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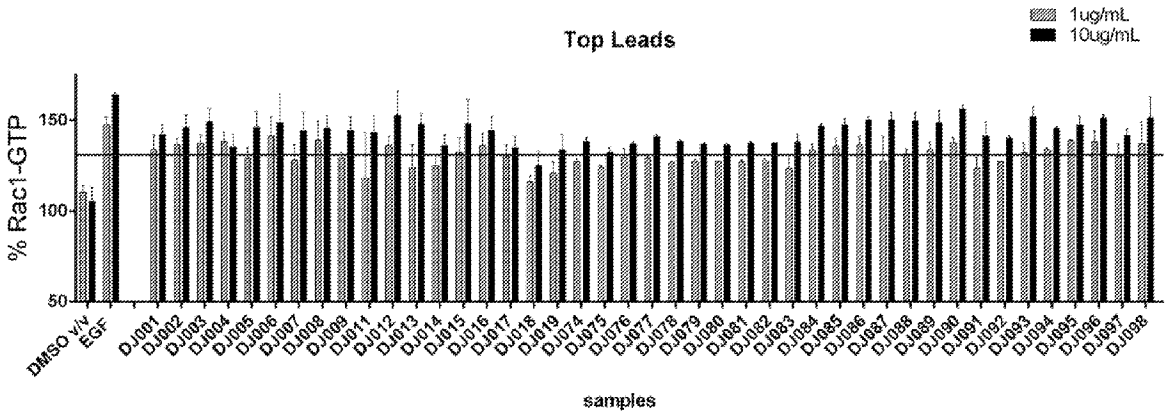

FIG. 9

(57) Abstract: The invention relates to compounds that promote hematopoietic regeneration. The invention further relates to methods of promoting hematopoietic regeneration using the novel compounds of the invention.

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COMPOUNDS AND METHODS FOR HEMATOPOIETIC REGENERATION

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/592,303, filed November 29, 2017, the contents of which are fully incorporated by reference herein.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with Government support under AI067769, awarded by the National Institutes of Health. The Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

Hematopoietic stem cells (HSCs) possess the unique capability to undergo self-renewal and give rise to all of the mature components of the hematologic and immune systems throughout the lifetime of an individual. HSC self-renewal is regulated by intrinsic mechanisms as well as extrinsic signaling emanating from the bone marrow (BM) microenvironment or niche. However, the precise mechanisms through which BM microenvironment cells regulate HSC self-renewal are incompletely understood. Furthermore, the mechanisms governing HSC regeneration, which is necessary for hematologic recovery to occur in patients receiving myelosuppressive chemotherapy, radiotherapy and hematopoietic cell transplantation, remain poorly understood.

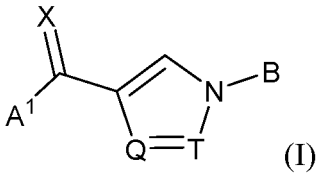
The transmembrane tyrosine phosphatase PTPσ (also known as PTPRS) has been discovered to regulate murine and human HSC self-renewal and regeneration in vivo. The loss of PTPσ substantially increases long-term HSC-repopulating capacity.

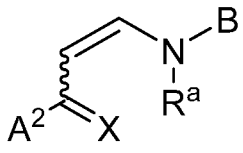
Currently, there are no FDA-approved systemic growth factors that promote human HSC regeneration or multilineage hematologic recovery in patients. Granulocyte colony stimulating factor (GCSF, Neupogen) is a white blood cell (WBC)-specific growth factor that accelerates neutrophil recovery in patients receiving chemotherapy and likely is detrimental to HSC function. Erythropoietin (Epogen) is a red blood cell (RBC)-specific growth factor which promotes RBC production in anemic patients due to chronic illness. Since PTPσ inhibitors target HSCs which give rise to entirety of the hematopoietic and immune systems, our proposed product would complement or possibly supercede indications for GCSF or erythropoietin.

Thus, there is a need for new systemic therapies that can promote the self-renewal or regeneration of hematopoietic stem cells in vivo, and specifically for inhibitors of PTPσ that can have that effect.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides compounds having the structure of formula (I), formula (II), formula (III) or formula (IV):


(I)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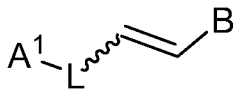
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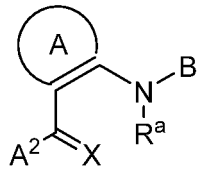

(IV)

and pharmaceutically acceptable salts and/or prodrugs thereof, wherein the variables are as defined herein. The compounds are typically selective inhibitors of PTPσ: In some embodiments, the compounds promote hematopoietic reconstitution in a subject in need thereof. Compounds of formula (I), formula (II), formula (III) and formula (IV) can be used to treat conditions described herein.

The present disclosure also provides compositions (such as pharmaceutical compositions) that comprise the compounds of this disclosure. The disclosure also includes the use of the compounds or compositions disclosed herein in the manufacture of a medicament for the treatment of one or more of the conditions described herein.

Another aspect of the disclosure provides methods for treating the conditions described herein using the compounds or compositions disclosed herein, including methods for promoting hematopoietic reconstitution in a subject in need thereof.

DETAILED DESCRIPTION OF THE DRAWINGS

FIG. 1 shows that PTPσ inhibition improves hematologic recovery and survival of irradiated mice.

FIG. 2A and 2B show that Novel PTPσ inhibitor, DJ003 increases hematopoietic colony formation (2A) and improves survival of irradiated mice (2B).

FIG. 3 shows the effect of various compounds on Rac1 activation in bone marrow cells.

FIG. 4 shows the survival of mice subjected to750 cGy of radiation, and treated with either DJ009 or a control (water).

FIG. 5A and 5B show the effect of various compounds on Rac1 activation in bone marrow cells.

FIG. 6A and 6B show the inhibition of PTPσ by various compounds.

FIG. 7 shows the results of a mechanistic study on DJ001.

FIG. 8 shows the activity of various compounds against Rac1-GTP.

FIG. 9 shows the activity of various compounds against Rac1-GTP.

FIG. 10 shows the inhibition of PTPσ by various compounds.

FIG. 11 shows the inhibition of PTPσ by various compounds.

FIG. 12 shows the hematopoietic recovery of certain cells treated with various compounds and a vehicle.

FIG. 13 shows the hematopoietic recovery of certain cells treated with various compounds and a vehicle.

FIG. 14 shows the serum stability of various compounds.

FIG. 15 shows the survival and anti-apoptotic effects of human hematopoietic progenitor cells treated with various compounds. Specifically, CD34+ cord blood cells irradiated and treated for 36 hours.

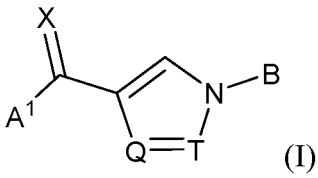
FIG. 16 shows the progenitor potential of human CD34+ cord blood mononuclear (CBMNCs) cells after treatment with various compounds for 72 hours.

FIG. 17 shows the survival of mice following irradiation with 750cGy who were subsequently treated with vehicle or various compounds at a dose of 100 ug. Notably, mice treated with compound survived longer than those treat with the vehicle.

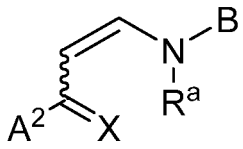
FIG. 18 shows the colony forming capacity of WBM cells post irradiation after treatment with either vehicle or various compounds.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the present invention provides compounds having the structure of formula (I), formula (II), formula (III) or formula (IV).



(I)



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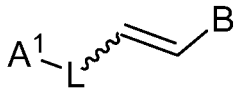

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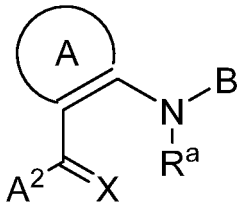


(IV)

wherein,

ring A is a pyridinylene;

A^1 is cycloalkyl, heterocyclyl, aryl, or heteroaryl;

A^2 is aryl, heteroaryl, cycloalkyl, or heterocyclyl;

B is cycloalkyl, heterocyclyl, aryl, or heteroaryl;

L is $-N(R^b)C(=X)-$ or $-C(=X)N(R^b)-$;

Q is N or CH;

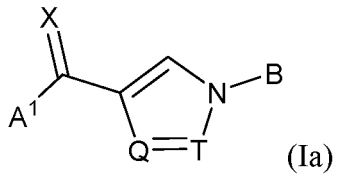
T is N or CH;

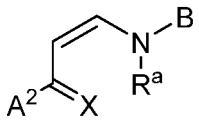
X is O, NR^a or S;

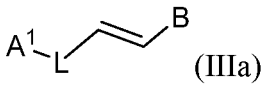
R^a is hydrogen or alkyl; and

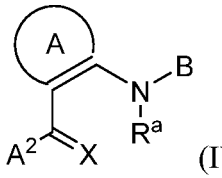
R^b is hydrogen or alkyl.

In some embodiments, the compound has the structure of formula Ia, formula IIa, formula IIIa, formula IVa or a pharmaceutically acceptable salt or prodrug thereof:


(Ia)


(IIa)


(IIIa)


(IVa)

wherein,

ring A is a pyridinylene;

A^1 is cycloalkyl, heterocyclyl, aryl, or heteroaryl;

A^2 is cycloalkyl or heterocyclyl;

B is cycloalkyl, heterocyclyl, aryl, or heteroaryl;

L is $-N(R^b)C(=X)-$ or $-C(=X)N(R^b)-$;

Q is N or CH;

T is N or CH;

X is O, NR^a or S;

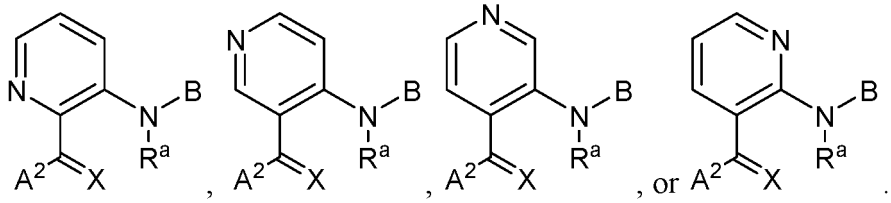
R^a is hydrogen or alkyl; and

R^b is hydrogen or alkyl.

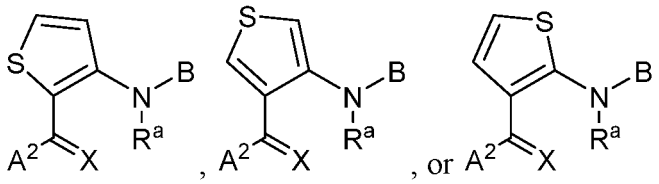
In some embodiments, the compound is a compound of Formula (I). In some embodiments of Formula (I), A^1 is phenyl. In some embodiments of Formula (I), Q and T are both CH. In other embodiments, Q and T are both N.

In some embodiments, the compound is a compound of Formula (II). In some embodiments of Formula (II), the alkene stereochemistry is in the E configuration.

In some embodiments, the compound is a compound of Formula (IV). In some embodiments of Formula (IV), the compound is represented by one of the following formulas:



In some embodiments of Formula (IV), the compound is represented by one of the following formulas:



In some embodiments of Formula (II) or (IV), A^2 is cycloalkyl or heterocyclyl. In other embodiments, A^2 is aryl or heteroaryl, such as phenyl. In some such embodiments, A^2 is aryl, such as chlorophenyl (e.g., dichlorophenyl) or methoxyphenyl (e.g., dimethoxyphenyl). In other such embodiments, A^2 is heteroaryl, such as pyridyl.

In some embodiments of Formula (II) or (IV), R^a is hydrogen.

In some embodiments the compound is represented by Formula (III). In some embodiments of Formula (III), A^1 is aryl, e.g., phenyl, fluorophenyl (such as 3,5-difluorophenyl), cyanophenyl (such as 3-cyanophenyl), or nitrophenyl (such as 4-nitrophenyl, 3-nitrophenyl or 2-nitrophenyl).

In some embodiments of Formula (III), L is $-N(R^b)C(=X)-$. In other embodiments, L is $-C(=X)N(R^b)-$.

In some embodiments of Formula (III), R^b is hydrogen.

In some embodiments of Formula (III), the alkene stereochemistry is in the Z configuration.

In some preferred embodiments of any one of Formulas (I), (II), (III), or (IV), X is oxygen.

In some embodiments of any one of Formulas (I), (II), (III), or (IV), B is aryl. In some preferred embodiments, B is phenyl, e.g., unsubstituted phenyl, fluorophenyl (such as 3,5-difluorophenyl), cyanophenyl (such as 3-cyanophenyl), or nitrophenyl (such as 4-nitrophenyl, 3-nitrophenyl or 2-nitrophenyl). In some preferred embodiments, B is methoxyphenyl (e.g., dimethoxyphenyl), trifluoromethylphenyl (e.g., 3-trifluoromethylphenyl), nitrofluorophenyl (e.g., 3-fluoro-5-nitrophenyl), amidophenyl (e.g., phenyl-3-carboxamide), alkynylphenyl (e.g., 3-ethynylphenyl).

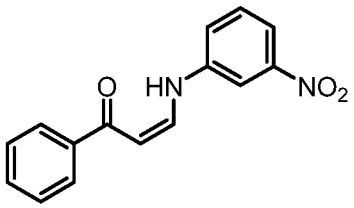
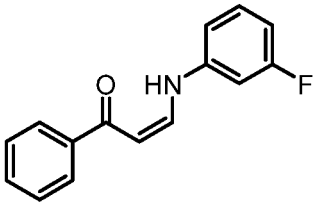
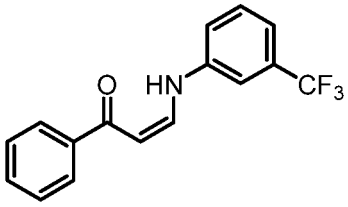
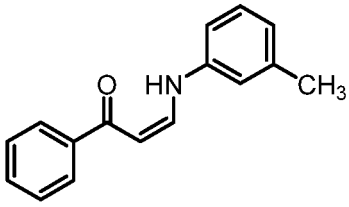
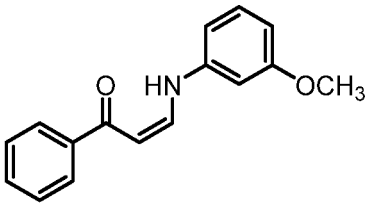
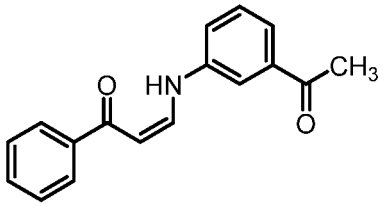
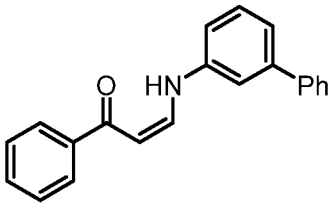
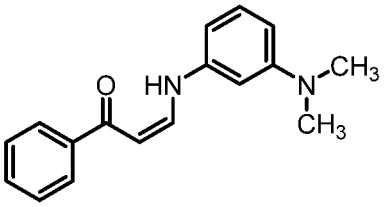
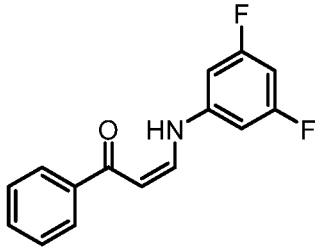
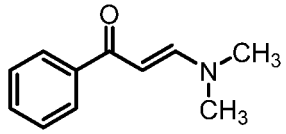
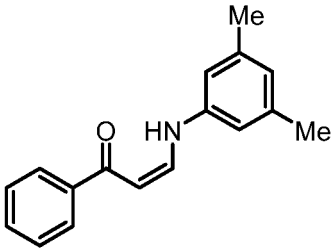
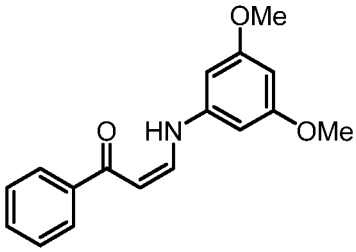
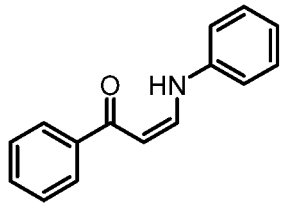
Certain compounds of the invention are prone to E/Z isomerization in solution and typically exist as a mixture of E and Z isomers. Certain embodiments of the invention are not prone to isomerization in solution. In certain embodiments, compounds of the invention may be enriched in either the E or Z isomer. For example, a compound of the invention may have greater than 50%, 60%, 70%, 80%, 90%, or 95% or more of the E or Z isomer. Those compounds that isomerize in solution in certain solvents may still be prepared in isomerically enriched form in other solvents, or in solid form.

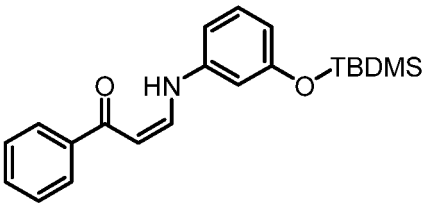
In certain embodiments, compounds of the invention may be racemic. In certain embodiments, compounds of the invention may be enriched in one enantiomer. For example, a compound of the invention may have greater than 30% ee, 40% ee, 50% ee, 60% ee, 70% ee, 80% ee, 90% ee, or even 95% or greater ee. In certain embodiments, compounds of the invention may have more than one stereocenter. In certain such embodiments, compounds of the invention may be enriched in one or more diastereomers. For example, a compound of the invention may have greater than 30% de, 40% de, 50% de, 60% de, 70% de, 80% de, 90% de, or even 95% or greater de.

In certain embodiments, the present invention provides pharmaceutical compositions comprising one or more of the compounds of the present invention. In certain embodiments, the pharmaceutical compositions further comprise a pharmaceutically acceptable excipient.

In certain embodiments, the present invention relates to methods of treatment with a compound selected from Table 1, or a pharmaceutically acceptable salt thereof. In certain embodiments, the therapeutic preparation may be enriched to provide predominantly one enantiomer or isomer of a compound (e.g., of a compound selected from Table 1). An enantiomerically enriched mixture may comprise, for example, at least 60 mol percent of one enantiomer, or more preferably at least 75, 90, 95, or even 99 mol percent. In certain

embodiments, the compound enriched in one enantiomer is substantially free of the other enantiomer, wherein substantially free means that the substance in question makes up less than 10%, or less than 5%, or less than 4%, or less than 3%, or less than 2%, or less than 1% as compared to the amount of the other enantiomer, *e.g.*, in the composition or compound mixture. For example, if a composition or compound mixture contains 98 grams of a first enantiomer and 2 grams of a second enantiomer, it would be said to contain 98 mol percent of the first enantiomer and only 2% of the second enantiomer.

In some embodiments, the compound is not  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .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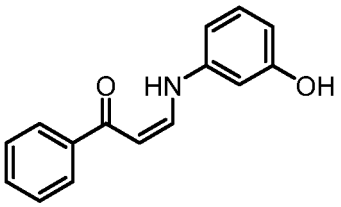
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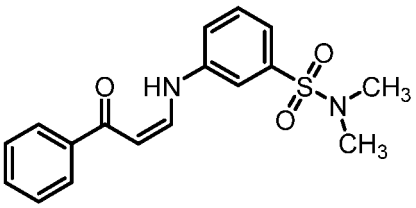
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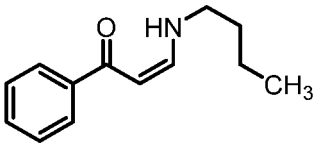
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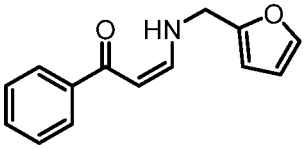
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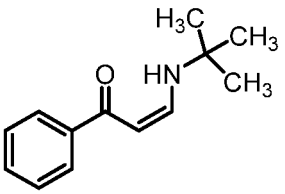
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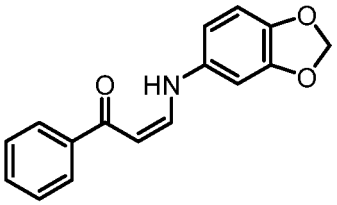
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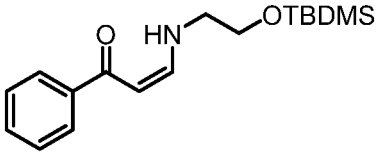
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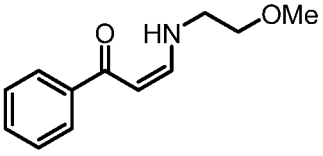
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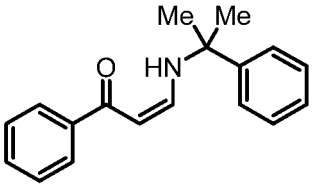
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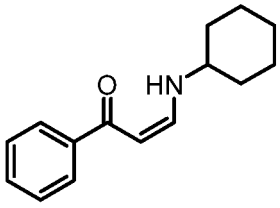
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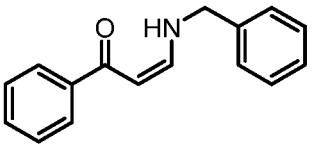
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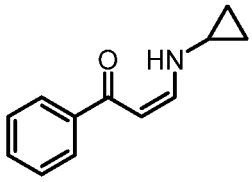
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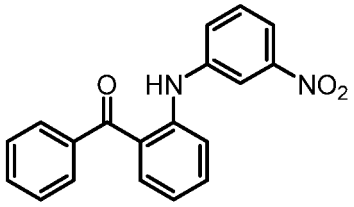
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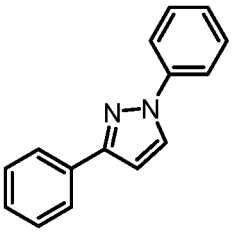
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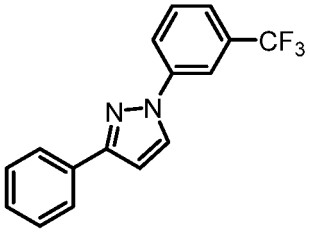
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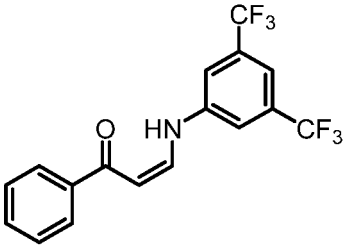
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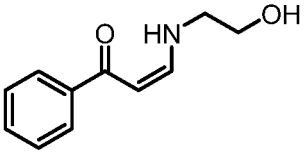
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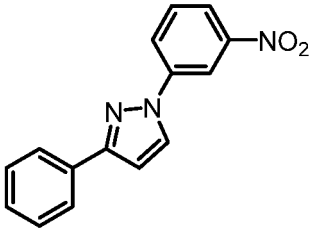
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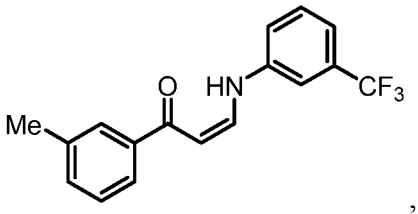
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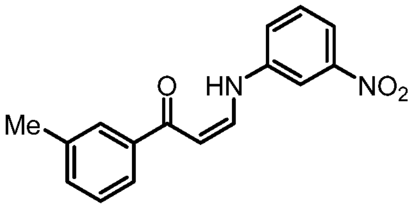
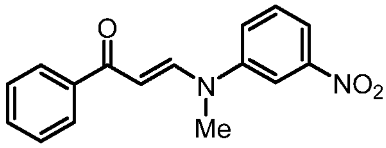
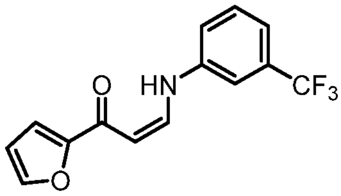
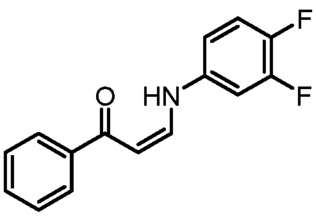
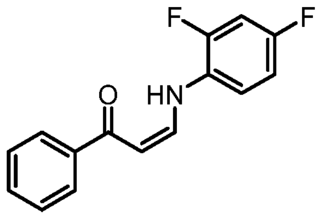
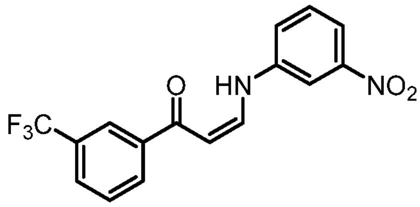
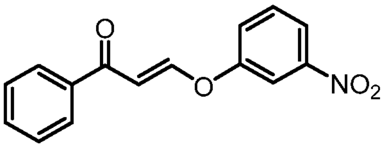
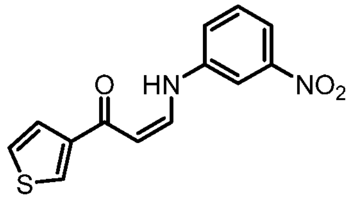
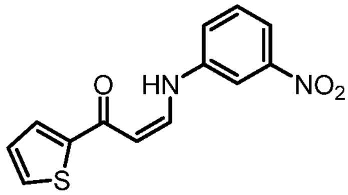
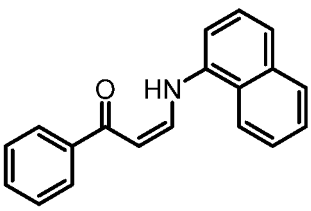
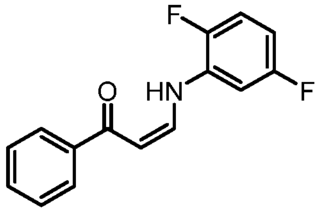
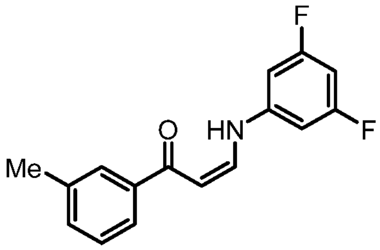
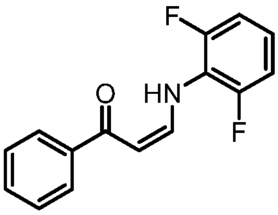
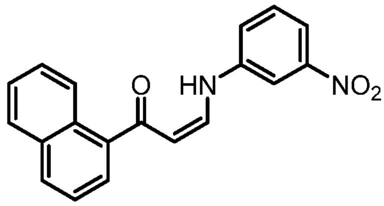
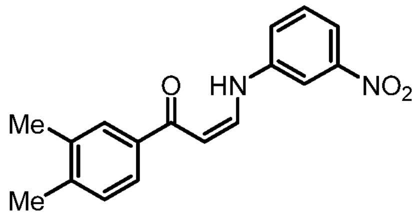
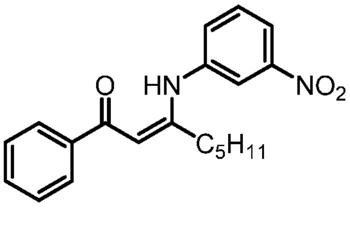
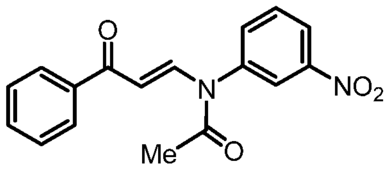
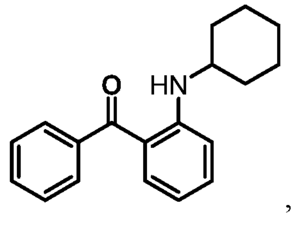
 ,  ,  ,

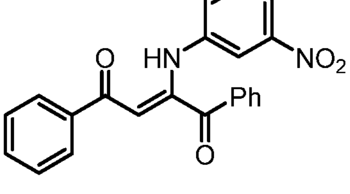
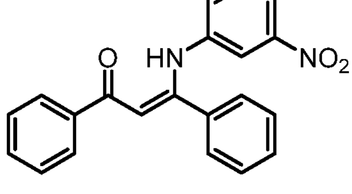
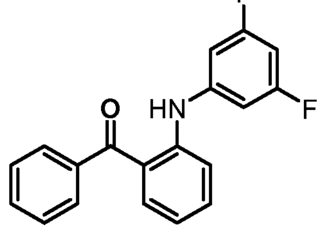
 ,  ,  ,

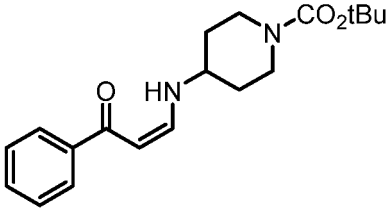
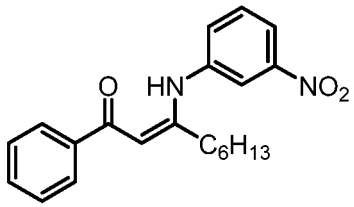
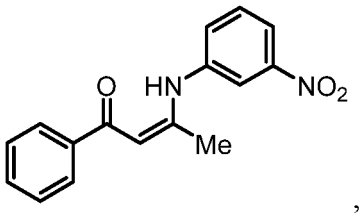
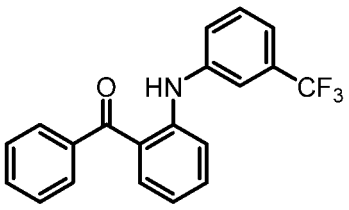
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

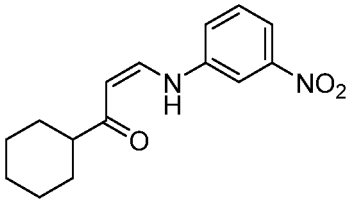
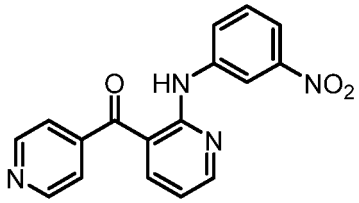
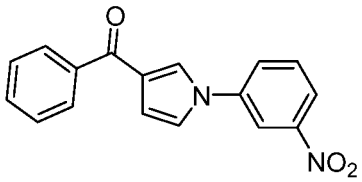
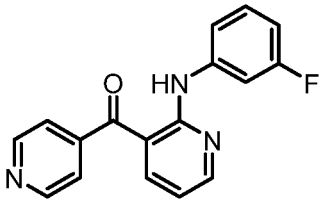
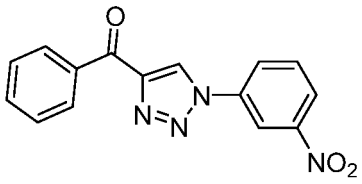
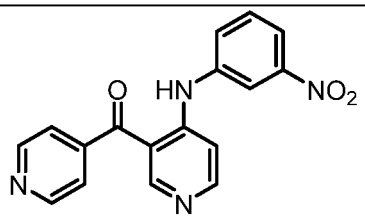
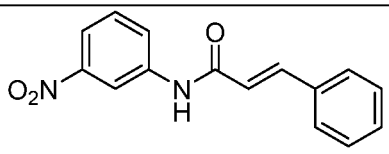
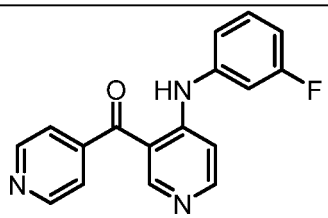
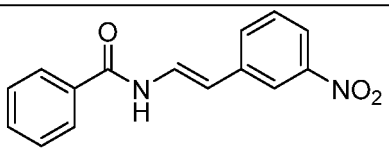
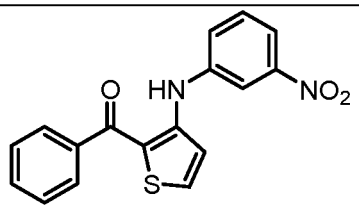
 ,  ,  ,

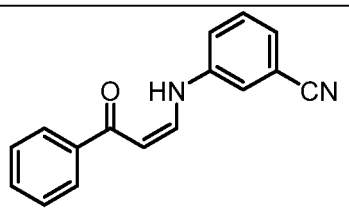
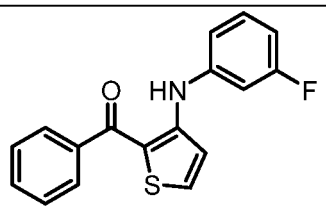
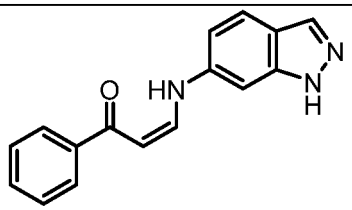
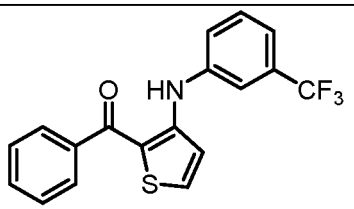
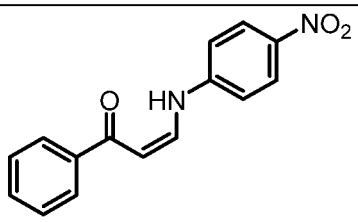
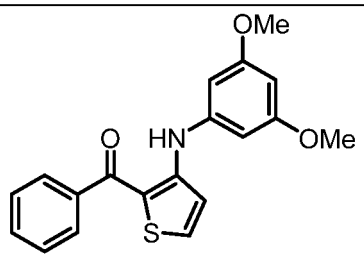
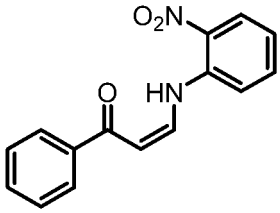
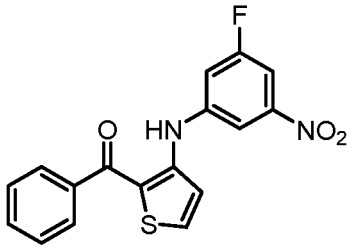
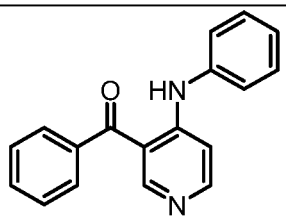
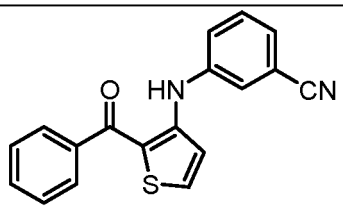
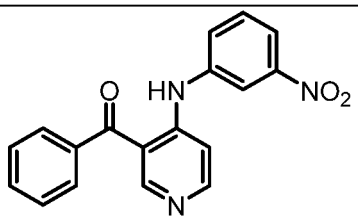
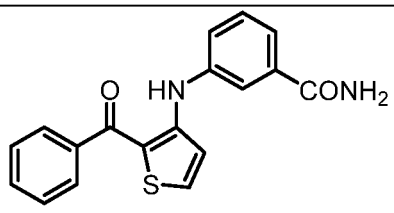
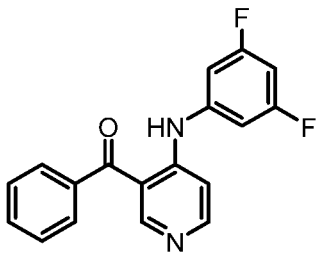
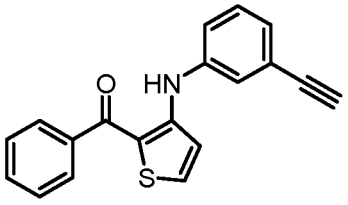





, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is selected from the compounds of Table 1 or a pharmaceutically acceptable salt thereof:

Table 1: Exemplary Compounds of the Disclosure

Number	Structure	Number	Structure
DJ041		**DJ079**	
DJ042		**DJ080**	
DJ051		**DJ081**	
DJ054		**DJ082**	
DJ063		**DJ083**	

Number	Structure	Number	Structure
DJ064		**DJ084**	
DJ065		**DJ085**	
DJ066		**DJ086**	
DJ067		**DJ087**	
DJ068		**DJ088**	
DJ069		**DJ089**	
DJ070		**DJ090**	

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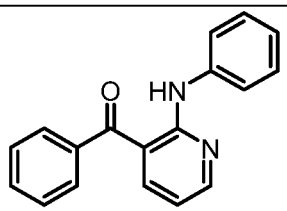
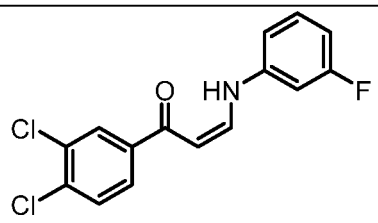
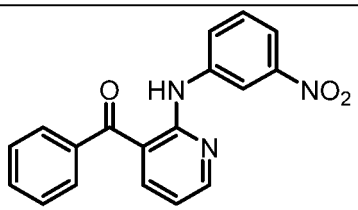
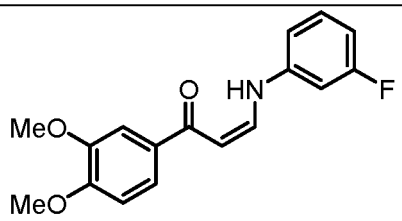
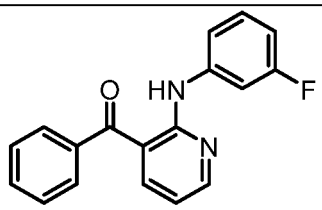
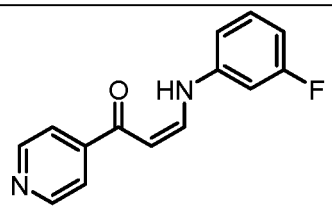
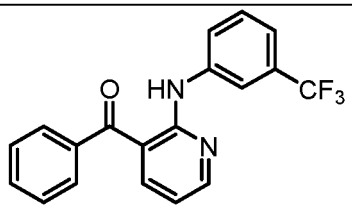
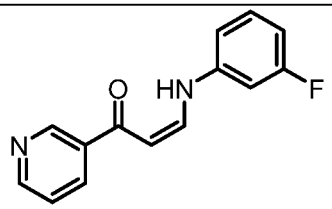
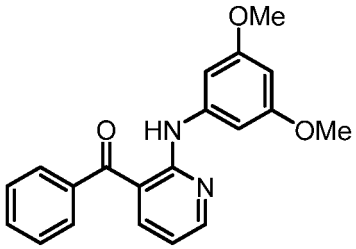
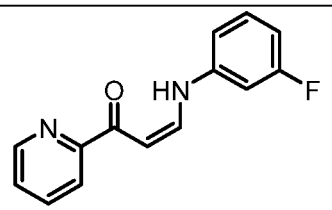
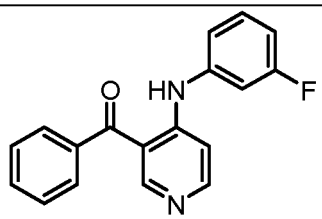
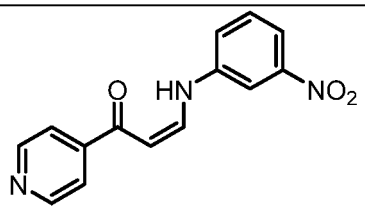
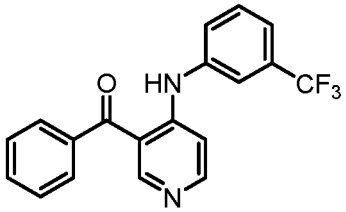
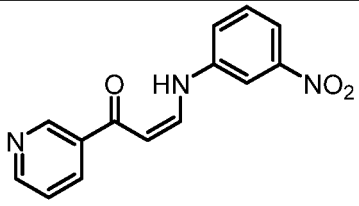
DJ071		**DJ091**	
DJ072		**DJ092**	
DJ073		**DJ093**	
DJ074		**DJ094**	
DJ075		**DJ095**	
DJ076		**DJ096**	
DJ077		**DJ097**	

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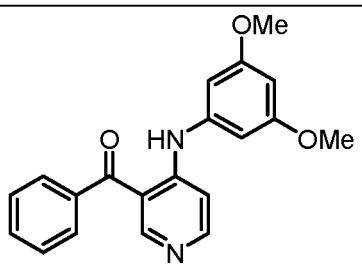
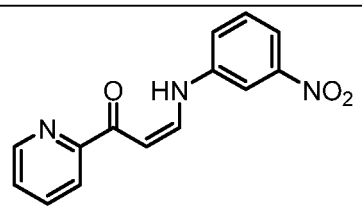
DJ078		**DJ098**	

In certain embodiments, the therapeutic preparation may be enriched to provide predominantly one diastereomer of a compound (e.g., of a compound selected from Table 1). A diastereomerically enriched mixture may comprise, for example, at least 60 mol percent of one diastereomer, or more preferably at least 75, 90, 95, or even 99 mol percent.

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

In certain embodiments, the therapeutic preparation may be enriched to provide predominantly one diastereomer of a compound (e.g., of a compound selected from Table 1). A diastereomerically enriched mixture may comprise, for example, at least 60 mol percent of one diastereomer, or more preferably at least 75, 90, 95, or even 99 mol percent.

In certain embodiments, the present invention provides a pharmaceutical preparation suitable for use in a human patient, comprising any of the compounds shown above (e.g., a compound of the invention, such as a compound selected from Table 1), and one or more pharmaceutically acceptable excipients. In certain embodiments, the pharmaceutical preparations may be for use in treating or preventing a condition or disease as described

herein. In certain embodiments, the pharmaceutical preparations have a low enough pyrogen activity to be suitable for use in a human patient.

Compounds of any of the above structures may be used in the manufacture of medicaments for the treatment of any diseases or conditions disclosed herein.

