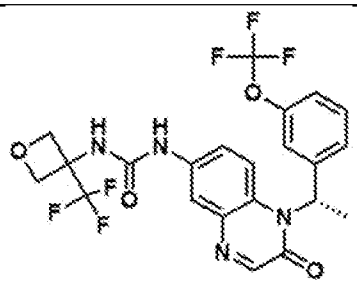
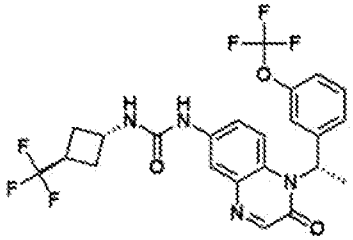
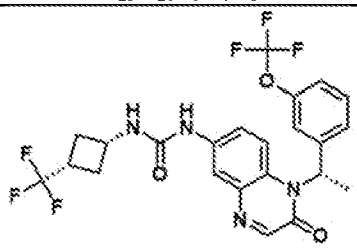
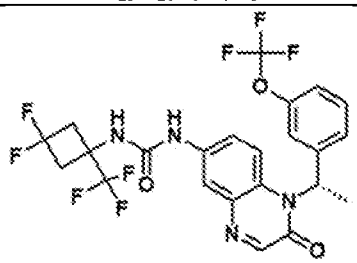
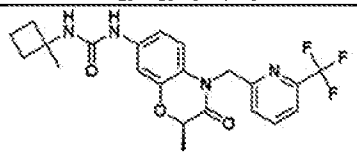
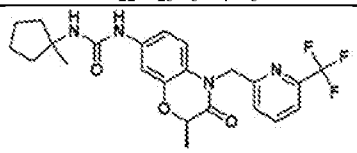
198	 $C_{20}H_{19}F_3N_4O_2$	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1,1,1-trifluoro-2-methylpropan-2-yl)urea
199	 $C_{20}H_{20}F_2N_4O_2$	1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1,1-difluoro-2-methylpropan-2-yl)urea
200	 $C_{23}H_{23}F_3N_4O_3$	(S)-1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
201	 $C_{23}H_{25}F_3N_4O_3$	(S)-1-neopentyl-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
202	 $C_{27}H_{21}F_6N_3O_3$	(S)-N-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)phenyl)propanamide

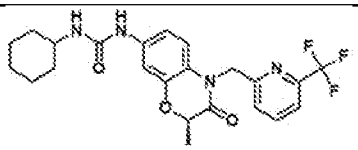
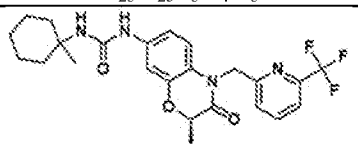
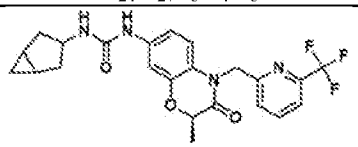
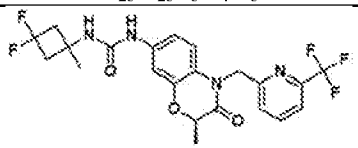
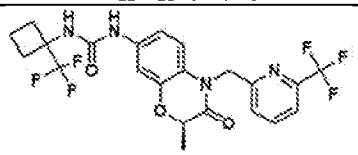
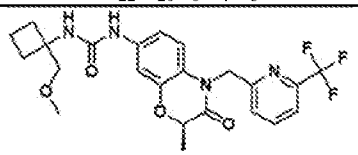
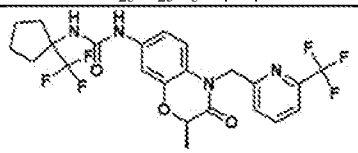
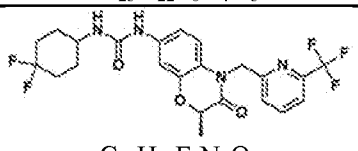
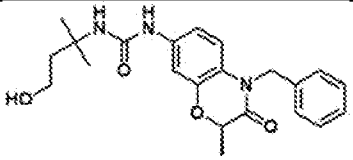
203	 $C_{24}H_{25}F_3N_4O_3$	(S)-1-(1-methylcyclopentyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
204	 $C_{22}H_{19}F_5N_4O_3$	(S)-1-(3,3-difluorocyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
205	 $C_{22}H_{21}F_3N_4O_3$	(S)-1-cyclobutyl-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
206	 $C_{23}H_{21}F_3N_4O_3$	(S)-1-(bicyclo[1.1.1]pentan-1-yl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
207	 $C_{23}H_{25}F_3N_4O_3$	(S)-1-isopentyl-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

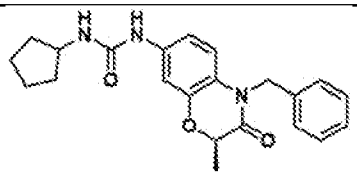
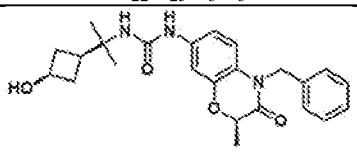
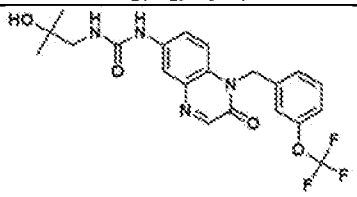
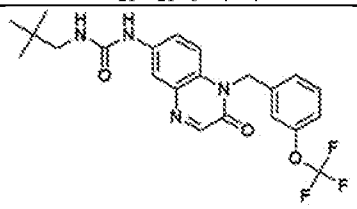
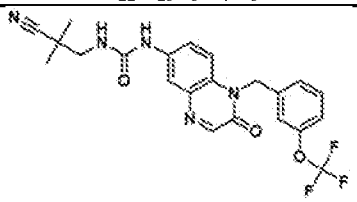
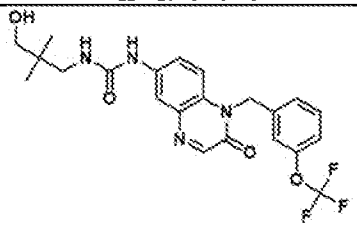
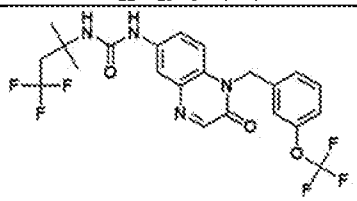
208	 $C_{22}H_{20}F_6N_4O_3$	(S)-1-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(1,1,1-trifluoro-2-methylpropan-2-yl)urea
209	 $C_{23}H_{25}F_3N_4O_3$	(S)-1-(tert-butyl)-3-(5-methyl-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
210	 $C_{25}H_{27}F_3N_4O_3$	(S)-1-(1-methylcyclohexyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
211	 $C_{25}H_{25}F_3N_4O_3$	(S)-1-(bicyclo[2.2.1]heptan-1-yl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
212	 $C_{22}H_{21}F_3N_4O_4$	(S)-1-(3-methyloxetan-3-yl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

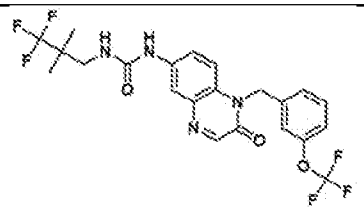
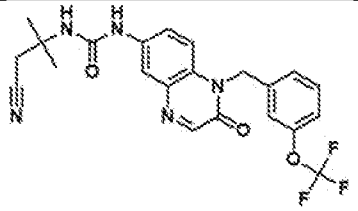
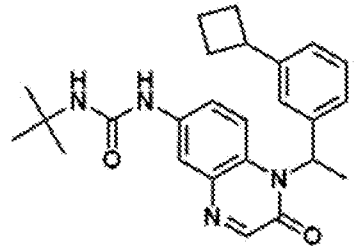
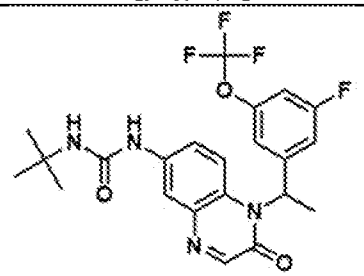
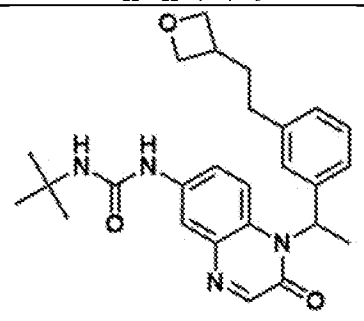
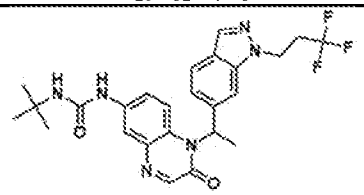
213	 $C_{24}H_{23}F_3N_4O_3$	(S)-1-(bicyclo[2.1.1]hexan-1-yl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
214	 $C_{23}H_{20}F_6N_4O_3$	(S)-1-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(1-(trifluoromethyl)cyclobutyl)urea
215	 $C_{24}H_{25}F_3N_4O_4$	(S)-1-(1-(methoxymethyl)cyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
216	 $C_{24}H_{23}F_5N_4O_3$	(S)-1-(4,4-difluorocyclohexyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
217	 $C_{24}H_{22}F_6N_4O_3$	(S)-1-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(1-(trifluoromethyl)cyclopentyl)urea