Definitions

Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, chemistry, cell and tissue culture, molecular biology, cell and cancer biology, neurobiology, neurochemistry, virology, immunology, microbiology, pharmacology, genetics and protein and nucleic acid chemistry, described herein, are those well-known and commonly used in the art.

The term “acyl” is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)-, preferably alkylC(O)-.

The term “acylamino” is art-recognized and refers to an amino group substituted with an acyl group and may be represented, for example, by the formula hydrocarbylC(O)NH-.

The term “acyloxy” is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)O-, preferably alkylC(O)O-.

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

The term “alkoxyalkyl” refers to an alkyl group substituted with an alkoxy group and may be represented by the general formula alkyl-O-alkyl.

The term “alkenyl”, as used herein, refers to an aliphatic group containing at least one double bond and is intended to include both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the alkenyl group. Such substituents may occur on one or more carbons that are included or not included in one or more double bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed below, except where stability is prohibitive. For example, substitution of alkenyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

An “alkyl” group or “alkane” is a straight chained or branched non-aromatic hydrocarbon which is completely saturated. Typically, a straight chained or branched alkyl group has from 1 to about 20 carbon atoms, preferably from 1 to about 10 unless otherwise

defined. Examples of straight chained and branched alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, pentyl, hexyl, pentyl and octyl. A C_1-C_6 straight chained or branched alkyl group is also referred to as a "lower alkyl" group.

Moreover, the term "alkyl" (or "lower alkyl") as used throughout the specification, examples, and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents, if not otherwise specified, can include, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), -CF_3, -CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxys, alkylthios, aminoalkyls, carbonyl-substituted alkyls, -CF_3, -CN, and the like.

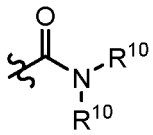
The term "C_{x-y}" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. For example, the term "C_{x-y}alkyl" refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from x to y carbons in the chain, including haloalkyl groups such as trifluoromethyl and 2,2,2-tirfluoroethyl, etc. C_0 alkyl indicates a hydrogen where the group is in a terminal position, a bond if internal. The terms "C_{2-y}alkenyl" and "C_{2-y}alkynyl" refer to substituted or unsubstituted unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

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

The term “alkylthio”, as used herein, refers to a thiol group substituted with an alkyl group and may be represented by the general formula alkylS-.

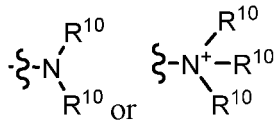
The term “alkynyl”, as used herein, refers to an aliphatic group containing at least one triple bond and is intended to include both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the alkynyl group. Such substituents may occur on one or more carbons that are included or not included in one or more triple bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed above, except where stability is prohibitive. For example, substitution of alkynyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

The term “amide”, as used herein, refers to a group



wherein each R^{10} independently represent a hydrogen or hydrocarbyl group, or two R^{10} are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

The terms “amine” and “amino” are art-recognized and refer to both unsubstituted and substituted amines and salts thereof, e.g., a moiety that can be represented by



wherein each R^{10} independently represents a hydrogen or a hydrocarbyl group, or two R^{10} are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

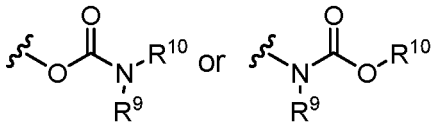
The term “aminoalkyl”, as used herein, refers to an alkyl group substituted with an amino group.

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

The term “aryl” as used herein include substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably the ring is a 5- to 7-membered ring, more preferably a 6-membered ring. The term “aryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are

common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like.

The term "carbamate" is art-recognized and refers to a group



wherein R^9 and R^{10} independently represent hydrogen or a hydrocarbyl group, such as an alkyl group, or R^9 and R^{10} taken together with the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

The terms "carbocycle", and "carbocyclic", as used herein, refers to a saturated or unsaturated ring in which each atom of the ring is carbon. The term carbocycle includes both aromatic carbocycles and non-aromatic carbocycles. Non-aromatic carbocycles include both cycloalkane rings, in which all carbon atoms are saturated, and cycloalkene rings, which contain at least one double bond. "Carbocycle" includes 5-7 membered monocyclic and 8-12 membered bicyclic rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated and aromatic rings. Carbocycle includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term "fused carbocycle" refers to a bicyclic carbocycle in which each of the rings shares two adjacent atoms with the other ring. Each ring of a fused carbocycle may be selected from saturated, unsaturated and aromatic rings. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, is included in the definition of carbocyclic. Exemplary "carbocycles" include cyclopentane, cyclohexane, bicyclo[2.2.1]heptane, 1,5-cyclooctadiene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]oct-3-ene, naphthalene and adamantane. Exemplary fused carbocycles include decalin, naphthalene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]octane, 4,5,6,7-tetrahydro-1H-indene and bicyclo[4.1.0]hept-3-ene. "Carbocycles" may be substituted at any one or more positions capable of bearing a hydrogen atom.

A "cycloalkyl" group is a cyclic hydrocarbon which is completely saturated. "Cycloalkyl" includes monocyclic and bicyclic rings. Typically, a monocyclic cycloalkyl group has from 3 to about 10 carbon atoms, more typically 3 to 8 carbon atoms unless

otherwise defined. The second ring of a bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings. Cycloalkyl includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term "fused cycloalkyl" refers to a bicyclic cycloalkyl in which each of the rings shares two adjacent atoms with the other ring. The second ring of a fused bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings. A "cycloalkenyl" group is a cyclic hydrocarbon containing one or more double bonds.

The term "carbocyclylalkyl", as used herein, refers to an alkyl group substituted with a carbocycle group.

The term "carbonate" is art-recognized and refers to a group $-OCO_2-R^{10}$, wherein R^{10} represents a hydrocarbyl group.

The term "carboxy", as used herein, refers to a group represented by the formula $-CO_2H$.

The term "ester", as used herein, refers to a group $-C(O)OR^{10}$ wherein R^{10} represents a hydrocarbyl group.

The term "ether", as used herein, refers to a hydrocarbyl group linked through an oxygen to another hydrocarbyl group. Accordingly, an ether substituent of a hydrocarbyl group may be hydrocarbyl-O-. Ethers may be either symmetrical or unsymmetrical. Examples of ethers include, but are not limited to, heterocycle-O-heterocycle and aryl-O-heterocycle. Ethers include "alkoxyalkyl" groups, which may be represented by the general formula alkyl-O-alkyl.

The terms "halo" and "halogen" as used herein means halogen and includes chloro, fluoro, bromo, and iodo.

The terms "hetaralkyl" and "heteroaralkyl", as used herein, refers to an alkyl group substituted with a hetaryl group.

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

The terms "heteroaryl" and "hetaryl" include substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heteroaryl" and "hetaryl" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is

heteroaromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like.

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

The terms "heterocyclyl", "heterocycle", and "heterocyclic" refer to substituted or unsubstituted non-aromatic ring structures, preferably 3- to 10-membered rings, more preferably 3- to 7-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heterocyclyl" and "heterocyclic" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heterocyclyl groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, lactones, lactams, and the like.

The term "heterocyclylalkyl", as used herein, refers to an alkyl group substituted with a heterocycle group.

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

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

The term "lower" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups where there are ten or fewer non-hydrogen atoms in the substituent, preferably six or fewer. A "lower alkyl", for example, refers to an alkyl group that contains ten or fewer carbon atoms, preferably six or fewer. In certain embodiments, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy substituents

defined herein are respectively lower acyl, lower acyloxy, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyalkyl and aralkyl (in which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyl substituent).

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

The term "silyl" refers to a silicon moiety with three hydrocarbyl moieties attached thereto.

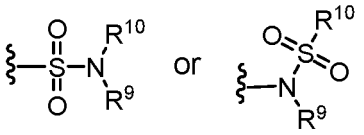
The term "silyloxy" refers to an oxygen moiety with a silyl attached thereto.

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 alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by

those skilled in the art that 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.

The term "sulfate" is art-recognized and refers to the group $-OSO_3H$, or a pharmaceutically acceptable salt thereof.

The term "sulfonamide" is art-recognized and refers to the group represented by the general formulae



wherein R^9 and R^{10} independently represents hydrogen or hydrocarbyl, such as alkyl, or R^9 and R^{10} taken together with the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

The term "sulfoxide" is art-recognized and refers to the group $-S(O)-R^{10}$, wherein R^{10} represents a hydrocarbyl.

The term "sulfonate" is art-recognized and refers to the group SO_3H, or a pharmaceutically acceptable salt thereof.

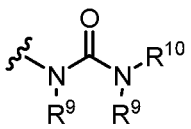
The term "sulfone" is art-recognized and refers to the group $-S(O)_2-R^{10}$, wherein R^{10} represents a hydrocarbyl.

The term "thioalkyl", as used herein, refers to an alkyl group substituted with a thiol group.

The term "thioester", as used herein, refers to a group $-C(O)SR^{10}$ or $-SC(O)R^{10}$ wherein R^{10} represents a hydrocarbyl.

The term "thioether", as used herein, is equivalent to an ether, wherein the oxygen is replaced with a sulfur.

The term "urea" is art-recognized and may be represented by the general formula



wherein R^9 and R^{10} independently represent hydrogen or a hydrocarbyl, such as alkyl, or either occurrence of R^9 taken together with R^{10} and the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

"Protecting group" refers to a group of atoms that, when attached to a reactive functional group in a molecule, mask, reduce or prevent the reactivity of the functional group. Typically, a protecting group may be selectively removed as desired during the course of a synthesis. Examples of protecting groups can be found in Greene and Wuts, *Protective Groups in Organic Chemistry,* 3rd Ed., 1999, John Wiley & Sons, NY and Harrison et al., *Compendium of Synthetic Organic Methods*, Vols. 1-8, 1971-1996, John Wiley & Sons, NY. Representative nitrogen protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), tert-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("TES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("FMOC"), nitro-veratryloxycarbonyl ("NVOC") and the like. Representative hydroxylprotecting groups include, but are not limited to, those where the hydroxyl group is either acylated (esterified) or alkylated such as benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers (e.g., TMS or TIPS groups), glycol ethers, such as ethylene glycol and propylene glycol derivatives and allyl ethers.

As used herein, a therapeutic that "prevents" a disorder or condition refers to a compound that, in a statistical sample, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control sample, or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated control sample. For example, a compound that prevents epilepsy may reduce the frequency of seizures and/or reduce the severity of seizures.

The term "treating" includes prophylactic and/or therapeutic treatments. 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 phrases "conjoint administration" and "administered conjointly" refer to any form of administration of two or more different therapeutic compounds such that the second compound is administered while the previously administered therapeutic compound is still effective in the body (*e.g.*, the two compounds are simultaneously effective in the patient,

which may include synergistic effects of the two compounds). For example, the different therapeutic compounds can be administered either in the same formulation or in a separate formulation, either concomitantly or sequentially. In certain embodiments, the different therapeutic compounds can be administered within one hour, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, or a week of one another. Thus, an individual who receives such treatment can benefit from a combined effect of different therapeutic compounds.

The term "prodrug" is intended to encompass compounds which, under physiologic conditions, are converted into the therapeutically active agents of the present invention (e.g., a compound selected from Table 1). A common method for making a prodrug is to include one or more selected moieties which are hydrolyzed under physiologic conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal. For example, esters or carbonates (e.g., esters or carbonates of alcohols or carboxylic acids) are preferred prodrugs of the present invention. In certain embodiments, some or all of the compounds selected from Table 1 in a formulation represented above can be replaced with the corresponding suitable prodrug, e.g., wherein a hydroxyl in the parent compound is presented as an ester or a carbonate or carboxylic acid present in the parent compound is presented as an ester.

The term "myelosuppressive" refers to therapies, treatments, or other actions taken on a subject that have the effect of decreasing the production of leukocytes, erythrocytes, and/or thrombocytes in that subject. The term "myelosuppressed" refers to a subject whose production of leukocytes, erythrocytes, and/or thrombocytes has been decreased below the normal level in that subject.

The terms "agonist", "antagonist", and "inhibitor" are used herein to denote a chemical compound (such as an organic or inorganic compound, a mixture of chemical compounds), a biological macromolecule (such as a nucleic acid, an antibody, including parts thereof as well as humanized, chimeric and human antibodies and monoclonal antibodies, a protein or portion thereof, *e.g.*, a peptide, a lipid, a carbohydrate), or an extract made from biological materials such as bacteria, plants, fungi, or animal cells or tissues. They include, for example, agents whose structure is known, and those whose structure is not known. An agonist refers to an agent that increases the activity of a protein. For example, a Rac1 agonist may increase the amount of Rac1-GTP in a cell. The terms "antagonist" and "inhibitor" are used interchangeably herein. An inhibitor may, for example, reduce the phosphatase activity of PTPσ. The inhibitor may inhibit a target such as PTPσ by reducing the amount of

translation of a PTPσ mRNA, e.g., the inhibitor may be an interfering nucleic acid. Similarly, an inhibitor may reduce the phosphatase activity of PTPσ by, for example, binding to a conformation of PTPσ that has reduced phosphatase activity.

Populations of cells

In some aspects, the invention relates to a population of mammalian cells comprising hematopoietic stem cells ("HSCs"), wherein the population is substantially free of cells that express protein tyrosine phosphatase sigma ("PTPσ"). The population may further comprise an inhibitor of the PTPσ pathway.

The term "substantially free of cells that express", such as in a "population of cells that is substantially free of cells that express PTPσ", may refer to compositions in which cells that express a high level of the molecule have been substantially removed and cells that express a low level of the molecule remain. The skilled artisan will recognize that a population of cells that is substantially free of cells that express PTPσ may comprise cells that express a detectable amount of PTPσ. Further, the skilled artisan will recognize that the threshold for distinguishing cells that express a high level of a molecule from cells that express a low level of a molecule may vary according to the overall context in which the distinction is being made. When two discrete populations of cell cannot be identified, the term "substantially free of cells that express [a molecule]" refers to the selection of cells that express low levels of the molecule. For example, Figure 1D shows various flow cytometry gates that do not distinguish two discrete populations of cells. In this case, the term substantially free of cells that express PTPσ refers to cells that are gated as low-expressing cells. A population of cells that is substantially free of cells that express PTPσ may therefore be obtained, for example, by collecting the gated cells. The placement of the gate may be arbitrary. Thus, the population of cells that is substantially free of cells that express PTPσ may be generated, for example, by gating a population of cells that comprises less than 0.000001%, 0.00001%, 0.0001%, 0.001%, 0.01%, 0.1%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, or 25% of the cells in a sample, wherein the gated cells were determined to express the least amount PTPσ. Similarly, the population of cells that is substantially free of cells that express PTPσ may be generated, for example, by removing at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, or 70% of the cells that express the most PTPσ from the sample.

Those with skill in the art will know that the gate may be adjusted based on other gates, for example, based on gates that select for other characteristics of HSCs.

In some embodiments, the invention relates to a population of mammalian cells comprising HSCs, wherein the population is enriched in PTPσ $^-$ cells. The population may further comprise an inhibitor of the PTPσ pathway.

The term "enriched" refers to a population that has been processed to either collect cells that possess the enriched characteristic or to remove cells that do not possess the characteristic. The skilled artisan will recognize that a characteristic such as PTPσ $^-$ or PTPσ$^+$ may be arbitrarily defined. As described herein, PTPσ$^+$ cells express more PTPσ on average than PTPσ $^-$ cells, such as during the sorting of a population of cells. A population is enriched in PTPσ $^-$ cells if the population is obtained by preferentially collecting cells that express low levels of PTPσ relative to cells that express higher levels of PTPσ, for example by FACS or MACS. Similarly, a population is enriched in PTPσ $^-$ cells if the population is obtained by preferentially removing cells that express high levels of PTPσ relative to cells that express lower levels of PTPσ.

In some aspects, the invention relates to a population of mammalian cells comprising HSCs and an inhibitor of the PTPσ pathway.

In some embodiments, the invention relates to a cell population, wherein the population is enriched in CD34$^+$, CD38$^-$, CD45RA$^-$, CD90$^+$, lin$^-$, Rho^{lo}, CD49f $^{+-}$, and/or CD33$^-$ cells. The population may be enriched, for example, in CD34$^+$CD38$^-$CD45RA$^-$Lin$^-$ cells or CD34$^+$CD38$^-$CD45RA$^-$Lin$^-$PTPσ$^-$ cells. Similarly, in some embodiments, the invention relates to a cell population, wherein the population is substantially free of CD34$^-$, CD38$^+$, CD45RA$^+$, CD90$^-$, lin$^+$, Rho^{hi}, CD49f$^-$, and/or CD33$^+$ cells. The HSCs of the invention may be, for example, mice or human HSCs. In some embodiments, the HSCs are cord blood or bone marrow HSCs.

Uses of the Compounds

In certain embodiments, the compounds of the present invention can inhibit PTPσ. In certain embodiments, administration of the compounds of the present invention can cause the rapid recovery of HSCs, hematopoietic reconstitution and improved survival. In certain embodiments, administration of the compounds of the present invention promotes the self-renewal or regeneration of hematopoietic stem cells in vivo in mammals, such as humans or mice. In certain embodiments, administration of the compounds of the present invention

promotes the self-renewal or regeneration of hematopoietic stem cells in patients that are myelosuppressed. In certain embodiments, administration of the compounds of the present invention promote the self-renewal or regeneration of hematopoietic stem cells in patients receiving myelosuppressive therapy, such as chemo- or radiotherapy, patients undergoing hematopoietic cell transplantation and patients with aplastic anemia and degenerative hematologic diseases.

In certain embodiments, the present invention provides methods of inhibiting PTPσ using a compound or composition of the present invention. In certain embodiments, the present invention provides methods of promoting rapid recovery of HSCs, hematopoietic reconstitution and improved survival. In certain embodiments, the present invention provides methods of promoting the self-renewal or regeneration of hematopoietic stem cells in vivo in mammals, such as humans or mice, by administering a therapeutically effective amount of compound or composition of the present invention. In certain embodiments, the present invention provides methods of promoting self-renewal or regeneration of hematopoietic stem cells in patients that are myelosuppressed. In certain embodiments, the present invention provides methods of promoting the self-renewal or regeneration of hematopoietic stem cells in patients receiving myelosuppressive therapy, such as chemo- or radiotherapy, patients undergoing hematopoietic cell transplantation and patients with aplastic anemia and degenerative hematologic diseases.

In some embodiments, the invention relates to methods for promoting hematopoietic reconstitution in a subject in need thereof, the method comprising administering to the subject an inhibitor of a PTPσ pathway. The subject may have received an implant comprising hematopoietic cells, such as a transplant comprising hematopoietic cells. For example, the subject may require an allogeneic bone marrow transplantation. In some embodiments, the implant is a cord blood or bone marrow implant. In some embodiments, the method further comprises administering hematopoietic cells to the patient, e.g., before the subject receives the implant, simultaneously with the implant, and/or after the subject receives the implant.

In some embodiments, the subject has compromised hematopoietic function. For example, the compounds of the present invention may be administered to accelerate the subject's own hematopoietic reconstitution process.

In some embodiments, the compounds of the present invention are administered systemically. The inhibitor may accelerate hematologic recovery.

The subject may need hematopoietic reconstitution to counteract the effects of myelosuppressive therapy, e.g., because the subject has received myelosuppressive therapy. In some embodiments, the myelosuppressive therapy is chemotherapy. In some embodiments, the subject is a chemotherapy patient and the inhibitor is administered prior to administering the chemotherapy. In some embodiments, the subject is a chemotherapy patient and the inhibitor is administered concurrently with the chemotherapy. In some embodiments, the subject is a chemotherapy patient and the inhibitor is administered after administering the chemotherapy.

In other embodiments, the myelosuppressive therapy is radiation. In some embodiments, the inhibitor is administered prior to administering a radiation treatment. In some embodiments, the inhibitor is administered concurrently with radiation treatment. In some embodiments, the inhibitor is administered after administering radiation treatment.

In some embodiments, the subject has been exposed to radiation.

In some embodiments, the subject is a mammal. For example, the subject may be a mouse or a human.

Pharmaceutical Compositions

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

can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as an eye drop.

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

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

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. 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.

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

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

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

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

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

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

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

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

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

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

formulations of the pharmaceutical compositions for rectal, vaginal, or urethral administration may be presented as a suppository, which may be prepared by mixing one or

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

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

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

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

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

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

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

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

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention. Exemplary ophthalmic

formulations are described in U.S. Publication Nos. 2005/0080056, 2005/0059744, 2005/0031697 and 2005/004074 and U.S. Patent No. 6,583,124, the contents of which are incorporated herein by reference. If desired, liquid ophthalmic formulations have properties similar to that of lacrimal fluids, aqueous humor or vitreous humor or are compatible with such fluids. A preferred route of administration is local administration (*e.g.*, topical administration, such as eye drops, or administration via an implant).

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion. Pharmaceutical compositions suitable for parenteral administration comprise one or more active compounds in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

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

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

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

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

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

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

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

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

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the therapeutically effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the pharmaceutical composition or compound at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. By "therapeutically effective amount" is meant the concentration of a compound that is sufficient to elicit the desired therapeutic effect. It is generally understood that the effective amount of the compound will vary according to the weight, sex, age, and medical history of the subject. Other factors which influence the effective amount may include, but are not limited to, the severity of the patient's condition, the disorder being treated, the stability of the compound, and, if desired, another type of therapeutic agent being administered with the compound of the invention. A larger total dose can be delivered by multiple administrations of the agent. Methods to determine efficacy and dosage are known to those skilled in the art (Isselbacher *et al.* (1996) Harrison's Principles of Internal Medicine 13 ed., 1814-1882, herein incorporated by reference).

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

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

The patient receiving this treatment is any animal in need, including primates, in particular humans, and other mammals such as equines, cattle, swine and sheep; and poultry and pets in general.

In certain embodiments, compounds of the invention may be used alone or conjointly administered with another type of therapeutic agent.

This invention includes the use of pharmaceutically acceptable salts of compounds of the invention in the compositions and methods of the present invention. In certain embodiments, contemplated salts of the invention include, but are not limited to, alkyl, dialkyl, trialkyl or tetra-alkyl ammonium salts. In certain embodiments, contemplated salts

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

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

The term "pharmaceutically acceptable basic addition salt" as used herein means any non-toxic organic or inorganic base addition salt of any acid compounds. Illustrative inorganic bases which form suitable salts include lithium, sodium, potassium, calcium, magnesium, or barium hydroxide. Illustrative organic bases which form suitable salts include aliphatic, alicyclic, or aromatic organic amines such as methylamine, trimethylamine and picoline or ammonia. The selection of the appropriate salt will be known to a person skilled in the art.

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

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

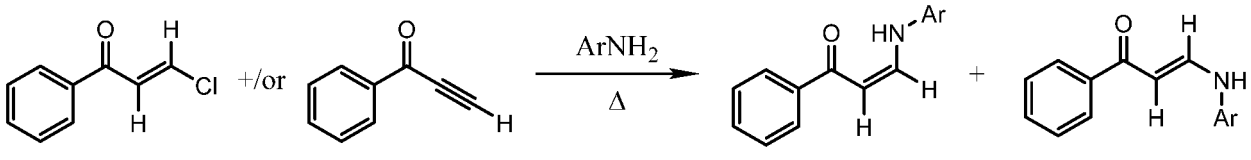
The invention now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of

certain aspects and embodiments of the present invention, and are not intended to limit the invention.

EXAMPLES

Example 1: Synthetic Protocols

DJ001 (also identified as UCLA 5483071) and its analogues were prepared by either of two simple methods. Heating the readily available aryl 2-chloroenone **1001** or the aryl enynone **1002** with any of several aryl amines gave the desired aryl 2-arylamino enones:



1001 1002 1003 (Z) 1004 (E)

Scheme 1

Procedures for the synthesis of ketones 1001 and 1002

The acetylenic ketones were synthesized according to a literature procedure (*Helv. Chim. Acta* **1979**, *62*, 852; *Org. Lett.* **2012**, *14 (22)*, 5756; *Org. Lett.* **2011**, *13 (17)*, 4680; *Chem. Eur. J.* **2014**, *20 (35)*, 11101; *Synth. Commun.* **2010**, *40*, 1280).

The β-E-chlorovinylketones were synthesized according to a literature procedure (*Chim. Acta Turcica* **1990**, *18*, 125 and *Gazz. Chim. Ital.* **1947**, *77*, 549).

General procedure A for the synthesis of compounds DJ (e.g., DJ001-DJ009, DJ011, DJ013-DJ016)

The aniline (1.2-1.5 equiv.) dissolved in pyridine was added to the chlorovinylketone **1001** and the reaction mixture was stirred at 65°C for 2 hours. The reaction mixture was concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (Hexanes/EtOAc).

DJ015 was synthesized according to procedure A followed by deprotection according to the literature (*Org. Lett.* **2015**, *17 (10)*, 2298).

Synthesis of *(Z)*-3-((3-nitrophenyl)amino)-1-phenylprop-2-en-1-one (DJ001)

A mixture of 1-phenylprop-2-yn-1-one* (0.303 g, 2.3 mmol), 3-nitroaniline (0.427 g, 3.0 mmol) and copper (I) iodide (0.078 g, 0.4 mmol) in DMF (6 mL) and water (60 μL) was stirred at 85 °C for 16 h. After 16 h, the reaction mixture was allowed to cool down to 21°C and was diluted with water (50 mL) and extracted with ethyl acetate (3 X 50 mL). The combined organic layer was washed with NH_4Cl/NH_3 (1:1 v/v, 3 X 20 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue

was purified by column chromatography (n-hexane/ethyl acetate = 20:1) to obtain DJ001 (140 mg, 0.52 mmol, 23%) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.26 (d, NH, J = 11.6 Hz), 7.96-7.91 (m, 3H), 7.90 (ddd, 1H, J = 8.0, 2.0, 0.8 Hz), 7.56-7.46 (m, 5H), 7.37 (ddd, 1H, J = 8.0, 2.4, 0.8 Hz), 6.16 (d, 1H, J = 8.0 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 149.4, 143.4, 141.6, 138.6, 132.2, 130.6, 128.6, 127.5, 122.3, 117.8, 110.0, 95.7. *1-Phenylprop-2-yn-1-one was prepared by oxidation of 1-phenylprop-2-yn-1-ol in a two-step procedure from benzaldehyde and trimethylsilylacetylene.

Synthesis of (Z)-3-((3,5-difluorophenyl)amino)-1-phenylprop-2-en-1-one (DJ009)

DJ009 (117.9 mg, 0.455 mmol, 59 %, yellow powder) was prepared from 1-phenylprop-2-yn-1-one (100 mg, 0.768 mmol), 3, 5-difluoroaniline (108.5 mg, 0.840 mmol) and copper (I) iodide (29.3 mg, 0.154 mmol) in DMF (1 mL) using same procedure described for DJ001. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.0 (d, J = 11.7 Hz, 1H), 7.94 (dt, J = 6.9, 1.6 Hz, 2H), 7.55–7.50 (m, 1), 7.48–7.45 (m, 2H), 7.38 (dd, J = 11.7, 8.2 Hz, 1H), 6.64–6.57 (m, 2H), 6.54–6.47 (m, 1H), 6.09 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.7, 164.0 (dd, J = 249, 15 Hz), 143.5, 142.8 (t, J = 13 Hz), 138.7, 132.1, 128.6, 127.5, 99.3 (dd, J = 20, 8 Hz), 98.5 (t, J = 26 Hz), 95.3; ^{19}F NMR (CDCl3, 376 MHz) δ (ppm): -107.9.

General procedure B for the synthesis of compounds DJ starting from the acetylenic ketones (e.g., DJ012, DJ030)

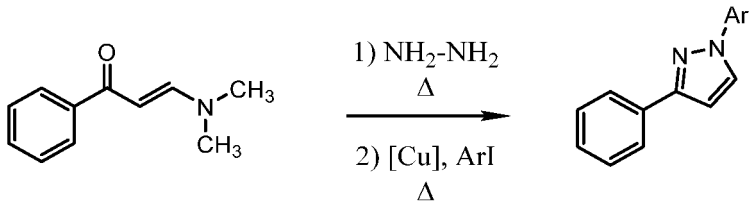
A mixture of the acetylenic ketone **1002**, the aniline (1.5 equiv.), and copper iodide (20-40 mol%) in DMF/H_2O was stirred under argon at 85°C for 20 hours. After cooling down to room temperature, the reaction mixture was diluted with H_2O and extracted with EtOAc. The gathered organic phases were washed with NH_4Cl/NH_3 (v/v : 1/1), brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (Hexanes/EtOAc).

General procedure C for the synthesis of compounds DJ starting from the acetylenic ketones (e.g., DJ017-DJ026, DJ031)

The amine (1.5 equiv.) was added to a solution of the acetylenic ketone **1002** in PhMe and the reaction mixture was stirred at room temperature or 80°C (DJ020) overnight. The reaction mixture was concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (Hexanes/EtOAc).

DJ031 was synthesized according to procedure C followed by deprotection according to the literature (*Org. Lett.* **2015**, *17 (10)*, 2298).

General procedure D for the synthesis of compounds DJ starting from acetophenone (e.g., DJ028, DJ029, DJ032)

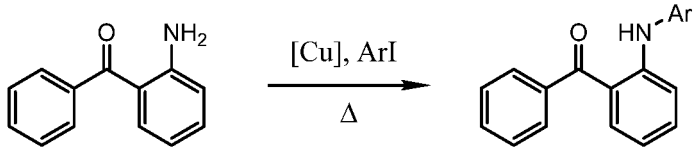


A mixture of acetophenone and dimethylformamide dimethylacetal (2.0 equiv.) was refluxed overnight. The reaction mixture was allowed to cool down to room temperature and was concentrated under reduced pressure. The remaining residue was suspended in hexanes and filtered. The filter cake was washed with plenty of hexanes. (E)- 3-(dimethylamino)-1-phenylprop-2-en-1-one was obtained.

Hydrazine-monohydrate (5.0 equiv.) was added to a solution of (*E*)- 3-(dimethylamino)-1-phenylprop-2-en-1-one in EtOH and the resulting reaction mixture was refluxed for 2 hours. The reaction was then allowed to cool down to room temperature and was concentrated under reduced pressure. The remaining residue was diluted with H_2O and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was considered pure enough by ^{1}H-NMR (>95%) to be used without further purification.

A mixture of phenylpyrazole, iodoarene (1.0 equiv.), copper iodide (20 mol%), trans-1,2-diaminocyclohexane (25 mol%), potassium carbonate (2.0 equiv.) in dioxane was stirred at 100°C under argon for 16 hours. After cooling down to room temperature, the reaction mixture was diluted with H_2O and extracted with EtOAC. The gathered organic phases were washed with NH_4Cl/NH_3 (v/v : 1/1), brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (Hexanes/EtOAc).

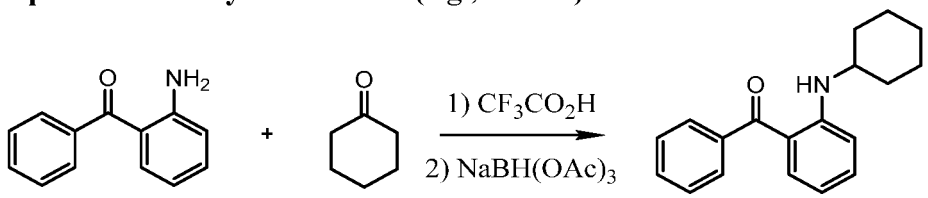
General procedure E for the synthesis of compounds DJ starting from 2-aminobenzophenone and iodoarene (e.g., DJ027, DJ058, and DJ062)



A mixture of 2-aminobenzophenone, iodoarene (1.5 equiv.), copper (1.5 equiv.), 18-Crown-6 (15 mol%), potassium carbonate (1.5 equiv.) in DMF was stirred under argon at 120°C for 24 hours. After cooling down to room temperature, the reaction mixture was diluted with H_2O and extracted with EtOAc. The gathered organic phases were washed with NH_4Cl/NH_3 (v/v : 1/1), brine, dried over $MgSO_4$, filtered and concentrated under reduced

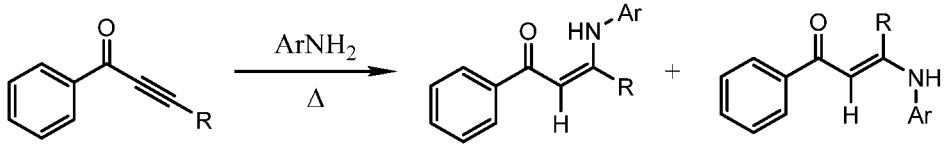
pressure. The remaining residue was purified by column chromatography on silica gel (Hexanes/EtOAc).

General procedure F for the synthesis of compounds DJ starting from 2-aminobenzophenone and cycloalkanone (e.g., DJ055)



Trifluoroacetic acid (1.5 equiv.) was added to a solution of 2-aminobenzophenone and cyclohexanone (1.1 equiv.) in 1,2-dichloroethane (2 mL) at 0°C and stirred at the same temperature for one hour. Sodium triacetoxyborohydride (2.2 equiv.) was then added in one portion and the reaction mixture was allowed to warm up to room temperature and was stirred overnight. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (100 mL), extracted with CH_2Cl_2 (3 x 50 mL). The gathered organic phases were washed brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (Hexanes/EtOAc).

General procedure G for the synthesis of compounds DJ starting from 1005 and $ArNH_2$ (e.g., DJ052, DJ060, DJ057)

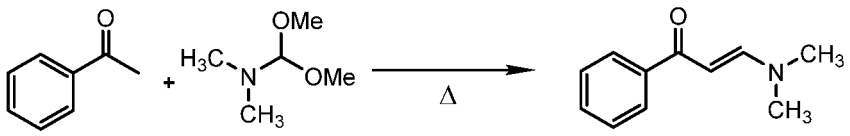


1005 1006 (Z) 1007 (E)

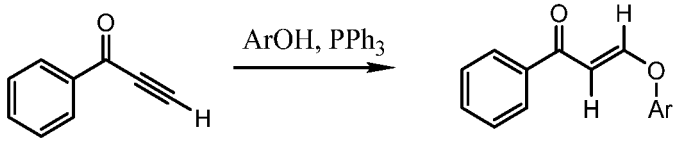
A solution of **1005** and aniline (2.5 equiv.) was refluxed for 72 hours, while being monitored by thin layer chromatography. The reaction mixture was allowed to cool down to room temperature and was concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (Hexanes/EtOAc).

Other Synthetic Procedures

DJ010 was prepared by heating the readily available acetophenone and dimethylformamide dimethylacetal (DMF-DMA).

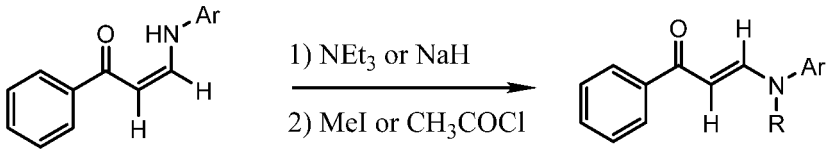


DJ040 was prepared by reacting the readily available aryl enynone **1002** with a phenol in the presence of triphenylphosphine at room temperature.



1002

DJ035 and DJ053 were prepared by reacting DJ001 with triethylamine or NaH, followed by addition of iodomethane or acetyl chloride.

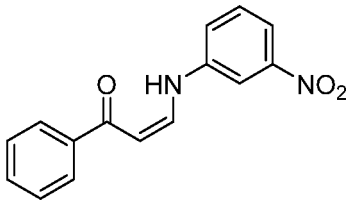


The compounds DJ001-DJ019, and other compounds capable of forming internal hydrogen bonds, were formed as the Z-isomer shown. However, when the compounds were dissolved in solvents such as DMSO, the pure Z-isomer was converted quickly to a roughly 1:1 mixture of the Z- and E-isomers.

DJ041, 042, 051, 054 and 063 may be prepared by methods analogous to those described herein.

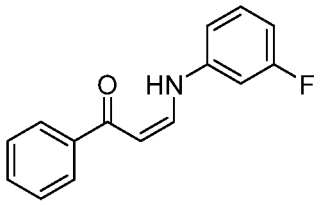
NMR Data

The identity of compounds synthesized according to the methods described above was confirmed by NMR spectroscopy. Exemplary spectroscopic data is listed below.



DJ001

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.25 (d, J = 11.3 Hz, 1H), 7.98–7.93 (m, 3H), 7.91 (ddd, J = 8.1, 2.1, 0.9 Hz, 1H), 7.56–7.45 (m, 5H), 7.37 (ddd, J = 8.2, 2.4, 0.9 Hz, 1H), 6.16 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.8, 149.4, 143.4, 141.7, 138.6, 132.2, 130.6, 128.6, 127.5, 122.3, 117.8, 110.0, 95.7.

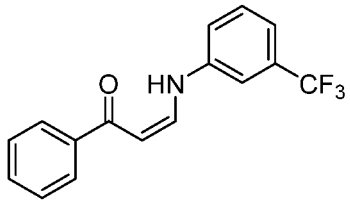


DJ002

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.11 (d, J = 10.7 Hz, 1H), 7.94 (dt, J = 8.5, 1.2 Hz, 2H), 7.53–7.43 (m, 4H), 7.32–7.26 (m, 1H), 6.87 (dd, J = 8.1, 1.5 Hz, 1H), 6.82 (dt, J = 10.4, 2.2 Hz, 1H), 6.77 (tdd, J = 8.3, 2.4, 0.1 Hz, 1H), 6.02 (d, J = 7.7 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.4, 163.8 (d, J = 246 Hz), 144.2, 142.0 (d, J = 10.2 Hz), 138.9, 131.8, 131.1 (d, J = 5.7 Hz), 128.5, 127.4, 112.1 (d, J = 2.8 Hz), 110.2 (d, J = 21.3 Hz), 103.3 (d, J = 25.4 Hz), 94.5.

^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm): -110.

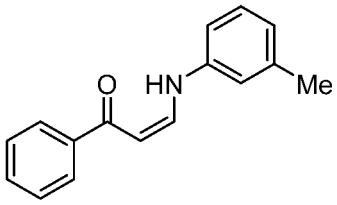


DJ003

^{1}H NMR (CDCl3, 400 MHz) δ (ppm): 12.33 (d, J = 12.5 Hz, 1H), 7.95 (dt, J = 9.7, 0.2 Hz, 2H), 7.54–7.44 (m, 5H), 7.34–7.30 (m, 2H), 7.25 (dd, J = 7.9, 1.9 Hz, 1H), 6.06 (d, J = 7.8 Hz, 1H).

^{13}C NMR (CDCl3, 100 MHz) δ (ppm): 191.5, 144.0, 140.9, 138.9, 132.3 (q, J = 33 Hz), 131.9, 130.4, 128.5, 127.4, 123.8 (q, J = 272 Hz), 119.9 (q, J = 3.7 Hz), 119.5, 112.6 (q, J = 3.8 Hz), 94.9.

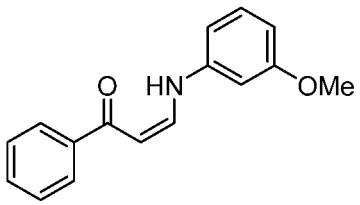
^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm): -62.9.



DJ004

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.1 (d, J = 11.6 Hz, 1H), 7.94 (dt, J = 6.7, 1.4 Hz, 2H), 7.55–7.43 (m, 4H), 7.23 (t, J = 7.8 Hz, 1H), 6.93–6.89 (m, 3H), 6.01 (d, J = 7.9 Hz, 1H), 2.36 (s, 3H).

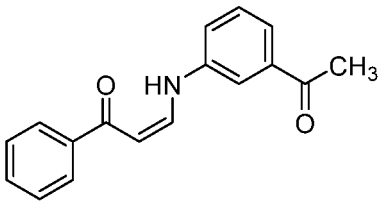
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.9, 145.1, 140.2, 139.8, 139.3, 131.5, 129.6, 128.4, 127.3, 124.6, 117.2, 113.5, 93.6, 21.5.



DJ005

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.1 (d, J = 11.6 Hz, 1H), 7.94 (dt, J = 9.6, 1.2 Hz, 2H), 7.53–7.43 (m, 4H), 7.26–7.23 (m, 1H), 6.71 (dt, J = 1.3, 0.2 Hz, 1H), 6.64–6.62 (m, 2H), 6.51 (d, J = 6.5 Hz, 1H), 3.82 (s, 3H).

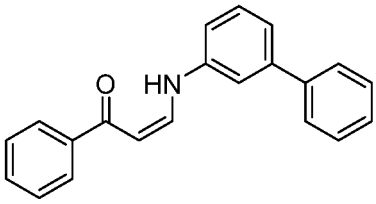
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.0, 160.9, 144.9, 144.5, 139.2, 131.6, 130.6, 128.5, 127.3, 109.2, 108.7, 102.4, 93.8, 55.4.



DJ006

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.2 (d, J = 12.1 Hz, 1H), 7.95 (dt, J = 6.9, 1.2 Hz, 2H), 7.73 (t, J = 2.1 Hz, 1H), 7.64 (dt, J = 7.8, 1.2 Hz, 1H), 7.58 (dd, J = 12.1, 7.9 Hz, 1H), 7.54–7.50 (m, 1H), 7.47–7.43 (m, 3H), 7.28 (tdd, J = 8.5, 2.5, 0.8 Hz, 1H), 6.09 (d, J = 7.9 Hz, 1H), 2.62 (s, 3H).

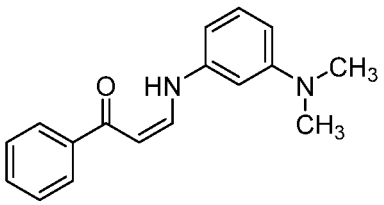
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 197.5, 191.4, 144.4, 140.8, 138.6, 138.5, 131.8, 130.0, 128.5, 127.4, 123.5, 121.0, 115.0, 94.6, 26.7.



DJ007

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.2 (d, J = 12.4 Hz, 1H), 7.95 (dt, J = 6.7, 1.3 Hz, 2H), 7.62–7.58 (m, 3H), 7.53–7.44 (m, 5H), 7.42–7.35 (m, 2H), 7.32–7.29 (m, 2H), 7.10 (ddd, J = 8.1, 1.7, 1.5 Hz, 1H), 6.06 (d, J = 8.1 Hz, 1H).

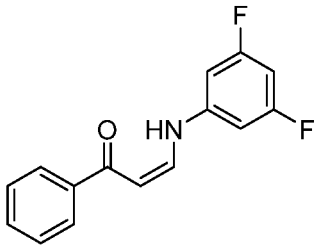
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.9, 144.8, 143.0, 140.7, 140.5, 139.2, 131.6, 130.1, 128.9, 128.5, 127.8, 127.4, 127.2, 122.6, 115.3, 115.1, 93.9.



DJ008

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.1 (d, J = 12.4 Hz, 1H), 7.94 (dt, J = 6.5, 1.3 Hz, 2H), 7.55 (dd, J = 12.4, 7.9 Hz, 1H), 7.51–7.42 (m, 3H), 7.19 (t, J = 8.2 Hz, 1H), 6.51–6.45 (m, 2H), 6.39 (t, J = 2.3 Hz, 1H), 6.00 (d, J = 7.9 Hz, 1H), 2.97 (s, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.8, 151.7, 145.4, 141.1, 139.4, 131.4, 130.2, 128.4, 127.3, 108.2, 103.8, 101.0, 93.2, 40.5.

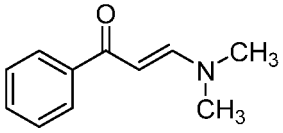


DJ009

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.0 (d, J = 11.7 Hz, 1H), 7.94 (dt, J = 6.9, 1.6 Hz, 2H), 7.55–7.50 (m, 1), 7.48–7.45 (m, 2H), 7.38 (dd, J = 11.7, 8.2 Hz, 1H), 6.64–6.57 (m, 2H), 6.54–6.47 (m, 1H), 6.09 (d, J = 8.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.7, 164.0 (dd, J = 249, 15 Hz), 143.5, 142.8 (t, J = 13 Hz), 138.7, 132.1, 128.6, 127.5, 99.3 (d, J = 30 Hz), 99.2 (d, J = 11 Hz), 98.5 (t, J = 26 Hz), 95.3.

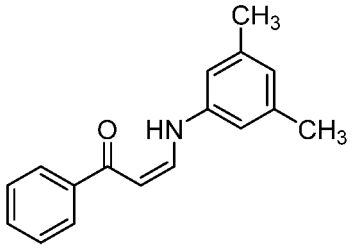
^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm): - 107.9.



DJ010

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.89 (dt, J = 6.5, 1.5 Hz, 2H), 7.79 (d, J = 12.5 Hz, 1H), 7.46–7.37 (m, 3H), 5.70 (d, J = 12.5 Hz, 1H), 3.12 (s, 3H), 2.91 (s, 3H).

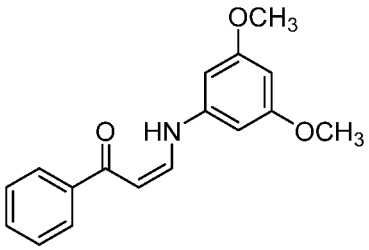
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 188.7, 154.2, 140.6, 130.9, 128.1, 127.7, 127.5, 92.3, 44.9, 37.3.



DJ011

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.08 (d, J = 12.4 Hz, 1H), 7.93 (dt, J = 6.7, 1.4 Hz, 2H), 7.54–7.42 (m, 4H), 6.74–6.73 (m, 3H), 5.99 (d, J = 7.9 Hz, 1H), 2.31 (s, 6H).

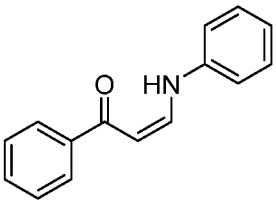
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.8, 145.1, 140.2, 139.6, 139.3, 131.5, 128.4, 127.3, 125.6, 114.3, 93.4, 21.4.



DJ012

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.07 (d, J = 12.4 Hz, 1H), 7.93 (dt, J = 6.8, 1.4 Hz, 2H), 7.52–7.43 (m, 4H), 6.26 (d, J = 2.2 Hz, 2H), 6.20 (t, J = 2.2 Hz, 1H), 6.01 (d, J = 7.8 Hz, 1H), 3.79 (s, 6H).

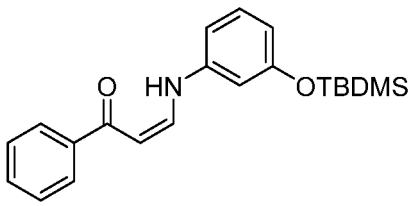
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.1, 161.9, 144.8, 142.1, 139.2, 131.7, 128.5, 127.3, 95.8, 95.0, 93.8, 55.5.



DJ013

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.15 (d, J = 11.5 Hz, 1H), 7.94 (dt, J = 6.6, 1.2 Hz, 2H), 7.53 (dd, J = 12.3, 7.8 Hz, 1H), 7.52–7.43 (m, 3H), 7.35 (t, J = 8.2 Hz, 2H), 7.15–7.06 (m, 3H), 6.03 (d, J = 7.7 Hz, 1H).

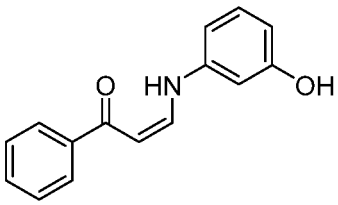
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.9, 145.0, 140.3, 139.2, 131.6, 129.8, 128.5, 127.3, 123.7, 116.4, 93.7.



DJ014

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.05 (d, J = 12.9 Hz, 1H), 7.93 (dt, J = 6.7, 1.4 Hz, 2H), 7.52–7.43 (m, 4H), 7.18 (t, J = 8.1 Hz, 1H), 6.71 (dd, J = 8.1, 2.1 Hz, 1H), 6.59–6.55 (m, 2H), 6.02 (d, J = 7.9 Hz, 1H), 0.99 (s, 9H), 0.22 (s, 6H).

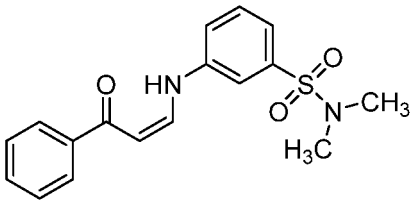
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.0, 157.0, 144.9, 141.5, 139.2, 131.6, 130.5, 128.5, 127.3, 115.5, 109.4, 108.5, 93.7, 25.7, 18.2, -4.4.



DJ015

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.05 (d, J = 11.9 Hz, 1H), 7.93 (dt, J = 6.9, 1.4 Hz, 2H), 7.53–7.43 (m, 4H), 7.19 (t, J = 8.2 Hz, 1H), 6.68 (dd, J = 8.1, 2.2 Hz, 1H), 6.64 (t, J = 2.2 Hz, 1H), 6.56 (ddd, J = 8.2, 2.3, 0.9 Hz, 1H), 6.02 (d, J = 7.9 Hz, 1H), 5.62 (br s, 1H).

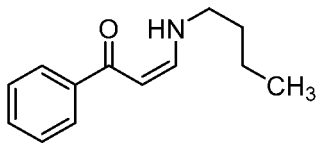
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.1, 157.2, 145.1, 139.3, 131.7, 130.8, 128.5, 127.4, 111.0, 109.7, 108.7, 103.7, 93.9.



DJ016

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.2 (d, J = 11.9 Hz, 1H), 7.95 (dt, J = 7.0, 1.9 Hz, 2H), 7.55–7.43 (m, 7H), 7.30 (ddd, J = 8.0, 2.4, 1.0 Hz, 1H), 6.13 (d, J = 8.0 Hz, 1H), 2.77 (s, 6H).

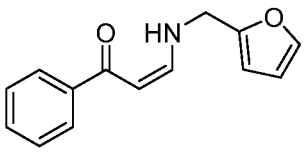
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.7, 143.8, 141.2, 138.8, 137.5, 132.0, 130.5, 128.6, 127.5, 122.1, 120.3, 114.6, 95.3, 38.0.



DJ017

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.39 (br s, 1H), 7.87 (dd, J = 8.0, 1.5 Hz, 2H), 7.45–7.37 (m, 3H), 6.94 (dd, J = 12.9, 7.4 Hz, 1H), 5.68 (d, J = 7.5 Hz, 1H), 3.27 (q, J = 6.5 Hz, 2H), 1.59 (qt, J = 6.5 Hz, 2H), 1.41 (sext, J = 6.7 Hz, 2H), 0.94 (t, J = 6.7 Hz, 3H).

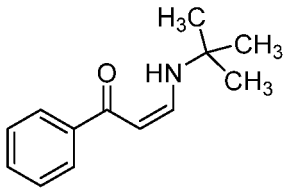
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.8, 154.4, 139.9, 130.8, 128.2, 127.0, 89.9, 49.0, 33.1, 19.8, 13.7.



DJ018

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.42 (br s, 1H), 7.87 (dt, J = 6.5, 1.4 Hz, 2H), 7.47–7.38 (m, 4H), 7.00 (dd, J = 12.6, 7.6 Hz, 1H), 6.33 (dd, J = 3.2, 1.9 Hz, 1H), 6.26 (dd, J = 3.3, 0.70 Hz, 1H), 5.77 (d, J = 7.5 Hz, 1H), 4.40 (d, J = 5.9 Hz, 2H).

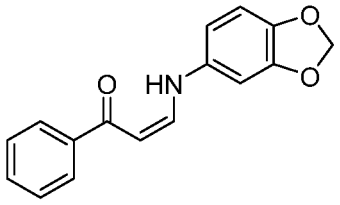
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.4, 153.6, 150.9, 142.8, 139.6, 131.0, 128.3, 127.1, 110.5, 107.9, 91.2, 45.4.



DJ019

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.71 (br s, 1H), 7.87 (dd, J = 8.0, 1.6 Hz, 2H), 7.42–7.38 (m, 3H), 7.13 (dd, J = 13.2, 7.5 Hz, 1H), 5.71 (d, J = 7.5 Hz, 1H), 1.35 (s, 9H).

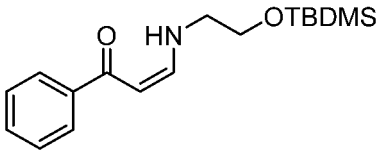
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.5, 149.9, 140.0, 130.7, 128.2, 127.0, 89.9, 52.2, 30.1.



DJ020

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.15 (d, J = 12.3 Hz, 1H), 7.93 (dt, J = 6.7, 1.3 Hz, 2H), 7.49–7.44 (m, 3H), 7.38 (dd, J = 12.3, 7.6 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.66 (d, J = 2.2 Hz, 1H), 6.55 (dd, J = 8.2, 2.3 Hz, 1H), 5.98 (d, J = 8.5 Hz, 1H), 5.97 (s, 2H).

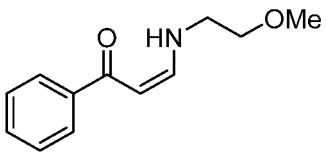
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.7, 148.8, 145.6, 144.3, 139.3, 135.2, 131.5, 128.4, 127.3, 109.7, 108.9, 101.5, 98.6, 93.2.



DJ021

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.34 (br s, 1H), 7.87 (dt, J = 6.3, 1.5 Hz, 2H), 7.44–7.37 (m, 3H), 6.96 (dd, J = 12.8, 7.4 Hz, 1H), 5.69 (d, J = 7.4 Hz, 1H), 3.73 (t, J = 5.4 Hz, 2H), 3.35 (q, J = 6.4 Hz, 2H), 0.89 (s, 9H), 0.05 (s, 6H).

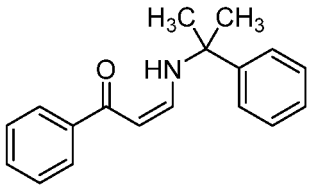
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.0, 155.0, 139.9, 130.7, 128.2, 127.1, 90.3, 63.1, 51.2, 25.9, 18.3, -5.4.



DJ022

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.36 (br s, 1H), 7.87 (dt, J = 6.5, 1.5 Hz, 2H), 7.43–7.37 (m, 3H), 6.97 (dd, J = 12.8, 7.5 Hz, 1H), 5.71 (d, J = 7.6 Hz, 1H), 3.52 (t, J = 5.6 Hz, 2H), 3.42 (q, J = 5.6 Hz, 2H), 3.38 (s, 3H).

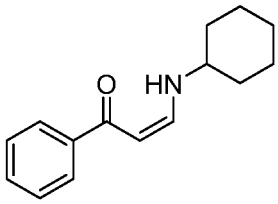
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.1, 154.6, 139.8, 130.9, 128.2, 127.1, 90.5, 72.2, 59.1, 48.9.



DJ023

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.95 (d, J = 12.4 Hz, 1H), 7.89 (dt, J = 6.7, 1.4 Hz, 2H), 7.47–7.34 (m, 7H), 7.27 (tt, J = 7.2 Hz, 1.4 Hz, 1H), 6.93 (dd, J = 12.4, 7.6 Hz, 1H), 5.75 (d, J = 7.8 Hz, 1H), 1.71 (s, 6H).

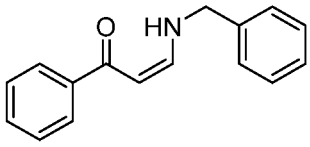
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.9, 151.2, 146.6, 139.8, 130.9, 128.6, 128.3, 127.2, 127.1, 125.7, 90.8, 57.7, 30.5.



DJ024

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.45 (br s, 1H), 7.87 (dt, J = 7.6, 1.4 Hz, 2H), 7.45–7.37 (m, 3H), 7.02 (dd, J = 13.0, 7.4 Hz, 1H), 5.69 (d, J = 7.5 Hz, 1H), 3.17–3.09 (m, 1H), 2.02–1.92 (m, 2H), 1.83–1.75 (m, 2H), 1.46–1.18 (m, 6H).

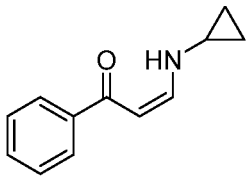
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.6, 152.3, 139.9, 130.7, 128.2, 127.0, 89.8, 57.4, 34.1, 25.3, 24.6.



DJ025

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.61 (br s, 1H), 7.88 (dt, J = 6.5, 1.5 Hz, 2H), 7.47–7.27 (m, 8H), 7.01 (dd, J = 12.5, 7. 3 Hz, 1H), 5.78 (d, J = 7.6 Hz, 1H), 4.46 (d, J = 6.1 Hz, 2H).

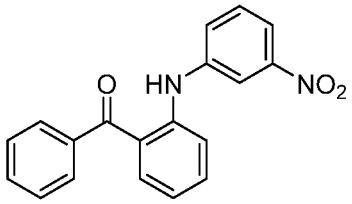
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.2, 154.1, 139.7, 137.7, 131.0, 128.9, 128.3, 127.8, 127.3, 127.1, 90.9, 52.7.



DJ026

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.28 (brs, 1H), 7.86 (dt, J = 8.0, 1.5 Hz, 2H), 7.44–7.38 (m, 3H), 7.07 (dd, J = 12.8, 7.4 Hz, 1H), 5.72 (d, J = 7.7 Hz, 1H), 2.84–2.78 (m, 1H), 0.80–0.68 (m, 4H).

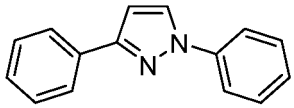
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.1, 154.3, 140.2, 131.0, 128.2, 127.1, 90.9, 29.0, 6.5.



DJ027

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.10 (br s, 1H), 8.16 (t, J = 2.1 Hz, 1H), 7.85 (ddd, J = 7.9, 2.2, 1.3 Hz, 1H), 7.34 (dt, J = 7.1, 1.4 Hz, 2H), 7.58 (tt, J = 7.5, 1.4 Hz, 2H), 7.53–7.45 (m, 6H), 6.89 (ddd, J = 7.8, 6.3, 1.9 Hz, 1H).

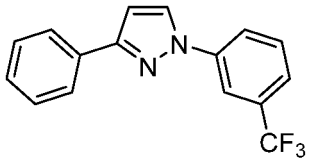
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 199.1, 149.3, 145.5, 142.6, 139.1, 134.9, 134.3, 132.0, 130.2, 129.7, 128.3, 126.3, 121.9, 118.9, 117.1, 115.6, 114.3.



DJ028

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.96 (d, J = 2.6 Hz, 1H), 7.93–7.90 (m, 2H), 7.79–7.76 (m, 2H), 7.49–7.41 (m, 4H), 7.36–7.26 (m, 2H), 6.78 (d, J = 2.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 153.0, 140.3, 133.1, 129.4, 128.7, 128.0, 128.0, 126.3, 125.9, 119.1, 105.0.

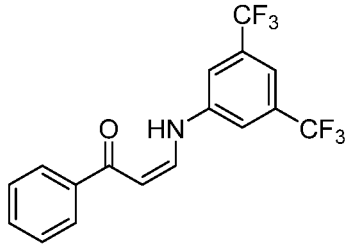


DJ029

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.08 (br s, 1H), 8.00 (d, J = 2.6 Hz, 1H), 7.98–7.91 (m, 3H), 7.61–7.51 (m, 2H), 7.46 (tt, J = 7.2, 1.5 Hz, 2H), 7.37 (tt, J = 7.4, 1.4 Hz, 1H), 6.82 (d, J = 2.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 153.6, 140.5, 132.7, 132.2 (q, J = 32.0 Hz), 130.1, 128.7, 128.4, 128.0, 125.9, 123.8 (q, J = 273 Hz), 122.7 (q, J = 3.9 Hz), 121.7, 121.7, 115.7 (q, J = 3.9 Hz).

^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm): - 62.7.

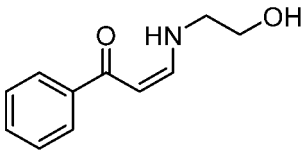


DJ030

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.32 (d, J = 11.8 Hz, 1H), 7.95 (dt, J = 7.1, 1.4 Hz, 2H), 7.56–7.46 (m, 7H), 6.18 (d, J = 8.3 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.9, 142.9, 141.9, 138.5, 133.2 (q, J = 33 Hz), 132.3, 128.6, 127.6, 123.0 (q, J = 273 Hz), 116.3 (q, J = 3 Hz), 115.7 (q, J = 3 Hz), 96.2.

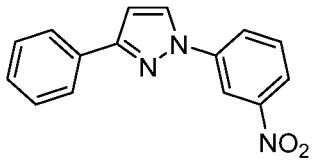
^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm): -63.2.



DJ031

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.35 (br s, 1H), 7.86 (dt, J = 6.7, 1.7 Hz, 2H), 7.47–7.38 (m, 3H), 6.98 (dd, J = 12.6, 7.4 Hz, 1H), 5.71 (d, J = 7.6 Hz, 1H), 3.76 (t, J = 5.2 Hz, 2H), 3.40 (q, J = 5.8 Hz, 2H), 2.51 (br s, 1H).

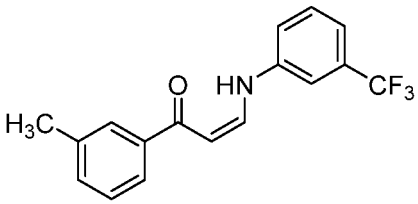
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.3, 154.9, 139.7, 131.0, 128.3, 127.1, 90.7, 62.4, 51.4.



DJ032

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.64 (t, J = 2.1 Hz, 1H), 8.18–8.11 (m, 2H), 8.05 (d, J = 2.6 Hz, 1H), 7.93 (dt, J = 7.0, 1.5 Hz, 2H), 7.65 (t, J = 8.2 Hz, 1H), 7.48–7.44 (m, 2H), 7.38 (tt, J = 7.4, 2.1 Hz, 1H), 6.86 (d, J = 2.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 154.0, 149.0, 140.9, 132.4, 130.4, 128.8, 128.6, 128.0, 125.9, 124.1, 120.6, 113.5, 106.3.

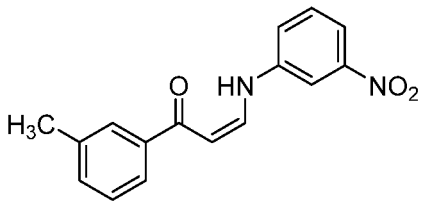


DJ033

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.2 (d, J = 11.6 Hz, 1H), 7.76 (s, 1H), 7.73 (dt, J = 6.4, 2.3 Hz, 1H), 7.49 (dd, J = 11.6, 7.9 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.37–7.30 (m, 4H), 7.26–7.23 (m, 1H), 6.09 (d, J = 7.9 Hz, 1H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.8, 143.8, 140.9, 138.9, 138.3, 132.7, 132.3 (q, J = 33 Hz), 130.4, 128.4, 128.1, 124.6, 123.7 (q, J = 273 Hz), 119.9 (q, J = 4 Hz), 119.4, 112.6 (q, J = 4 Hz), 95.1, 21.5.

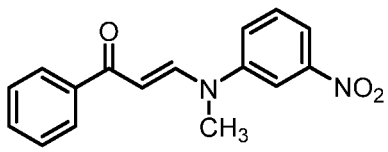
^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm): -62.3.



DJ034

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.2 (d, J = 11.9 Hz, 1H), 7.97 (t, J = 2.3 Hz, 1H), 7.89 (ddd, J = 8.1, 1.9, 0.9 Hz, 1H), 7.76 (s, 1H), 7.75–7.73 (m, 1H), 7.55–7.47 (m, 2H), 7.38–7.33 (m, 3H), 6.14 (d, J = 8.1 Hz, 1H), 2.44 (s, 3H).

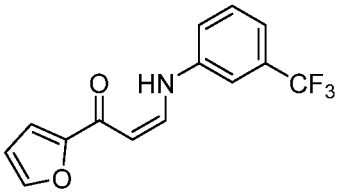
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 192.1, 149.5, 143.2, 141.7, 138.7, 138.4, 132.9, 130.6, 128.5, 128.1, 124.7, 122.3, 117.7, 109.9, 95.9, 21.5.



DJ035

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.22 (d, J = 12.8 Hz, 1H), 8.05–8.03 (m, 1H), 8.02–7.97 (m, 1H), 7.97–7.93 (m, 2H), 7.58–7.54 (m, 2H), 7.53 (tt, J = 7.2, 2.5 Hz, 1H), 7.46 (tt, J = 7.2, 1.5 Hz, 2H), 6.26 (d, J = 12.8 Hz, 1H), 3.46 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.4, 149.1, 148.0, 147.3, 139.4, 131.9, 130.5, 128.4, 127.8, 125.3, 118.9, 114.3, 99.2, 36.9.

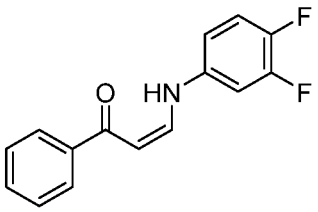


DJ036

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 11.95 (d, J = 11.4 Hz, 1H), 7.56 (dd, J = 1.7, 0.8 Hz, 1H), 7.46 (dd, J = 12.0, 8.0 Hz, 1H), 7.46–7.42 (m, 1H), 7.31–7.29 (m, 2H), 7.21 (dd, J = 8.3, 1.9 Hz, 1H), 7.13 (dd, J = 3.5, 0.7 Hz, 1H), 6.53 (dd, J = 3.5, 1.7 Hz, 1H), 5.99 (d, J = 7.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 180.4, 153.5, 145.4, 143.9, 140.8, 132.3 (q, J = 33 Hz), 130.4, 123.8 (q, J = 277 Hz), 119.9 (q, J = 4 Hz), 119.4, 114.8, 112.5 (q, J = 4 Hz), 112.3, 94.7.

^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm): -62.9.

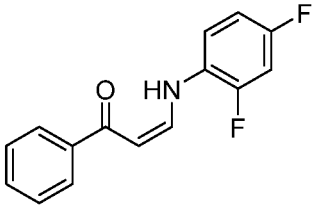


DJ037

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.11 (d, J = 11.8 Hz, 1H), 7.95–7.90 (m, 2H), 7.54–7.43 (m, 3H), 7.36 (dd, J = 11.8, 7.8 Hz, 1H), 7.17–7.10 (m, 1H), 6.96–6.89 (m, 1H), 6.82–6.77 (m, 1H), 6.05 (d, J = 7.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.4, 150.9 (d, J = 249, 14 Hz), 146.8 (d, J = 244, 12 Hz), 144.6, 138.8, 137.2 (d, J = 4 Hz), 131.9, 128.5, 127.4, 118.2 (dd, J = 18, 2 Hz), 112.2 (dd, J = 5, 3 Hz), 105.4 (d, J = 21 Hz), 94.5.

^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm): -134.7 (d), -144.0 (d).

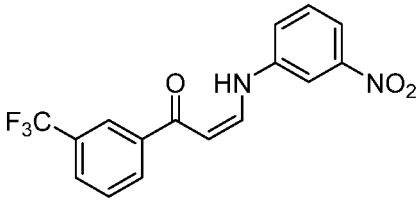


DJ038

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.13 (d, J = 11.4 Hz, 1H), 7.98–7.92 (m, 2H), 7.54–7.38 (m, 4H), 7.19–7.13 (m, 1H), 6.96–6.85 (m, 2H), 6.10 (d, J = 7.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.3, 158.3 (dd, J = 245, 11 Hz), 152.4 (dd, J = 248, 11 Hz), 144.4, 138.9, 131.8, 128.5, 127.4, 125.6 (dd, J = 11, 4 Hz), 116.4 (dd, J = 9, 3 Hz), 111.7 (dd, J = 23, 4 Hz), 104.9 (dd, J = 26, 23 Hz), 94.9.

^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm): -116.5 (d), -125.6 (d).

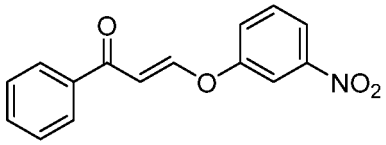


DJ039

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.28 (d, J = 11.8 Hz, 1H), 8.19 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 8.00 (t, J = 2.3 Hz, 1H), 7.94 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.63–7.51 (m, 3H), 7.40 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H), 6.14 (d, J = 7.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.9, 149.4, 144.4, 141.3, 129.3, 131.1 (q, J = 33 Hz), 130.7, 130.6, 129.2, 128.5 (q, J = 4 Hz), 124.4 (q, J = 4 Hz), 123.8 (q, J = 273 Hz), 122.4, 118.2, 110.3, 95.1.

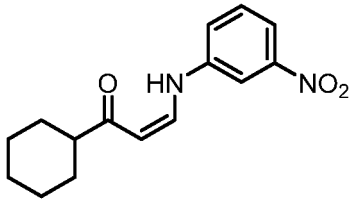
^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm): -62.7.



DJ040

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.09 (ddd, J = 8.3, 2.3, 0.9 Hz, 1H), 8.01 (t, J = 2.3 Hz, 1H), 7.97 (d, J = 11.8 Hz, 1H), 7.95–7.93 (m, 2H), 7.62–7.56 (m, 2H), 7.52–7.46 (m, 3H), 6.86 (d, J = 11.8 Hz, 1H).

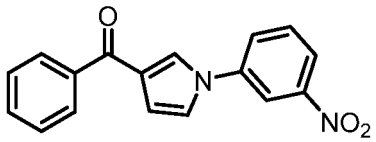
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.9, 157.8, 156.4, 149.3, 137.9, 133.1, 130.9, 128.7, 128.2, 123.8, 119.8, 113.1, 108.5.



DJ041

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 11.8 (d, J = 11.4 Hz, 1H), 7.88–7.83 (m, 2H), 7.45 (t, J = 8.3 Hz, 1H), 7.30–7.25 (m, 2H), 5.45 (d, J = 7.7 Hz, 1H), 2.38–2.30 (m, 1H), 1.92–1.62 (m, 5H), 1.46–1.16 (m, 5H).

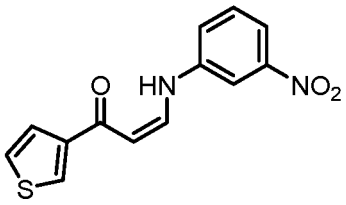
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 206.0, 149.4, 141.93, 141.90, 130.5, 122.0, 117.4, 109.5, 97.9, 50.5, 29.3, 25.9, 25.9.



DJ042

1H NMR (CDCl3, 400 MHz) δ (ppm): 8.30 (t, J = 2.1 Hz, 1H), 8.19 (ddd, J = 8.2, 2.1, 1.0 Hz, 1H), 7.90–7.87 (m, 2H), 7.78 (ddd, J = 8.2, 2.4, 1.1 Hz, 1H), 7.69–7.66 (m, 2H), 7.58 (tt, J = 7.4, 1.4 Hz, 1H), 7.52–7.48 (m, 2H), 7,19 (dd, J = 3.1, 1.5 Hz, 1H), 6.93 (dd, J = 3.0, 1.6 Hz, 1H).

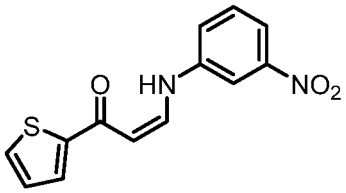
13C NMR (CDCl3, 100 MHz) δ (ppm): 190.5, 149.2, 140.6, 139.4, 131.9, 130.9, 128.9, 128.4, 127.3, 126.4, 125.5, 121.5, 120.9, 115.8, 113.5.



DJ043

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.08 (d, J = 11.5 Hz, 1H), 8.00 (dd, J = 2.9, 1.2 Hz, 1H), 7.94 (t, J = 2.1 Hz, 1H), 7.88 (ddd, J = 8.2, 2.0, 0.8 Hz, 1H), 7.55 (dd, J = 5.1, 1.1 Hz, 1H), 7.51–7.44 (m, 2H), 7.36–7.31 (m, 2H), 5.97 (d, J = 8.0 Hz, 1H).

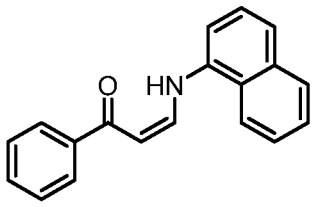
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 186.2, 149.4, 143.3, 143.0, 141.6, 130.6, 130.0, 126.7, 126.4, 122.1, 117.7, 109.9, 96.8.



DJ044

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 11.96 (d, J = 12.1 Hz, 1H), 7.92 (t, J = 2.2 Hz, 1H), 7.88 (ddd, J = 8.1, 2.2, 0.8 Hz, 1H), 7.68 (dd, J = 3.8, 1.1 Hz, 1H), 7.59 (dd, J = 4.9, 1.1 Hz, 1H), 7.50–7.44 (m, 2H), 7.32 (ddd, J = 8.1, 2.3, 0.8 Hz, 1H), 7.13 (dd, J = 4.9, 3.8 Hz, 1H), 5.99 (d, J = 7.9 Hz, 1H).

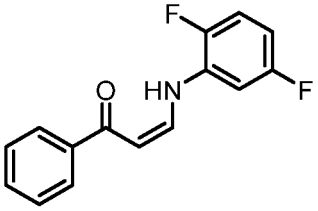
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 184.4, 149.4, 145.6, 142.9, 141.6, 132.5, 130.6, 129.8, 128.2, 122.2, 117.7, 109.8, 95.8.



DJ045

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 13.08 (d, J = 11.2 Hz, 1H), 8.26 (d, J = 8.6 Hz, 1H), 8.02–7.99 (m, 2H), 7.87 (dt, J = 8.2, 0.7 Hz, 1H), 7.72 (dd, J = 11.6, 7.8 Hz, 1H), 7.64–7.60 (m, 2H), 7.52–7.43 (m, 5H), 7.29 (d, J = 7.9 Hz, 1H), 6.17 (d, J = 7.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.4, 146.2, 139.3, 136.5, 134.4, 131.7, 128.5, 127.4, 126.7, 126.6, 125.8, 124.9, 124.2, 121.1, 111.1, 94.7.

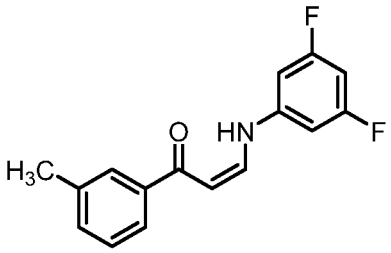


DJ046

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.14 (d, J = 11.5 Hz, 1H), 7.97–7.94 (m, 2H), 7.52 (tt, J = 7.6, 2.4 Hz, 1H), 7.48–7.44 (m, 2H), 7.39 (dd, J = 11.5, 7.9 Hz, 1H), 7.12–7.06 (m, 1H), 6.94–6.90 (m, 1H), 6.71–6.64 (m, 1H), 6.15 (d, J = 7.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.6, 159.2 (dd, J = 243, 3 Hz), 148.4 (dd, J = 241, 3 Hz), 142.9, 138.8, 132.0, 130.0 (dd, J = 13, 10 Hz), 128.5, 127.5, 116.8 (dd, J = 21, 10 Hz), 109.1 (dd, J = 24, 8 Hz), 102.3 (dd, J = 28, 3 Hz), 95.9.

^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm): -136.3 (d), -116.3 (d).

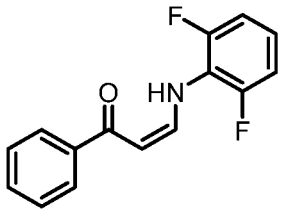


DJ047

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.06 (d, J = 11.8 Hz, 1H), 7.75 (s, 1H), 7.73–7.70 (m, 1H), 7.36 (dd, J = 11.7, 8.2 Hz, 1H), 7.36–7.33 (m, 2H), 6.64–6.56 (m, 2H), 6.49 (tt, J = 8.9, 2.1 Hz, 1H), 6.08 (d, J = 8.2 Hz, 1H), 2.43 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.9, 164.0 (dd, J = 247, 14 Hz), 143.3, 142.9 (d, J = 13 Hz), 138.7, 138.3, 132.9, 128.4, 128.1, 124.6, 99.2 (dd, J = 20, 9 Hz), 98.5 (t, J = 26 Hz), 95.5, 21.4.

^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm): -107.9.

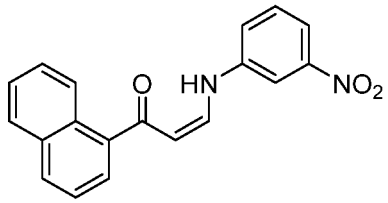


DJ048

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.16 (d, J = 10.9 Hz, 1H), 7.97–7.94 (m, 2H), 7.72 (dd, J = 12, 8 Hz, 1H), 7.51 (tt, J = 7.3, 2.7 Hz, 1H), 7.48–7.43 (m, 2H), 6.99–6.93 (m, 3H), 6.10 (d, J = 8.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.6, 153.5 (dd, J = 247, 7 Hz), 147.6 (t, J = 6 Hz), 138.9, 131.8, 128.5, 127.5, 122.6 (t, J = 9 Hz), 112.2 (dd, J = 17, 7 Hz), 95.3.

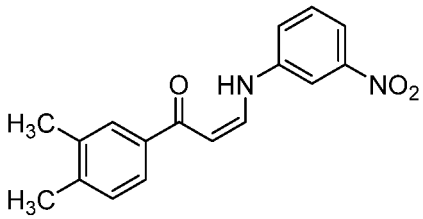
^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm): -125.5.



DJ049

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.26 (d, J = 11.8 Hz, 1H), 8.52 (dd, J = 8.3, 0.8 Hz, 1H), 8.01 (t, J = 2.1 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.92 (ddd, J = 8.3, 2.1, 1.1 Hz, 1H), 7.89 (dd, J = 8.2, 1.4 Hz, 1H), 7.76 (dd, J = 7.2, 1.2 Hz, 1H), 7.60–7.49 (m, 5H), 7.41 (ddd, J = 8.2, 2.3, 0.9 Hz, 1H), 5.98 (d, J = 8.0 Hz, 1H).

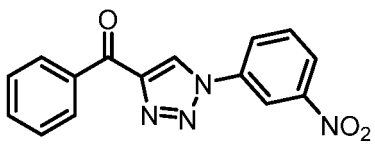
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 196.1, 149.5, 143.1, 141.7, 138.2, 133.9, 131.3, 130.7, 130.1, 128.5, 127.2, 126.4, 126.3, 125.7, 124.7, 122.4, 117.9, 110.1, 100.2.



DJ050

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.2 (d, J = 11.6 Hz, 1H), 7.95 (t, J = 2.1 Hz, 1H), 8.87 (ddd, J = 8.2, 2.2, 0.9 Hz, 1H), 7.73 (s, 1H), 7.67 (dd, J = 7.9, 1.7 Hz, 1H), 7.50 (dd, J = 11.6, 8.2 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.35 (ddd, J = 8.1, 2.3, 0.9 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 6.13 (d, J = 8.2 Hz, 1H), 2.33 (s, 3H), 2.32 (s, 3H).

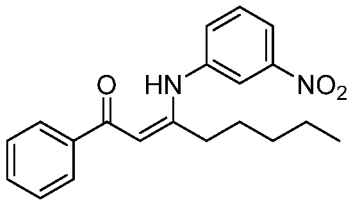
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.8, 149.4, 142.9, 141.8, 141.6, 136.9, 136.4, 130.6, 129.8, 128.7, 125.2, 122.2, 117.6, 109.8, 95.8, 20.0, 19.9.



DJ051

1H NMR (d6 DMSO, 400 MHz) δ (ppm): 9.78 (s, 1H), 8.85 (t, J = 2.2 Hz, 1H), 8.49 (ddd, J = 8.2, 2.2, 1.0 Hz, 1H), 8.35 (ddd, J = 8.2, 2.2, 1.0 Hz, 1H), 8.24–8.21 (m, 2H), 7.91 (t, J = 8.3 Hz, 1H), 7.70 (tt, J = 7.4, 1.5 Hz, 1H), 7.59 (tt, J = 7.9, 1.5 Hz, 2H).

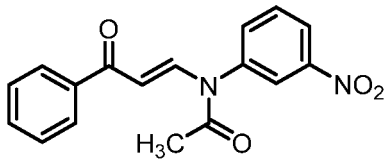
13C NMR (d6 DMSO, 100 MHz) δ (ppm): 185.4, 149.0, 147.6, 137.2, 136.9, 134.0, 132.0, 130.4, 129.2, 129.1, 127.3, 124.3, 116.1.



DJ052

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 13.29 (s, 1H), 8.09–8.04 (m, 2H), 7.95–7.90 (m, 2H), 7.52–7.48 (m, 5H), 6.02 (s, 1H), 2.49 (t, J = 7.6 Hz, 2H), 1.63–1.55 (m, 2H), 1.36–1.22 (m, 4H), 0.85 (t, J = 7.0 Hz, 3H).

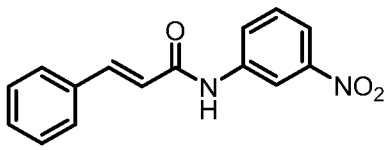
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.9, 165.2, 148.8, 140.2, 139.6, 131.4, 130.3, 130.1, 128.4, 127.2, 120.1, 119.0, 94.8, 32.4, 31.4, 28.0, 22.2, 13.8.



DJ053

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.67 (d, J = 13.6 Hz, 1H), 8.41 (ddd, J = 8.4, 2.2, 0.9 Hz, 1H), 8.17 (t, J = 2.2 Hz, 1H), 7.80 (t, J = 8.2 Hz, 1H), 7.72–7.69 (m, 2H), 7.62 (ddd, J = 7.8, 2.0, 0.8 Hz, 1H), 7.51 (tt, J = 7.4, 1.4 Hz, 1H), 7.42–7.37 (m, 2H), 5.74 (d, J = 13.6 Hz, 1H), 2.20 (brs, 3H).

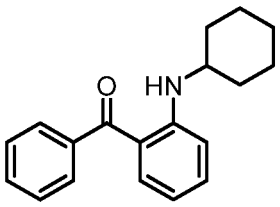
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.8, 169.2, 149.5, 142.8, 139.5, 138.1, 134.7, 132.7, 131.5, 128.5, 128.1, 124.5, 123.9, 107.3, 23.2.



DJ054

1H NMR (d6 DMSO, 400 MHz) δ (ppm): 10.66 (s, 1H), 8.71 (t, J = 2.1 Hz, 1H), 7.96 (ddd, J = 8.2, 2.0, 0.9 Hz, 1H), 7.89 (ddd, J = 8.2, 2.4, 0.9 Hz, 1H), 7.64–7.58 (m, 4H), 7.45–7.38 (m, 3H), 6.78 (d, J = 15.7 Hz, 1H).