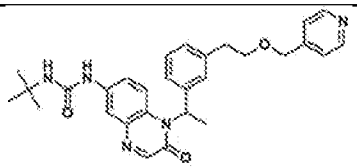
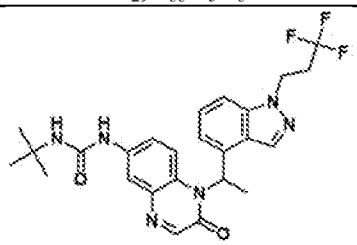
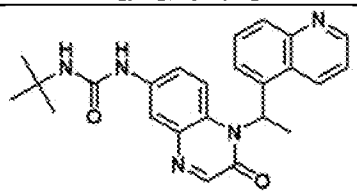
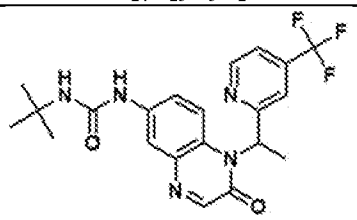
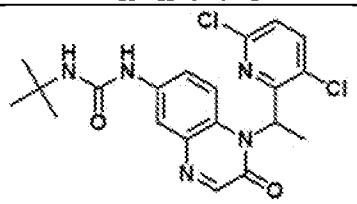
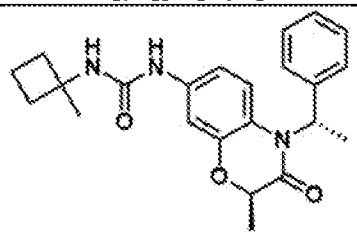
218	 $C_{22}H_{22}ClF_3N_4O_3$	(S)-1-(tert-butyl)-3-(5-chloro-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
219	 $C_{24}H_{24}F_3N_3O_3$	(R)-2,2-dimethyl-N-(2-oxo-1-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)cyclobutane-1-carboxamide
220	 $C_{24}H_{24}F_3N_3O_3$	(S)-2,2-dimethyl-N-(2-oxo-1-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)cyclobutane-1-carboxamide
221	 $C_{23}H_{21}F_5N_4O_3$	(S)-1-(3,3-difluoro-1-methylcyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

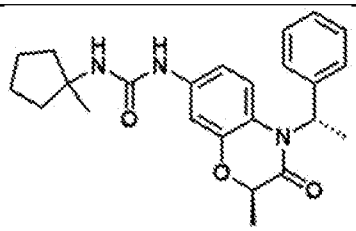
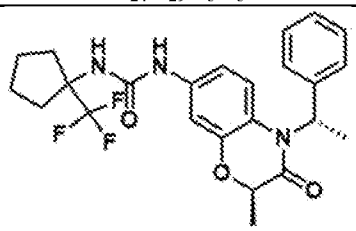
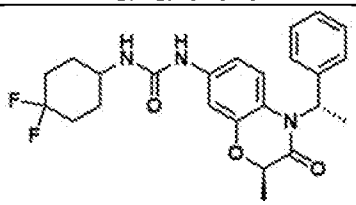
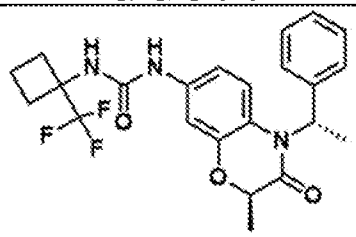
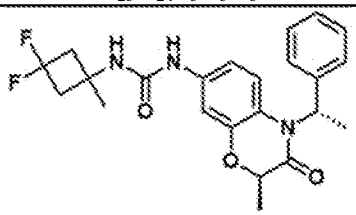
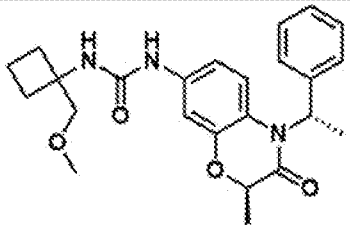
222	 $C_{22}H_{18}F_6N_4O_4$	(S)-1-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)oxetan-3-yl)urea
223	 $C_{23}H_{20}F_6N_4O_3$	1-(2-oxo-1-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-((1r,3S)-3-(trifluoromethyl)cyclobutyl)urea
224	 $C_{23}H_{20}F_6N_4O_3$	1-(2-oxo-1-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-((1s,3R)-3-(trifluoromethyl)cyclobutyl)urea
225	 $C_{23}H_{18}F_8N_4O_3$	(S)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
226	 $C_{22}H_{23}F_3N_4O_3$	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclobutyl)urea
227	 $C_{23}H_{25}F_3N_4O_3$	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea

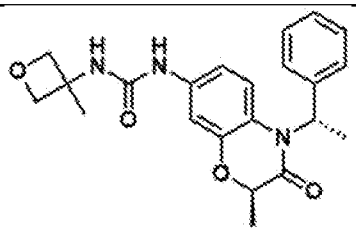
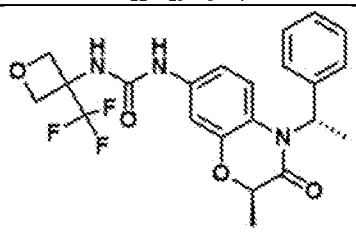
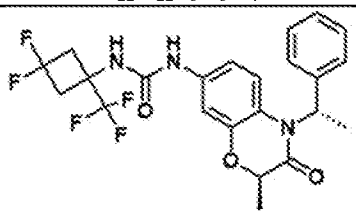
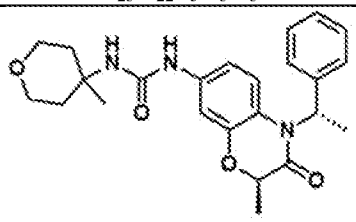
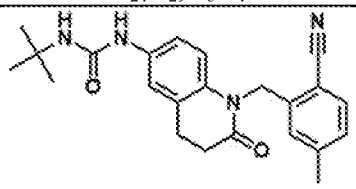
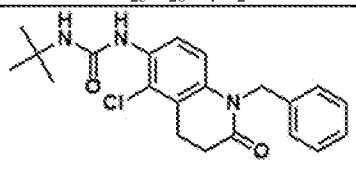
228	 $C_{23}H_{25}F_3N_4O_3$	(R)-1-cyclohexyl-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
229	 $C_{24}H_{27}F_3N_4O_3$	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclohexyl)urea
230	 $C_{23}H_{23}F_3N_4O_3$	1-(bicyclo[3.1.0]hexan-3-yl)-3-((R)-2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
231	 $C_{22}H_{21}F_5N_4O_3$	(R)-1-(3,3-difluoro-1-methylcyclobutyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
232	 $C_{22}H_{20}F_6N_4O_3$	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-(trifluoromethyl)cyclobutyl)urea
233	 $C_{23}H_{25}F_3N_4O_4$	(R)-1-(1-(methoxymethyl)cyclobutyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
234	 $C_{23}H_{22}F_6N_4O_3$	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-(trifluoromethyl)cyclopentyl)urea
235	 $C_{23}H_{23}F_5N_4O_3$	(R)-1-(4,4-difluorocyclohexyl)-3-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
236	 $C_{22}H_{27}N_3O_4$	(R)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(4-hydroxy-2-methylbutan-2-yl)urea

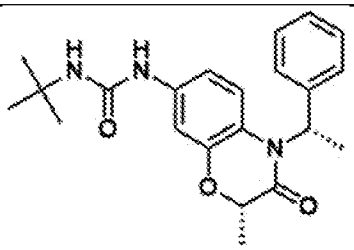
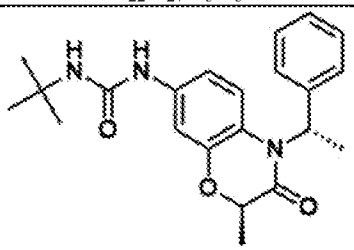
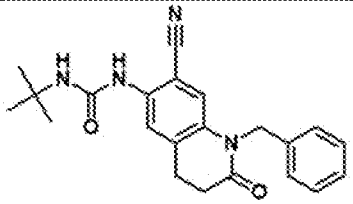
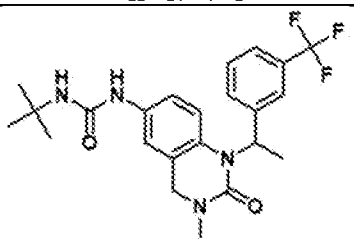
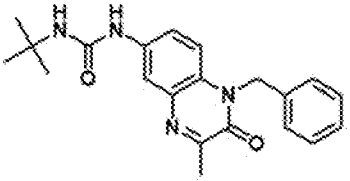
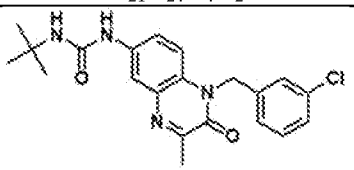
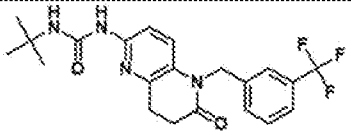
237	 $C_{22}H_{25}N_3O_3$	(R)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-cyclopentylurea
238	 $C_{24}H_{29}N_3O_4$	1-((R)-4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(2-((1s,3S)-3-hydroxycyclobutyl)propan-2-yl)urea
239	 $C_{21}H_{21}F_3N_4O_4$	1-(2-hydroxy-2-methylpropyl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
240	 $C_{22}H_{23}F_3N_4O_3$	1-neopentyl-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
241	 $C_{22}H_{20}F_3N_5O_3$	1-(2-cyano-2-methylpropyl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
242	 $C_{22}H_{23}F_3N_4O_4$	1-(3-hydroxy-2,2-dimethylpropyl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
243	 $C_{22}H_{20}F_6N_4O_3$	1-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)-3-(4,4,4-trifluoro-2-methylbutan-2-yl)urea

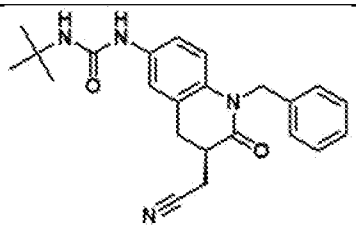
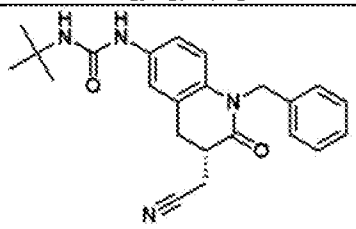
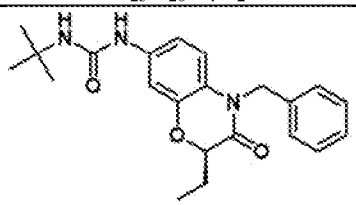
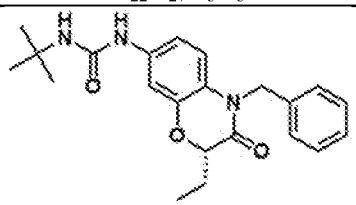
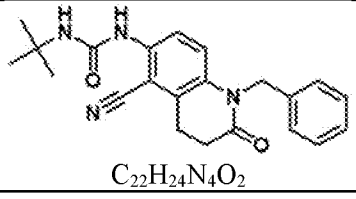
244	 $C_{22}H_{20}F_6N_4O_3$	1-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)-3-(3,3,3-trifluoro-2,2-dimethylpropyl)urea
245	 $C_{22}H_{20}F_3N_5O_3$	1-(1-cyano-2-methylpropan-2-yl)-3-(2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
246	 $C_{25}H_{30}N_4O_2$	1-(tert-butyl)-3-(1-(1-(3-cyclobutylphenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
247	 $C_{22}H_{22}F_4N_4O_3$	1-(tert-butyl)-3-(1-(1-(3-fluoro-5-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
248	 $C_{26}H_{32}N_4O_3$	1-(tert-butyl)-3-(1-(1-(3-(2-(oxetan-3-yl)ethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
249	 $C_{25}H_{27}F_3N_6O_2$	1-(tert-butyl)-3-(2-oxo-1-(1-(1-(3,3,3-trifluoropropyl)-1H-indazol-6-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

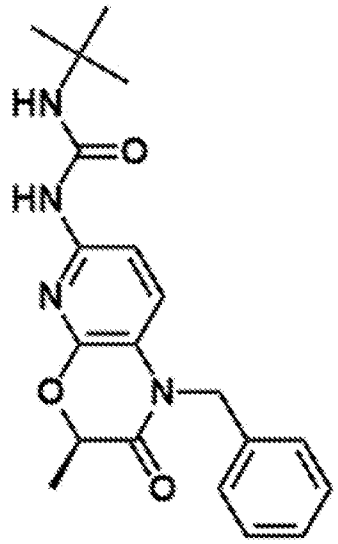
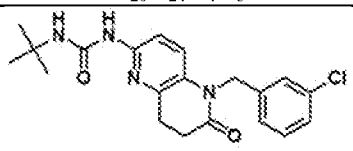
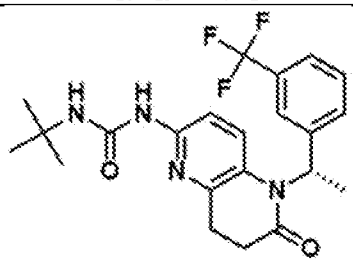
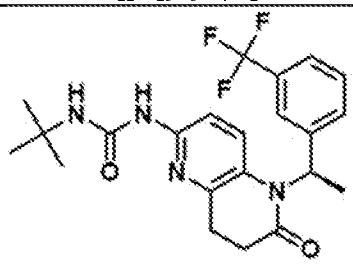
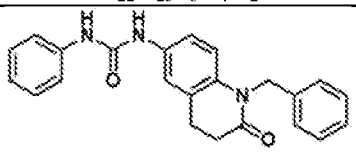
250	 $C_{29}H_{33}N_5O_3$	1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2-(pyridin-4-ylmethoxy)ethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
251	 $C_{25}H_{27}F_3N_6O_2$	1-(tert-butyl)-3-(2-oxo-1-(1-(1-(3,3,3-trifluoropropyl)-1H-indazol-4-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
252	 $C_{24}H_{25}N_5O_2$	1-(tert-butyl)-3-(2-oxo-1-(1-(quinolin-5-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
253	 $C_{21}H_{22}F_3N_5O_2$	1-(tert-butyl)-3-(2-oxo-1-(1-(4-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
254	 $C_{20}H_{21}Cl_2N_5O_2$	1-(tert-butyl)-3-(1-(1-(3,6-dichloropyridin-2-yl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
255	 $C_{23}H_{27}N_3O_3$	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclobutyl)urea

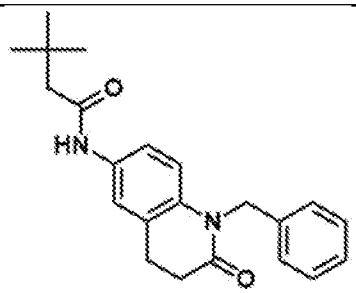
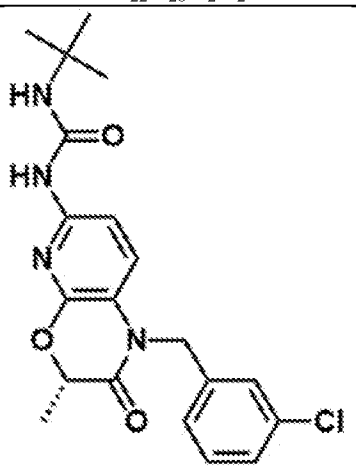
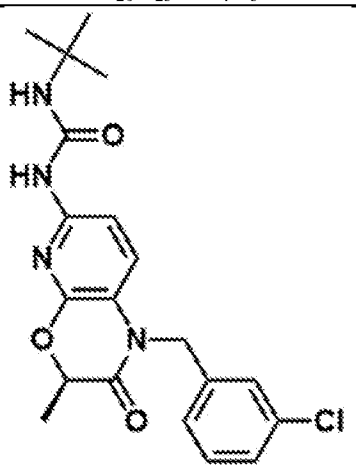
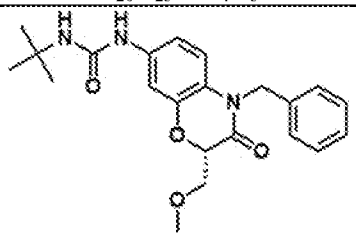
256	 $C_{24}H_{29}N_3O_3$	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea
257	 $C_{24}H_{26}F_3N_3O_3$	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-(trifluoromethyl)cyclopentyl)urea
258	 $C_{24}H_{27}F_2N_3O_3$	1-(4,4-difluorocyclohexyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
259	 $C_{23}H_{24}F_3N_3O_3$	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-(trifluoromethyl)cyclobutyl)urea
260	 $C_{23}H_{25}F_2N_3O_3$	1-(3,3-difluoro-1-methylcyclobutyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
261	 $C_{24}H_{29}N_3O_4$	1-(1-(methoxymethyl)cyclobutyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

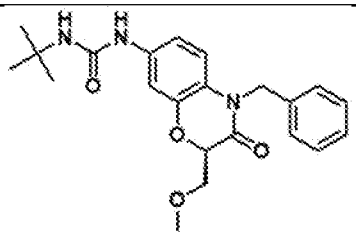
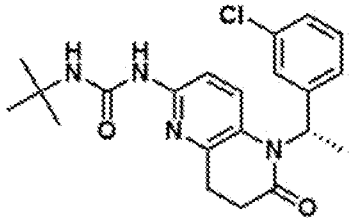
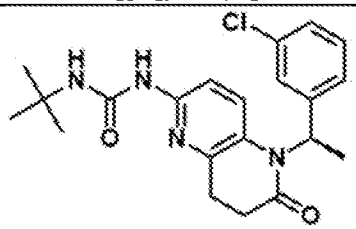
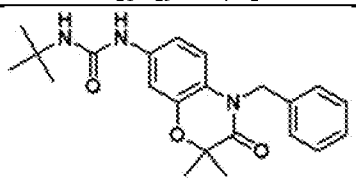
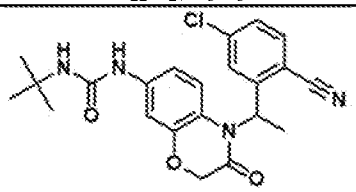
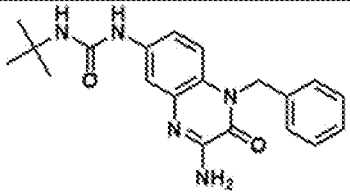
262	 $C_{22}H_{25}N_3O_4$	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(3-methyloxetan-3-yl)urea
263	 $C_{22}H_{22}F_3N_3O_4$	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(3-(trifluoromethyl)oxetan-3-yl)urea
264	 $C_{23}H_{22}F_5N_3O_3$	1-(3,3-difluoro-1-(trifluoromethyl)cyclobutyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
265	 $C_{24}H_{29}N_3O_4$	1-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(4-methyltetrahydro-2H-pyran-4-yl)urea
266	 $C_{23}H_{26}N_4O_2$	1-(tert-butyl)-3-(1-(2-cyano-5-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
267	 $C_{21}H_{24}ClN_3O_2$	1-(1-benzyl-5-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

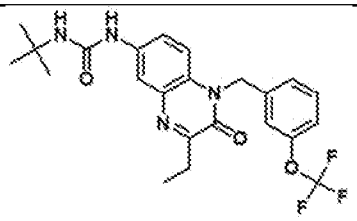
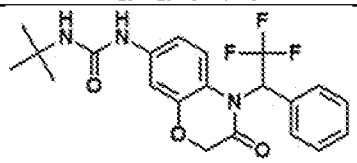
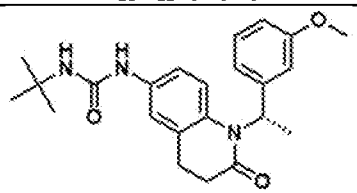
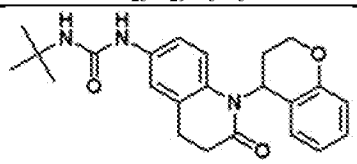
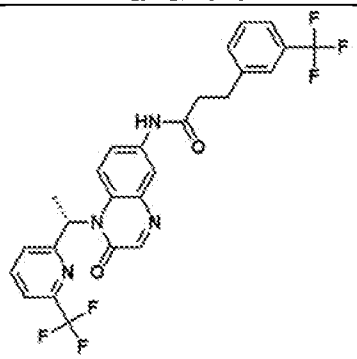
268	 $C_{22}H_{27}N_3O_3$	1-(tert-butyl)-3-((S)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
269	 $C_{22}H_{27}N_3O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
270	 $C_{22}H_{24}N_4O_2$	1-(1-benzyl-7-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
271	 $C_{23}H_{27}F_3N_4O_2$	1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea
272	 $C_{21}H_{24}N_4O_2$	1-(1-benzyl-3-methyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea
273	 $C_{21}H_{23}ClN_4O_2$	1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
274	 $C_{21}H_{23}F_3N_4O_2$	1-(tert-butyl)-3-(6-oxo-5-(3-(trifluoromethyl)benzyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea