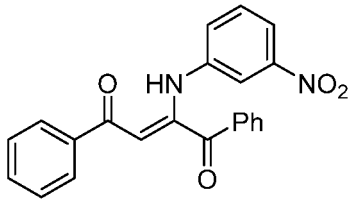
13C NMR (d6 DMSO, 100 MHz) δ (ppm): 164.6, 148.5, 141.7, 140.8, 134.9, 130.7, 130.5, 129.5, 128.4, 125.6, 121.9, 118.3, 113.8.



DJ055

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.75 (d, J = 6.6 Hz, 1H), 7.62–7.57 (m, 2H), 7.52–7.41 (m, 4H), 7.34 (tdd, J = 7.3, 1.7, 1.4 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 6.46 (tdd, J = 7.0, 1.2, 1.0 Hz, 1H), 3.54–3.44 (m, 1H), 2.11–2.00 (m, 2H), 1.88–1.73 (m, 2H), 1.67–1.58 (m, 1H), 1.49–1.26 (m, 5H).

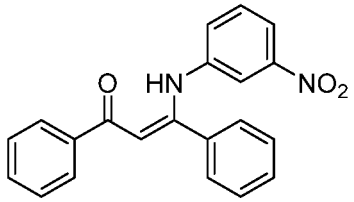
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 199.3, 151.1, 140.8, 135.8, 134.9, 130.6, 129.0, 128.0, 116.8, 113.1, 112.0, 50.5, 32.7, 25.9, 24.6.



DJ056

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.61 (s, 1H), 8.03–7.98 (m, 2H), 7.97–7.92 (m, 2H), 7.85–7.81 (m, 2H), 7.60 (tt, J = 7.5, 1.3 Hz, 1H), 7.55 (tt, J = 7.3, 1.4 Hz, 1H), 7.50–7.43 (m, 4H), 7.33 (t, J = 7.1 Hz, 1H), 7.25 (dt, J = 8.5, 1.8 Hz, 1H), 6.26 (s, 1H).

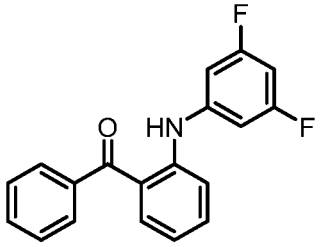
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.7, 191.6, 155.1, 148.7, 140.2, 138.5, 134.9, 134.5, 132.6, 130.1, 129.8, 129.1, 128.7, 127.6, 126.7, 119.2, 115.9, 97.5.



DJ057

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.91 (s, 1H), 8.00–7.96 (m, 2H), 7.81 (ddd, J = 8.1, 2.1, 1.0 Hz, 1H), 7.58 (t, J = 2.1 Hz, 1H), 7.53 (tt, J = 7.3, 1.3 Hz, 1H), 7.49–7.37 (m, 7H), 7.28 (t, J = 8.4 Hz, 1H), 7.07 (dd, J = 8.1, 2.1 Hz, 1H), 6.22 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.6, 160.2, 148.5, 141.1, 139.3, 134.9, 131.9, 130.4, 129.5, 129.1, 128.5, 128.2, 128.1, 127.5, 118.3, 117.1, 98.9.

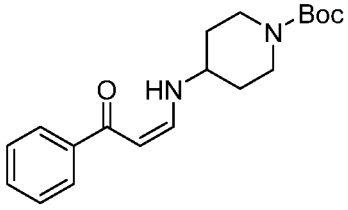


DJ058

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 9.95 (s, 1H), 7.74–7.71 (m, 2H), 7.60–7.55 (m, 2H), 7.52–7.46 (m, 3H), 7.46–7.41 (m, 1H), 6.88–6.83 (m, 1H), 6.80–6.74 (m, 2H), 6.45 (tt, J = 8.8, 2.1 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 199.1, 163.9 (dd, J = 246, 15 Hz), 145.4, 143.8 (t, J = 13 Hz), 139.1, 134.7, 134.1, 132.0, 129.7, 128.3, 122.0, 118.7, 116.4, 102.7 (dd, J = 20, 8 Hz), 97.7 (dd, J = 27, 26 Hz).

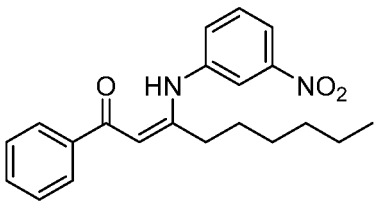
^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm): -109.3.



DJ059

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.43 (dd, J = 12.0, 7.9 Hz, 1H), 7.87–7.84 (m, 2H), 7.46–7.37 (m, 3H), 7.00 (dd, J = 12.8, 7.6 Hz, 1H), 5.72 (d, J = 7.6 Hz, 1H), 4.07–3.96 (m, 2H), 3.32–3.22 (m, 1H), 2.92 (t, J = 11.9 Hz, 2H), 1.97–1.86 (m, 2H), 1.62–1.48 (m, 2H), 1.45 (s, 9H).

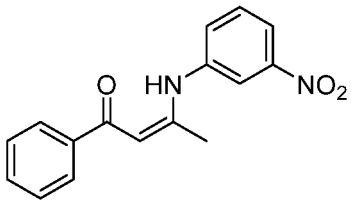
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.1, 154.7, 151.9, 139.6, 131.0, 128.3, 127.1, 90.6, 79.9, 55.5, 42.1, 33.0, 28.4.



DJ060

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 13.3 (s, 1H), 8.07–8.04 (m, 2H), 7.95–7.89 (m, 2H), 7.58–7.42 (m, 5H), 6.02 (s, 1H), 2.49 (t, J = 8.3 Hz, 1H), 1.63–1.53 (m, 2H), 1.38–1.17 (m, 6H), 0.85 (t, J = 6.7 Hz, 3H).

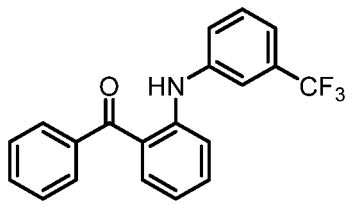
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.9, 165.2, 148.8, 140.2, 139.6, 131.4, 130.3, 130.1, 128.4, 127.2, 120.0, 119.0, 94.8, 32.5, 31.4, 28.9, 28.3, 22.4, 14.0.



DJ061

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 13.3 (s, 1H), 8.06–8.01 (m, 2H), 7.94–7.89 (m, 2H), 7.56–7.41 (m, 5H), 5.99 (s, 1H), 2.24 (s, 3H).

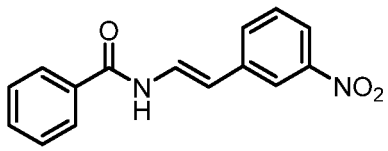
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.7, 160.4, 148.8, 140.3, 139.4, 131.5, 130.1, 129.7, 128.4, 127.2, 119.8, 118.5, 96.1, 20.6.



DJ062

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.09 (s, 1H), 7.74–7.70 (m, 2H), 7.59–7.53 (m, 3H), 7.51–7.46 (m, 2H), 7.46–7.39 (m, 4H), 7.31–7.27 (m, 1H), 6.83–6.78 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 199.2, 146.6, 141.6, 139.4, 134.9, 134.3, 131.9 (q, J =32 Hz), 131.8, 130.0, 129.6, 128.2, 124.2, 124.0 (q, J = 273 Hz), 121.0, 119.4 (q, J = 4 Hz), 117.9, 117.6 (q, J = 4 Hz), 115.1.

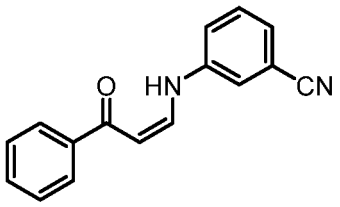


DJ063

A mixture of benzamide (0.072 g, 0.59 mmol), (*E*)-1-(2-bromovinyl)-3-nitrobenzene (0.119 g, 0.52 mmol), copper (I) iodide (0.027 g, 0.14 mmol), K_2CO_3 (0.138 g, 1.0 mmol) and dimethyl-ethylenediamine (DMEDA, 0.030 mL, 0.27 mmol) in THF (20 mL) was stirred under argon at 80 °C for 18 h. After 18 h, the reaction mixture was allowed to cool down to 21 °C, diluted with NH_4Cl/NH_3 (50 mL) and extracted with EtOAc (2 X 50 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (*n*-hexane/ethyl acetate = 5:1, 3:1, 2:1 to 3:2) to obtain **DJ063**.

^{1}H NMR (DMSO-d6, 400 MHz) δ (ppm): 10.78 (d, J = 9.9 Hz, 1H, NH), 8.13 (t, J = 1.9 Hz, 1H), 7.98–7.92 (m, 3H), 7.86 (d, J = 8.1 Hz, 1H), 7.80 (dd, J = 14.7, 9.9 Hz, 1H), 7.61–7.47 (m, 4H), 6.52 (d, J = 14.7 Hz, 1H).

^{13}C NMR (DMSO, 100 MHz) δ (ppm): 164.8, 148.8, 139.3, 133.5, 132.6, 131.8, 130.6, 129.0, 128.2, 127.4, 121.0, 120.0, 111.1.

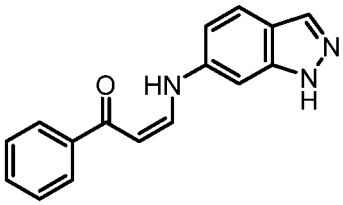


DJ064

DJ064 (81.8 mg, 0.330 mmol, 43%, yellow powder) was prepared from 1-phenylprop-2-yn-1-one (EDB-346, 100 mg, 0.768 mmol), 3-aminobenzonitrile (108.9 mg, 0.922 mmol) and copper (I) iodide (29.3 mg, 0.154 mmol) in DMF (1 mL) using the same procedure as that described for **DJ001**.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.15 (d, J = 12.0 Hz, 1H, NH), 7.94-7.92 (m, 2H), 7.53-7.41 (m, 5H), 7.35-7.27 (m, 3H), 6.12 (d, J = 8.0 Hz, 1H).

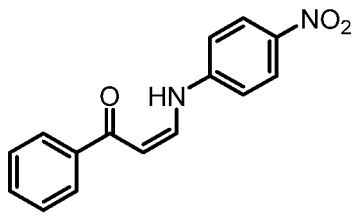
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.8, 143.4, 141.2, 138.7, 132.1, 130.7, 128.6, 127.5, 126.7, 120.7, 118.7, 113.9, 95.5 (one carbon not observed or overlapping).



DJ065

DJ065 (38.4 mg, 0.146 mmol, 32%, yellow powder) was prepared from 1-phenylprop-2-yn-1-one (EDB-346, 70.4 mg, 0.541 mmol) and 1*H*-indazol-6-amine (HJG170809, 108.9 mg, 0.922 mmol) in toluene (1.5 mL) using the same procedure as that described for **DJ058**.

^{1}H NMR (acetone-d_6, 400 MHz) δ (ppm): 12.33 (br s, 1H, NH), 7.99-7.96 (m, 3H), 7.90 (dd, J = 12.0, 8.0 Hz, 1H), 7.76 (dd, J = 8.4, 0.4 Hz, 1H), 7.54-7.45 (m, 4H), 7.42 (s, 1H), 7.10 (dd, J = 8.8, 2.0 Hz, 1H), 6.16 (d, J = 8.0 Hz, 1H).

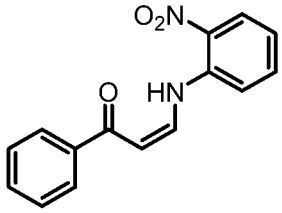


DJ066

DJ066 (57 mg, 0.213 mmol, 33%, yellow powder) was prepared from 1-phenylprop-2-yn-1-one (EDB-346, 85 mg, 0.653 mmol), *p*-nitroaniline (99 mg, 0.718 mmol) and copper (I) iodide (24.9 mg, 0.131 mmol) in DMF (0.5 mL) using the same procedure as that described for **DJ001**.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.27 (d, J = 11.6 Hz, 1H, NH), 8.25 (d, J = 9.2 Hz, 2H), 7.96-7.94 (m, 2H), 7.57-7.46 (m, 4H), 7.16 (d, J = 9.2 Hz, 2H), 6.21 (d, J = 8.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 192.0, 145.8, 142.4, 138.5, 132.4, 128.7, 127.6, 126.1, 115.3, 97.0 (one carbon not observed or overlapping).

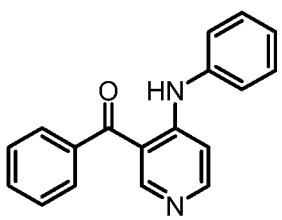


DJ067

DJ067 (45.8 mg, 0.171 mmol, 22%, orange powder) was prepared from 1-phenylprop-2-yn-1-one (EDB-346, 100 mg, 0.768 mmol), *o*-nitroaniline (116.8 mg, 0.845 mmol) and copper (I) iodide (29.3 mg, 0.154 mmol) in DMF (0.7 mL) using the same procedure as that described for **DJ001**.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 13.50 (d, J = 11.2 Hz, 1H, NH), 8.25 (dd, J = 8.4, 1.6 Hz, 1H), 8.02-7.99 (m, 2H), 7.61 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 7.55-7.41 (m, 5H), 7.90 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 6.28 (d, J = 8.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.0, 140.7, 138.6, 137.4, 136.2, 135.6, 132.2, 128.5, 127.8, 126.9, 121.8, 115.7, 98.6.



DJ068

A solution of (4-chloropyridin-3-yl)(phenyl)methanone (see next entry) (100 mg, 0.460 mmol) and aniline (47 mg, 0.505 mmol) in DMF (0.5 mL) was stirred at 21 °C for 10 min and heated to 160 °C with stirring for 1 h. After 1 h, the reaction mixture was cooled, diluted with water and extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over MgSO4, filtered and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography (*n*-hexane: ethyl acetate = 3:2 then dichloromethane: acetone = 8:1) to obtain desired product (66.2 mg, 0.460 mmol, 53 %) as a pale yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.52 (s, 1H, NH), 8.65 (s, 1H), 8.23 (d, J = 6.0 Hz, 1H), 7.72-7.69 (m, 2H), 7.57 (m, 1H), 7.49 (m, 2H), 7.41 (m, 2H), 7.29 (d, J = 7.2 Hz, 2H), 7.23 (dd, J = 7.6, 7.2 Hz, 1H), 7.03 (d, J = 6.0 Hz, 1H).

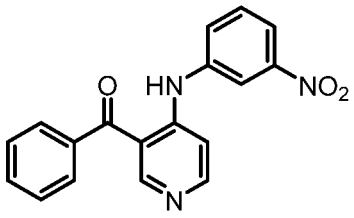
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 198.6, 156.2, 153.3, 152.4, 138.7, 137.9, 131.8, 129.6, 129.3, 128.3, 125.7, 124.0, 115.0, 107.7.

(4-Chloropyridin-3-yl)(phenyl)methanone

To a solution of diisopropylamine (1.7 g, 16.757 mmol) in anhydrous THF (16 mL) was slowly added at -78 °C a 1.6 M solution of *n*-BuLi in hexane (10.5 mL, 16.757 mmol) and the mixture was stirred at 0 °C for 20 min. The LDA solution was cooled to -78 °C and a slurry of 4-chloropyridine hydrochloride (1.14 g, 7.617 mmol) in THF (2 mL) was added to the reaction mixture and it was stirred at -78 °C for 10 min. Then *N, N*-dimethylbenzamide (1.25 g, 8.379 mmol) in THF (4 mL) was added to the reaction mixture at -78 °C and it was stirred for 5 h. After it had stirred for 5 h, an aqueous NH_4Cl solution was added to the reaction mixture and it was stirred at 21 °C. The reaction mixture was extracted with ethyl acetate, washed with 1N HCl and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography (*n*-hexane: ethyl acetate = 2:1) to obtain the desired product (976.6 mg, 4.487 mmol, 59%) as a pale yellow liquid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.64 (d, J = 5.2 Hz, 1H), 8.60 (d, J = 0.4 Hz, 1H), 7.83-7.80 (m, 2H), 7.64 (m, 1H), 7.52-7.47 (m, 2H), 7.45 (dd, J = 5.2, 0.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 192.9, 151.7, 149.7, 141.7, 136.2, 134.5, 134.3, 130.0, 128.9, 125.0.

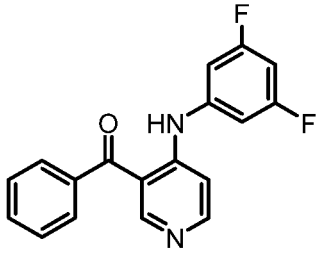


DJ069

DJ069 (34.3 mg, 0.107 mmol, 23%, pale yellow powder) was prepared from (4-chloropyridin-3-yl)(phenyl)methanone (100 mg, 0.460 mmol) and 3-nitroaniline (69.8 mg, 0.505 mmol) in DMF (0.5 mL) using the same procedure as that described for **DJ068**.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.67 (s, 1H, NH), 8.72 (s, 1H), 8.37 (d, J = 6.0 Hz, 1H), 8.20 (dd, J = 2.4, 2.0 Hz, 1H), 8.05 (ddd, J = 7.6, 2.0, 1.6 Hz, 1H), 7.74-7.71 (m, 2H), 7.73-7.57 (m, 3H), 7.54-7.50 (m, 2H), 7.13 (d, J = 6.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 198.8, 156.3, 153.3, 152.1, 149.2, 139.8, 138.3, 132.4, 130.6, 129.6, 129.0, 128.6, 119.9, 117.8, 116.0, 107.8.

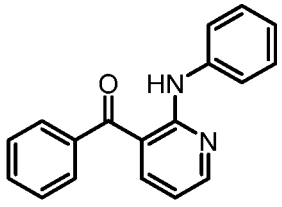


DJ070

DJ070 (35 mg, 0.113 mmol, 45%, pale yellow powder) was prepared from (4-chloropyridin-3-yl)(phenyl)methanone (54 mg, 0.248 mmol) and 3,5-difluoroaniline (51.2 mg, 0.397 mmol) in DMF (0.3 mL) using the same procedure as that described for **DJ068**.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.52 (s, 1H, NH), 8.69 (s, 1H), 8.35 (d, J = 6.0 Hz, 1H), 7.72-7.70 (m, 2H), 7.60 (m, 1H), 7.53-7.49 (m, 2H), 7.19 (d, J = 6.0 Hz, 1H), 6.85 (dd, J = 8.0, 2.0 Hz, 2H), 6.45 (ddd, J = 8.8, 6.4, 2.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 198.7, 163.8 (d, J = 247.2 Hz), 156.1, 153.1, 152.0, 140.9 (dd, J = 12.6, 12.4 Hz), 138.3, 132.4, 129.5, 128.5, 116.0, 108.3, 106.0 (d, J = 27.5 Hz), 100.7 (t, J = 25.4 Hz).



DJ071

DJ071 (9.1 mg, 0.107 mmol) was prepared from (2-chloropyridin-3-yl)(phenyl)methanone (see next entry) (102 mg, 0.469 mmol) and aniline (48 mg, 0.516 mmol) in DMF (0.5 mL) using the same procedure as that described for **DJ068**.

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 10.89 (s, 1H, NH), 8.46 (dd, J = 4.5, 1.8 Hz, 1H), 7.91 (dd, J = 7.8, 2.1 Hz, 1H), 7.80 (dd, J = 8.4, 1.2 Hz, 2H), 7.72-7.68 (m, 2H), 7.64 (m, 1H), 7.57-7.51 (m, 2H), 7.42 (ddd, J = 8.4, 2.1, 1.8 Hz, 2H), 7.13 (dt, J = 7.2, 1.2 Hz, 1H), 6.74 (dd, J = 7.8, 4.8 Hz, 1H).

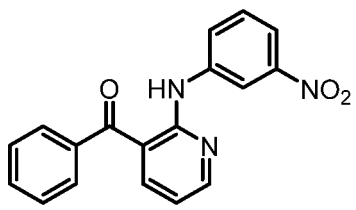
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 198.4, 156.4, 153.6, 143.5, 139.5, 139.1, 131.7, 129.2, 128.9, 128.4, 123.3, 121.4, 113.5, 112.6.

(2-Chloropyridin-3-yl)(phenyl)methanone

To a solution of tetramethylethylenediamine (TMEDA, 581.2 mg, 5.0 mmol) in THF (6 mL) was added at -78 °C a 1.6 M solution of n-BuLi in hexane (6.25 mL, 10.0 mmol) and the mixture was stirred at 0 °C for 10 min. Then 2,2,6,6-tetramethylpiperidine (1.41 g, 10.0 mmol) and copper (I) chloride (495 mg, 5.0 mmol) were added to the reaction mixture at 0 °C and it was stirred for 15 min. To the mixture was slowly added at 0 °C 2-chloropyridine (567.7 mg, 5.0 mmol) in THF (3 mL) and the mixture was warmed to 21 °C for 2 h. To the reaction mixture was added benzoyl chloride (1.41 g, 10.0 mmol) and it was stirred at 40 °C overnight. The reaction mixture was diluted with water and diethyl ether and extracted with diethyl ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography (*n*-hexane: ethyl acetate = 5:1) to obtain desired product (385 mg, 1.769 mmol, 35%) as pale yellow liquid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.54 (dd, J = 4.8, 2.0 Hz, 1H), 7.81-7.78 (m, 2H), 7.73 (dd, J = 7.6, 2.0 Hz, 1H), 7.62 (m, 1H), 7.48 (m, 2H), 7.83 (dd, J = 7.6, 4.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 193.4, 150.9, 147.8, 138.0, 135.8, 134.9, 134.2, 130.0, 128.9, 122.3.

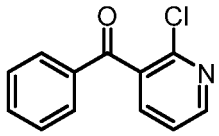


DJ072

(2-((3-Nitrophenyl)amino)pyridin-3-yl)(phenyl)methanone

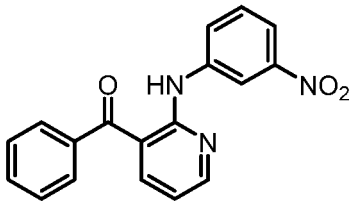
DJ072 (3.8 mg, 0.107 mmol) was prepared from (2-chloropyridin-3-yl)(phenyl)methanone (99 mg, 0.455 mmol) and 3-nitroaniline (69.1 mg, 0.500 mmol) in DMF (0.5 mL) using the same procedure as that described for **DJ068**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 11.08 (s, 1H, NH), 8.93 (dd, J = 2.0, 1.6 Hz, 1H), 8.49 (dd, J = 3.6, 1.6 Hz, 1H), 7.94 (dd, J = 6.4, 1.6 Hz, 2H), 7.90 (ddd, J = 6.4, 2.0, 0.8 Hz, 1H), 7.67-7.65 (m, 2H), 7.61 (m, 1H), 7.54-7.51 (m, 2H), 7.48 (t, J = 6.4 Hz, 1H), 6.83 (dd, J = 6.4, 4.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 198.5, 155.6, 153.3, 148.8, 143.5, 140.8, 138.6, 132.2, 129.4, 129.3, 128.5, 126.3, 117.3, 115.4, 114.2, 114.0.

Further Synthetic Methods



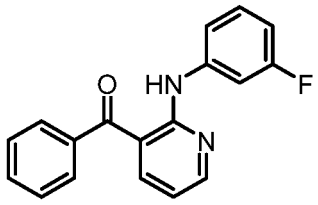
(2-Chloropyridin-3-yl)(phenyl)methanone

To a solution of tetramethylethylenediamine (581.2 mg, 5.0 mmol) in THF (6 mL) was added *n*-BuLi (1.6 M solution in *n*-hexane, 6.25 mL, 10.0 mmol) at -78 °C and the reaction mixture was stirred at 0 °C for 10 min. Then 2,2,6,6-tetramethylpiperidine (1.41 g, 10.0 mmol) and copper (I) chloride (495 mg, 5.0 mmol) were added to the reaction mixture at 0 °C and it was stirred for 15 min. To the mixture was slowly added at 0 °C 2-chloropyridine (567.7 mg, 5.0 mmol) in THF (3 mL) and the reaction mixture was warmed to 21 °C. After 2 h, benzoyl chloride (1.41 g, 10.0 mmol) was added to the reaction mixture and it was stirred at 40 °C for overnight. The reaction mixture was diluted with water and Et_2O and the aqueous layer was extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (*n*-hexane: EtOAc = 5:1) to obtain the desired product (385 mg, 1.769 mmol, 35%) as pale yellow liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.54 (dd, J = 4.8, 2.0 Hz, 1H), 7.81-7.78 (m, 2H), 7.73 (dd, J = 7.6, 2.0 Hz, 1H), 7.62 (m, 1H), 7.48 (m, 2H), 7.83 (dd, J = 7.6, 4.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 193.4, 150.9, 147.8, 138.0, 135.8, 134.9, 134.2, 130.0, 128.9, 122.3.



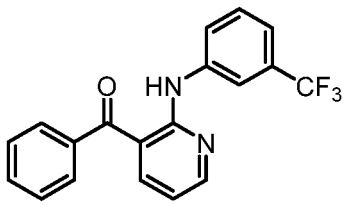
(2-((3-Nitrophenyl)amino)pyridin-3-yl)(phenyl)methanone (DJ072)

A solution of (2-chloropyridin-3-yl)(phenyl)methanone (59.5 mg, 0.273 mmol), 3-nitroaniline (45.3 mg, 0.328 mmol), $Pd(OAc)_2$ (3.1 mg, 0.014 mmol), Xantphos (15.8 mg, 0.027 mmol) and Cs_2CO_3 (133.3 mg, 0.410 mmol) in 1,4-dioxane (0.7 mL) was stirred at 100 °C for 1 h. After it was cooled, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (*n*-hexane: EtOAc = 6:1) to obtain the desired product DJ072 (78 mg, 0.244 mmol, 89 %) as a light yellow solid. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 11.07 (br s, NH), 8.91 (dd, J = 2.4, 2.0 Hz, 1H), 8.47 (dd, J = 4.8, 2.0 Hz, 1H), 7.91-7.94 (m, 2H), 7.88 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H), 7.64-7.66 (m, 2H), 7.58-7.62 (m, 1H), 7.49-7.53 (m, 2H), 7.47 (t, J = 8.0 Hz, 1H), 6.83 (dd, J = 8.0, 4.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 198.4, 155.5, 153.2, 148.7, 143.4, 140.8, 138.5, 132.1, 129.3, 129.2, 128.4, 126.2, 117.2, 115.3, 114.1, 113.9.



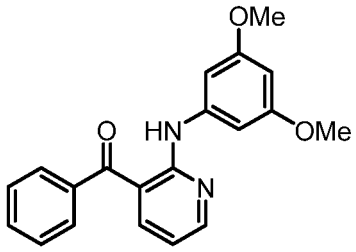
(2-((3-Fluorophenyl)amino)pyridin-3-yl)(phenyl)methanone (DJ073)

DJ073 (106.1 mg, 0.363 mmol, 86%, light yellow powder) was prepared from (2-chloropyridin-3-yl)(phenyl)methanone (92 mg, 0.423 mmol), 3-fluoroaniline (56.4 mg, 0.507 mmol), $Pd(OAc)_2$ (4.7 mg, 0.021 mmol), Xantphos (24.5 mg, 0.044 mmol) and Cs_2CO_3 (206.6 mg, 0.634 mmol) in 1,4-dioxane (1 mL) using the same procedure as described for DJ072. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.95 (br s, NH), 8.43 (dd, J = 4.8, 2.0 Hz, 1H), 7.90 (ddd, J = 11.6, 2.4, 2.0 Hz, 1H), 7.87 (dd, J = 8.0, 2.0 Hz, 1H), 7.63-7.66 (m, 2H), 7.56-7.61 (m, 1H), 7.48-7.52 (m, 2H), 7.32 (ddd, J = 8.0, 2.0, 1.2 Hz, 1H), 7.25-7.30 (m, 1H), 6.77 (ddd, J = 8.0, 2.4, 1.2 Hz, 1H), 6.74 (dd, J = 8.0, 4.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 198.3, 163.0 (d, J = 241.7 Hz), 155.8, 153.2, 143.3, 141.1 (d, J = 11.1 Hz), 138.7, 131.9, 129.6 (d, J = 9.6 Hz), 129.1, 128.3, 116.1 (d, J = 2.7 Hz), 113.7, 113.1, 109.3 (d, J = 21.4 Hz), 107.9 (d, J = 26.2 Hz).



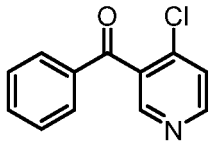
Phenyl(2-((3-(trifluoromethyl)phenyl)amino)pyridin-3-yl)methanone (DJ074)

DJ074 (88.6 mg, 0.259 mmol, 90%, yellow powder) was prepared from (2-chloropyridin-3-yl)(phenyl)methanone (62.8 mg, 0.289 mmol), 3-trifluoromethylaniline (55.8 mg, 0.346 mmol), $Pd(OAc)_2$ (3.2 mg, 0.014 mmol), Xantphos (16.7 mg, 0.029 mmol) and Cs_2CO_3 (141 mg, 0.433 mmol) in 1,4-dioxane (0.7 mL) using the same procedure as described for DJ072. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 11.00 (br s, NH), 8.45 (dd, J = 4.8, 2.0 Hz, 1H), 8.20 (s, 1H), 7.90 (dd, J = 8.0, 2.0 Hz, 2H), 7.64-7.67 (m, 2H), 7.58-7.62 (m, 1H), 7.49-7.53 (m, 2H), 7.46 (dd, J = 8.0, 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 6.77 (d, J = 7.6, 4.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 198.3, 155.8, 153.2, 143.3, 140.1, 138.6, 131.9, 131.1 (q, J = 32.0 Hz), 129.1, 128.4, 124.1 (q, J = 270.8 Hz), 123.8 (d, J = 1.0 Hz), 119.2 (q, J = 3.9 Hz), 117.4 (q, J = 3.9 Hz), 113.8, 113.4.



(2-((3,5-Dimethoxyphenyl)amino)pyridin-3-yl)(phenyl)methanone (DJ075)

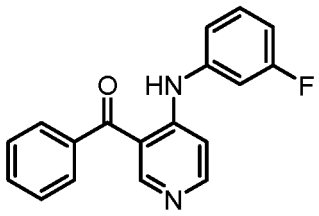
DJ075 (99 mg, 0.296 mmol, 92%, yellow solid) was prepared from (2-chloropyridin-3-yl)(phenyl)methanone (69.7 mg, 0.320 mmol), 3,5-dimethoxyaniline (58.9 mg, 0.384 mmol), $Pd(OAc)_2$ (3.6 mg, 0.016 mmol), Xantphos (18.5 mg, 0.032 mmol) and Cs_2CO_3 (156.5 mg, 0.480 mmol) in 1,4-dioxane (0.8 mL) using the same procedure as described for DJ072. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.85 (br s, NH), 8.42 (dd, J = 4.8, 2.0 Hz, 1H), 7.86 (dd, J = 7.6, 2.0 Hz, 1H), 7.62-7.65 (m, 2H), 7.55-7.59 (m, 1H), 7.47-7.51 (m, 2H), 7.04 (d, J = 2.4 Hz, 2H), 6.70 (dd, J = 8.0, 4.8 Hz, 1H), 6.23 (t, J = 2.4 Hz, 1H), 3.82 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 198.3, 160.9, 156.1, 153.4, 143.3, 141.1, 138.9, 131.7, 129.1, 128.3, 113.6, 112.7, 99.4, 95.5, 55.3.



(4-Chloropyridin-3-yl)(phenyl)methanone

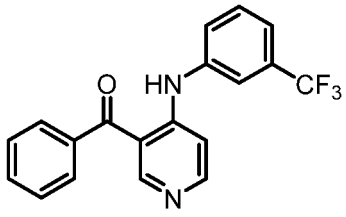
To a solution of diisopropylamine (1.7 g, 16.757 mmol) in anhydrous THF (16 mL) was slowly added *n*-BuLi (1.6 M solution in *n*-hexane, 10.5 mL, 16.757 mmol) at -78 °C and the reaction mixture was stirred at 0°C for 20 min. The LDA solution was cooled to -78 °C

and a slurry of 4-chloropyridine hydrochloride (1.14 g, 7.617 mmol) in THF (2 mL) was added and the reaction mixture was stirred at -78 °C for 10 min. Then *N,N*-dimethylbenzamide (1.25 g, 8.379 mmol) in THF (4 mL) was added to the reaction mixture at -78 °C and it was warmed to 21 °C. After 5 h, aqueous NH_4Cl solution was added to the reaction mixture and it was stirred for 10 min. The reaction mixture was extracted with EtOAc, washed with 1N HCl and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (*n*-hexane: EtOAc= 2:1) to obtain the desired product (976.6 mg, 4.487 mmol, 59%) as pale yellow liquid. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.64 (d, J = 5.2 Hz, 1H), 8.60 (d, J = 0.4 Hz, 1H), 7.83-7.80 (m, 2H), 7.64 (m, 1H), 7.52-7.47 (m, 2H), 7.45 (dd, J = 5.2, 0.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 192.9, 151.7, 149.7, 141.7, 136.2, 134.5, 134.3, 130.0, 128.9, 125.0.



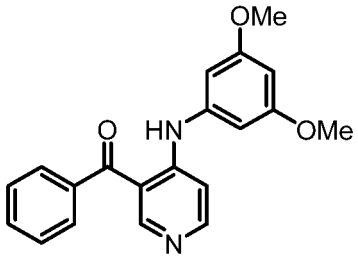
(4-((3-Fluorophenyl)amino)pyridin-3-yl)(phenyl)methanone (DJ076)

DJ076 (41.3 mg, 0.141 mmol, 44%, light yellow powder) was prepared from (4-chloropyridin-3-yl)(phenyl)methanone (70 mg, 0.322 mmol) and 3-fluoroaniline (42.9 mg, 0.386 mmol) in DMF (0.3 mL) using the same procedure as described for DJ068. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.52 (br s, NH), 8.68 (s, 1H), 8.30 (d, J = 6.4 Hz, 1H), 7.70-7.73 (m, 2H), 7.58-7.62 (m, 1H), 7.49-7.53 (m, 2H), 7.38 (td, J = 8.0, 6.4 Hz, 1H), 7.03-7.13 (m, 3H), 6.93 (ddd, J = 8.0, 2.4, 0.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 198.8, 163.4 (d, J = 245.8 Hz), 156.3, 152.9, 152.8, 139.9 (d, J = 9.8 Hz), 138.6, 132.2, 130.9 (d, J = 9.4 Hz), 129.5, 128.5, 119.3 (d, J = 3.0 Hz), 115.5, 112.4 (d, J = 21.0 Hz), 110.8 (d, J = 23.5 Hz), 108.0.



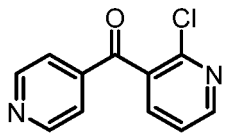
Phenyl(4-((3-(trifluoromethyl)phenyl)amino)pyridin-3-yl)methanone (DJ077)

DJ077 (22.8 mg, 0.067 mmol, 27%, light yellow solid) was prepared from (4-chloropyridin-3-yl)(phenyl)methanone (50 mg, 0.244 mmol), 3-trifluoromethylaniline (47 mg, 0.292 mmol), $Pd(OAc)_2$ (2.7 mg, 0.012 mmol), Xantphos (14 mg, 0.024 mmol) and Cs_2CO_3 (113 mg, 0.365 mmol) in 1,4-dioxane (0.6 mL) using the same procedure as described for DJ072. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.60 (br s, NH), 8.70 (s, 1H), 8.32 (d, J = 6.0 Hz, 1H), 7.71-7.74 (m, 2H), 7.48-7.63 (m, 7H), 7.06 (d, J = 6.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 198.7, 156.2, 152.9, 152.7, 138.9, 138.4, 132.2 (q, J = 32.5 Hz), 132.2, 130.3, 129.4, 128.5, 126.9, 123.6 (q, J = 270.9 Hz), 122.1 (q, J = 4.0 Hz), 120.4 (q, J = 3.4 Hz), 115.6, 107.6.



(4-((3,5-Dimethoxyphenyl)amino)pyridin-3-yl)(phenyl)methanone (DJ078)

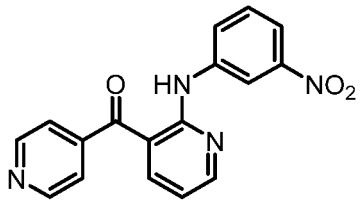
DJ078 (25.2 mg, 0.075 mmol, 29%, yellow solid) was prepared from (4-chloropyridin-3-yl)(phenyl)methanone (56 mg, 0.257 mmol), 3,5-dimethoxyaniline (47.3 mg, 0.309 mmol), $Pd(OAc)_2$ (2.9 mg, 0.013 mmol), Xantphos (14.9 mg, 0.026 mmol) and Cs_2CO_3 (125.7 mg, 0.386 mmol) in 1,4-dioxane (0.6 mL) using the same procedure as described for DJ072. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.46 (br s, NH), 8.64 (s, 1H), 8.25 (d, J = 6.0 Hz, 1H), 7.70-7.72 (m, 2H), 7.57-7.61 (m, 1H), 7.48-7.52 (m, 2H), 7.15 (d, J = 6.0 Hz, 1H), 6.46 (d, J = 2.0 Hz, 2H), 6.34 (t, J = 2.0 Hz, 1H), 3.80 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 198.7, 161.6, 156.2, 153.1, 152.5, 139.8, 138.7, 132.0, 129.4, 128.4, 115.2, 108.3, 102.1, 97.8, 55.4.



(2-Chloropyridin-3-yl)(pyridin-4-yl)methanone

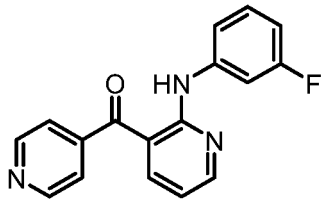
To a solution of 2,2,6,6-tetramethylpiperidine (357.2 mg, 2.529 mmol) in THF (2.5 mL) was slowly added *n*-BuLi (1.6 M solution in *n*-hexane, 1.47 mL, 2.349 mmol) at -78 °C and the reaction mixture was stirred at 0 °C for 30 min. Then 2-chloropyiridine (246.1 mg, 2.168 mmol) was added to the reaction mixture at -78 °C and it was stirred for 30 min. And a solution of *N*-methoxy-*N*-methylisonicotinamide (300 mg, 1.807 mmol) in THF (2.5 mL) was

added dropwise to the reaction mixture and it was stirred for a while before being warmed to 21 °C. After 4 h, the reaction mixture was quenched with saturated NH_4Cl solution and stirred for 10 min. Then the mixture was diluted and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (*n*-hexane: EtOAc = 1:1) to obtain the desired product (138.8 mg, 0.635 mmol, 35%) as a yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.81 (d, J = 6.0 Hz, 2H), 8.57 (dd, J = 4.8, 2.0 Hz, 1H), 7.77 (dd, J = 7.6, 2.0 Hz, 1H), 7.55 (d, J = 6.0 Hz, 2H), 7.41 (dd, J = 7.6, 4.8 Hz, 1H).^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 192.8, 151.8, 151.1, 147.9, 141.9, 138.5, 133.5, 122.5, 122.3.



(2-((3-Nitrophenyl)amino)pyridin-3-yl)(pyridin-4-yl)methanone (DJ079)

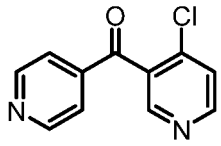
DJ079 (38.1 mg, 0.119 mmol, 50%, yellow solid) was prepared from (2-chloropyridin-3-yl)(pyridin-4-yl)methanone (51.6 mg, 0.236 mmol), 3-nitroaniline (39.1 mg, 0.283 mmol), $Pd(OAc)_2$ (2.6 mg, 0.012 mmol), Xantphos (13.7 mg, 0.024 mmol) and Cs_2CO_3 (115.3 mg, 0.354 mmol) in 1,4-dioxane (0.5 mL) using the same procedure as described for DJ072. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 11.11 (br s, NH), 8.90 (dd, J = 2.4, 2.0 Hz, 1H), 8.83 (d, J = 5.6 Hz, 2H), 8.52 (dd, J = 4.8, 2.0 Hz, 1H), 7.93 (tdd, J = 8.4, 1.2, 0.8 Hz, 2H), 7.84 (dd,, J = 8.0, 2.0 Hz, 1H), 7.46-7.51 (m, 1H), 7.47 (d, J = 5.6 Hz, 2H), 6.84 (dd, J = 8.0, 4.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 196.6, 155.7, 154.4, 150.5, 148.7, 145.5, 143.3, 140.3, 129.4, 126.6., 122.2, 117.8, 115.8, 114.1, 112.9.



(2-((3-Fluorophenyl)amino)pyridin-3-yl)(pyridin-4-yl)methanone (DJ080)

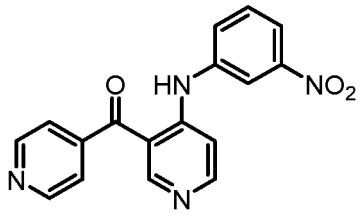
DJ080 (32 mg, 0.109 mmol, 52%, pale yellow solid) was prepared from (2-chloropyridin-3-yl)(pyridin-4-yl)methanone (46.1 mg, 0.211 mmol), 3-fluoroaniline (28.1 mg, 0.253 mmol), $Pd(OAc)_2$ (2.4 mg, 0.011 mmol), Xantphos (12.2 mg, 0.021 mmol) and Cs_2CO_3 (103 mg, 0.316 mmol) in 1,4-dioxane (0.5 mL) using the same procedure as

described for DJ072. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.98 (br s, NH), 8.82 (d, J = 5.6 Hz, 2H), 8.48 (dd, J = 4.8, 2.0 Hz, 1H), 7.86 (dt, J = 11.6, 2.0 Hz, 1H), 7.79 (dd, J = 7.6, 2.0 Hz, 1H), 7.46 (d, J = 6.0 Hz, 2H), 7.26-7.35 (m, 2H), 6.78-6.82 (m, 1H), 6.76 (dd, J = 8.0, 4.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 196.5, 163.1 (d, J = 242.3 Hz), 156.0, 154.6, 150.3, 145.8, 143.3, 140.7 (d, J = 11.0 Hz), 129.8 (d, J = 9.5 Hz), 122.2, 116.6 (d, J = 2.7 Hz), 113.4, 112.5, 110.1 (d, J = 21.3 Hz), 108.5 (d, J = 26.2 Hz).