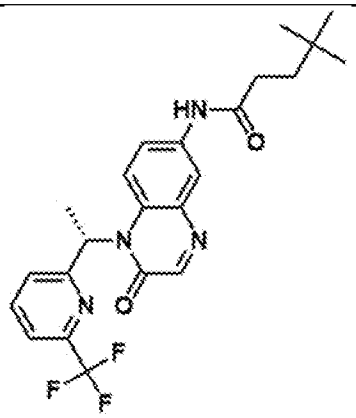
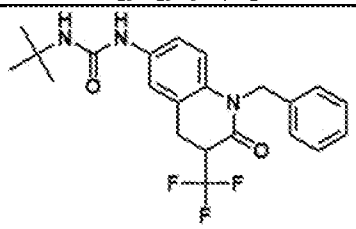
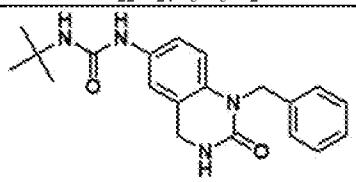
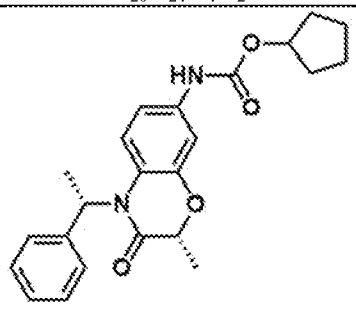
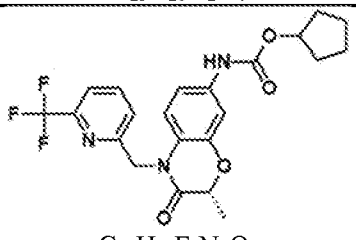
275	 $C_{23}H_{26}N_4O_2$	(R)-1-(1-benzyl-3-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
276	 $C_{23}H_{26}N_4O_2$	(S)-1-(1-benzyl-3-(cyanomethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
277	 $C_{22}H_{27}N_3O_3$	(R)-1-(4-benzyl-2-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
278	 $C_{22}H_{27}N_3O_3$	(S)-1-(4-benzyl-2-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
279	 $C_{22}H_{24}N_4O_2$	1-(1-benzyl-5-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

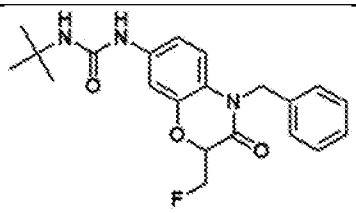
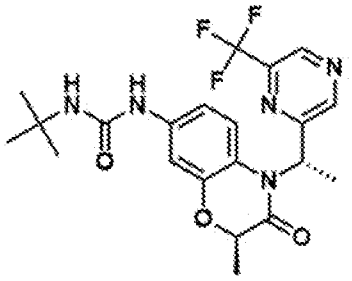
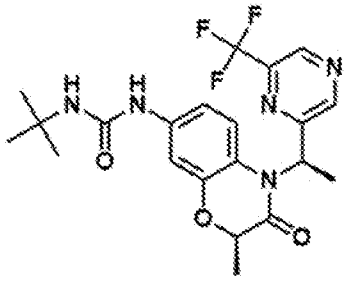
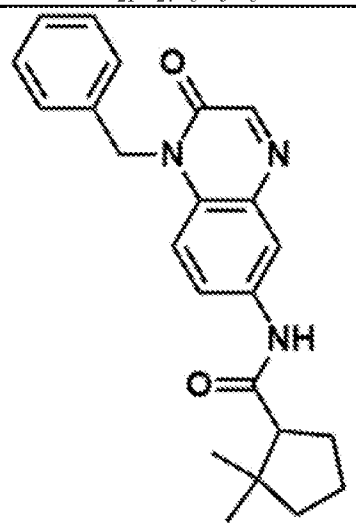
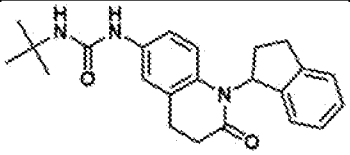
280	 $C_{20}H_{24}N_4O_3$	(R)-1-(1-benzyl-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea
281	 $C_{20}H_{23}ClN_4O_2$	1-(tert-butyl)-3-(5-(3-chlorobenzyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea
282	 $C_{22}H_{25}F_3N_4O_2$	(S)-1-(tert-butyl)-3-(6-oxo-5-(1-(3-(trifluoromethyl)phenyl)ethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea
283	 $C_{22}H_{25}F_3N_4O_2$	(R)-1-(tert-butyl)-3-(6-oxo-5-(1-(3-(trifluoromethyl)phenyl)ethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea
284	 $C_{23}H_{21}N_3O_2$	1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-phenylurea

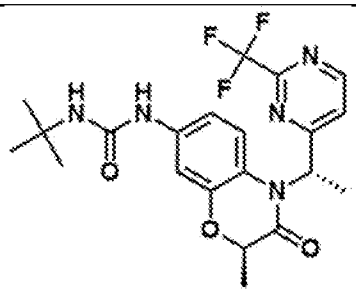
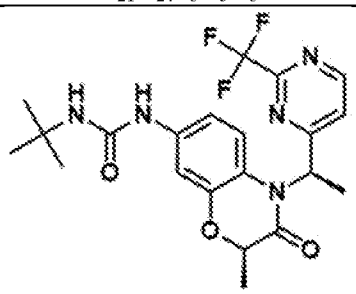
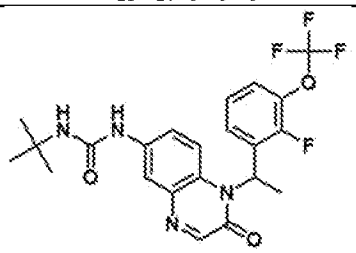
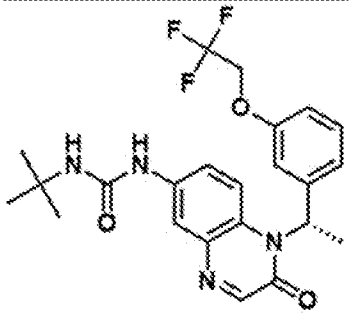
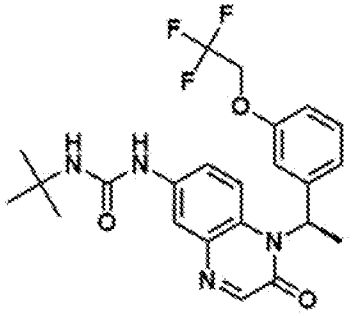
285	 $C_{22}H_{26}N_2O_2$	N-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3,3-dimethylbutanamide
286	 $C_{20}H_{23}ClN_4O_3$	(S)-1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea
287	 $C_{20}H_{23}ClN_4O_3$	(R)-1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea
288	 $C_{22}H_{27}N_3O_4$	(S)-1-(4-benzyl-2-(methoxymethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea

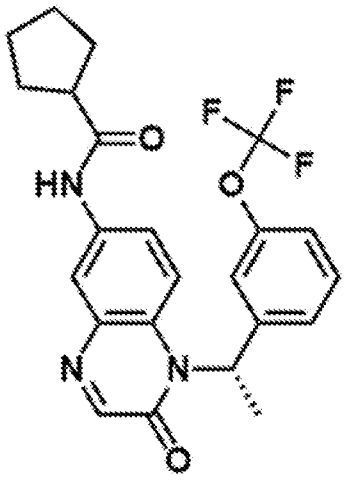
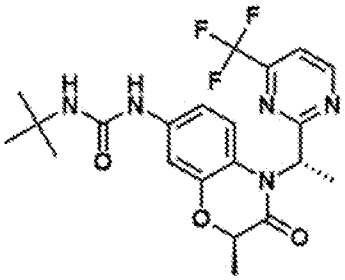
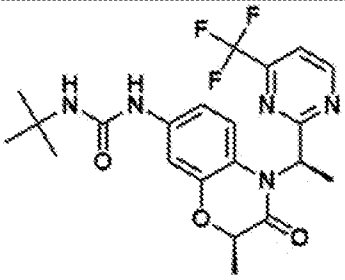
289	 $C_{22}H_{27}N_3O_4$	(R)-1-(4-benzyl-2-(methoxymethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
290	 $C_{21}H_{25}ClN_4O_2$	(S)-1-(tert-butyl)-3-(5-(1-(3-chlorophenyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea
291	 $C_{21}H_{25}ClN_4O_2$	(R)-1-(tert-butyl)-3-(5-(1-(3-chlorophenyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea
292	 $C_{22}H_{27}N_3O_3$	1-(4-benzyl-2,2-dimethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
293	 $C_{22}H_{23}ClN_4O_3$	1-(tert-butyl)-3-(4-(1-(5-chloro-2-cyanophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
294	 $C_{20}H_{23}N_5O_2$	1-(3-amino-1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea

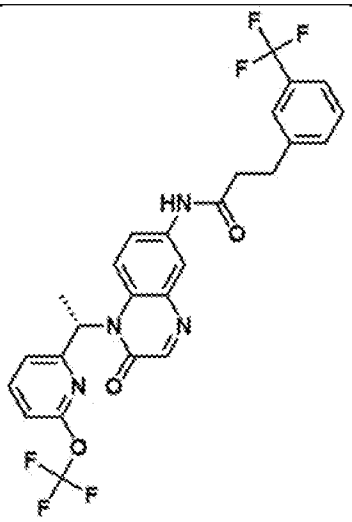
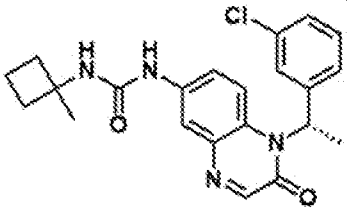
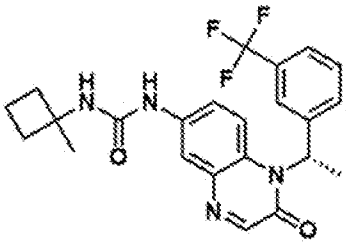
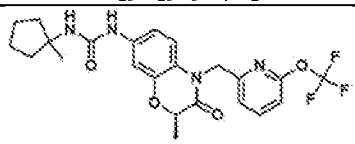
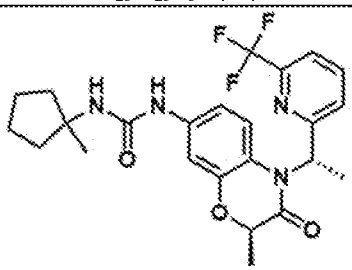
295	 $C_{23}H_{25}F_3N_4O_3$	1-(tert-butyl)-3-(3-ethyl-2-oxo-1-(3-(trifluoromethoxy)benzyl)-1,2-dihydroquinoxalin-6-yl)urea
296	 $C_{21}H_{22}F_3N_3O_3$	1-(tert-butyl)-3-(3-oxo-4-(2,2,2-trifluoro-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
297	 $C_{23}H_{29}N_3O_3$	(S)-1-(tert-butyl)-3-(1-(1-(3-methoxyphenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
298	 $C_{23}H_{27}N_3O_3$	1-(tert-butyl)-3-(1-(chroman-4-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
299	 $C_{26}H_{20}F_6N_4O_2$	(S)-N-(2-oxo-1-(1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)phenyl)propanamide