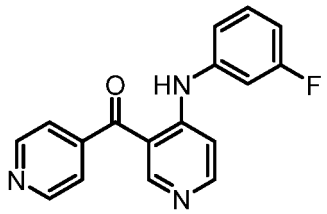
(4-Chloropyridin-3-yl)(pyridin-4-yl)methanone

This compound (200.3 mg, 0.916 mmol, yellow oil) was prepared from 4-chloropyridine hydrochloride (325.2 mg, 2.168 mmol) and *N*-methoxy-*N*-methylisonicotinamide (300 mg, 1.807 mmol) in THF (8 mL) with *in situ* LiTMP (4.516 mmol) using the same procedure as described for (2-chloropyridin-3-yl)(pyridin-4-yl)methanone. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.78 (d, J = 6.0 Hz, 2H), 8.62 (d, J = 6.4 Hz, 1H), 8.58 (s, 1H), 7.53 (d, J = 6.0 Hz, 2H), 7.41 (d, J = 6.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 192.2, 152.4, 150.9, 149.9, 142.0, 141.8, 132.8, 125.0, 122.1.



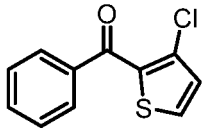
(4-((3-Nitrophenyl)amino)pyridin-3-yl)(pyridin-4-yl)methanone (DJ081)

DJ081 (64.1 mg, 0.200 mmol, 86%, yellow solid) was prepared from (4-chloropyridin-3-yl)(pyridin-4-yl)methanone (51 mg, 0.233 mmol), 3-nitroaniline (35.4 mg, 0.257 mmol), $Pd(OAc)_2$ (2.6 mg, 0.012 mmol), Xantphos (13.5 mg, 0.023 mmol) and Cs_2CO_3 (114 mg, 0.350 mmol) in 1,4-dioxane (0.5 mL) using the same procedure as described for DJ072. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.71 (br s, NH), 8.82 (d, J = 6.0 Hz, 2H), 8.62 (s, 1H), 8.36 (d, J = 6.0 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 8.09 (ddd, J = 6.8, 2.4, 1.6 Hz, 1H), 7.61-7.63 (m, 2H), 7.51 (d, J = 5.6 Hz, 2H), 7.08 (d, J = 6.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 197.2, 156.2, 153.8, 152.6, 150.4, 149.1, 145.0, 139.1, 130.6, 129.6, 122.3, 120.5, 118.4, 114.7, 107.7.



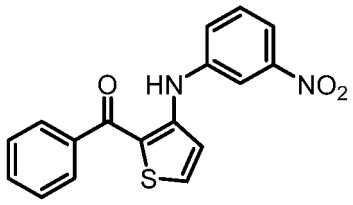
(4-((3-Fluorophenyl)amino)pyridin-3-yl)(pyridin-4-yl)methanone (DJ082)

DJ082 (69.7 mg, 0.238 mmol, 88%, pale yellow solid) was prepared from (4-chloropyridin-3-yl)(pyridin-4-yl)methanone (58.8 mg, 0.269 mmol), 3-fluoroaniline (35.9 mg, 0.323 mmol), $Pd(OAc)_2$ (3.0 mg, 0.013 mmol), Xantphos (15.5 mg, 0.027 mmol) and Cs_2CO_3 (131.4 mg, 0.403 mmol) in 1,4-dioxane (0.5 mL) using the same procedure as described for DJ072. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.57 (br s, NH), 8.80 (d, J = 5.6 Hz, 2H), 8.56 (s, 1H), 8.28 (dd, J = 6.0, 0.4 Hz, 1H), 7.49 (d, J = 6.0 Hz, 2H), 7.38 (td, J = 8.0, 6.4 Hz, 1H), 7.01-7.09 (m, 3H), 6.95 (tdd, J = 8.0, 2.4, 0.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 197.1, 163.3 (d, J = 246.3 Hz), 156.2, 153.4, 153.1, 150.3, 145.3, 139.2 (d, J = 9.8 Hz), 130.9 (d, J = 9.3 Hz), 122.3, 119.7 (d, J = 3.1 Hz), 114.3, 113.0 (d, J = 20.9 Hz), 111.3 (d, J = 23.3 Hz), 107.9.



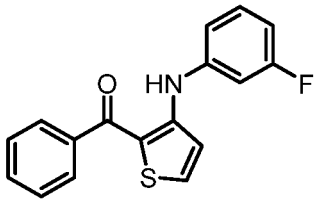
(3-Chlorothiophen-2-yl)(phenyl)methanone

This compound (678 mg, 2.91 mmol, 58%, pale yellow oil) was prepared from 3-chlorothiophene (593 mg, 5 mmol), benzoyl chloride (1.41 g, 10 mmol), 2,2,6,6-tetramethylpiperidine (1.41 g, 10 mmol), *n*-BuLi (1.6 M solution in *n*-hexane, 6.25 mL, 10 mmol), tetramethylethylenediamine (581.2 mg, 5 mmol) and CuCl (495 mg, 5 mmol) in THF (13 mL) using the same procedure as described for (2-chloropyridin-3-yl)(phenyl)methanone. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.82-7.84 (m, 2H), 7.57-7.61 (m, 1H), 7.56 (d, J = 5.2 Hz, 1H), 7.45-7.49 (m, 2H), 7.05 (d, J = 5.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 187.6, 137.8, 134.3, 132.8, 130.5, 130.0, 129.5, 128.3. One low-field carbon not observed.



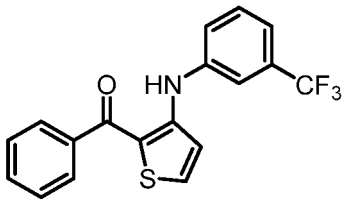
(3-((3-Nitrophenyl)amino)thiophen-2-yl)(phenyl)methanone (DJ083)

DJ083 (65.3 mg, 0.201 mmol, 76%, yellow solid) was prepared from (3-chlorothiophen-2-yl)(phenyl)methanone (59 mg, 0.265 mmol), 3-nitroaniline (43.9 mg, 0.318 mmol), $Pd(OAc)_2$ (3 mg, 0.013 mmol), Xantphos (15.3 mg, 0.027 mmol) and Cs_2CO_3 (129.5 mg, 0.397 mmol) in 1,4-dioxane (0.5 mL) using the same procedure as described for DJ072. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.75 (br s, NH), 8.15 (m, 1H), 7.86-7.92 (m, 3H), 7.60 (d, J = 5.2 Hz, 1H), 7.48-7.58 (m, 5H), 7.29 (d, J = 5.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.6, 151.5, 149.2, 142.4, 140.2, 135.2, 131.6, 130.2, 128.4, 128.1, 125.8, 117.5, 117.4, 114.5, 113.9.



(3-((3-Fluorophenyl)amino)thiophen-2-yl)(phenyl)methanone (DJ084)

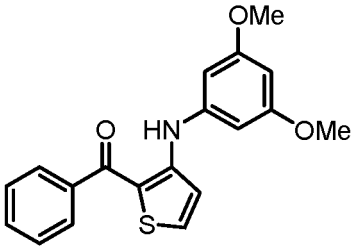
DJ084 (61.2 mg, 0.206 mmol, 76%, yellow solid) was prepared from (3-chlorothiophen-2-yl)(phenyl)methanone (60.4 mg, 0.271 mmol), 3-fluoroaniline (36.2 mg, 0.326 mmol), $Pd(OAc)_2$ (3 mg, 0.013 mmol), Xantphos (15.7 mg, 0.027 mmol) and Cs_2CO_3 (132.5 mg, 0.407 mmol) in 1,4-dioxane (0.5 mL) using the same procedure as described for DJ072. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.60 (br s, NH), 7.85-7.87 (m, 2H), 7.52 (d, J = 5.2 Hz, 1H), 7.47-7.56 (m, 3H), 7.26-7.33 (m, 1H), 7.24 (d, J = 5.6 Hz, 1H), 6.98-7.03 (m, 2H), 6.79 (tdd, J = 8.0, 2.0, 0.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.2, 163.5 (d, J = 244.3 Hz), 152.7, 142.7 (d, J = 10.2 Hz), 140.5, 134.9, 131.4, 130.6 (d, J = 9.6 Hz), 128.4, 128.0, 117.7, 116.2 (d, J = 2.8 Hz), 113.2, 110.1 (d, J = 21.2 Hz), 107.4 (d, J = 24.2 Hz).



Phenyl(3-((3-(trifluoromethyl)phenyl)amino)thiophen-2-yl)methanone (DJ085)

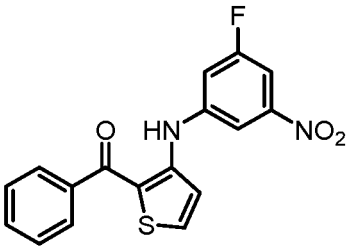
DJ085 (80.5 mg, 0.232 mmol, 79%, yellow solid) was prepared from (3-chlorothiophen-2-yl)(phenyl)methanone (65.3 mg, 0.293 mmol), 3-trifluoromethylaniline (56.7 mg, 0.352 mmol), $Pd(OAc)_2$ (3.3 mg, 0.015 mmol), Xantphos (17 mg, 0.029 mmol) and Cs_2CO_3 (143.3 mg, 0.440 mmol) in 1,4-dioxane (0.6 mL) using the same procedure as described for DJ072. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.68 (br s, NH), 7.86-7.88 (m,

2H), 7.45-7.58 (m, 5H), 7.55 (d, J = 5.6 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 5.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.3, 152.5, 141.6, 140.4, 135.0, 131.9 (q, J = 32.2 Hz), 131.4, 130.0, 128.4, 128.0, 123.8 (q, J = 270.8 Hz), 123.5 (d, J = 1.1 Hz), 119.9 (q, J = 3.7 Hz), 117.4, 116.9 (q, J = 3.7 Hz), 113.5.



(3-((3,5-Dimethoxyphenyl)amino)thiophen-2-yl)(phenyl)methanone (DJ086)

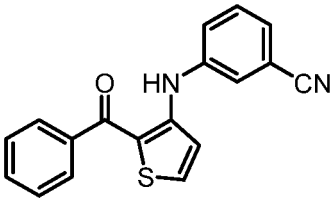
DJ086 (76 mg, 0.224 mmol, 89%, yellow liquid) was prepared from (3-chlorothiophen-2-yl)(phenyl)methanone (55.9 mg, 0.251 mmol), 3,5-dimethoxyaniline (46.1 mg, 0.301 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), Xantphos (14.5 mg, 0.025 mmol) and Cs_2CO_3 (122.7 mg, 0.377 mmol) in 1,4-dioxane (0.5 mL) using the same procedure as described for DJ072. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.57 (br s, NH), 7.84-7.87 (m, 2H), 7.49 (d, J = 5.6 Hz, 1H), 7.46-7.54 (m, 3H), 7.28 (d, J = 5.6 Hz, 1H), 6.43 (d, J = 2.4 Hz, 2H), 6.24 (t, J = 2.4 Hz, 1H), 3.80 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.0, 161.5, 153.5, 142.6, 140.7, 134.8, 131.2, 128.3, 128.0, 118.1, 112.5, 99.2, 95.8, 55.4.



(3-((3-Fluoro-5-nitrophenyl)amino)thiophen-2-yl)(phenyl)methanone (DJ087)

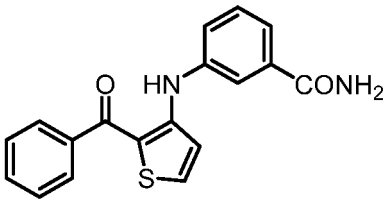
DJ087 (38.1 mg, 0.111 mmol, 36%, yellow solid) was prepared from (3-chlorothiophen-2-yl)(phenyl)methanone (68 mg, 0.305 mmol), 5-fluoro-3-nitroaniline (57.2 mg, 0.366 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), Xantphos (17.7 mg, 0.031 mmol) and Cs_2CO_3 (149.3 mg, 0.458 mmol) in 1,4-dioxane (0.6 mL) using the same procedure as described for DJ072. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.79 (br s, NH), 7.93 (d, J = 0.4 Hz, 1H), 7.86-7.88 (m, 2H), 7.64 (d, J = 5.6 Hz, 1H), 7.56-7.60 (m, 2H), 7.49-7.53 (m, 2H), 7.32 (d, J = 5.2 Hz, 1H), 7.25 (ddd, J = 10.0, 2.4, 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.8, 163.0 (d, J = 248.5 Hz), 150.4, 149.9 (d, J = 10.9 Hz), 143.8 (d, J = 11.0 Hz),

139.9, 135.2, 131.9, 128.5, 128.2, 117.7, 115.6, 111.8 (d, J = 24.7 Hz), 109.6 (d, J = 3.0 Hz), 104.8 (d, J = 26.9 Hz).



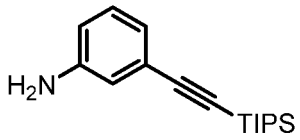
3-((2-Benzoylthiophen-3-yl)amino)benzonitrile (DJ088)

DJ088 (99.6 mg, 0.327 mmol, 93%, yellow solid) was prepared from (3-chlorothiophen-2-yl)(phenyl)methanone (78.6 mg, 0.353 mmol), 3-aminobenzonitrile (50 mg, 0.424 mmol), $Pd(OAc)_2$ (4 mg, 0.018 mmol), Xantphos (20.4 mg, 0.035 mmol) and Cs_2CO_3 (172.5 mg, 0.530 mmol) in 1,4-dioxane (0.7 mL) using the same procedure as described for DJ072. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.63 (br s, NH), 7.84-7.87 (m, 2H), 7.53-7.58 (m, 3H), 7.47-7.51 (m, 2H), 7.43-7.45 (m, 2H), 7.34 (m, 1H), 7.20 (d, J = 5.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.5, 151.7, 142.0, 140.2, 135.1, 131.6, 130.4, 128.4, 126.5, 124.6, 122.7, 118.5, 117.4, 114.2, 113.5. One low-field carbon not observed.



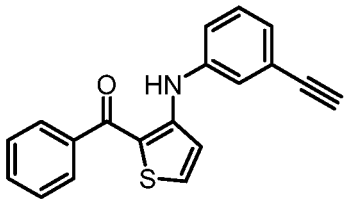
3-((2-Benzoylthiophen-3-yl)amino)benzamide (DJ089)

To a solution of DJ088 (59.6 mg, 0.196 mmol) in *N*-methyl-2-pyrrolidone (0.7 mL) was added 30% H_2O_2 solution (0.3 mL) and 6N NaOH (0.15 mL) and the reaction mixture was stirred at 50 °C for 1 h. After it was cooled, water (10 mL) was added to the reaction mixture and it was stirred for 5 min. Then precipitated solid was filtered and washed with water (20 mL). The crude solid was dried under air and washed with Et_2O and cold dichloromethane to remove the remaining starting material. Then the yellow solid was dried *in vacuo* to obtain the desired product DJ089 (33.9 mg, 0.105 mmol, 54%) as a yellow powder. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 10.52 (br s, NH), 8.00-8.02 (m, 2H), 7.78-7.82 (m, 3H), 7.54-7.60 (m, 4H), 7.41-7.47 (m, 3H), 7.32 (d, J = 5.2 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 188.1, 167.5, 152.4, 140.6, 140.3, 137.0, 135.7, 131.5, 129.5, 128.6, 127.6, 122.9, 122.4, 119.0, 118.1, 112.3.



3-((Triisopropylsilyl)ethynyl)aniline

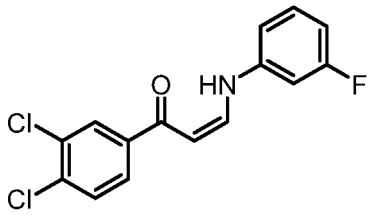
To a solution of 3-bromoaniline (500 mg, 2.907 mmol), triisopropylsilylacetylene (795.2 mg, 4.360 mmol) and copper (I) iodide (55.4 mg, 0.291 mmol) in TEA (3 mL) and DMF (3 mL) was added $Pd(PPh_3)_4$ (336.3 mg 0.291 mmol) and the reaction mixture was stirred at 80 °C for 2 h. After it was cooled, the reaction mixture was diluted with EtOAc and aqueous NH_4Cl solution. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting brown oil was purified by flash column chromatography (*n*-hexane: EtOAc = 4:1) to obtain the desired product (588.6 mg, 2.152 mmol, 74%) as a pale yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.08 (dd, J = 8.0, 7.6 Hz, 1H), 6.89 (dd, J = 7.6, 1.2 Hz, 1H), 6.81 (dd, J = 2.0, 1.6 Hz, 1H), 6.63 (ddd, J = 8.0, 2.4, 0.8 Hz, 1H), 3.57 (br s, NH_2), 1.13 (m, 21H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 146.1, 129.1, 124.2, 122.5, 118.3, 115.3, 107.4, 89.7, 18.6, 11.3.



(3-((3-Ethynylphenyl)amino)thiophen-2-yl)(phenyl)methanone (DJ090)

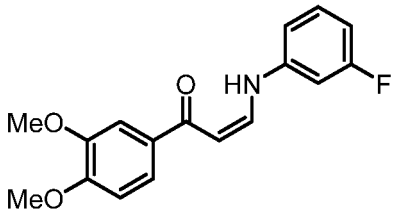
Phenyl(3-((3-((triisopropylsilyl)ethynyl)phenyl)amino)thiophen-2-yl)methanone (99.6 mg, 0.217 mmol) was prepared from (3-chlorothiophen-2-yl)(phenyl)methanone (60.8 mg, 0.273 mmol), 3-((triisopropylsilyl)ethynyl)aniline (90 mg, 0.328 mmol), $Pd(OAc)_2$ (3.1 mg, 0.014 mmol), Xantphos (15.8 mg, 0.027 mmol) and Cs_2CO_3 (133.4 mg, 0.410 mmol) in 1,4-dioxane (0.6 mL) using the same procedure as described for DJ072. Then the yellow liquid obtained was treated with TBAF (1.0 M solution in THF, 0.43 mL) in THF (3 mL) at 0 °C for 40 min. After the reaction was completed, Et_2O (10 mL) and aqueous NH_4Cl was added to the reaction mixture and it was stirred for 10 min. Then the biphasic mixture was separated and aqueous layer was extracted with Et_2O (2 X 10 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (*n*-hexane: EtOAc = 6:1) to obtain the desired product DJ090 (49.8 mg, 0.164 mmol, 76%) as an orange solid. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.55 (s, NH), 7.85-7.87 (m, 2H), 7.46-7.56 (m, 4H), 7.42 (t, J = 1.6 Hz,

1H), 7.30-7.33 (m, 1H), 7.22-7.25 (m, 2H), 7.19 (d, J = 5.6 Hz, 1H), 3.10 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.1, 153.1, 141.0, 140.6, 134.9, 131.3, 129.4, 128.3, 128.0, 127.2, 124.0, 123.2, 121.5, 117.6, 112.8, 83.1, 77.6.



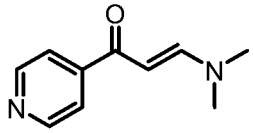
(*Z*)-1-(3,4-Dichlorophenyl)-3-((3-fluorophenyl)amino)prop-2-en-1-one (DJ091)

DJ091 (105.5 mg, 0.340 mmol, 68%, yellow powder) was prepared from 1-(3,4-dichlorophenyl)prop-2-yn-1-one (EDB-235, 100 mg, 0.502 mmol), 3-fluoroaniline (67 mg, 0.603 mmol) and copper (I) iodide (28.7 mg, 0.151 mmol) in DMF (0.5 mL) using the same procedure as described for DJ001. ^{1}H NMR (CDCl3, 400 MHz) δ (ppm): 12.09 (d, J = 10.8 Hz, NH), 8.00 (d, J = 1.6 Hz, 1H), 7.74 (dd, J = 8.4, 2.0 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.48 (dd, J = 12.4, 8.0 Hz, 1H), 7.30 (dd, J = 14.8, 8.0 Hz, 1H), 6.78-6.88 (m, 3H), 5.96 (d, J = 8.0 Hz, 1H). ^{13}C NMR (CDCl3, 100 MHz) δ (ppm): 188.4, 163.7 (d, J = 245.2 Hz), 145.2, 141.6 (d, J = 10.2 Hz), 138.6, 136.0, 133.0, 131.1 (d, J = 10.5 Hz), 130.5, 129.4, 126.4, 112.3 (d, J = 2.7 Hz), 110.7 (d, J = 21.1 Hz), 103.5 (d, J = 25.3 Hz), 93.8.



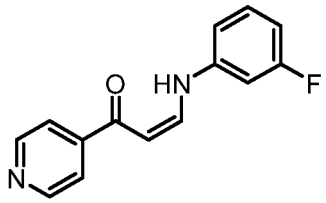
(*Z*)-1-(3,4-Dimethoxyphenyl)-3-((3-fluorophenyl)amino)prop-2-en-1-one (DJ092)

DJ092 (124 mg, 0.412 mmol, 78%, yellow powder) was prepared from 1-(3,4-dimethoxyphenyl)prop-2-yn-1-one (EDB-245, 100 mg, 0.526 mmol), 3-fluoroaniline (70 mg, 0.631 mmol) and copper (I) iodide (30 mg, 0.158 mmol) in DMF (0.5 mL) using the same procedure as described for DJ001. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.04 (d, J = 12.0 Hz, NH), 7.54 (d, J = 2.0 Hz, 1H), 7.52 (dd, J = 8.4, 2.0 Hz, 1H), 7.38 (dd, J = 12.0, 8.0 Hz, 1H), 7.24 (td, J = 8.0, 6.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.70-6.82 (m, 3H), 6.00 (d, J = 8.4 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.1, 163.7 (d, J = 244.5 Hz), 152.3, 149.0, 143.5, 142.0 (d, J = 10.1 Hz), 131.8, 131.0 (d, J = 10.6 Hz), 121.2, 111.8 (d, J = 2.7 Hz), 110.1, 100.9 (d, J = 21.2 Hz), 109.8, 102.9 (d, J = 25.3 Hz), 94.1, 55.9, 55.8.



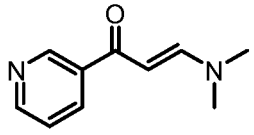
(*E*)-3-(Dimethylamino)-1-(pyridin-4-yl)prop-2-en-1-one

To a solution of 4-acetylpyridine (500 mg, 4.128 mmol) in EtOH (4 mL) was added *N*,*N*-dimethylforamide dimethyl acetal (737.7 mg, 6.191 mmol) and the reaction mixture was stirred under reflux for 5 h. After it was cooled, the reaction mixture was concentrated under reduced pressure. The crude liquid was precipitated by addition of *n*-hexane. Then the solid was washed with *n*-hexane to obtain the desired product (385.2 mg 2.186 mmol, 53 %) as a dark orange solid which was used for further steps without purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.68 (d, J = 6.0 Hz, 2H), 7.82 (d, J = 12.0 Hz, 1H), 7.66 (d, J = 6.0 Hz, 2H), 5.63 (d, J = 12.4 Hz, 1H), 3.17 (s, 3H), 2.94 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 186.6, 155.2, 150.2, 147.2, 121.1, 91.7, 45.2, 37.4.



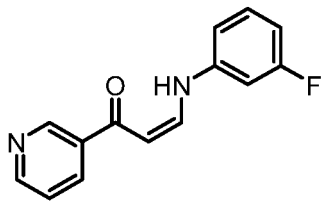
(*Z*)-3-((3-Fluorophenyl)amino)-1-(pyridin-4-yl)prop-2-en-1-one (DJ093)

A solution of (*E*)-3-(dimethylamino)-1-(pyridin-4-yl)prop-2-en-1-one (65.6 mg, 0.372 mmol) and 3-fluoroaniline (41.4 mg, 0.372 mmol) in acetic acid (0.5 mL) was stirred at 90 °C for 30 min. After it was cooled, the precipitated orange-colored solid was diluted with water and 1N NaOH solution. The mixture was extracted with EtOAc and the combined organic layer was washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (*n*-hexane: EtOAc = 1:1) to obtain the desired product DJ093 (60.2 mg, 0.249 mmol, 67 %) as a yellow crystalline solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.18 (d, J = 11.6 Hz, NH), 8.76 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 6.0 Hz, 2H), 7.54 (dd, J = 12.8, 8.0 Hz, 1H), 7.32 (td, J = 8.0, 6.4 Hz, 1H), 6.79-6.91 (m, 3H), 6.02 (d, J = 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.2, 163.7 (d, J = 245.4 Hz), 150.5, 145.8, 145.4, 141.4 (d, J = 9.9 Hz), 131.2 (d, J = 9.5 Hz), 120.8, 112.5 (d, J = 2.9 Hz), 111.0 (d, J = 21.2 Hz), 103.7 (d, J = 25.3 Hz), 94.0.



(*E*)-3-(dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one

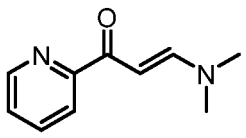
This compound (592.1 mg 3.36 mmol, 81%, orange crystalline solid) was prepared from 3-acetylpyridine (500 mg, 4.128 mmol) and *N*, *N*-dimethylforamide dimethyl acetal (737.7 mg, 6.191 mmol) in EtOH (4 mL) using the same procedure as described for (*E*)-3-(dimethylamino)-1-(pyridin-4-yl)prop-2-en-1-one. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 9.02 (d, J = 1.6 Hz, 1H), 8.60 (dd, J = 4.8, 1.6 Hz, 1H), 8.12 (ddd, J = 8.0, 2.0, 1.6 Hz, 1H), 7.77 (d, J = 12.0 Hz, 1H), 7.29 (dd, J = 8.0, 4.8 Hz, 1H), 5.61 (d, J = 11.6 Hz, 1H), 3.11 (s, 3H), 2.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 186.2, 154.5, 151.3, 148.8, 135.5, 134.9, 123.1, 91.7, 45.0, 37.2.



(*Z*)-3-((3-Fluorophenyl)amino)-1-(pyridin-3-yl)prop-2-en-1-one (DJ094)

DJ094 (86.7 mg, 0.358 mmol, 75%, yellow solid) was prepared from (*E*)-3-(dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one (84.4 mg, 0.479 mmol) and 3-fluoroaniline (53.3 mg 0.479 mmol) in acetic acid (0.5 mL) using the same procedure as described for DJ093.

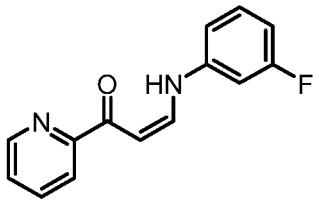
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.12 (d, J = 11.6 Hz, NH), 9.13 (d, J = 1.6 Hz, 1H), 8.72 (dd, J = 4.8, 1.6 Hz, 1H), 8.21 (dt, J = 8.0, 2.0 Hz, 1H), 7.50 (dd, J = 12.0, 8.0 Hz, 1H), 7.40 (ddd, J = 8.0, 4.8, 0.8 Hz, 1H), 7.30 (td, J = 8.0, 6.4 Hz, 1H), 6.77-6.90 (m, 3H), 6.03 (d, J = 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.2, 163.7 (d, J = 245.1 Hz), 152.2, 148.8, 145.2, 141.6 (d, J = 10.0 Hz), 134.8, 134.2, 131.1 (d, J = 9.6 Hz), 123.5, 112.3 (d, J = 2.9 Hz), 110.8 (d, J = 21.2 Hz), 103.6 (d, J = 25.3 Hz), 94.1.



(*E*)-3-(Dimethylamino)-1-(pyridin-2-yl)prop-2-en-1-one

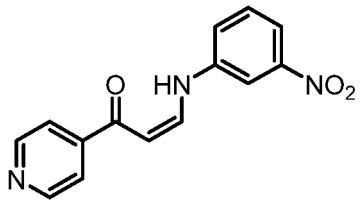
This compound (500.9 mg 2.842 mmol, 69%, light orange solid) was prepared from 2-acetylpyridine (500 mg, 4.128 mmol) and *N*, *N*-dimethylforamide dimethyl acetal (737.7

mg, 6.191 mmol) in EtOH (4 mL) using the same procedure as described for (*E*)-3-(dimethylamino)-1-(pyridin-4-yl)prop-2-en-1-one. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.61 (ddd, J = 4.8, 1.6, 0.8 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.89 (d, J = 12.8 Hz, 1H), 7.77 (td, J = 7.6, 1.6 Hz, 1H), 7.33 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 6.43 (d, J = 12.8 Hz, 1H), 3.15 (s, 3H), 2.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 186.9, 156.2, 154.7, 148.2, 136.6, 125.3, 122.0, 91.1, 45.1, 37.4.



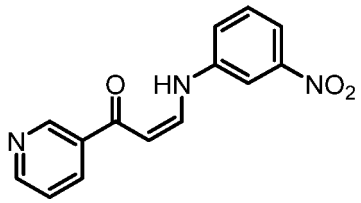
(*Z*)-3-((3-Fluorophenyl)amino)-1-(pyridin-2-yl)prop-2-en-1-one (DJ095)

DJ095 (48.8 mg, 0.201 mmol, 41%, beige solid) was prepared from (*E*)-3-(dimethylamino)-1-(pyridin-2-yl)prop-2-en-1-one (86.4 mg, 0.490 mmol) and 3-fluoroaniline (54.5 mg 0.490 mmol) in acetic acid (0.5 mL) using the same procedure as described for DJ093. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.09 (d, J = 11.2 Hz, NH), 8.67 (dd, J = 4.0, 0.8 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.85 (td, J = 7.6, 1.6 Hz, 1H), 7.55 (dd, J = 12.0, 8.0 Hz, 1H), 7.41 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.30 (td, J = 8.0, 6.4 Hz, 1H), 6.75-6.90 (m, 3H), 6.78 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.0, 163.7 (d, J = 244.9 Hz), 154.8, 148.7, 145.1, 141.9 (d, J = 10.2 Hz), 137.0, 131.0 (d, J = 9.5 Hz), 126.0, 121.8, 112.2 (d, J = 2.8 Hz), 110.4 (d, J = 21.3 Hz), 103.4 (d, J = 25.3 Hz), 94.1.



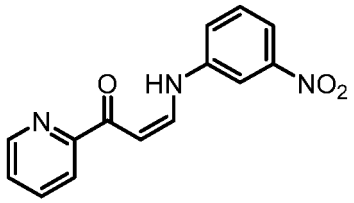
(*Z*)-3-((3-Nitrophenyl)amino)-1-(pyridin-4-yl)prop-2-en-1-one (DJ096)

DJ096 (65.6 mg, 0.244 mmol, 54%) was prepared from (*E*)-3-(dimethylamino)-1-(pyridin-4-yl)prop-2-en-1-one (79.2 mg, 0.449 mmol) and 3-nitroaniline (62.1 mg 0.449 mmol) in acetic acid (0.5 mL) using the same procedure as described for DJ093. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.30 (d, J = 11.6 Hz, NH), 8.78 (d, J = 6.0 Hz, 2H), 8.01 (dd, J = 2.4, 2.0 Hz, 1H), 7.96 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H), 7.73 (d, J = 6.0 Hz, 2H), 7.62 (dd, J = 12.0, 8.0 Hz, 1H), 7.54 (dd, J = 8.4, 8.0 Hz, 1H), 7.41 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H), 6.12 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.8, 150.6, 149.4, 145.1, 145.0, 141.1, 130.8, 122.6, 120.8, 118.5, 110.6, 95.1.



(*Z*)-3-((3-Nitrophenyl)amino)-1-(pyridin-3-yl)prop-2-en-1-one (DJ097)

DJ097 (83.4 mg, 0.310 mmol, 69%) was prepared from (*E*)-3-(dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one (78.9 mg, 0.448 mmol) and 3-nitroaniline (61.9 mg 0.448 mmol) in acetic acid (0.5 mL) using the same procedure as described for DJ093. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.25 (d, J = 11.6 Hz, NH), 9.16 (d, J = 1.6 Hz, 1H), 8.75 (dd, J = 4.8, 1.6 Hz, 1H), 8.24 (dt, J = 8.0, 2.0 Hz, 1H), 8.00 (dd, J = 2.4, 2.0 Hz, 1H), 7.94 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H), 7.60 (dd, J = 12.0, 8.0 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.39-7.45 (m, 2H), 6.13 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.7, 152.4, 149.4, 148.8, 144.5, 141.3, 135.0, 133.9, 130.7, 123.6, 122.4, 118.3, 110.4, 95.2.



(*Z*)-3-((3-Nitrophenyl)amino)-1-(pyridin-2-yl)prop-2-en-1-one (DJ098)

DJ098 (64.6 mg, 0.240 mmol, 49%) was prepared from (*E*)-3-(dimethylamino)-1-(pyridin-2-yl)prop-2-en-1-one (87 mg, 0.494 mmol) and 3-nitroaniline (68.2 mg 0.494 mmol) in acetic acid (0.5 mL) using the same procedure as described for DJ093. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 12.21 (d, J = 11.6 Hz, NH), 8.68 (d, J = 4.0 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.99 (dd, J = 2.4, 2.0 Hz, 1H), 7.91 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H), 7.86 (td, J = 8.0, 2.0 Hz, 1H), 7.62 (dd, J = 12.0, 8.0 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.28-7.45 (m, 2H), 6.89 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.6, 154.5, 149.4, 148.8, 144.2, 141.5, 137.0, 130.6, 126.2, 122.1, 121.9, 117.9, 110.3, 95.2.

Example 2: Effect of DJ001 and DJ003 on Survival of Irradiated Mice

DJ001 activates Rac1 signaling in HSCs, accelerates HSC regeneration in irradiated mice and dramatically increases mice survival following lethal dose irradiation, as shown in Figure 1. A) CFU-GEMMs produced by TSF media vs. TSF + GJ001 (p=0.001). B) Percentage of BM KSL cells expressing Rac1GTP (p=0.008). C) Survival of mice irradiated

with 750 cGy followed by treatment with DJ001 or vehicle (p=0.0007). D) % BM KSL cells (blue) and %ckit^{+}sca-1^{-}lin^{-} progenitors (gray) at day +21 in irradiated mice.

Figure 2 shows that DJ003 increases hematopoietic colony formation (Figure 2A) and improves survival of irradiated mice (Figure 2B).

Example 3: Rac1 Activation Assay

Cell cultures were incubated with each tested compound for 2 minutes at concentrations of 1 and 10 µg/mL, after which the cells were tested for Rac1 activation using a G-LISA activation assay. The cells were lysed and the lysates introduced into wells containing Rac-GTP-binding protein, then sequentially incubated with anti-Rac1 antibody and a horseradish peroxidase-linked secondary antibody. The amount of horseradish peroxidase was then quantitated to evaluate the Rac1 activation potency of each compound studied. The results are shown in Table 2.

Table 2

Compound	**Rac1 Activation**	**Potency relative to EGF control = ++++**
DJ001	yes	++++
DJ002	no	
DJ003	yes	++
DJ004	yes	++
DJ005	no	
DJ006	no	
DJ007	no	
DJ008	no	
DJ009	yes	++++
DJ011	yes	++++
DJ012	yes	++++
DJ013	yes	++++
DJ014	yes	++++
DJ015	yes	++++
DJ016	no	
DJ017	no	
DJ018	no	
DJ019	no	

Example 4: Rac1 Activation Assay

Compounds DJ001-DJ009 and DJ011-DJ036 were assayed as described in Example 3. The results are presented in Figures 3, 5A, and 5B.

Example 5: Mouse Survival Study

Mice were subjected to 750 cGy of radiation and treated with either water or DJ009. The results are depicted in Figure 4.

Example 6: In vitro Phosphatase Assay

The two interacellular catalytic domains (D1D2) of PTPRS were cloned into a pET28a vector and overexpressed in E. coli BL21 and purified as described in Jeon TJ, et al.. Structure of the Catalytic Domain of Protein Tyrosine Phosphatase Sigma in the Sulfenic Acid Form. Molecules and Cells. 2013;36(1):55-61. doi:10.1007/s10059-013-0033-x. Enzymatic activity of PTPRS was assayed using a modified version of the Malachite Green Assay (described in Lorenz U. Protein Tyrosine Phosphatase Assays. Current protocols in immunology / edited by John E Coligan . [et al]. 2011; CHAPTER:Unit-11.7. doi:10.1002/0471142735.im1107s93) and the Tyrosine Phosphatase Assay Kit (Promega Coorperation). Unless stated otherwise, standard assays were carried out using 50 nM PTPRS protein in 1x Buffer (10 mM Tris, 5 mM MgCl2, 10mM NaCl, 0.02% Tween) and Tyr Phosphopeptide as substrate (100uM for figure 1 and 50 – 1200 uM in figure 2) . Catalytic domains D1D2 were preincubated with the test compound or control for 15 min in the wells of a 96 well plate before the addition of 100 uM Tyr Phosphopeptide (DADA(pY)LIPQQG).

For IC_{50} determination, rates normalized relative to uninhibited controls (DMSO) were plotted against compound concentration and fitted using a four-parameter nonlinear regression curve fit ((y = [(A – D) (1 + {xC–1}B)–1] + D), (Prism 6.0, Graphpad Software). For mechanism studies and determination of the enyzme's K_m and V_{max}, data were analyzed using a nonlinear regression fit according to classical Mechaelis-Menten kinetics model $Y=V_{max}*X/(K_m+X)$ (Prism 6.0, Graphpad Software).

The IC50s measured are listed in Table 3. Activity data as a function of inhibitor concentration is shows in Figures 6A and 6B.

Table 3

Compound	IC_{50} (μM)
DJ001	1.43
DJ003	1.06
DJ006	3.03
DJ008	N/D
DJ009	1.37
DJ015	1.39
DJ027	0.91
DJ030	1.83
DJ033	0.95

Example 7: Mechanistic Study

Substrate titration of PTPσ showed that DJ001 (compound 3071) is a classical noncompetitive inhibitor that inhibits substrate catalysis (V_{max}) but not substrate binding (constant K_m). Plots of V_{max} and K_m as a function of DJ001 concentration are shown in Figure 7.

Example 8: Phosphatase Profiler Screen

DJ001 was evaluated in a PhosphataseProfiler screen at 10 μM and 1 μM (2.7 μg/mL and 0.27 μg/mL) concentrations at Eurofins Pharma Discovery Services UK (Study number UK022-0004033) against a panel of 21 Phosphatases. In each experiment, the respective reference antagonist/agonist was tested directly with DJ001, and the data were compared with historical values determined at Eurofins. DJ001 compound inhibition was calculated as percentage inhibition of the enzymatic activity compared to control.

Example 9: G-LISA Activation Assays

The RAC1-GTP activation levels in BM lin^- cells were measured using a colorimetric based RAC1-, G-LISA Activation Assay Kit (Cytoskeleton Inc.). BM cells from femurs and tibias were isolated from 12 week old *Ptprs*$^{+/+}$ and *Ptprs*$^{-/-}$ mice. Cells were then depleted of lineage-committed cells with Direct Lineage Cell Depletion Kit (Miltenyi Biotec). The BM lin^- cell fraction was then serum starved in Iscove's modified Dulbecco's medium (IMDM) and treated with either vehicle (equal amount of DMSO) or 1 μg/mL DJ001 for 10 minutes at 37° C. After treatment, cells were washed with ice-cold PBS and then placed in lysis buffer supplemented with protease inhibitor. Lysate concentrations were measured by Pierce™ BCA Protein Assay Kit (ThermoFisher Scientific). G-LISA was performed according to manufacturer's instructions. Briefly, 12.5 μg of lysates was added to a GTP-binding protein

pre-coated plate and active RAC1-GTP, levels were measured at 490nm using a PowerWave XS2 microplate reader (BioTek). Exemplary results of this assay are depicted in FIG. 8 and FIG. 9.

Example 10: Flow Cytometric Analysis

Femurs and tibiae were harvested from euthanized C57BL/6 or *Ptprs*$^{-/-}$ mice and flushed with IMDM containing 10% FBS and 1% penicillin-streptomycin for BM cells. PB was collected through sub-mandibular puncture. Cells were filtered through a 40 μM strainer and then treated with ACK lysis buffer (Sigma Aldrich) before antibody staining for flow cytometry. For KSL and CD150^{+}CD48^{-}KSL cell analysis, BM cells were stained with allophycocyanin (APC)-and Cy7-conjugated anti-Sca-1 (BD Biosciences), phycoerythrin (PE)-conjugated anti-c-kit (BD Biosciences), V450 lineage cocktail (BD Biosciences), Alexa Fluor 488-conjugated anti-CD48 (BioLegend), and Alexa Fluor 647-conjugated anti-CD150 (Biolegend) antibodies. For donor engraftment analysis in transplanted mice, PB or BM cells were stained with BV605 anti-CD45.2 (BioLegend), fluorescein isothiocyanate (FITC)-conjugated anti-CD45.1 (BD Biosciences), PE-conjugated anti-Mac-1 and anti-Gr-1 (BD Biosciences), V450-conjugated anti-CD3 (BD Biosciences), and APC-Cy7-conjugated anti-B220 (BD Biosciences) antibodies.

Intracellular flow cytometric analysis was performed on irradiated (300 cGy) or non-irradiated, sorted KSL cells after treatment with 1 μg/mL DJ001 or control (equal volumes of DMSO) for 24 hours. At 24 hours after irradiation, cells were fixed with 4% PFA for 10 min, followed by permeabilization using 0.25% saponin in PBS. Cells were washed again and stained with antibody at the recommended concentrations for 30 minutes at room temperature. Intracellular antibodies and phospho-flow antibodies used were: FITC-conjugated anti-BCL-X_L (Abcam #ab26148), active RAC1-GTP antibody (NewEast Biosciences #26903), and anti-PAK1 (phospho S144) + PAK2 (phospho S141) + PAK3 (phospho S154) antibody (Abcam #ab40795).

Example 11: Mouse Survival Study

All animal procedures were performed in accordance with animal use protocols approved by the UCLA animal care and use committee. *Ptprs*$^{-/-}$ mice were provided by Dr. Michel Tremblay (McGill University). *C57BL/6* mice, *B6.SJL* mice and *NOD.Cg-*

Prkdc^{scid}*Il2rg*^{tm1Wjl}*/SzJ (NSG)* mice between 8 to 12 weeks old were obtained from the Jackson Laboratory.

10 week old female C57BL/6 mice were irradiated with 750 cGy TBI, which is lethal for approximately 50% of C57BL/6 mice by day +30 (LD50/30), using a Shepherd Cesium-137 irradiator. Twenty four hours post-irradiation, mice were administered daily subcutaneous injections of 5 mg/kg DJ001 (or DJ009) or vehicle in a volume of 100 µL for 10 days. DJ001 injections were prepared in PBS, 0.5% Tween 80, and 10% DMSO. Corresponding vehicle injections contained PBS, 10% DMSO and 0.5% Tween 80. PB complete blood counts were measured using a Hemavet 950 instrument (Drew Scientific) at day +10 post-irradiation. For hematopoietic analysis, BM cells were collected at day +10 post-irradiation. To study whether DJ001 increased survival rates through activation of RAC signaling, the RAC inhibitor, EHT1864 (Selleckchem), was dissolved in PBS and administered intraperitoneally, 40 mg/kg every other day, to 750 cGy irradiated mice until day +10. For DJ009 studies, ten week old female C57BL/6 mice were irradiated with 550 cGy TBI and then given daily subcutaneous injections of 5 mg/kg of DJ009 or vehicle in a volume of 100 µL for 3 days. DJ009 injections were prepared in PBS, 0.5% Tween 80, and 10% DMSO. Vehicle injections contained 10% DMSO and 0.5% Tween 80. At day +3 post 550 cGy irradiation, we collected PB and BM cells for CBCs and hematopoietic analysis. Exemplary results of this assay are depicted in FIG. 8 and FIG. 17.

Example 12: Human BM cultures and human BM transplantation assays

Human BM mononuclear cells (MNCs) were purchased from AllCells. Cryopreserved human BM cells were recovered in IMDM + 10% FBS + 1% penicillin-streptomycin and then positively selected for $CD34^+$ stem/progenitor cells by using CD34 MicroBead Kit (Miltenyi Biotec). $CD34^+$ cells were cultured in human TSF media (IMDM, 10%FBS, 1% pen-strep, 20 ng/mL recombinant human Thrombopoietin (TPO), 125 ng/mL recombinant human Stem Cell Factor (SCF), 50 ng/mL recombinant human Flt3 ligand (R&D Systems). The progeny of 2 x 10^5 irradiated, human BM $CD34^+$ cultured for 36 hours and treated with DJ001 at 5 ug/mL, were transplanted via tail vein injection into 10-12 week old NSG mice preconditioned with 275 cGy TBI. Multilineage donor hematopoietic cell engraftment was monitored in the PB and BM by flow cytometry.

Example 13: CFC assays, HSC Cultures and Competitive Repopulation Assays

CFC assays (colony-forming unit-granulocyte monocyte (CFU-GM), burst-forming unit-erythroid (BFU-E), and colony-forming unit-granulocyte erythroid monocyte megakaryocyte (CFU-GEMM) were performed using MethoCult GF M3434 (Stemcell Technologies), as we have previously described[1,5]. For all in vitro assays, BM $CD34^-KSL$ cells, KSL cells, and Lin^- cells were cultured in TSF media (IMDM, 10% FBS, 1% pen-strep, 20 ng/mL recombinant mouse Thrombopoietin (TPO), 125 ng/mL recombinant mouse Stem Cell Factor (SCF), 50 ng/mL recombinant mouse Flt3 ligand) and treated as described. Recombinant mouse SCF, Flt-3 ligand, and TPO were purchased from R&D Systems. For competitive repopulation assays, BM cells were isolated from donor 10-12 week old female $CD45.2^+$ mice. Recipient 10 week old female $CD45.1^+$ B6.SJL mice were irradiated with 950 cGy TBI using a Cs137 irradiator, and donor BM cells were administered via tail vein injection along with a competing dose of 1×10^5 non-irradiated host BM cells. Multilineage donor hematopoietic cell engraftment was measured in the PB by flow cytometry.

Example 14: Isolation of BM HSCs

BM HSCs were collected from mice. Briefly, BM cells were first treated with ACK lysis buffer (Sigma Aldrich) and lineage committed cells were removed using a Direct Lineage Cell Depletion Kit (Miltenyi Biotec). Lin^- cells were stained with APC-Cy7-conjugated anti-sca-1, PE-conjugated anti-c-kit, FITC-conjugated anti-CD34, and V450 lineage cocktail (BD Biosciences) or with isotype controls. Sterile cell sorting was conducted on a BD FACS-Aria cytometer. Purified KSL cells and $CD34^-c\text{-}kit^+sca\text{-}1^+Lin^-$ ($CD34^-KSL$) cells were collected into IMDM (Life Technologies) + 10% FBS + 1% penicillin-streptomycin.

Example 15: *In silico* molecular docking studies

Molecular docking of DJ001 *(Z)*-isomer to the protein tyrosine phosphatase-σ (PDB ID: 2FH7) was carried out by AutoDock Vina, in which the Iterated Local Search Globule Optimizer was applied as optimization algorithm. Each structure of ligand was prepared in Maestro 10.5 (Schroedinger, LLC) and minimized with the OPLS_2005 force field. All hydrogen atoms were added to each protein and ligand to be docked and each coordinate file of protein and ligand was generated as PDBQT file using AutoDockTools-1.5.6. A grid box for binding site was set as 18 Å in the three dimensions (x, y and z) that covered the catalytic

site of the protein or 40 Å in the three dimensions for allosteric binding site. The box had 1.0 Å grid spacing and centered at the geometric center of the protein. In each docking experiment, the best binding mode was selected according to the binding affinity calculated by the scoring function in AutoDock Vina. Docking results were analyzed with PyMOL and visualized by VMD 1.9.2.

Example 16: Statistical Analysis

GraphPad Prism 6.0 was used for all statistical analyses. All data were checked for normal distribution and similar variance between groups. Data were derived from multiple independent experiments from distinct mice or cell culture plates. Sample sizes for in vitro studies were chosen based on observed effect sizes and standard errors from prior studies. For all animal studies, a power test was used to determine the sample size needed to observe a two-fold difference in means between groups with 0.8 power. A two-tailed Student's t test was utilized for all comparison excepts where otherwise noted in the Figure Legends. All animal studies were performed using sex- and age-matched animals, with wild-type littermates as controls. Animal studies were performed without blinding of the investigator. Values are reported as means ± SEM, unless stated otherwise. Results were considered significant when $P < 0.05$.

INCORPORATION BY REFERENCE

All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

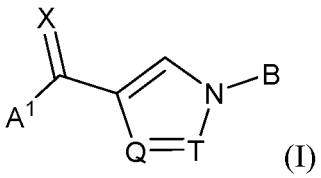
EQUIVALENTS

While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

CLAIMS

We claim:

1. A compound having the structure of formula I, formula II, formula III, formula IV or a pharmaceutically acceptable salt or prodrug thereof: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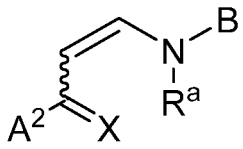
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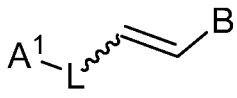
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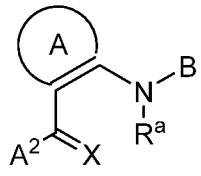

(IV)

wherein,

ring A is a pyridinylene;

A^1 is cycloalkyl, heterocyclyl, aryl, or heteroaryl;

A^2 is aryl, heteroaryl, cycloalkyl, or heterocyclyl;

B is cycloalkyl, heterocyclyl, aryl, or heteroaryl;

L is $-N(R^b)C(=X)-$ or $-C(=X)N(R^b)-$;

Q is N or CH;

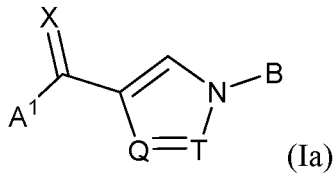
T is N or CH;

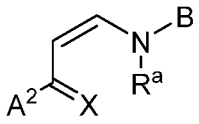
X is O, NR^a or S;

R^a is hydrogen or alkyl; and

R^b is hydrogen or alkyl.

2. The compound of claim 1, having the structure of formula Ia, formula IIa, formula IIIa, formula IVa or a pharmaceutically acceptable salt or prodrug thereof:


(Ia)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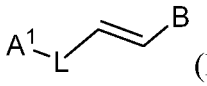
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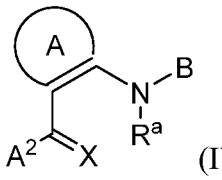

(IVa)

wherein,

ring A is a pyridinylene;

A^1 is cycloalkyl, heterocyclyl, aryl, or heteroaryl;

A^2 is cycloalkyl or heterocyclyl;

B is cycloalkyl, heterocyclyl, aryl, or heteroaryl;

L is $-N(R^b)C(=X)-$ or $-C(=X)N(R^b)-$;

Q is N or CH;

T is N or CH;

X is O, NR^a or S;

R^a is hydrogen or alkyl; and

R^b is hydrogen or alkyl.

3. The compound of claim 1 or 2, wherein the compound is represented by formula I.

4. The compound of claim 1 or 2, wherein A^1 is phenyl.

5. The compound of any one of claims 1-4, wherein Q and T are both CH.

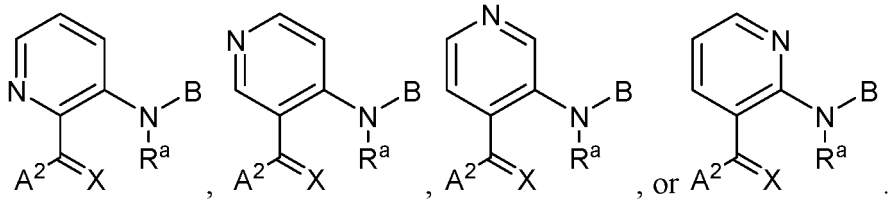
6. The compound of any one of claims 1-4, wherein Q and T are both N.

7. The compound of claim 1 or 2, wherein the compound is represented by formula II.

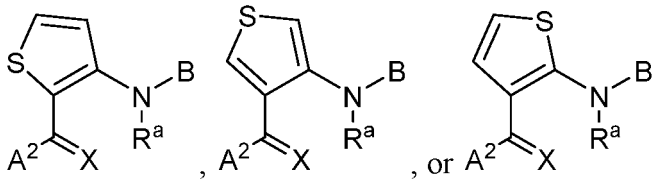
8. The compound of claim 7, wherein the alkene stereochemistry is in the E configuration.

9. The compound of claim 1 or 2, wherein the compound is represented by formula IV.

10. The compound of claim 6 or 7, wherein the compound is represented by one of the following formulas:



11. The compound of claim 6 or 7, wherein the compound is represented by one of the following formulas:



12. The compound of any one of claims 7-11, wherein A^2 is cycloalkyl or heterocyclyl.

13. The compound of any one of claims 7-12, wherein A^2 is cycloalkyl.

14. The compound of any one of claims 7-12, wherein A^2 is aryl or heteroaryl, such as phenyl.

15. The compound of claim 14, wherein A^2 is aryl, such as chlorophenyl (e.g., dichlorophenyl) or methoxyphenyl (e.g., dimethoxyphenyl).

16. The compound of claim 14, wherein A^2 is heteroaryl, such as pyridyl.

17. The compound of any one of claims 7-16, wherein R^a is hydrogen.

18. The compound of claim 1 or 2, wherein the compound is represented by formula III.

19. The compound of claim 18, wherein A^1 is aryl.

20. The compound of claim 18 or 19, wherein A^1 is phenyl, fluorophenyl (such as 3,5-difluorophenyl), cyanophenyl (such as 3-cyanophenyl), or nitrophenyl (such as 4-nitrophenyl, 3-nitrophenyl or 2-nitrophenyl).

21. The compound of any one claims 18-20, wherein L is $-N(R^b)C(=X)-$.

22. The compound of claims any one of claims 18-20, wherein L is $-C(=X)N(R^b)-$.

23. The compound of any one of claims 18-22, wherein R^b is hydrogen.

24. The compound of any one of claims 18-23, wherein the alkene stereochemistry is in the Z configuration.

25. The compound of any one of the preceding claims, wherein X is oxygen.

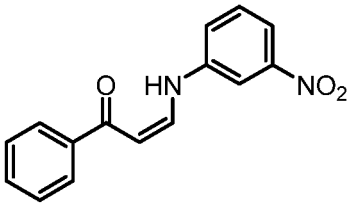
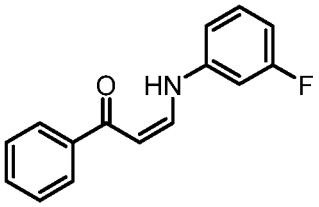
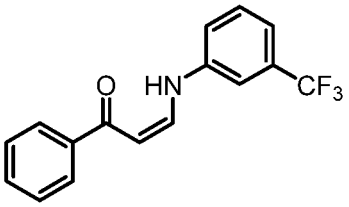
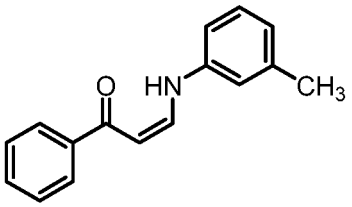
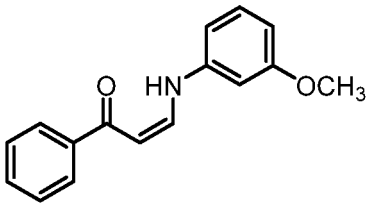
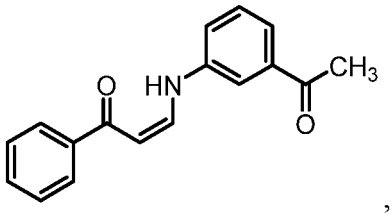
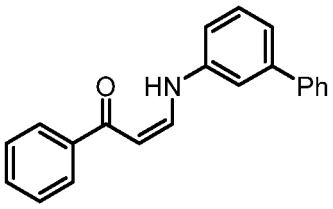
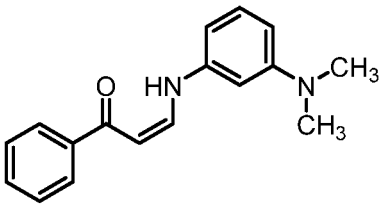
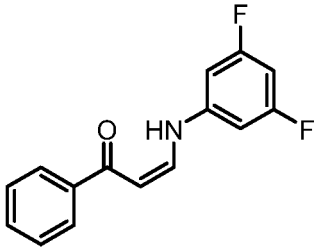
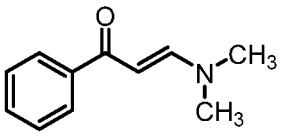
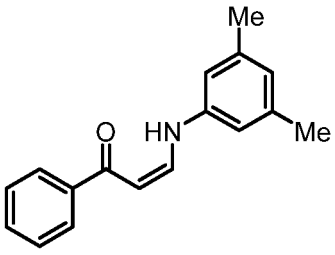
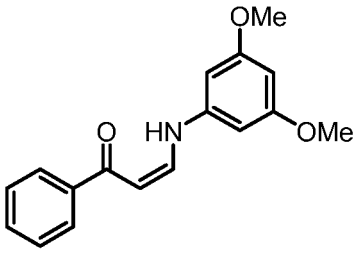
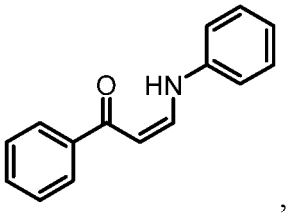
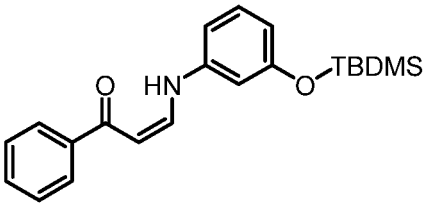
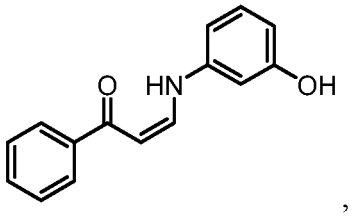
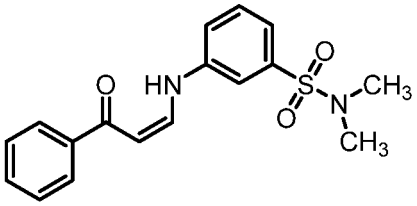
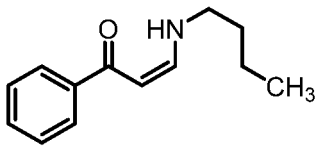
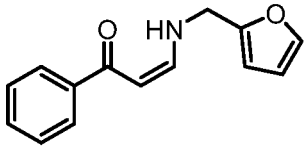
26. The compound of any one of the preceding claims, wherein B is aryl.

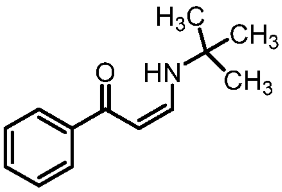
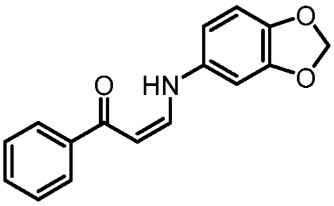
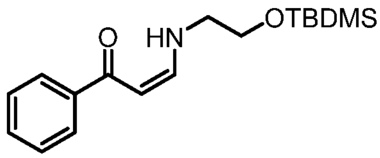
27. The compound of any one of the preceding claims, wherein B is phenyl, fluorophenyl (such as 3,5-difluorophenyl), cyanophenyl (such as 3-cyanophenyl), or nitrophenyl (such as 4-nitrophenyl, 3-nitrophenyl or 2-nitrophenyl).

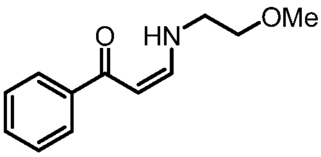
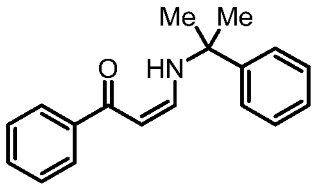
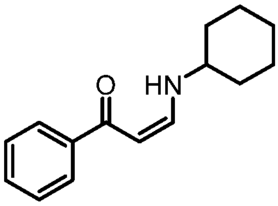
28. The compound of any one of claims 1-27, wherein B is methoxyphenyl (e.g., dimethoxyphenyl), trifluoromethylphenyl (e.g., 3-trifluoromethylphenyl), nitrofluorophenyl

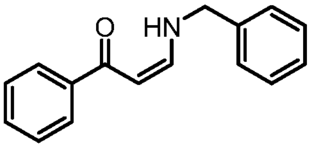
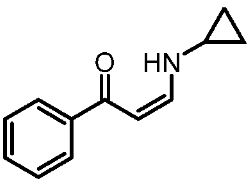
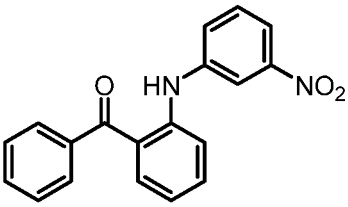
(e.g., 3-fluoro-5-nitrophenyl), amidophenyl (e.g., phenyl-3-carboxamide), alkynylphenyl (e.g., 3-ethynylphenyl).

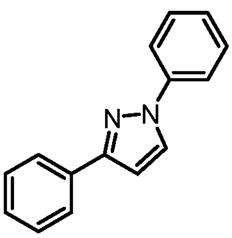
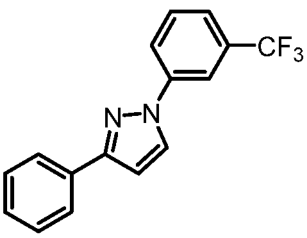
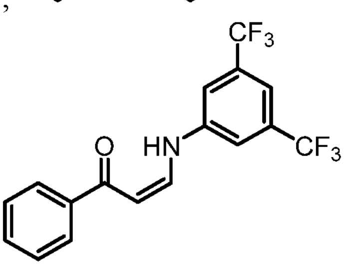
29. The compound of any one of claims 1-28, wherein the compound is not

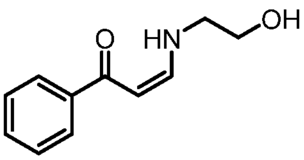
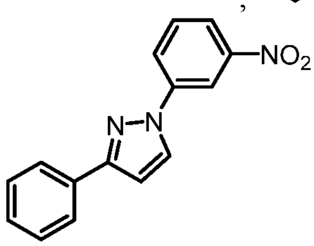
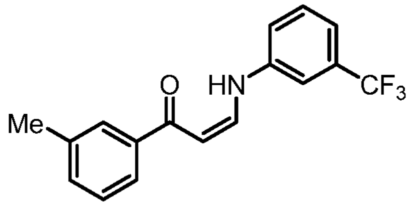



















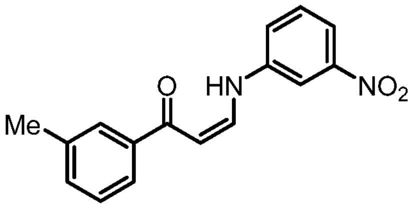
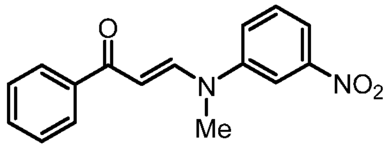
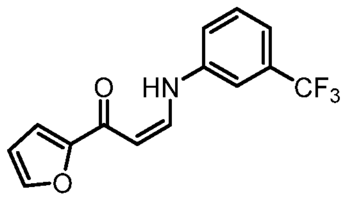
 ,
 ,
 ,

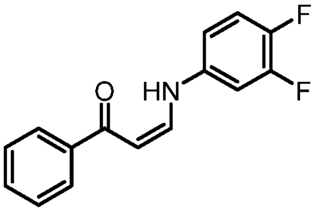
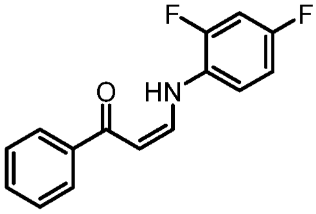
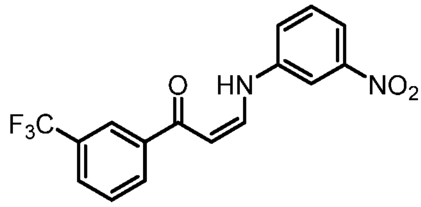
 ,
 ,
 ,

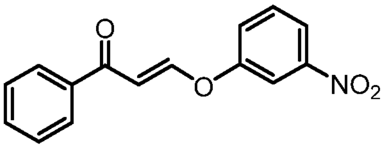
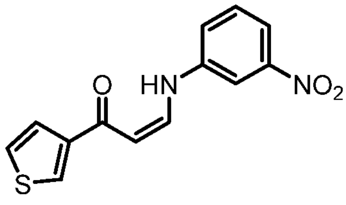
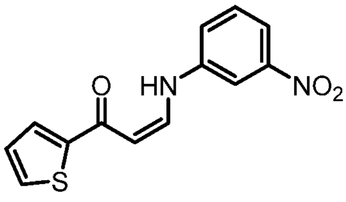
 ,
 ,
 ,

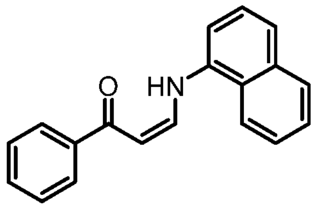
 ,
 ,
 ,

 ,
 ,
 ,

 ,
 ,
 ,

 ,
 ,
 ,

 ,
 ,
 ,



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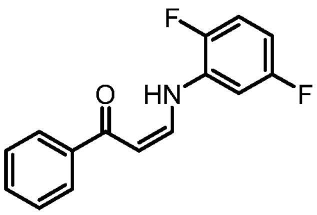

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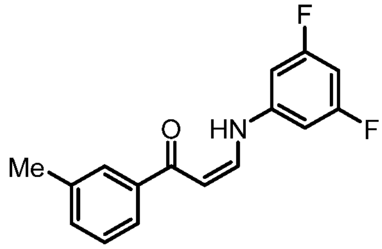

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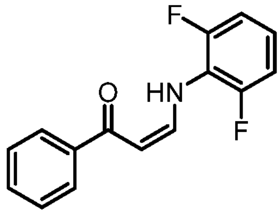

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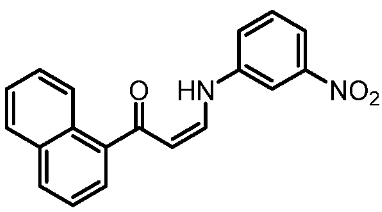

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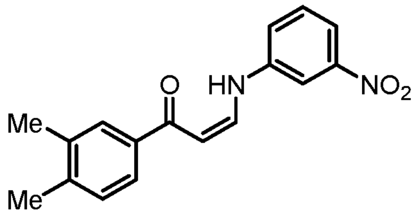

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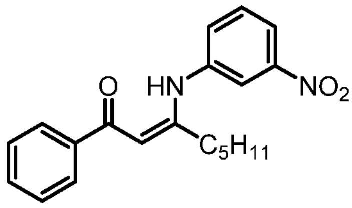

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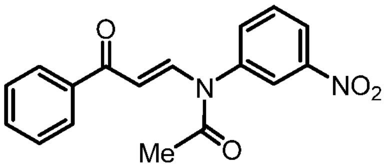

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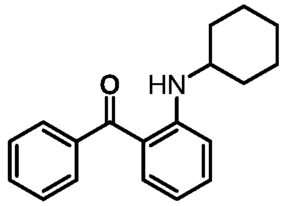

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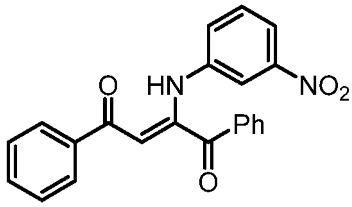

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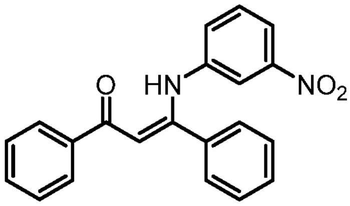

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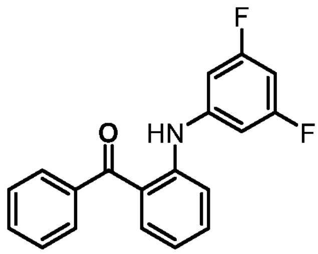

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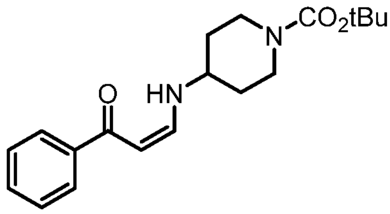

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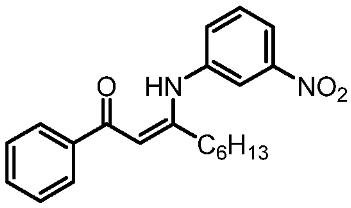

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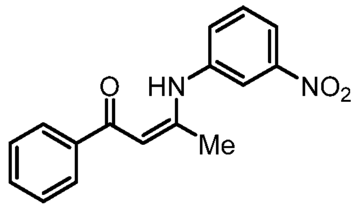

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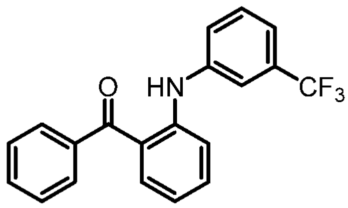
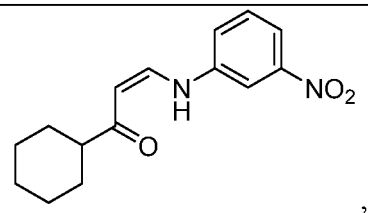
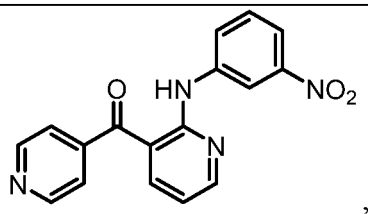
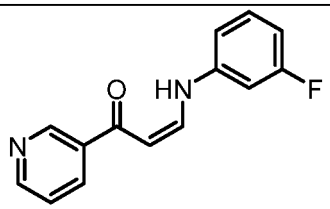
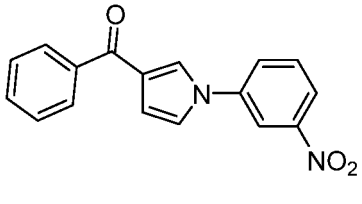
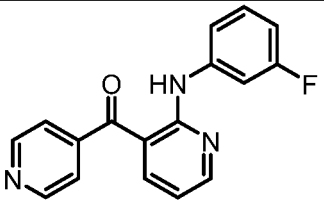
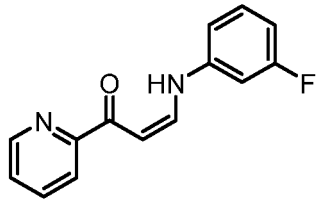
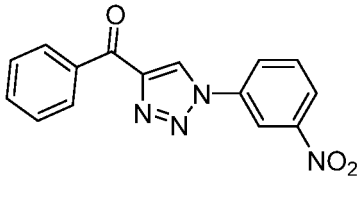
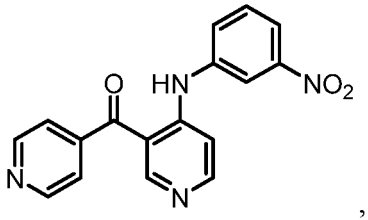
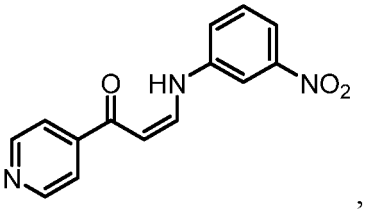
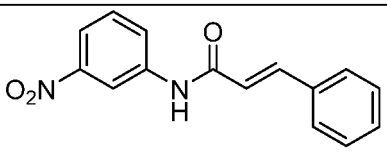
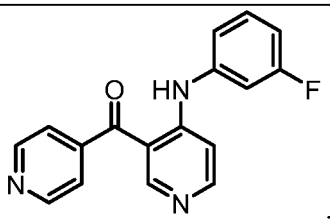
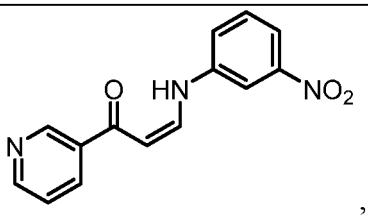
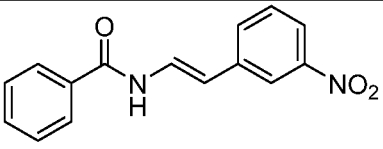
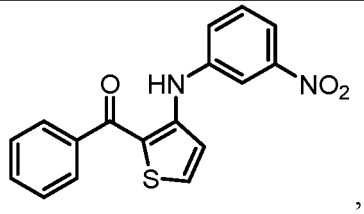
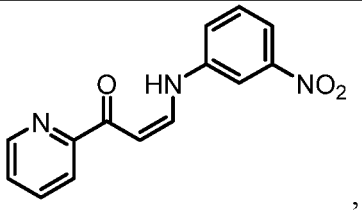
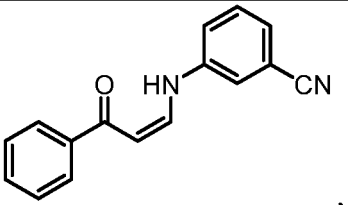
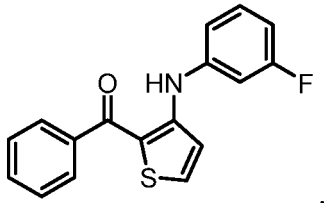
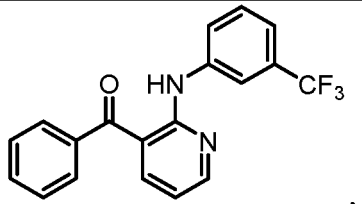
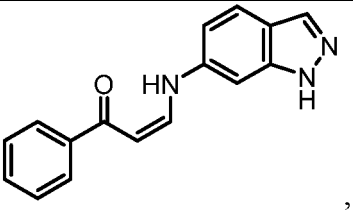
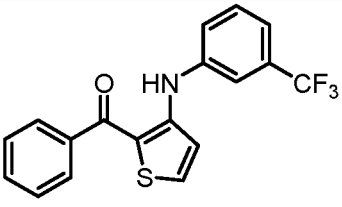
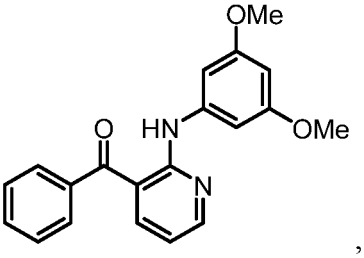
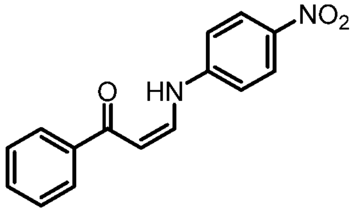
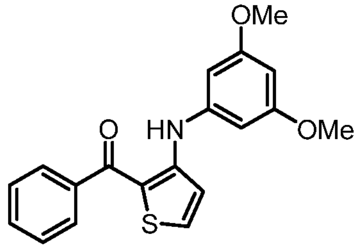
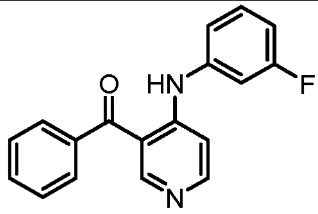
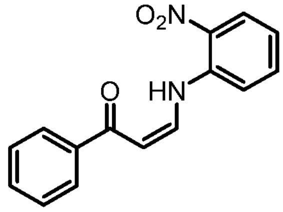
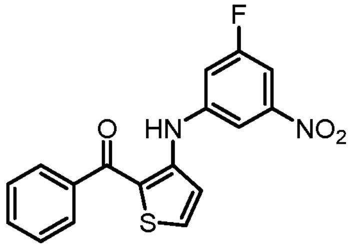
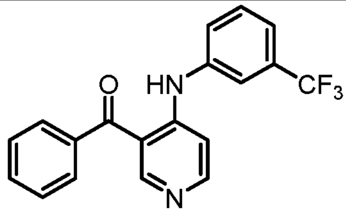
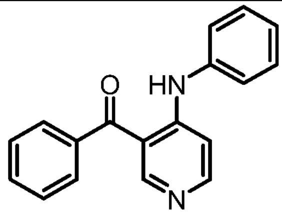
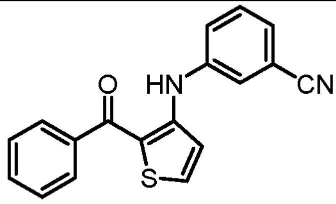
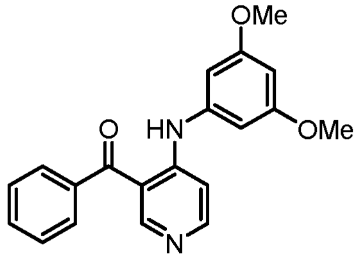
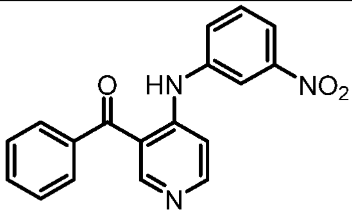
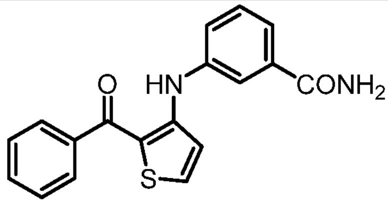
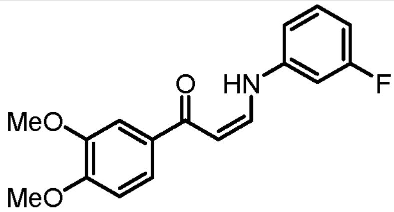
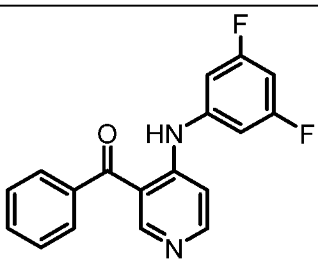
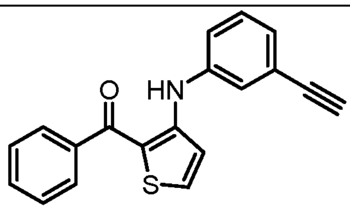
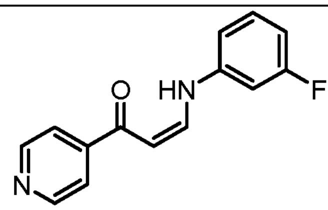
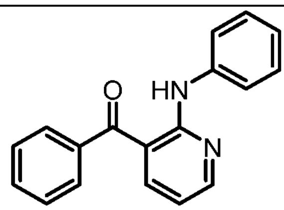
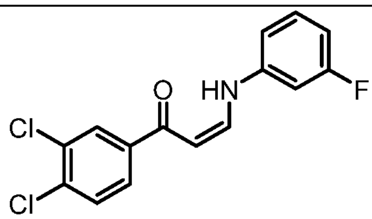
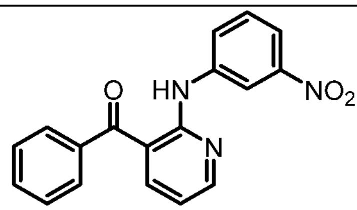
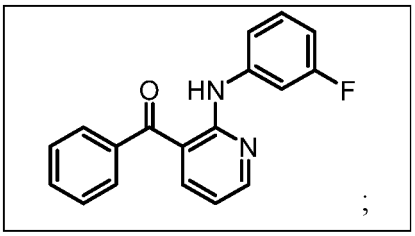


, or a pharmaceutically acceptable salt thereof.

30. The compound of any one of the preceding claims, wherein the compound is

 ,	 ,	
 ,	 ,	
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,

 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,



;

or a pharmaceutically acceptable salt thereof.

31. A pharmaceutical composition comprising a compound according to any one of the preceding claims and a pharmaceutically acceptable excipient.

32. A method of inhibiting PTPσ in a cell, comprising contacting the cell with a compound or composition according to any one of the previous claims.

33. A method of promoting the self-renewal or regeneration of hematopoietic stem cells comprising administering to a subject a therapeutically effective amount of a compound or composition according to any one of claims 1-31.

34. The method of claim 33, wherein the subject is myelosuppressed.

35. The method of claims 33 or 34, wherein the subject has received or is receiving myelosuppressive chemotherapy or radiotherapy, has undergone or is undergoing hematopoietic cell transplantation, or is suffering from with aplastic anemia or a degenerative hematologic disease.

36. The compound or composition of any one of claims 1-31, for use in inhibiting PTPσ in a subject.

37. The compound or composition of any one of claims 1-31, or 36, for use in promoting the self-renewal or regeneration of hematopoietic stem cells in a subject.

38. The compound or composition for use of claim 36 or 37, wherein the subject is myelosuppressed.

39. The compound or composition for use of any one of claims 36-38, wherein the subject has received or is receiving myelosuppressive chemotherapy or radiotherapy, has undergone

or is undergoing hematopoietic cell transplantation, or is suffering from with aplastic anemia or a degenerative hematologic disease.