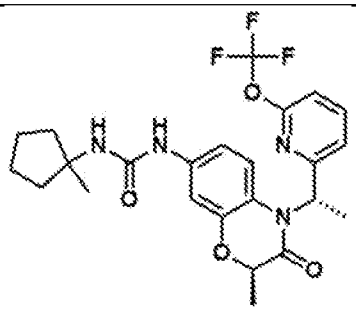
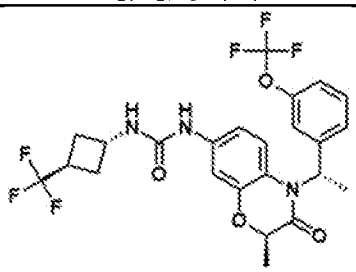
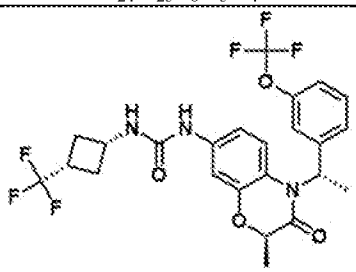
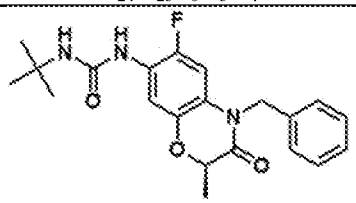
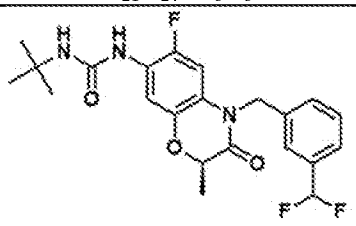
300	 $C_{23}H_{25}F_3N_4O_2$	(S)-4,4-dimethyl-N-(2-oxo-1-(1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)pentanamide
301	 $C_{22}H_{24}F_3N_3O_2$	1-(1-benzyl-2-oxo-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
302	 $C_{20}H_{24}N_4O_2$	1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-3-(tert-butyl)urea
303	 $C_{23}H_{26}N_2O_4$	cyclopentyl ((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)carbamate
304	 $C_{22}H_{22}F_3N_3O_4$	cyclopentyl (R)-(2-methyl-3-oxo-4-((6-(trifluoromethyl)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)carbamate

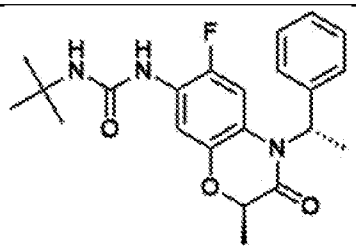
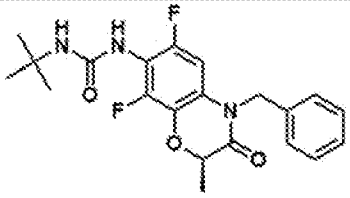
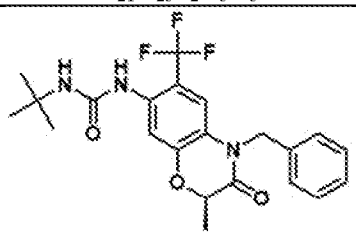
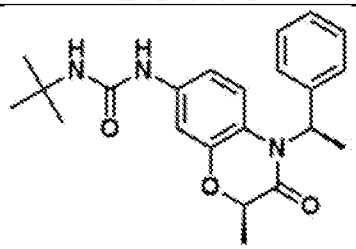
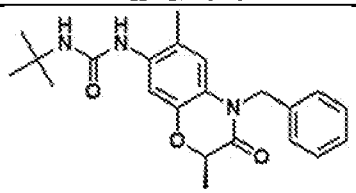
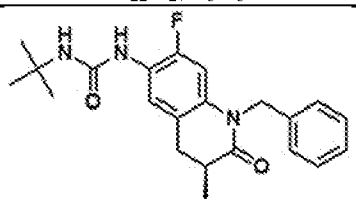
305	 $C_{21}H_{24}FN_3O_3$	1-(4-benzyl-2-(fluoromethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
306	 $C_{21}H_{24}F_3N_5O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethyl)pyrazin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
307	 $C_{21}H_{24}F_3N_5O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-(6-(trifluoromethyl)pyrazin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
308	 $C_{23}H_{25}N_3O_2$	N-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-2,2-dimethylcyclopentane-1-carboxamide
309	 $C_{23}H_{27}N_3O_2$	1-(tert-butyl)-3-(1-(2,3-dihydro-1H-inden-1-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

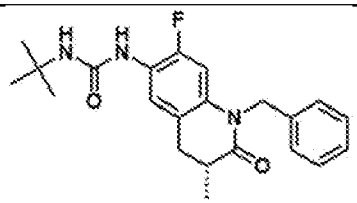
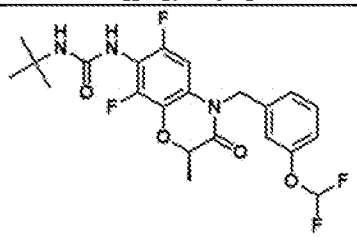
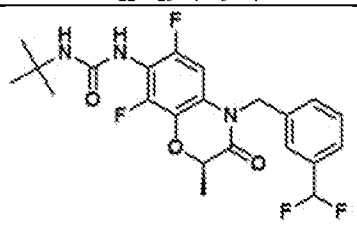
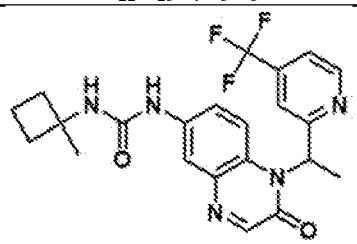
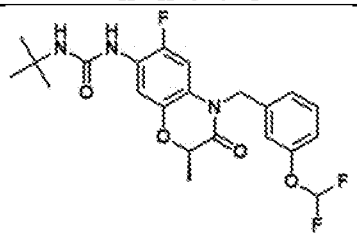
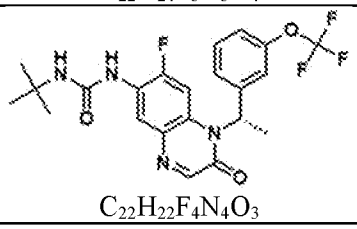
310	 $C_{21}H_{24}F_3N_5O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(2-(trifluoromethyl)pyrimidin-4-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
311	 $C_{21}H_{24}F_3N_5O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-(2-(trifluoromethyl)pyrimidin-4-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
312	 $C_{22}H_{22}F_4N_4O_3$	1-(tert-butyl)-3-(1-(1-(2-fluoro-3-(trifluoromethoxy)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
313	 $C_{23}H_{25}F_3N_4O_3$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
314	 $C_{23}H_{25}F_3N_4O_3$	(R)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

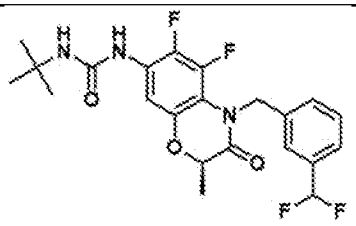
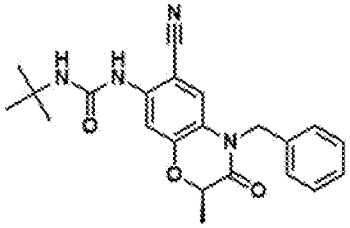
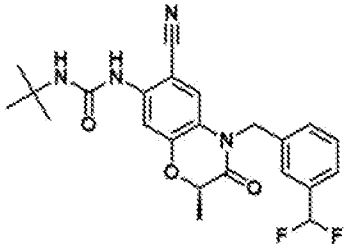
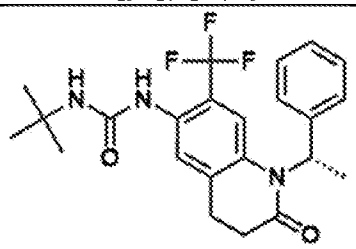
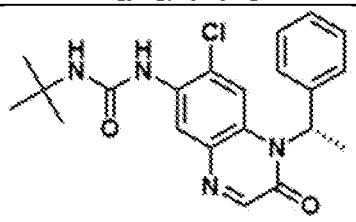
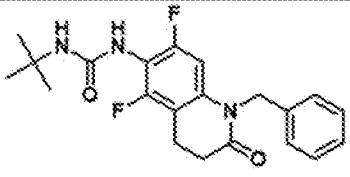
315	 $C_{23}H_{22}F_3N_3O_3$	(S)-N-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)cyclopentanecarboxamide
316	 $C_{21}H_{24}F_3N_5O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-(4-(trifluoromethyl)pyrimidin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
317	 $C_{21}H_{24}F_3N_5O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-(4-(trifluoromethyl)pyrimidin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