FIGURES

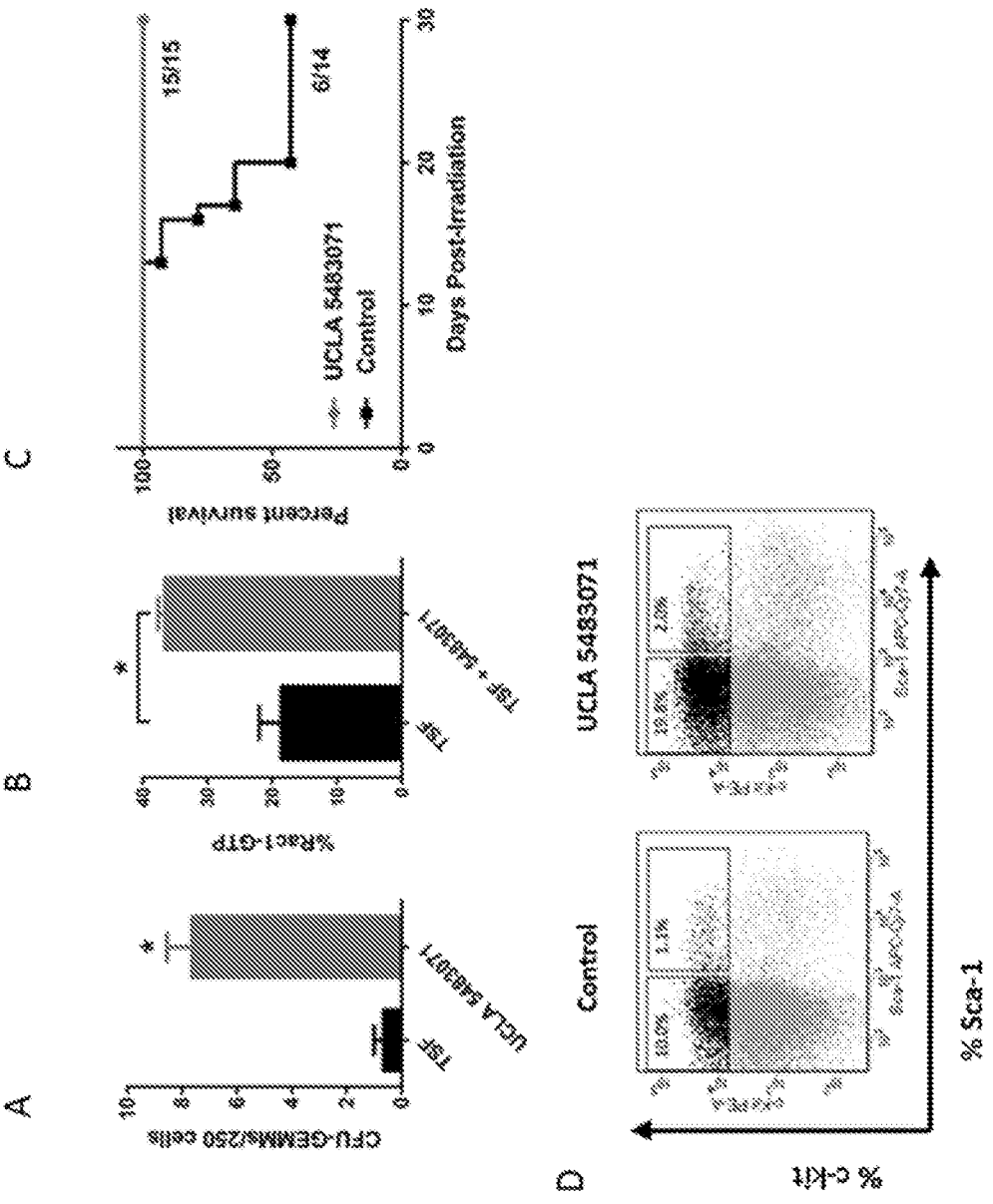


FIG. 1

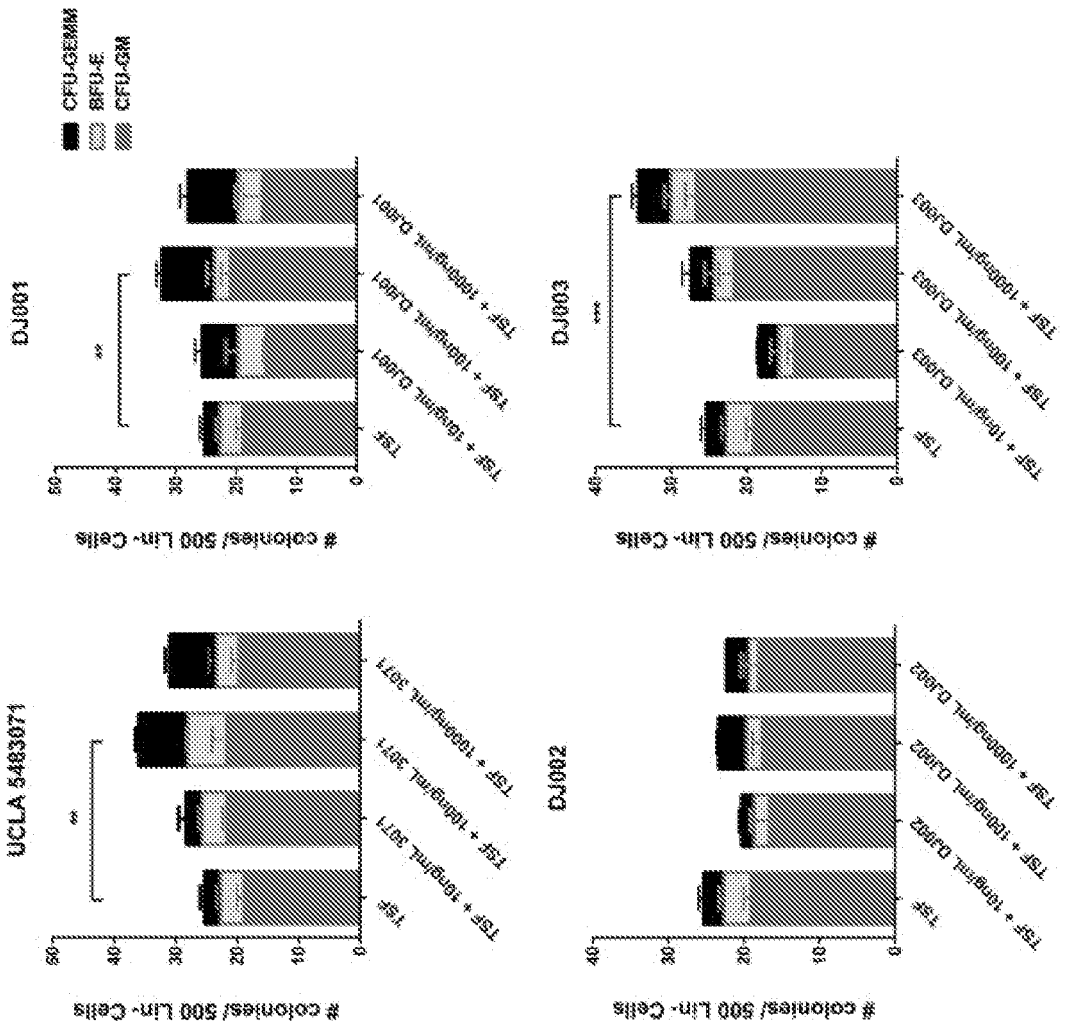

DJ001
DJ003
DJ002
UCLA 5483071
CFU-GEMM
BFU-E
CFU-GM
colonies/ 500 Lin- Cells
TSF
TSF + 10ng/mL DJ001
TSF + 100ng/mL DJ001
TSF + 1000ng/mL DJ001
TSF + 10ng/mL DJ003
TSF + 100ng/mL DJ003
TSF + 1000ng/mL DJ003
TSF + 10ng/mL DJ002
TSF + 100ng/mL DJ002
TSF + 1000ng/mL DJ002
TSF + 10ng/mL 3071
TSF + 100ng/mL 3071
TSF + 1000ng/mL 3071

FIG. 2A

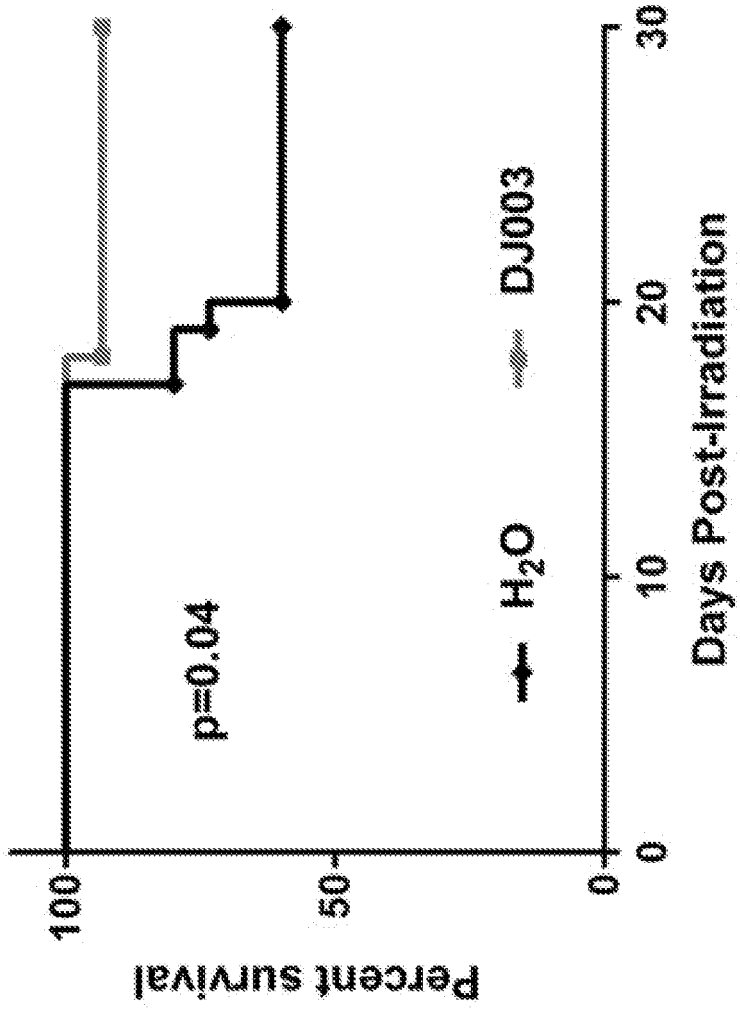

Percent survival
100
50
0
0
10
20
30
Days Post-Irradiation
p=0.04
H2O
DJ003

FIG. 2B

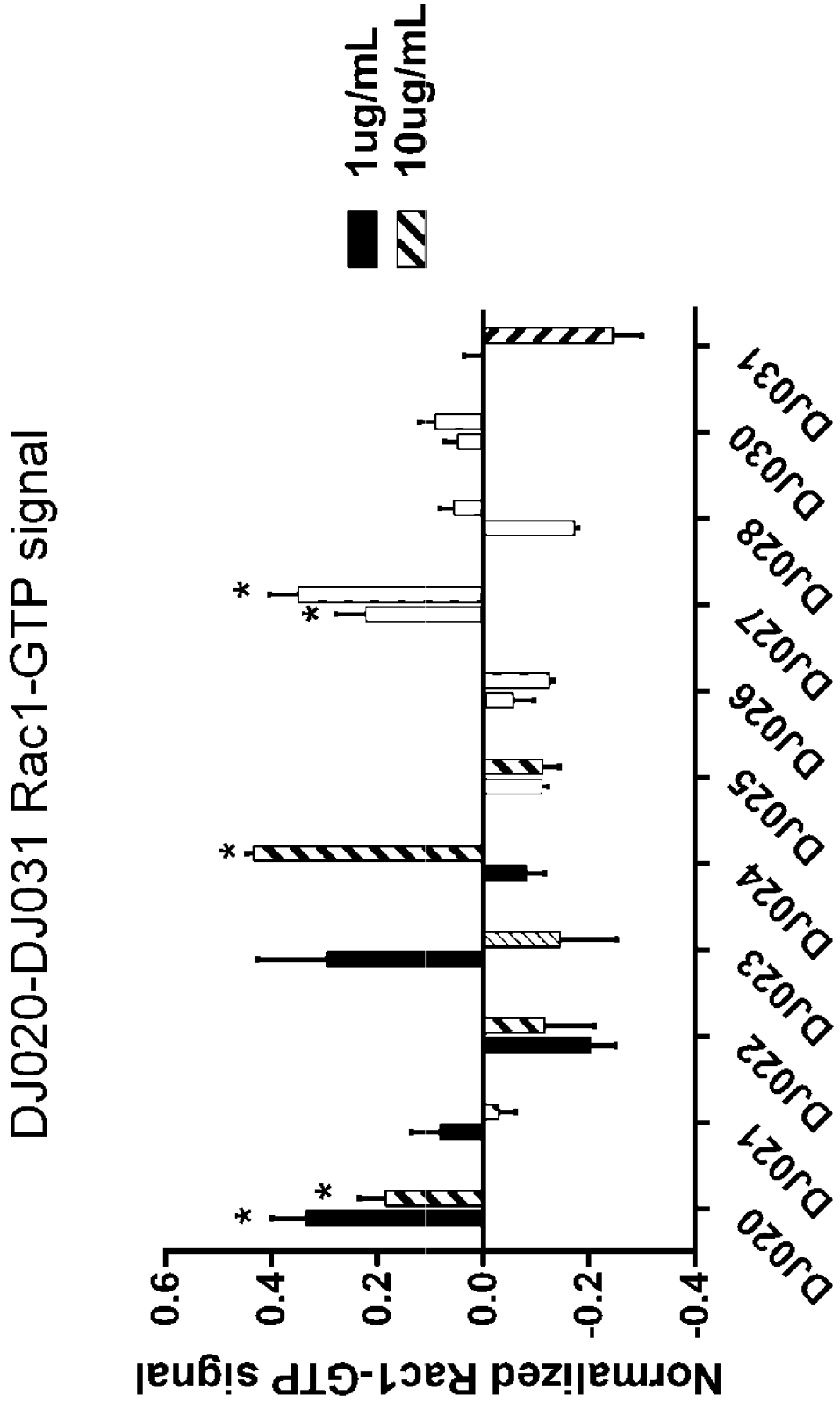

DJ020-DJ031 Rac1-GTP signal
1ug/mL
10ug/mL
Normalized Rac1-GTP signal
0.6
0.4
0.2
0.0
-0.2
-0.4
DJ020
DJ021
DJ022
DJ023
DJ024
DJ025
DJ026
DJ027
DJ028
DJ030
DJ031
*

FIG. 3

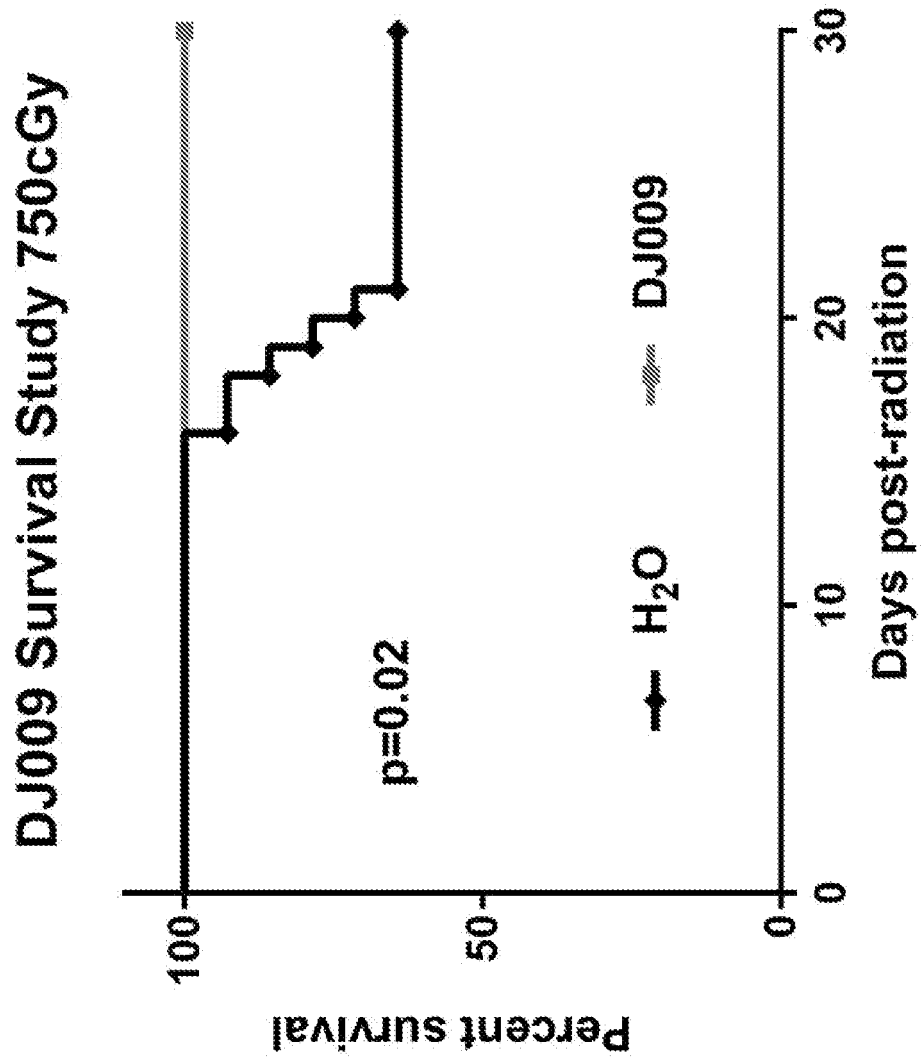

DJ009 Survival Study 750cGy
Percent survival
100
50
0
0
10
20
30
Days post-radiation
p=0.02
H2O
DJ009

FIG. 4

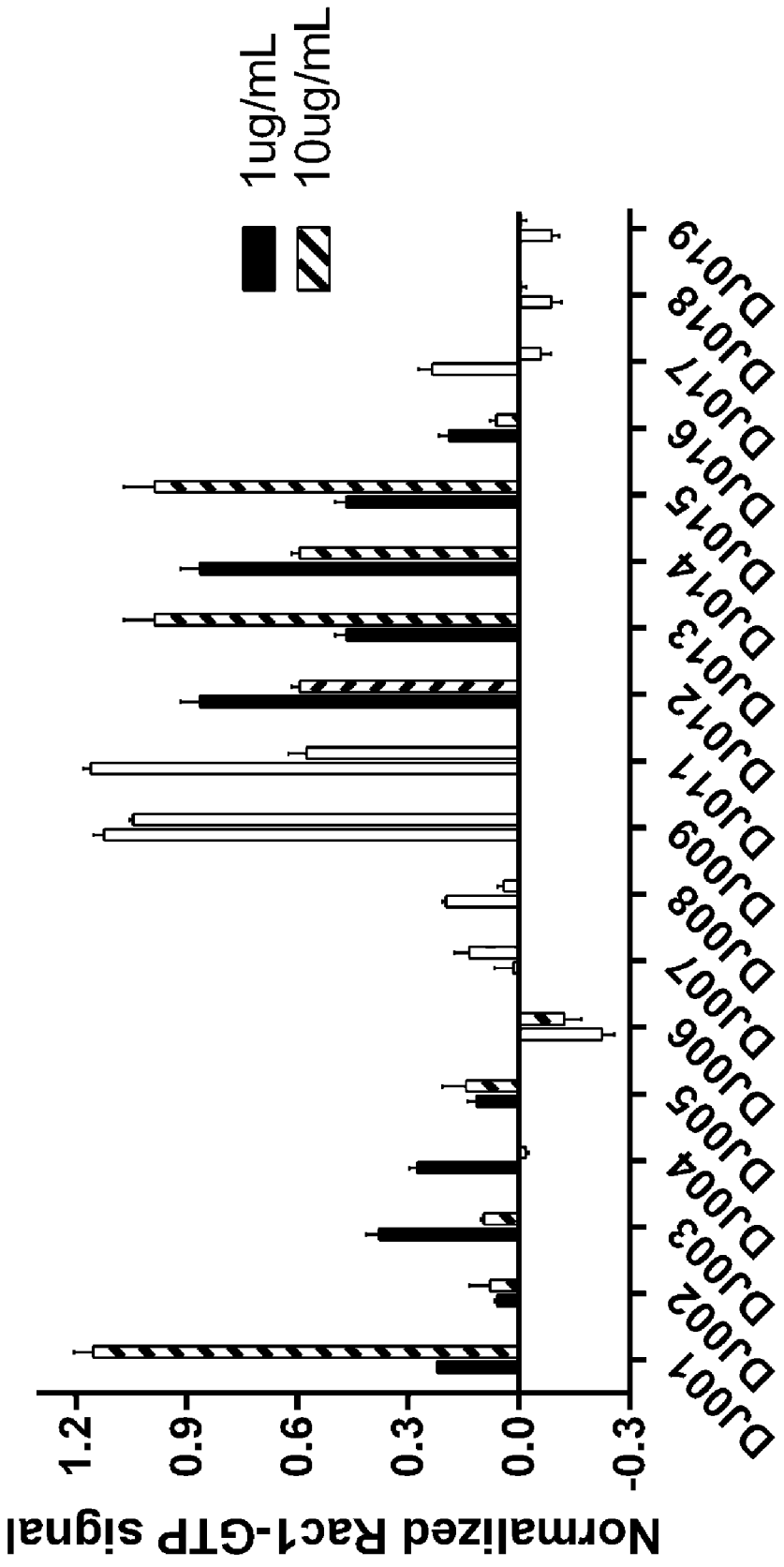

Normalized Rac1-GTP signal
1.2
0.9
0.6
0.3
0.0
-0.3
1ug/mL
10ug/mL
DJ001
DJ002
DJ003
DJ004
DJ005
DJ006
DJ007
DJ008
DJ009
DJ011
DJ012
DJ013
DJ014
DJ015
DJ016
DJ017
DJ018
DJ019

FIG. 5A

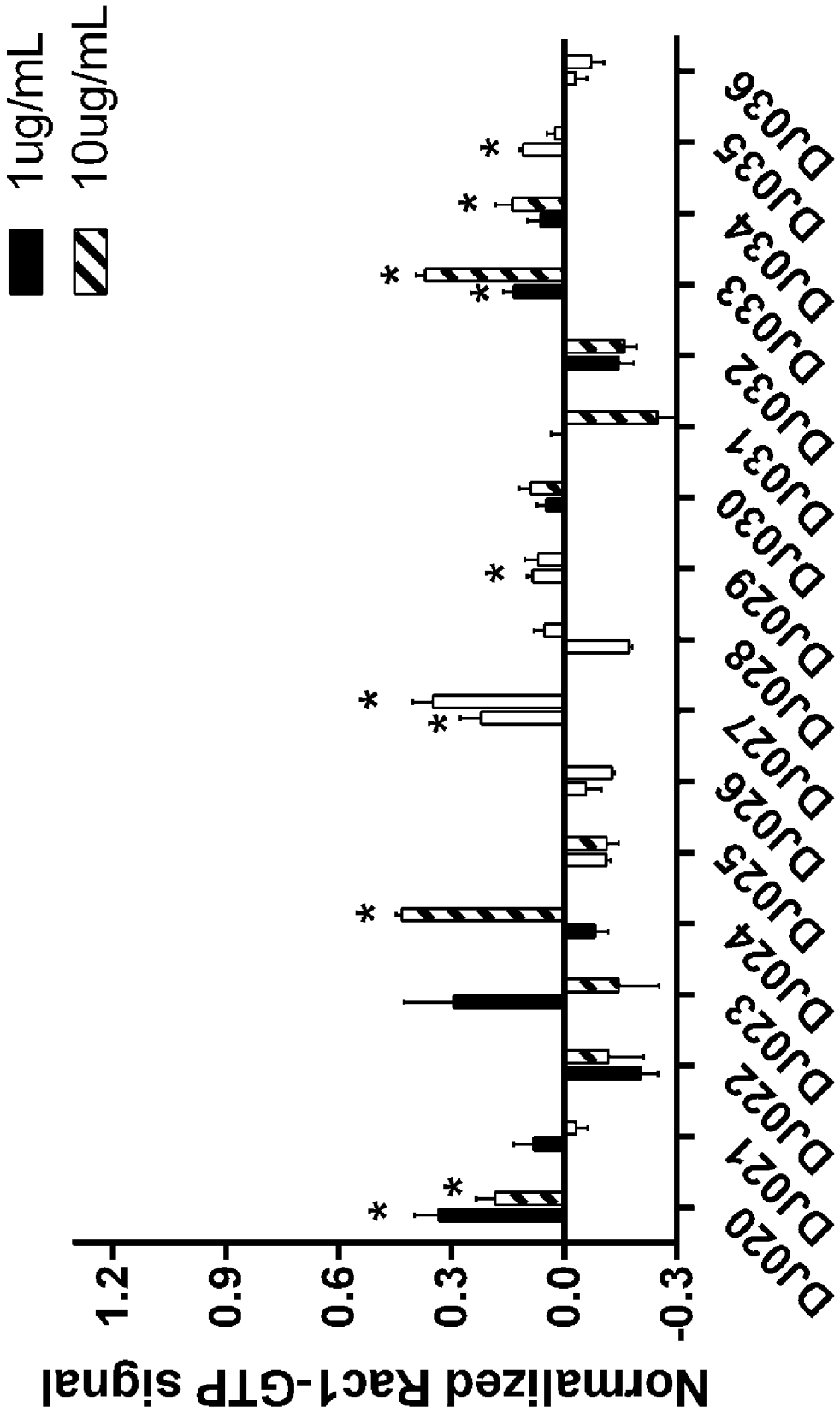

1ug/mL
10ug/mL
Normalized Rac1-GTP signal
1.2
0.9
0.6
0.3
0.0
-0.3
DJ020
DJ021
DJ022
DJ023
DJ024
DJ025
DJ026
DJ027
DJ028
DJ029
DJ030
DJ031
DJ032
DJ033
DJ034
DJ035
DJ036

FIG. 5B

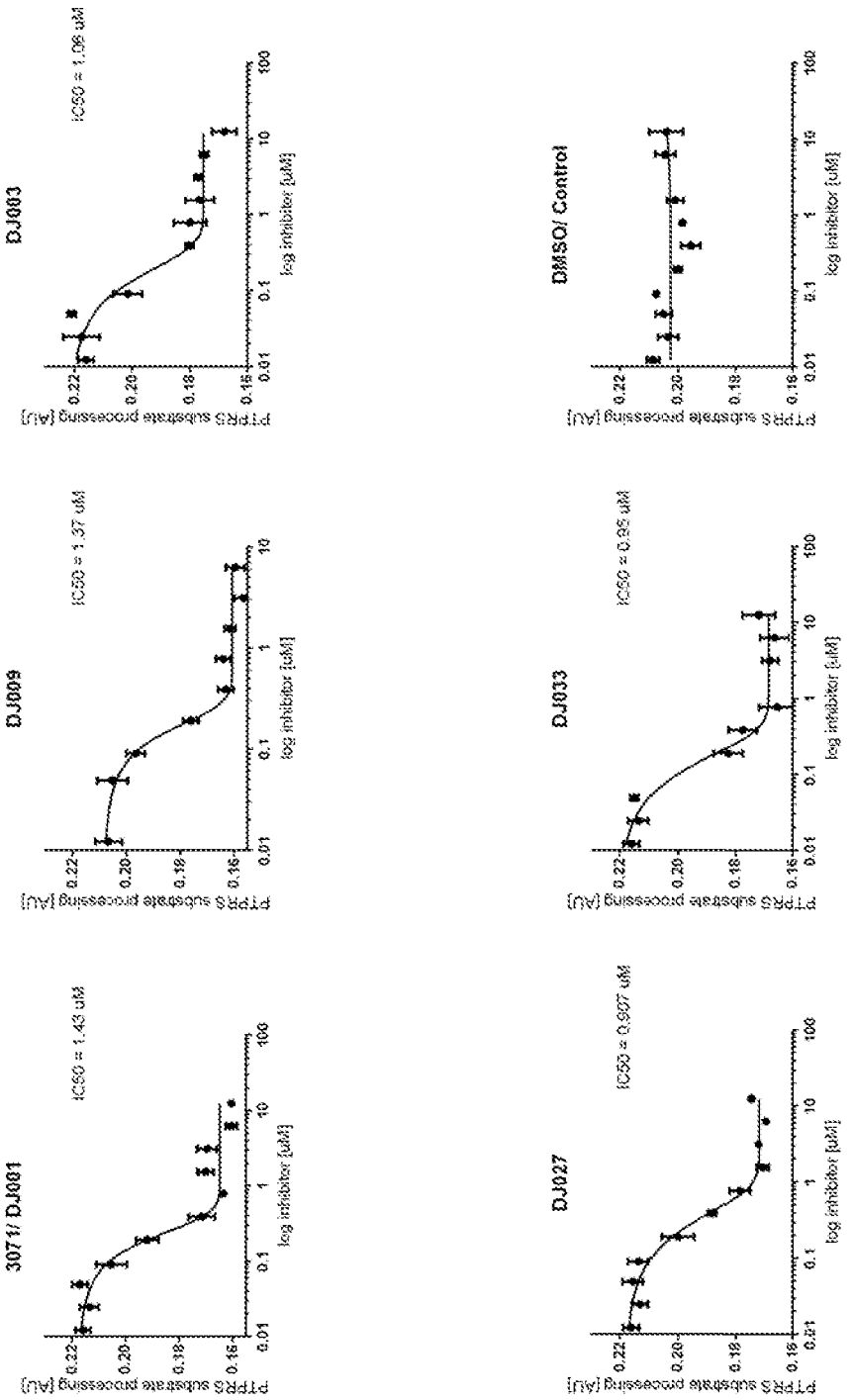

DJ003
IC50 = 1.06 uM
DMSO/ Control
DJ009
IC50 = 1.37 uM
DJ033
IC50 = 0.95 uM
3071/ DJ001
IC50 = 1.43 uM
DJ027
IC50 = 0.907 uM
PTPRS substrate processing [AU]
log inhibitor [uM]

FIG. 6A

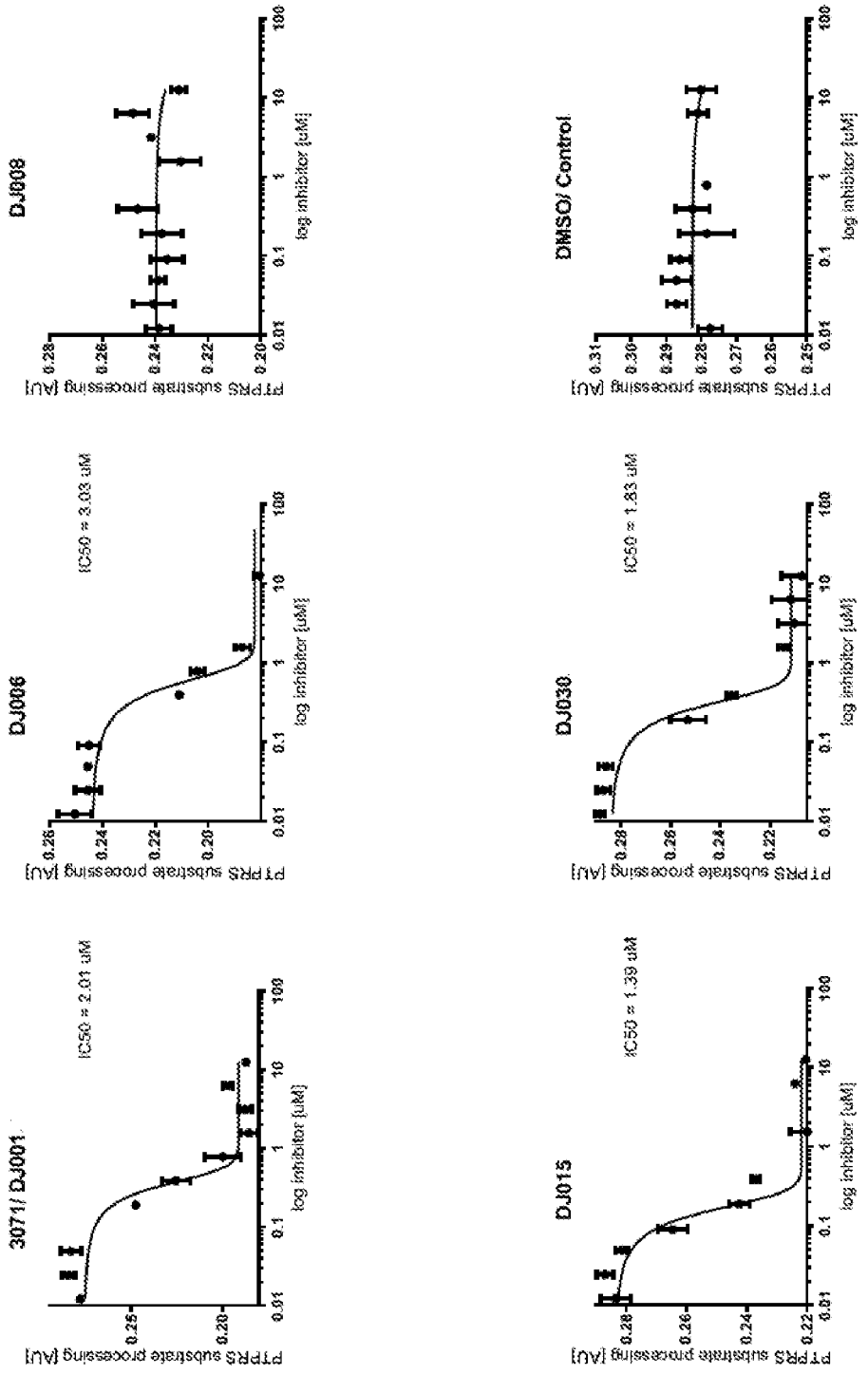

3071/ DJ001
IC50 = 2.01 uM
DJ006
IC50 = 3.03 uM
DJ015
IC50 = 1.39 uM
DJ030
IC50 = 1.83 uM
DJ009
DMSO/ Control
PTPRS substrate processing [AU]
log inhibitor [uM]

FIG. 6B

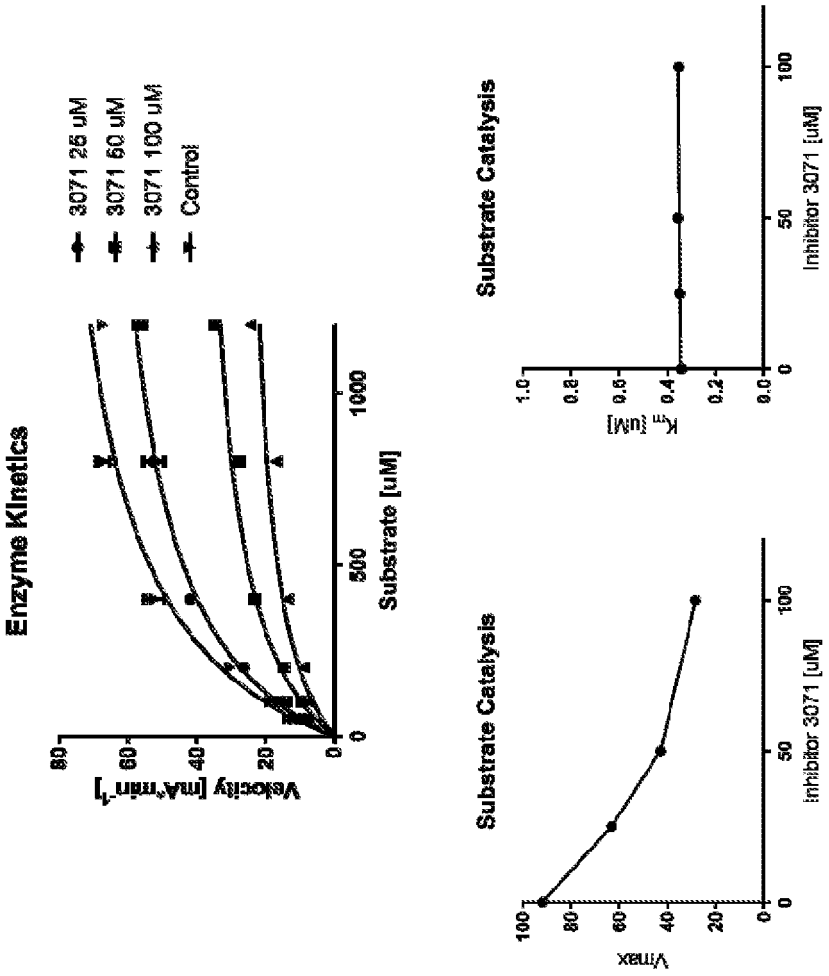

Enzyme Kinetics
3071 26 uM
3071 60 uM
3071 100 uM
Control
Velocity [mA*min-1]
Substrate [uM]
Substrate Catalysis
Vmax
Inhibitor 3071 [uM]
Substrate Catalysis
Km [uM]
Inhibitor 3071 [uM]

FIG. 7

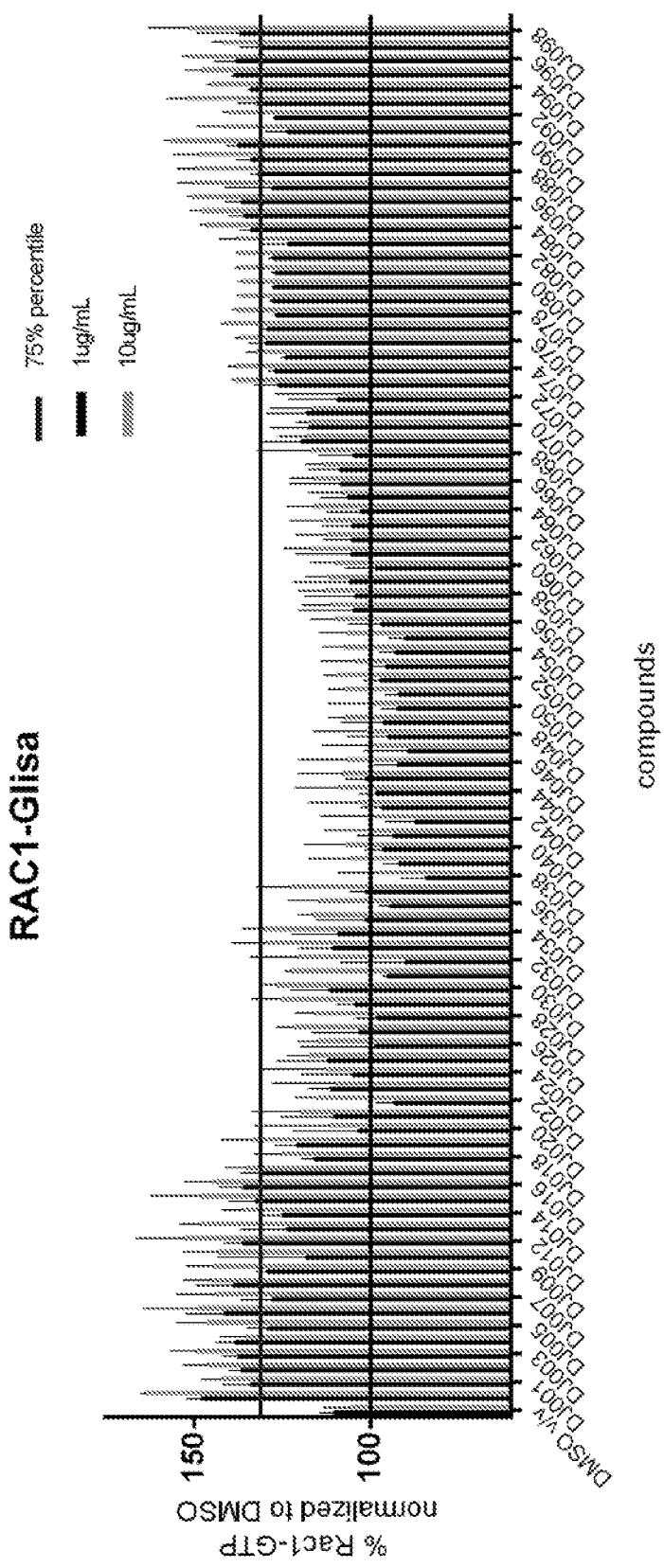

RAC1-Glisa
75% percentile
1ug/mL
10ug/mL
% Rac1-GTP
normalized to DMSO
150
100
DMSO
compounds

FIG. 8

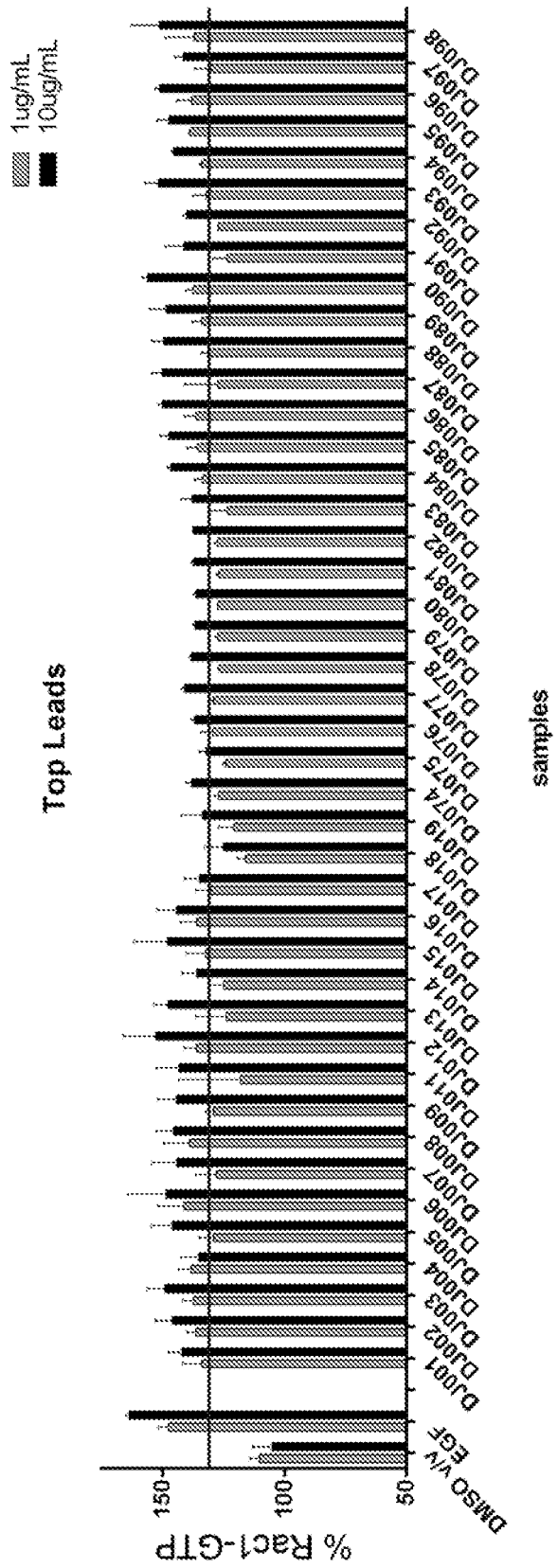

Top Leads
1ug/mL
10ug/mL
% Rac1-GTP
150
100
50
DMSO v/v
EGF
DJ001
DJ002
DJ003
DJ004
DJ005
DJ006
DJ007
DJ008
DJ009
DJ011
DJ012
DJ013
DJ014
DJ015
DJ016
DJ017
DJ018
DJ019
DJ074
DJ075
DJ076
DJ077
DJ078
DJ079
DJ080
DJ081
DJ082
DJ083
DJ084
DJ085
DJ086
DJ087
DJ088
DJ089
DJ090
DJ091
DJ092
DJ093
DJ094
DJ095
DJ096
DJ097
DJ098
samples