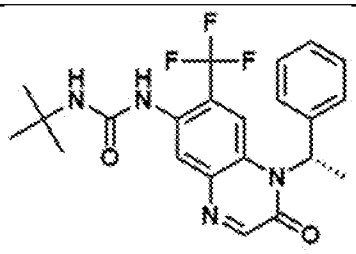
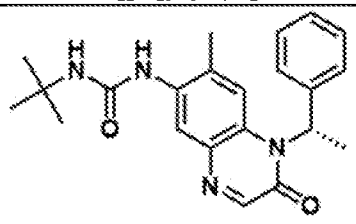
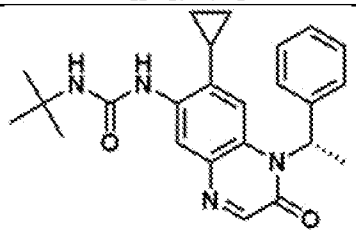
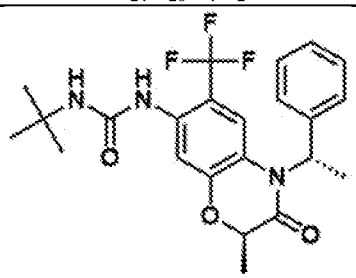
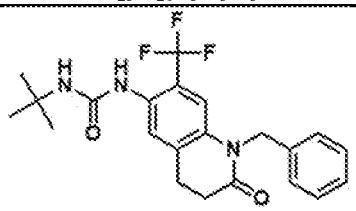
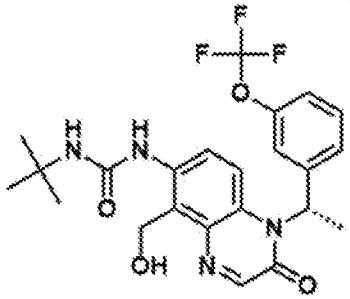
318	 $C_{26}H_{20}F_6N_4O_3$	(S)-N-(2-oxo-1-(1-(6-(trifluoromethoxy)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)phenyl)propanamide
319	 $C_{22}H_{23}ClN_4O_2$	(S)-1-(1-(1-(3-chlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(1-methylcyclobutyl)urea
320	 $C_{23}H_{23}F_3N_4O_2$	(S)-1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
321	 $C_{23}H_{25}F_3N_4O_4$	(R)-1-(2-methyl-3-oxo-4-((6-(trifluoromethoxy)pyridin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea
322	 $C_{24}H_{27}F_3N_4O_3$	1-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethyl)pyridin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea

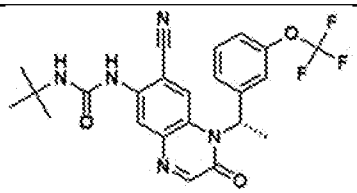
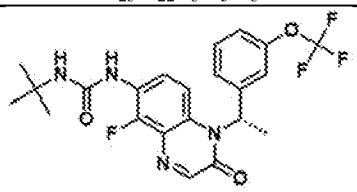
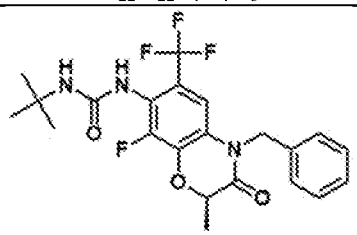
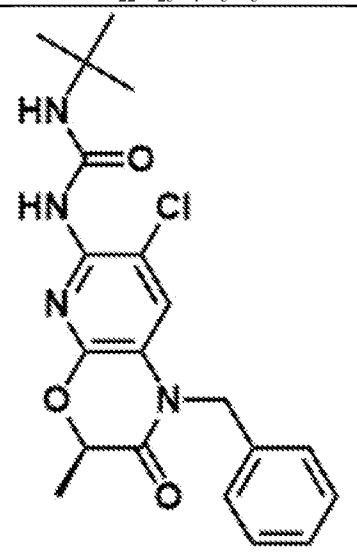
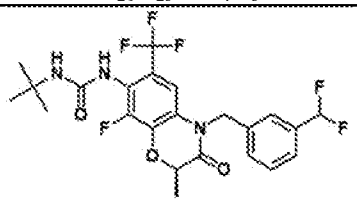
323	 $C_{24}H_{27}F_3N_4O_4$	1-((R)-2-methyl-3-oxo-4-((S)-1-(6-(trifluoromethoxy)pyridin-2-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1-methylcyclopentyl)urea
324	 $C_{24}H_{23}F_6N_3O_4$	1-((R)-2-methyl-3-oxo-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-((1r,3R)-3-(trifluoromethyl)cyclobutyl)urea
325	 $C_{24}H_{23}F_6N_3O_4$	1-((R)-2-methyl-3-oxo-4-((S)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-((1s,3S)-3-(trifluoromethyl)cyclobutyl)urea
326	 $C_{21}H_{24}FN_3O_3$	(R)-1-(4-benzyl-6-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
327	 $C_{22}H_{24}F_3N_3O_3$	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-6-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

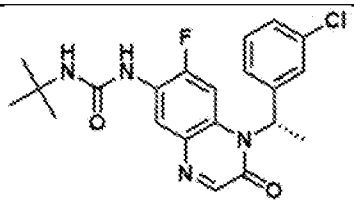
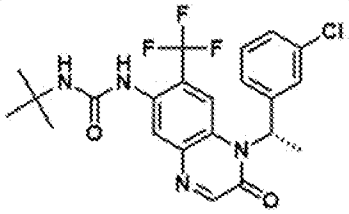
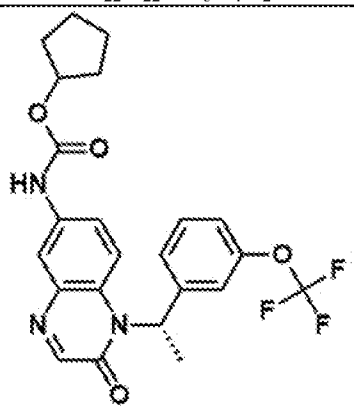
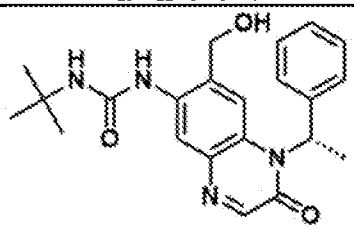
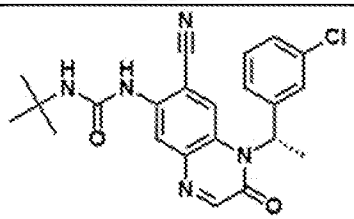
328	 $C_{22}H_{26}FN_3O_3$	1-(tert-butyl)-3-((R)-6-fluoro-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
329	 $C_{21}H_{23}F_2N_3O_3$	(R)-1-(4-benzyl-6,8-difluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
330	 $C_{22}H_{24}F_3N_3O_3$	(R)-1-(4-benzyl-2-methyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
331	 $C_{22}H_{27}N_3O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((R)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
332	 $C_{22}H_{27}N_3O_3$	(R)-1-(4-benzyl-2,6-dimethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
333	 $C_{22}H_{26}FN_3O_2$	(S)-1-(1-benzyl-7-fluoro-3-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

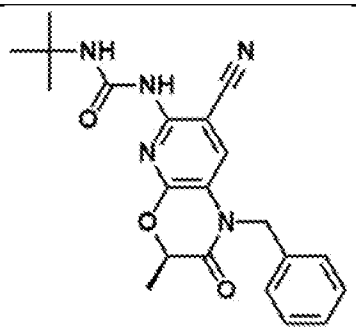
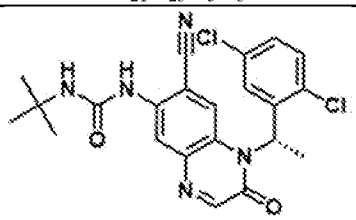
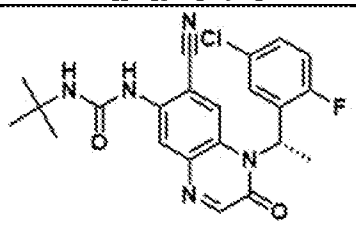
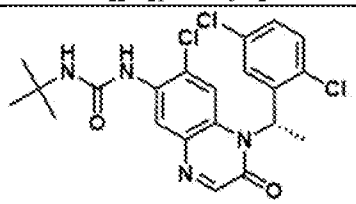
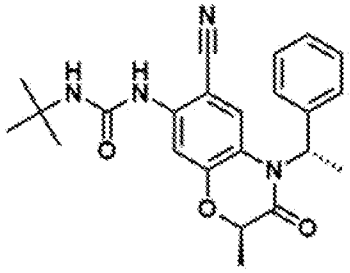
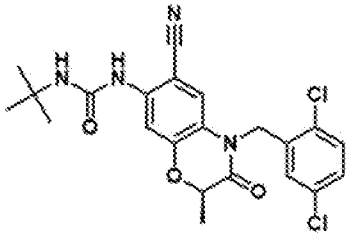
334	 $C_{22}H_{26}FN_3O_2$	(R)-1-(1-benzyl-7-fluoro-3-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
335	 $C_{22}H_{23}F_4N_3O_4$	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethoxy)benzyl)-6,8-difluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
336	 $C_{22}H_{23}F_4N_3O_3$	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-6,8-difluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
337	 $C_{22}H_{22}F_3N_5O_2$	1-(1-methylcyclobutyl)-3-(2-oxo-1-(1-(4-(trifluoromethyl)pyridin-2-yl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
338	 $C_{22}H_{24}F_3N_3O_4$	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethoxy)benzyl)-6-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
339	 $C_{22}H_{22}F_4N_4O_3$	(S)-1-(tert-butyl)-3-(7-fluoro-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

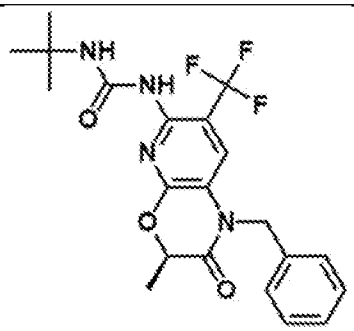
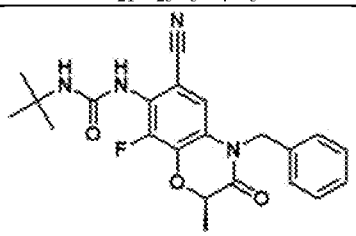
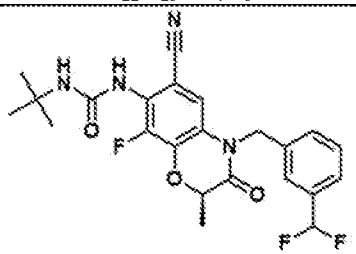
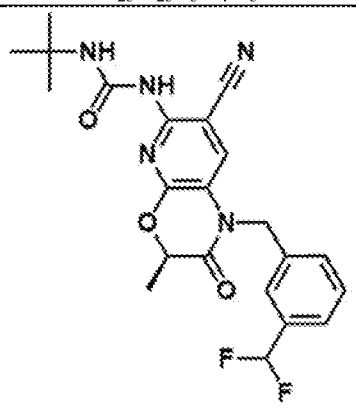
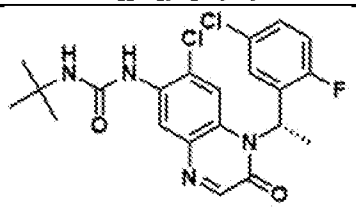
340	 $C_{22}H_{23}F_4N_3O_3$	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-5,6-difluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
341	 $C_{22}H_{24}N_4O_3$	(R)-1-(4-benzyl-6-cyano-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
342	 $C_{23}H_{24}F_2N_4O_3$	(R)-1-(tert-butyl)-3-(6-cyano-4-(3-(difluoromethyl)benzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
343	 $C_{23}H_{26}F_3N_3O_2$	(S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-7-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
344	 $C_{21}H_{23}ClN_4O_2$	(S)-1-(tert-butyl)-3-(7-chloro-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea
345	 $C_{21}H_{23}F_2N_3O_2$	1-(1-benzyl-5,7-difluoro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea

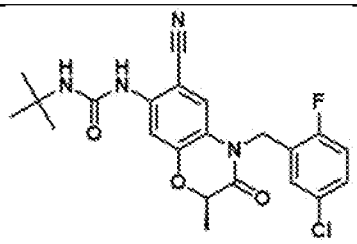
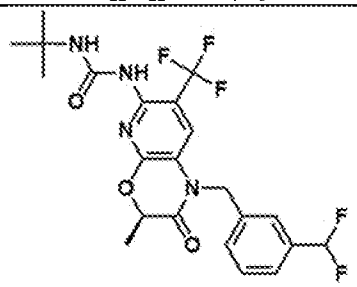
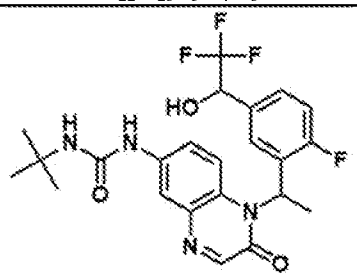
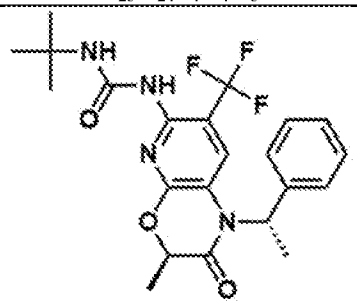
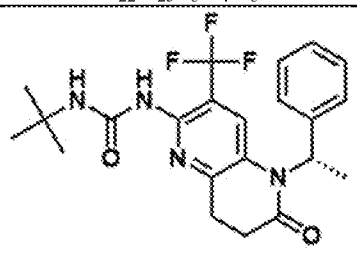
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347	 $C_{22}H_{26}N_4O_2$	(S)-1-(tert-butyl)-3-(7-methyl-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea
348	 $C_{24}H_{28}N_4O_2$	(S)-1-(tert-butyl)-3-(7-cyclopropyl-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea
349	 $C_{23}H_{26}F_3N_3O_3$	1-(tert-butyl)-3-((R)-2-methyl-3-oxo-4-((S)-1-phenylethyl)-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
350	 $C_{22}H_{24}F_3N_3O_2$	1-(1-benzyl-2-oxo-7-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
351	 $C_{23}H_{25}F_3N_4O_4$	(S)-1-(tert-butyl)-3-(5-(hydroxymethyl)-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea

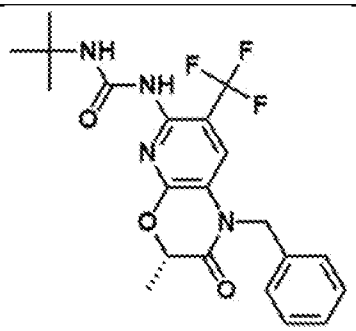
352	 $C_{23}H_{22}F_3N_5O_3$	(S)-1-(tert-butyl)-3-(7-cyano-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
353	 $C_{22}H_{22}F_4N_4O_3$	(S)-1-(tert-butyl)-3-(5-fluoro-2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)urea
354	 $C_{22}H_{23}F_4N_3O_3$	(R)-1-(4-benzyl-8-fluoro-2-methyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
355	 $C_{20}H_{23}ClN_4O_3$	(R)-1-(1-benzyl-7-chloro-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea
356	 $C_{23}H_{23}F_6N_3O_3$	(R)-1-(tert-butyl)-3-(4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-3-oxo-6-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

357	 $C_{21}H_{22}ClFN_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-7-fluoro-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
358	 $C_{22}H_{22}ClF_3N_4O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-2-oxo-7-(trifluoromethyl)-1,2-dihydroquinoxalin-6-yl)urea
359	 $C_{23}H_{22}F_3N_3O_4$	cyclopentyl (S)-(2-oxo-1-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1,2-dihydroquinoxalin-6-yl)carbamate
360	 $C_{22}H_{26}N_4O_3$	(S)-1-(tert-butyl)-3-(7-(hydroxymethyl)-2-oxo-1-(1-phenylethyl)-1,2-dihydroquinoxalin-6-yl)urea
361	 $C_{22}H_{22}ClN_5O_2$	(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-7-cyano-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

362	 $C_{21}H_{23}N_5O_3$	(R)-1-(1-benzyl-7-cyano-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea
363	 $C_{22}H_{21}Cl_2N_5O_2$	(S)-1-(tert-butyl)-3-(7-cyano-1-(1-(2,5-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
364	 $C_{22}H_{21}ClFN_5O_2$	(S)-1-(tert-butyl)-3-(1-(1-(5-chloro-2-fluorophenyl)ethyl)-7-cyano-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
365	 $C_{21}H_{21}Cl_3N_4O_2$	(S)-1-(tert-butyl)-3-(7-chloro-1-(1-(2,5-dichlorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
366	 $C_{23}H_{26}N_4O_3$	1-(tert-butyl)-3-((R)-6-cyano-2-methyl-3-oxo-4-((S)-1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
367	 $C_{22}H_{22}Cl_2N_4O_3$	(R)-1-(tert-butyl)-3-(6-cyano-4-(2,5-dichlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

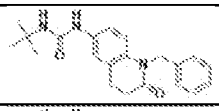
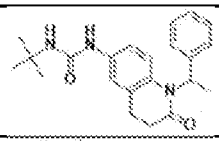
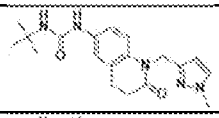
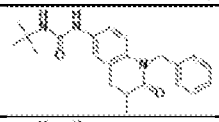
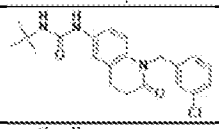
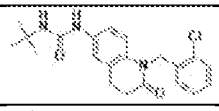
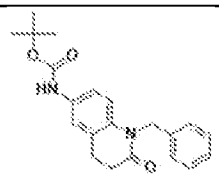
368	 $C_{21}H_{23}F_3N_4O_3$	(R)-1-(1-benzyl-3-methyl-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea
369	 $C_{22}H_{23}FN_4O_3$	(R)-1-(4-benzyl-6-cyano-8-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
370	 $C_{23}H_{23}F_3N_4O_3$	(R)-1-(tert-butyl)-3-(6-cyano-4-(3-(difluoromethyl)benzyl)-8-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
371	 $C_{22}H_{23}F_2N_5O_3$	(R)-1-(tert-butyl)-3-(7-cyano-1-(3-(difluoromethyl)benzyl)-3-methyl-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea
372	 $C_{21}H_{21}Cl_2FN_4O_2$	(S)-1-(tert-butyl)-3-(7-chloro-1-(1-(5-chloro-2-fluorophenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea

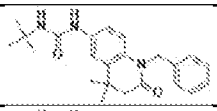
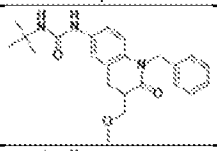
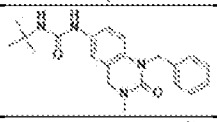
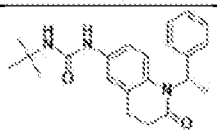
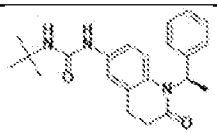
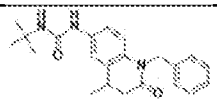
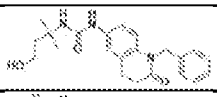
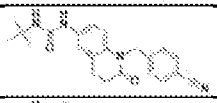
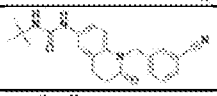
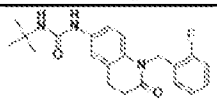
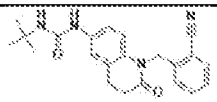
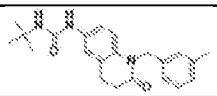
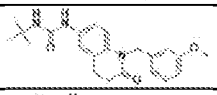
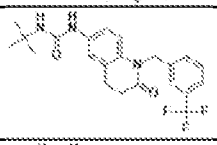
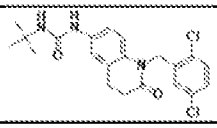
373	 $C_{22}H_{22}ClFN_4O_3$	(R)-1-(tert-butyl)-3-(4-(5-chloro-2-fluorobenzyl)-6-cyano-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
374	 $C_{22}H_{23}F_5N_4O_3$	(R)-1-(tert-butyl)-3-(1-(3-(difluoromethyl)benzyl)-3-methyl-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea
375	 $C_{23}H_{24}F_4N_4O_3$	1-(tert-butyl)-3-(1-(1-(2-fluoro-5-(2,2,2-trifluoro-1-hydroxyethyl)phenyl)ethyl)-2-oxo-1,2-dihydroquinoxalin-6-yl)urea
376	 $C_{22}H_{25}F_3N_4O_3$	1-(tert-butyl)-3-((R)-3-methyl-2-oxo-1-((S)-1-phenylethyl)-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)urea
377	 $C_{22}H_{25}F_3N_4O_2$	(S)-1-(tert-butyl)-3-(6-oxo-5-(1-phenylethyl)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)urea

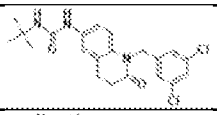
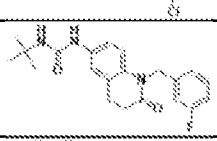
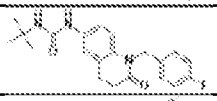
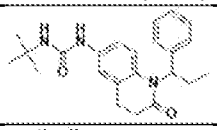
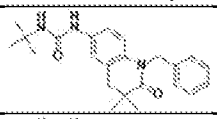
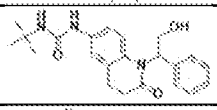
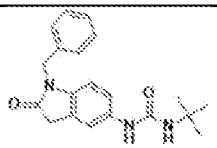
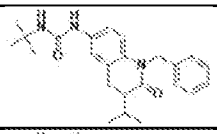
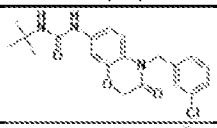
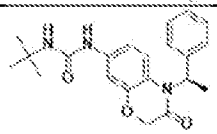
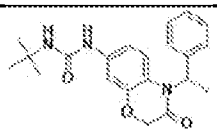
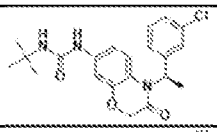
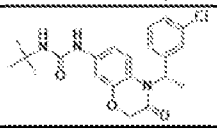
378	 $C_{21}H_{23}F_3N_4O_3$	(R)-1-(1-benzyl-3-methyl-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-6-yl)-3-(tert-butyl)urea

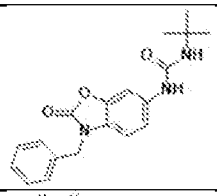
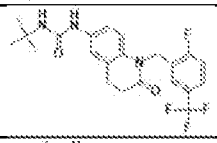
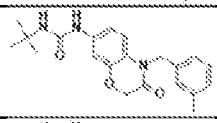
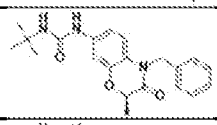
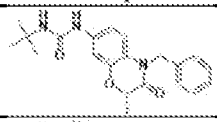
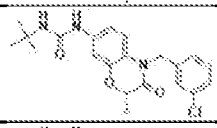
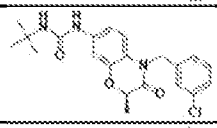
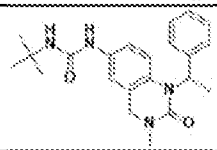
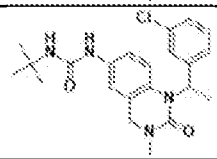
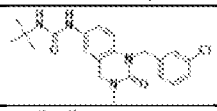
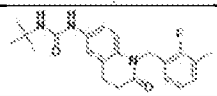
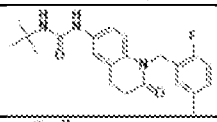
or a pharmaceutically acceptable salt thereof.

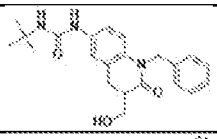
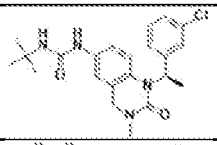
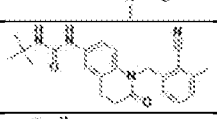
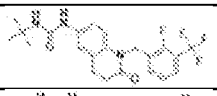
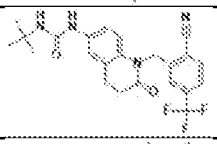
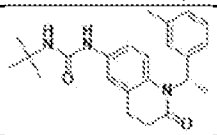
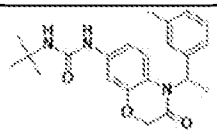
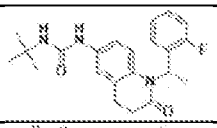
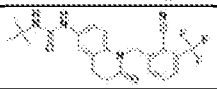
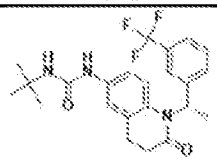
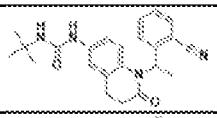
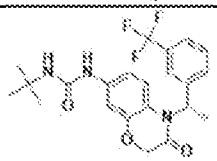
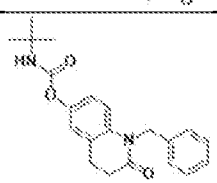
75. A compound selected from the following table:

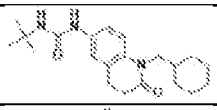
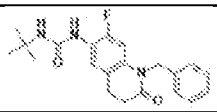
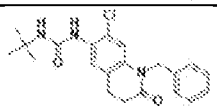
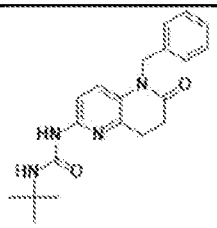
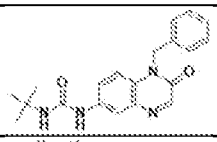
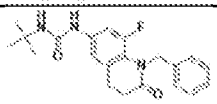
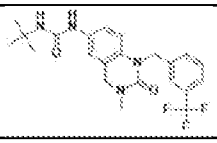
1		1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
2		1-(tert-butyl)-3-(2-oxo-1-(pyridin-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
3		1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
4		1-(tert-butyl)-3-(1-((1-methyl-1H-pyrazol-3-yl)methyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
5		1-(1-benzyl-3-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
6		1-(tert-butyl)-3-(1-(3-chlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
7		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
8		1-(tert-butyl)-3-(1-(2-chlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
9		tert-butyl (1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)carbamate

10		1-(1-benzyl-4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
11		1-(1-benzyl-3-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
12		1-(1-benzyl-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-3-(tert-butyl)urea
13		(S)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
14		(R)-1-(tert-butyl)-3-(2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
15		1-(1-benzyl-4-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
16		1-(1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-hydroxy-2-methylbutan-2-yl)urea
17		1-(tert-butyl)-3-(1-(4-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
18		1-(tert-butyl)-3-(1-(3-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
19		1-(tert-butyl)-3-(1-(2-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
20		1-(tert-butyl)-3-(1-(2-cyanobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
21		1-(tert-butyl)-3-(1-(3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
22		1-(tert-butyl)-3-(1-(3-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
23		1-(tert-butyl)-3-(2-oxo-1-(3-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
24		1-(tert-butyl)-3-(1-(2,5-dichlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea

25		1-(tert-butyl)-3-(1-(3,5-dichlorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
26		1-(tert-butyl)-3-(1-(3-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
27		1-(tert-butyl)-3-(1-(4-fluorobenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
28		1-(tert-butyl)-3-(2-oxo-1-(1-phenylpropyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
29		1-(1-benzyl-3,3-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
30		1-(tert-butyl)-3-(1-(2-hydroxy-1-phenylethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
31		1-(1-benzyl-2-oxoindolin-5-yl)-3-(tert-butyl)urea
32		1-(1-benzyl-3-isopropyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
33		1-(tert-butyl)-3-(4-(3-chlorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
34		(R)-1-(tert-butyl)-3-(3-oxo-4-(1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
35	 $C_{21}H_{25}N_3O_3$	(S)-1-(tert-butyl)-3-(3-oxo-4-(1-phenylethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
36		(R)-1-(tert-butyl)-3-(4-(1-(3-chlorophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
37		(S)-1-(tert-butyl)-3-(4-(1-(3-chlorophenyl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

38		1-(3-benzyl-2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)-3-(tert-butyl)urea
39		1-(tert-butyl)-3-(1-(2-fluoro-5-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
40		1-(tert-butyl)-3-(4-(3-methylbenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
41		(R)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
42		(S)-1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(tert-butyl)urea
43		(S)-1-(tert-butyl)-3-(4-(3-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
44		(R)-1-(tert-butyl)-3-(4-(3-chlorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
45		(S)-1-(tert-butyl)-3-(3-methyl-2-oxo-1-(1-phenylethyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea
46		(S)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea
47		1-(tert-butyl)-3-(1-(3-chlorobenzyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea
48		1-(tert-butyl)-3-(1-(2-fluoro-3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
49		1-(tert-butyl)-3-(1-(2-fluoro-5-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
50		1-(tert-butyl)-3-(3-oxo-4-(3-(trifluoromethyl)benzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea

51		1-(1-benzyl-3-(hydroxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
52		(R)-1-(tert-butyl)-3-(1-(1-(3-chlorophenyl)ethyl)-3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)urea
53		1-(tert-butyl)-3-(1-(2-cyano-3-methylbenzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
54		1-(tert-butyl)-3-(1-(2-fluoro-3-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
55		1-(tert-butyl)-3-(1-(2-cyano-5-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
56		(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(m-tolyl)ethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
57		(S)-1-(tert-butyl)-3-(3-oxo-4-(1-(m-tolyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
58		(S)-1-(tert-butyl)-3-(1-(1-(2-fluorophenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
59		1-(tert-butyl)-3-(1-(2-cyano-3-(trifluoromethyl)benzyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
60		(S)-1-(tert-butyl)-3-(2-oxo-1-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,2,3,4-tetrahydroquinolin-6-yl)urea
61		(S)-1-(tert-butyl)-3-(1-(1-(2-cyanophenyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
62		(S)-1-(tert-butyl)-3-(3-oxo-4-(1-(3-(trifluoromethyl)phenyl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)urea
63		1-benzyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl tert-butylcarbamate

64		1-(tert-butyl)-3-(1-(cyclohexylmethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)urea
65		1-(1-benzyl-7-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
66		1-(1-benzyl-7-chloro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea
67		1-(5-benzyl-6-oxo-5,6,7,8-tetrahydro-1,5-naphthyridin-2-yl)-3-(tert-butyl)urea
68		1-(1-benzyl-2-oxo-1,2-dihydroquinoxalin-6-yl)-3-(tert-butyl)urea
69		1-(1-benzyl-8-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(tert-butyl)urea; and
70		1-(tert-butyl)-3-(3-methyl-2-oxo-1-(3-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroquinazolin-6-yl)urea

or a pharmaceutically acceptable salt thereof.

76. A pharmaceutical composition, comprising a compound of any one of claims 1 to 75; and at least one pharmaceutically acceptable excipient.

77. A method of inhibiting a thyroid stimulating hormone receptor, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1 to 75.

78. A method of treating hyperthyroidism, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1 to 75.

79. The method of claim 78, wherein the subject has Graves' disease.

80. The method of claim 79 wherein the subject has Graves' ophthalmopathy.

81. The method of claim 79 or 80, wherein the subject has Graves' dermopathy.

82. The method of claim 78, wherein the subject has thyroid cancer.