FIG. 9

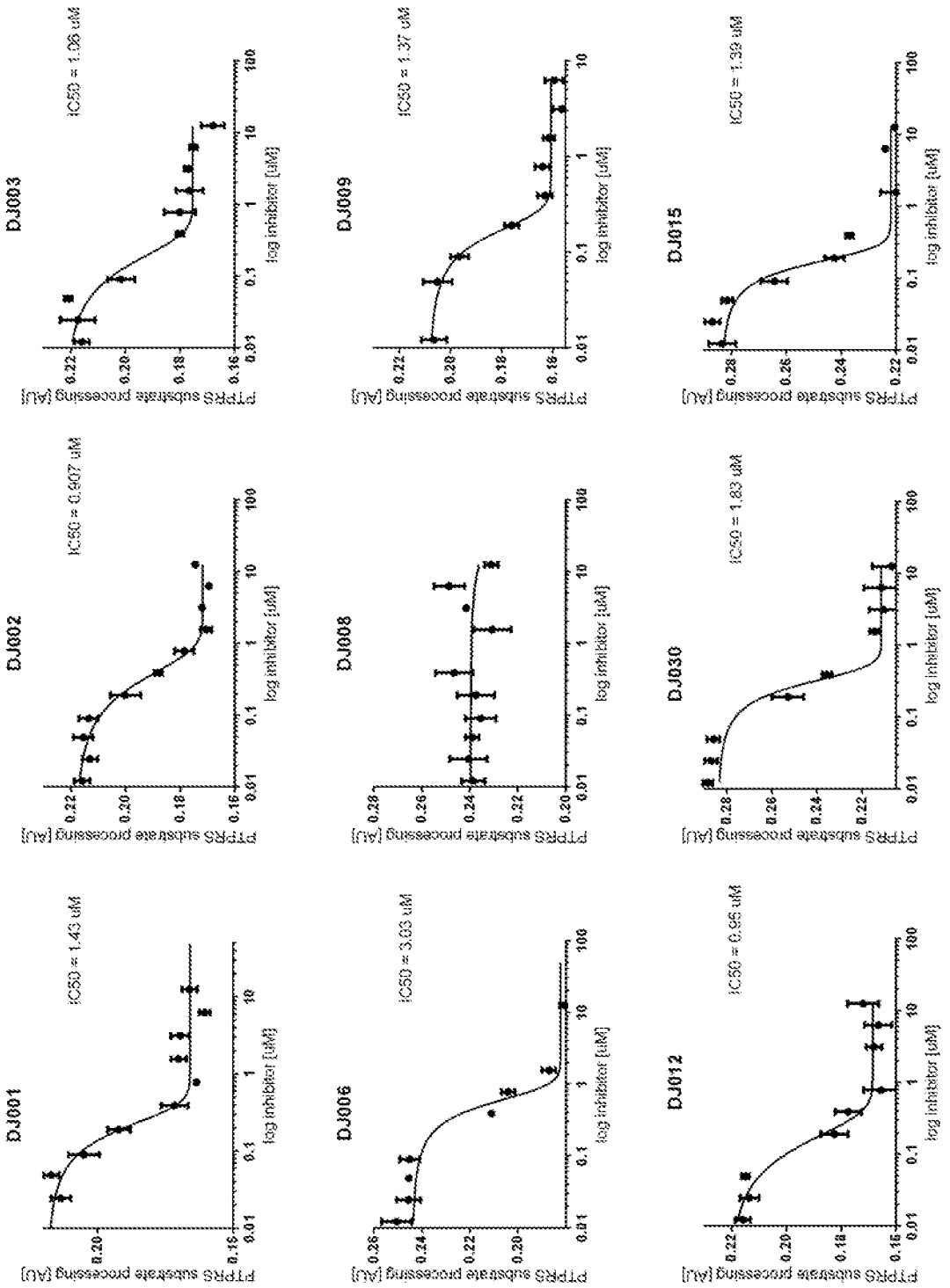

DJ003
IC50 = 1.06 uM
DJ009
IC50 = 1.37 uM
DJ015
IC50 = 1.39 uM
DJ002
IC50 = 0.907 uM
DJ008
DJ030
IC50 = 1.83 uM
DJ001
IC50 = 1.43 uM
DJ006
IC50 = 3.63 uM
DJ012
IC50 = 0.96 uM
PTPRS substrate processing [AU]
log inhibitor [uM]

FIG. 10

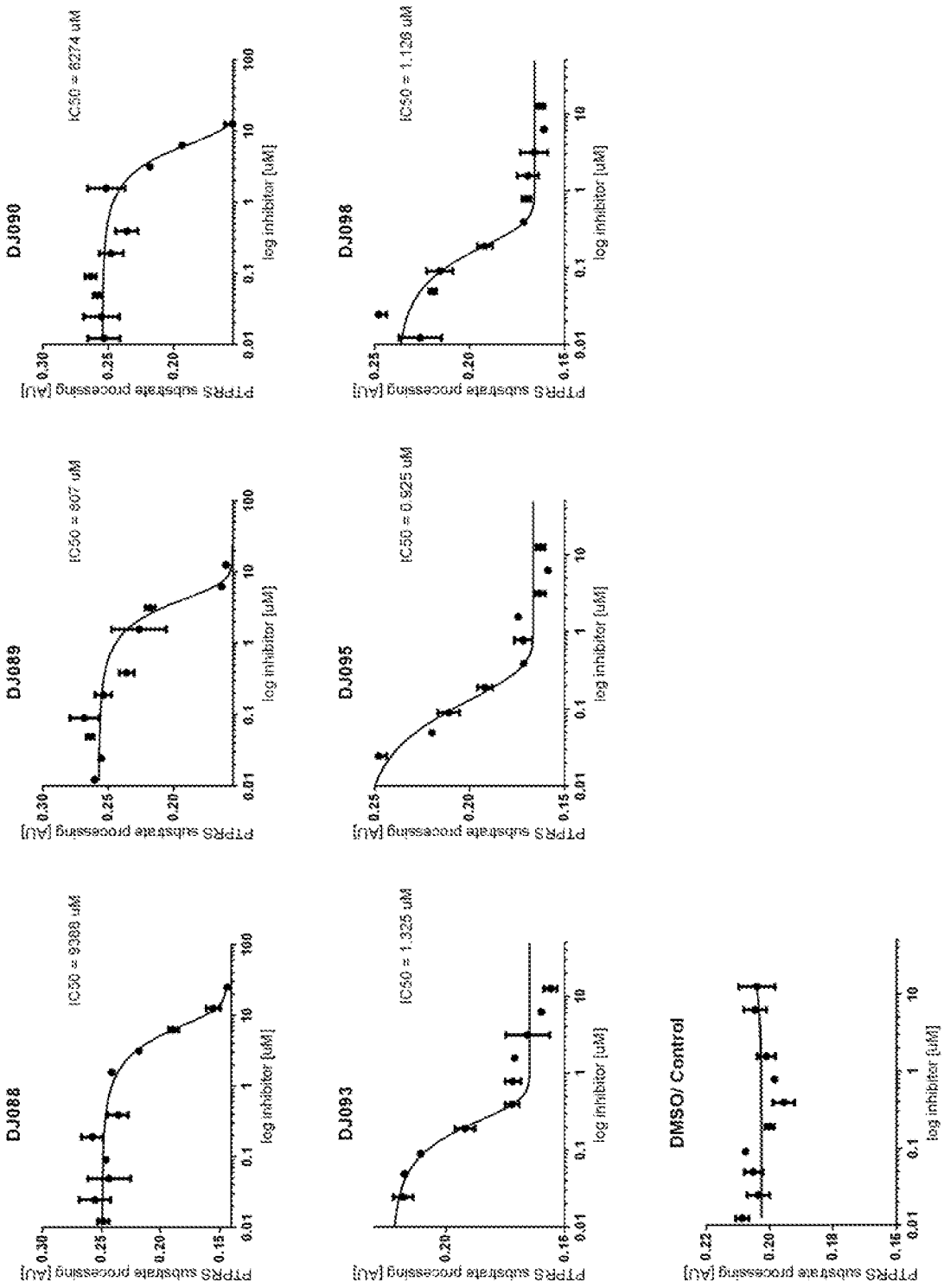

DJ090
IC50 = 6274 uM
DJ098
IC50 = 1.139 uM
DJ089
IC50 = 807 uM
DJ095
IC50 = 0.925 uM
DJ088
IC50 = 9388 uM
DJ093
IC50 = 1.325 uM
DMSO/ Control
PTPRS substrate processing [AU]
log inhibitor [uM]

FIG. 11

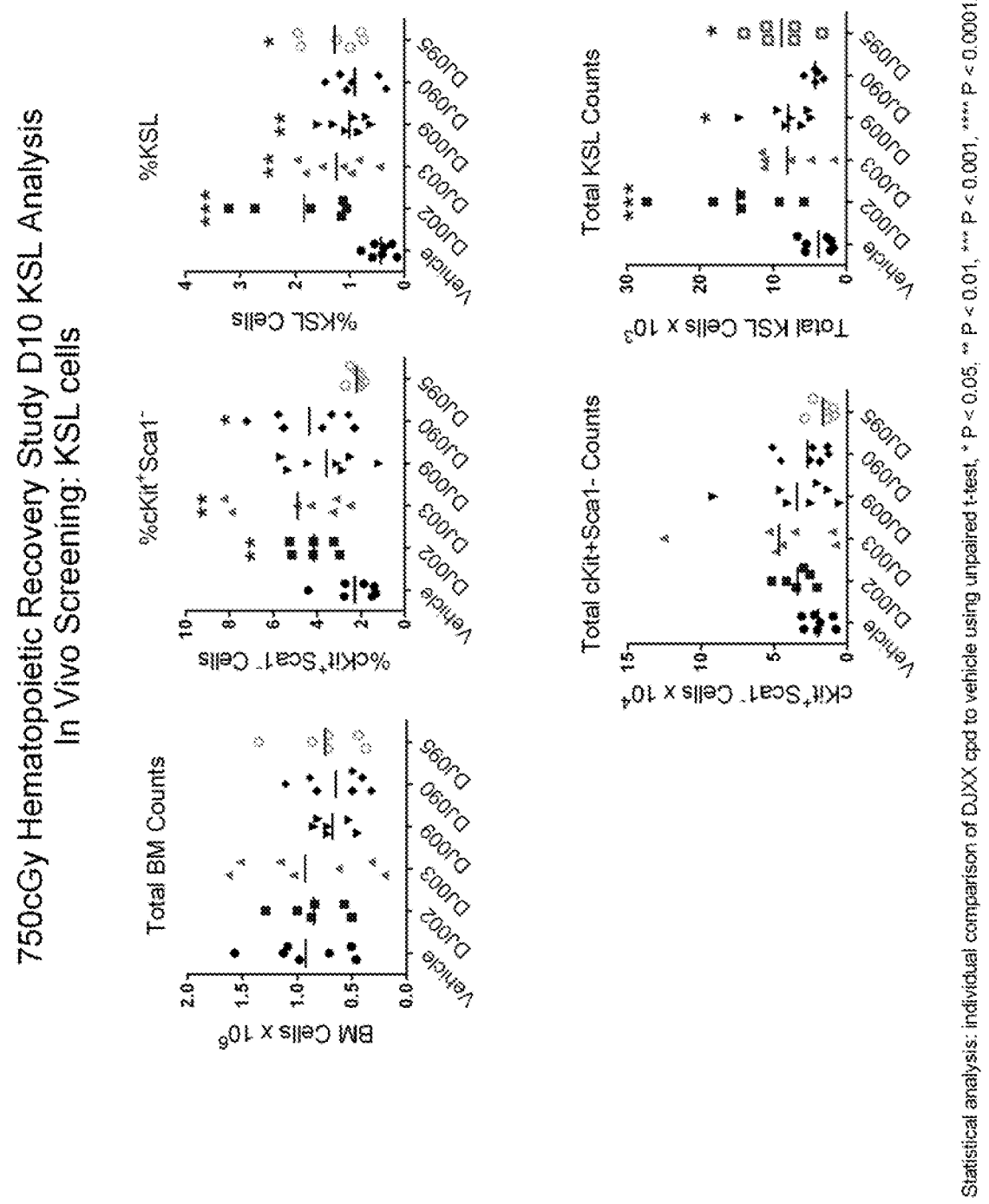

750cGy Hematopoietic Recovery Study D10 KSL Analysis
In Vivo Screening: KSL cells
Total BM Counts
BM Cells x 10^6
%cKit+Scal-
%cKit+Sca1- Cells
%KSL
%KSL Cells
Total cKit+Sca1- Counts
cKit+Scal- Cells x 10^4
Total KSL Counts
Total KSL Cells x 10^3
Vehicle
D.002
D.003
D.009
D.090
D.095
Statistical analysis: individual comparison of DJXX cpd to vehicle using unpaired t-test, * P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001.

FIG. 12

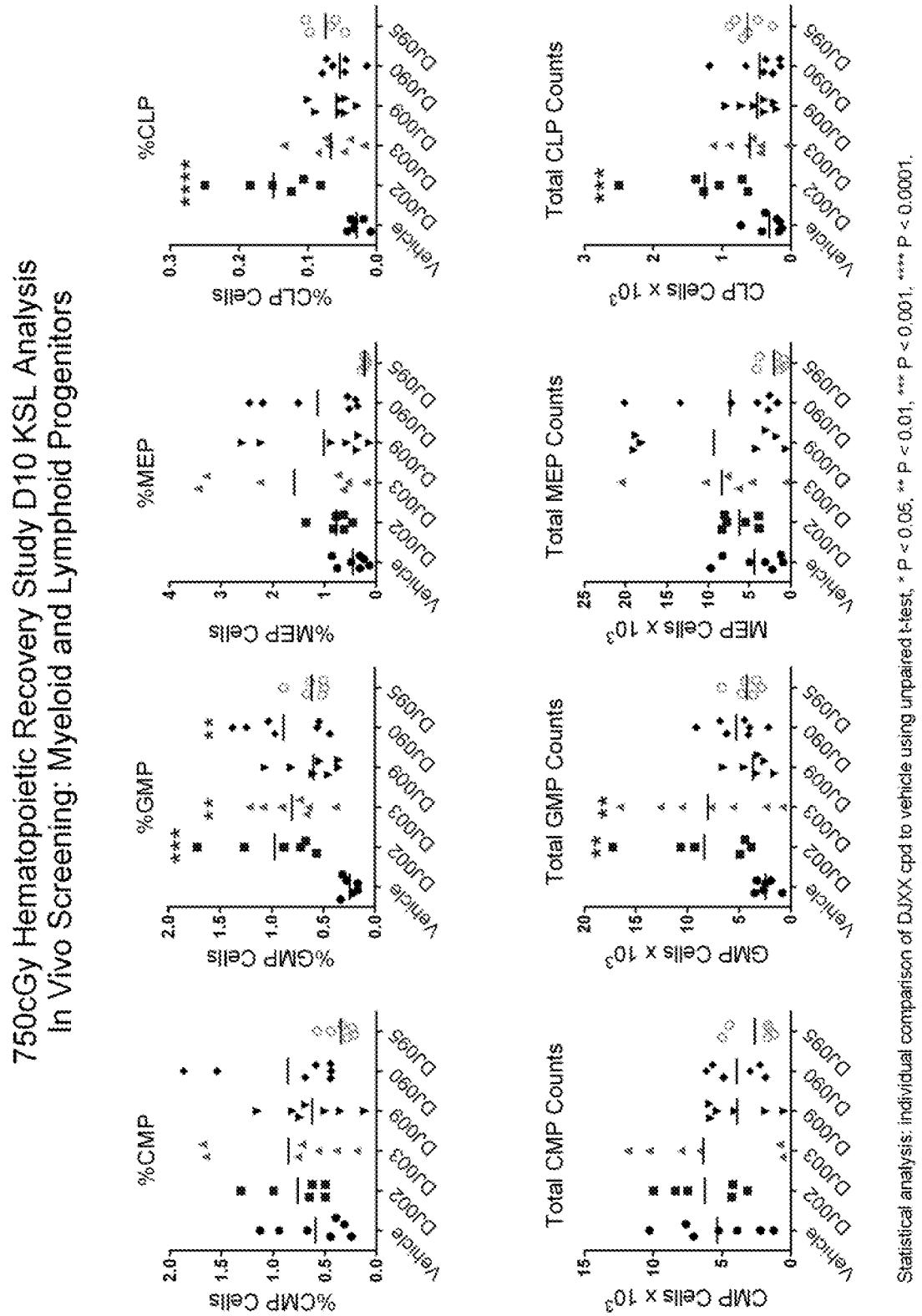

750cGy Hematopoietic Recovery Study D10 KSL Analysis
In Vivo Screening: Myeloid and Lymphoid Progenitors
%CMP
%CMP Cells
%GMP
%GMP Cells
%MEP
%MEP Cells
%CLP
%CLP Cells
Total CMP Counts
CMP Cells x 10^3
Total GMP Counts
GMP Cells x 10^3
Total MEP Counts
MEP Cells x 10^3
Total CLP Counts
CLP Cells x 10^3
Vehicle
DJ002
DJ003
DJ009
DJ090
DJ095
Statistical analysis: individual comparison of DJXX cpd to vehicle using unpaired t-test, * P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001.

FIG. 13

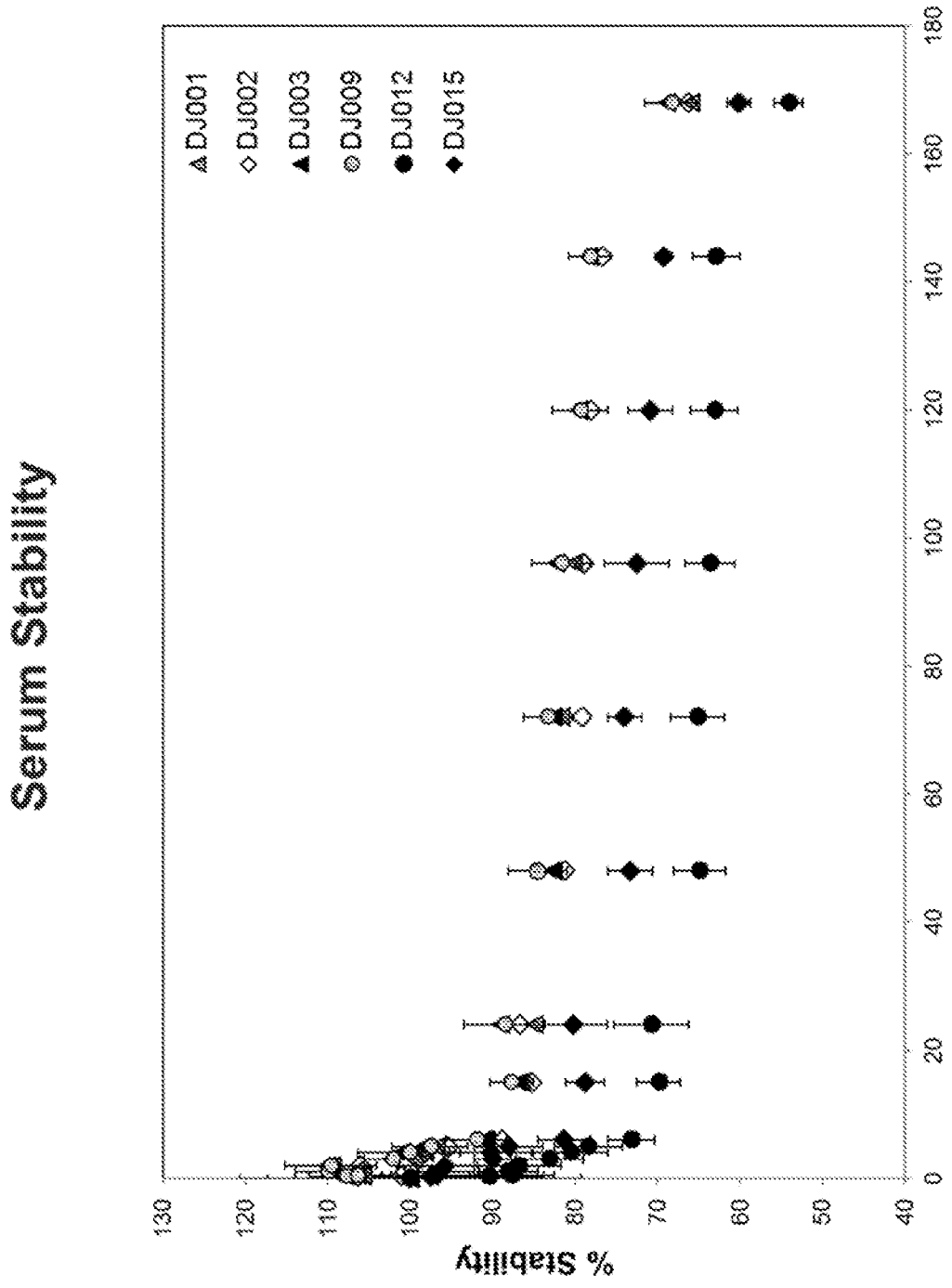

Serum Stability
DJ001
DJ002
DJ003
DJ009
DJ012
DJ015
% Stability
130
120
110
100
90
80
70
60
50
40
0
20
40
60
80
100
120
140
160
180
Time (h)

FIG. 14

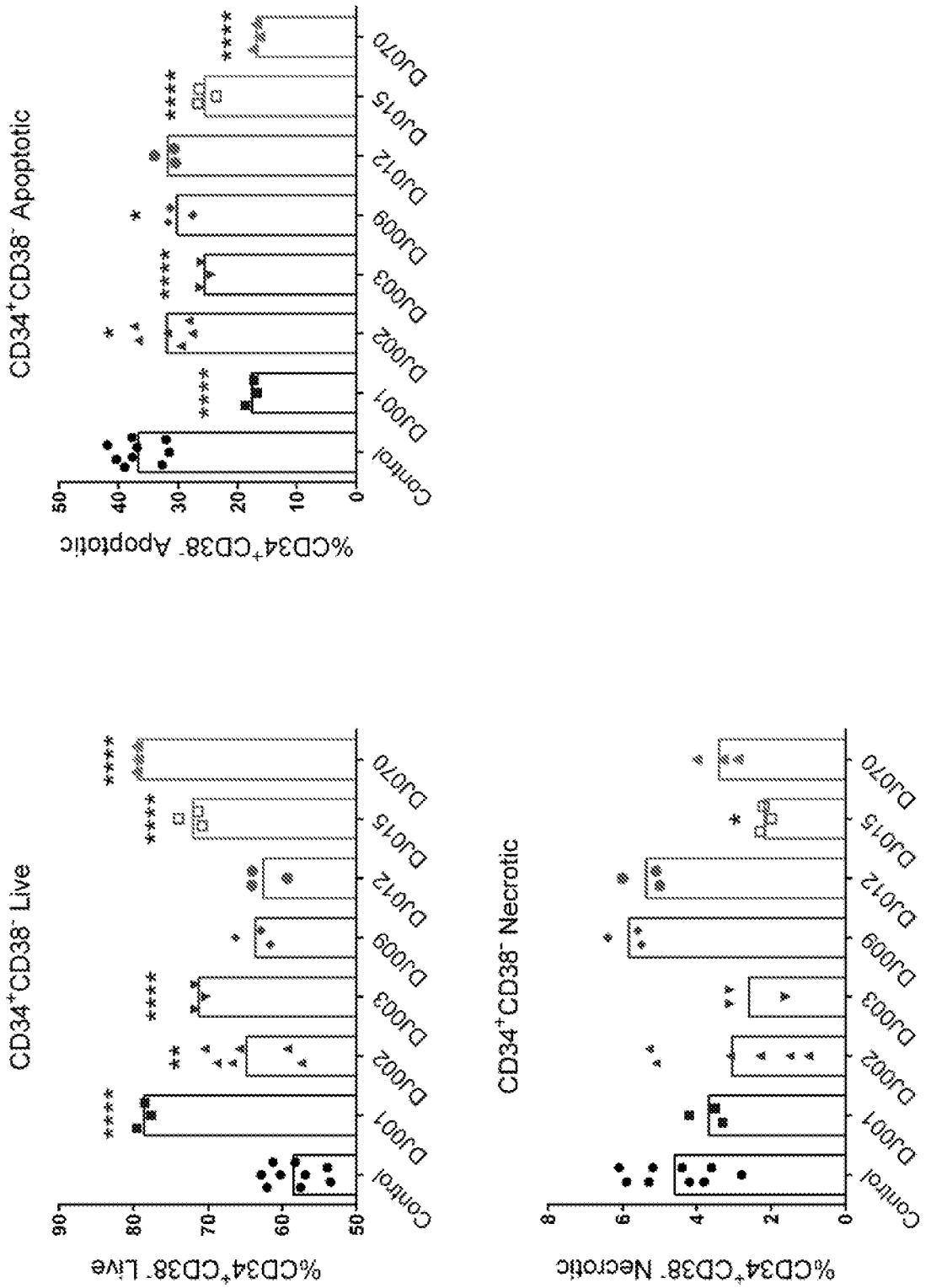

CD34+CD38- Apoptotic
%CD34+CD38- Apoptotic
CD34+CD38- Live
%CD34+CD38- Live
CD34+CD38- Necrotic
%CD34+CD38- Necrotic
Control
DJ001
DJ002
DJ003
DJ009
DJ012
DJ015
DJ070

FIG. 15

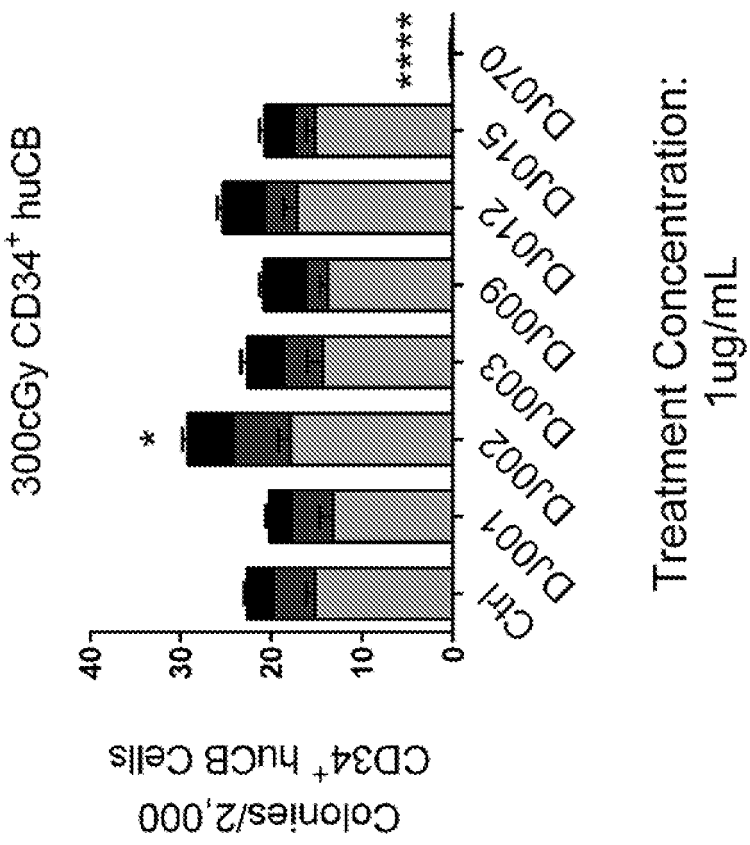

300cGy CD34+ huCB
Colonies/2,000 CD34+ huCB Cells
40
30
20
10
0
*
****
Ctrl
DJ001
DJ002
DJ003
DJ009
DJ012
DJ015
DJ070
Treatment Concentration: 1ug/mL

FIG. 16

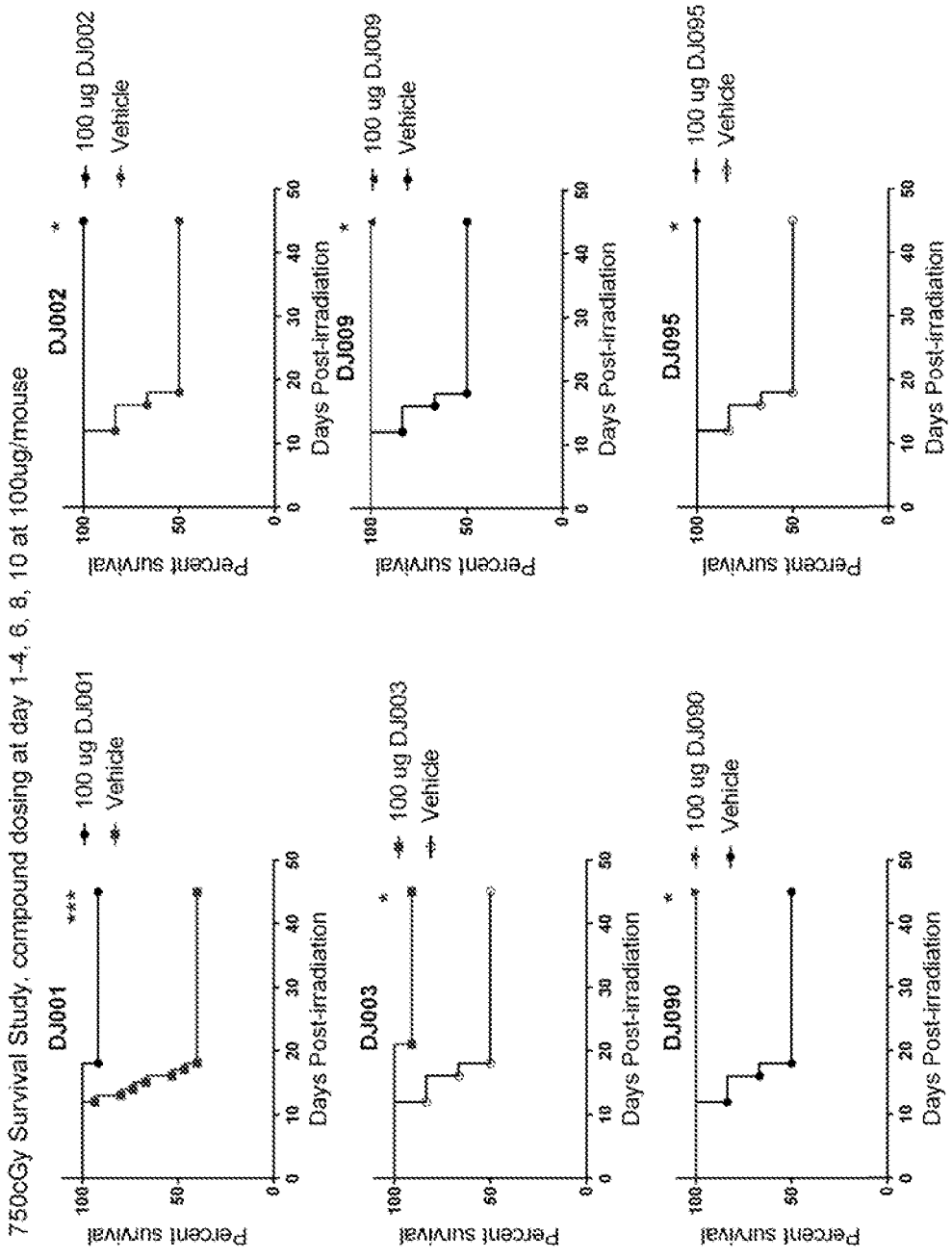

750cGy Survival Study, compound dosing at day 1-4, 6, 8, 10 at 100ug/mouse
DJ001
***
100 ug DJ001
Vehicle
DJ002
*
100 ug DJ002
Vehicle
DJ003
*
100 ug DJ003
Vehicle
DJ009
*
100 ug DJ009
Vehicle
DJ090
*
100 ug DJ090
Vehicle
DJ095
*
100 ug DJ095
Vehicle
Percent survival
Days Post-irradiation
0
50
100
0
10
20
30
40
50
Statistical analysis: Log-rank test, * P < 0.05, ** P < 0.01, *** P < 0.001

FIG. 17

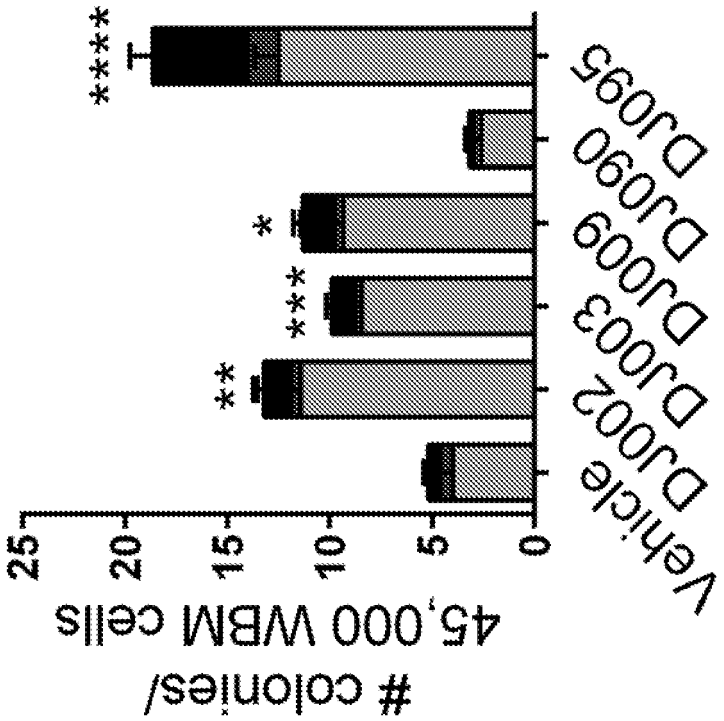

Vehicle
DJ002
DJ003
DJ009
DJ090
DJ095
0
5
10
15
20
25
colonies/
45,000 WBM cells
****
**
***
*
****

FIG. 18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/063074

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC (2019.01) C07C 225/22, C07C 233/11, C07C 233/36, C07D 207/333, C07D 213/50, C07D 213/74, C07D 231/56, C07D 333/36, C07D 249/06, C07D 401/06, A61K 135/00, A61K 31/166, A61K 31/167, A61K 31/381, A61K 31/402, A61K 31/416, A61K, A61K 31/44, A61P 7/00, A61P 43/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Databases consulted: Google Patents, CAPLUS, BIOSIS, EMBASE, MEDLINE, REGISTRY, Google Scholar
Search terms used: PTPsigma; protein tyrosine phosphatase sigma; hematopoiet*; HSC, stem cell, aplastic anemia; hematological.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PINA, M. C., et al. Synthesis and prototropic isomerization of 1-nitrophenyl-2-acylpyrroles. Chemistry of Heterocyclic Compounds, (1989), vol. 25, Issue 3, pages 268-271. 31 Dec 1989 (1989/12/31) Page 271 line 6.	1-5,25-30
X	CN 104119285 A (GUANGZHOU INST BIOMED & HEALTH) 29 Oct 2014 (2014/10/29) Compounds on pages 21-42.	1-4,6,25-29
X	CN 106279027 A (UNIV SHENYANG PHARMACEUTICAL) 04 Jan 2017 (2017/01/04) Pages 8-16, paragraphs [0042], [0051], [0060], [0069], [0078], [0087], [0096], [0150], [0114], [0123], [0132], [0141], [0150], [0168])	1-4,25-29
X	JP S63239273 A (MITSUI PETROCHEMICAL IND; SUNTORY LTD) 05 Oct 1988 (1988/10/05) Page 759 No. 23 and 25.	1-4,25-29
X	WO 2013/082751 A1 (LEO PHARMA AS [DK]) 13 Jun 2013 (2013/06/13) Page 23 lines 5-6 and 23-24, page 30 lines 3-4 and 17-18.	1-4,25,26,29

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search	Date of mailing of the international search report
03 Mar 2019	03 Mar 2019

Name and mailing address of the ISA:	Authorized officer
Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Facsimile No. 972-2-5651616	BARASH SHIFTAN Noga Telephone No. 972-2-5651672

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/063074

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHAO, Yushang, et al. Lewis acid-catalyzed cyclization of enaminones with propargylic alcohols: regioselective synthesis of multisubstituted 1, 2-dihydropyridines. The Journal of organic chemistry,(7 May 2013), Vol. 78, Issue 11, pages 5731-5736. Retrieved from URL:< http://or.nsfc.gov.cn/bitstream/00001903-5/438776/1/1000007306677.pdf> 07 May 2013 (2013/05/07) Page 5732, Table 2, 1a-1j.	1,2,7,12-17,25-27, 29,30
X	CAS Registry Number 416884-32-7. CA Index Name: 2-Propen-1-one, 3-[(2-nitrophenyl) amino]-1-phenyl-. STN Entry Date: 16 May 2002. 16 May 2002 (2002/05/16)	1,7,8,25-27,29,30
X	CAS Registry Number 380877-28-1. CA Index Name: 2-Propen-1-one, 1-(3,4-dichlorophenyl)-3-[(3-fluorophenyl)amino]-. STN Entry Date: 08 Jan 2002. 08 Jan 2002 (2002/01/08)	1,7,8,25-27,29,30
X	CAS Registry Number 369392-83-6. . CA Index Name: 2-Propen-1-one, 1-(3,4-dimethoxyphenyl)-3-[(3-fluorophenyl)amino]-. STN Entry Date: 13 Nov 2001. 13 Nov 2001 (2001/11/13)	1,7,8,25-27,29,30
X	WANG, Chengyu, et al. ZnCl2-catalyzed chemoselective cascade reactions of enaminones with 2-furylcarbinols: a versatile process for the synthesis of cyclopenta [b] pyrrole derivatives. Chemical Communications, (3 January 2014), Vol. 50, Issue17, pages 2164-2166. Retrieved from URL::<https://pubs.rsc.org/en/content/getauthorversionpdf/c3cc49191a> 03 Jan 2014 (2014/01/03) Page 2, Table 2, compounds 2a-2e, 2i and 2k-2m.	1,2,7,25-27,29,30
X	WO 2014/033122 A1 (UNIV MUENCHEN L MAXIMILIANS [DE]) 06 Mar 2014 (2014/03/06) Claim 8, 11, Formulas (II) – (VIII), pages 24-25, Figure 2B.	1,7,8,25,26,29-31
X	KING, Frank D.; CADDICK, Stephen. The triflic acid-mediated cyclisation of N-benzylcinnamanilides. Tetrahedron, (7 October 2013) Vol. 69, Issue 40, Pages 8592-8601. 07 Oct 2013 (2013/10/07) Page 8595,paragraph 4.2.2, compound 1c.	1,2,18,19,21,23,25, 26,29,30
X	CN 106631865 A (NANJING HUASHI NEW MAT CO LTD) 10 May 2017 (2017/05/10) Table of formula (1), page 4; compounds 13 and 14, page 7; 18, 19 and 21, page 8; 22, 24 and 25, page 9.	1,2,18,19,21,23,25, 26,29
X	CN 107325018 A (UNIV SUZHOU) 07 Nov 2017 (2017/11/07) Compounds 1a-1t, paragraphs [0045],[0067], [0071], [0075], [0079], [0083], [0087], [0091], [0095], [0099], [0103], [0107],[0111],[0115], [0119], [0123], [0127], [0131], [0135], [0139], pages 6, 8-17.	1,2,18-20,22,23, 25-29
X	WO 2013/096971 A1 (UNIV CALIFORNIA [US]) 27 Jun 2013 (2013/06/27) Compound 1, page 60.	1,18-20,22-27,29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/063074

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Radinov, R. et al. Benzo[b][1,6]naphthyridines and pyrimido[4,5-b]quinolines from 3-benzoyl-4-chloropyridine and 5-benzoyl-4,6-dichloropyrimidine. Izvestiya po Khimiya (1989), Vol. 22, Number 1, pages 144-57. 31 Dec 1989 (1989/12/31) Page 145, Scheme 1, 6a-6j and 7.	1,9,10,14,15,17, 25-30
X	EP 0779291 A1 (YAMANOUCHI PHARMA CO [JP]) 18 Jun 1997 (1997/06/18) Page 20 lines 45 and 55; page 21 line 5.	1,9,10,14,15,17, 25-27,30
X	WO 2008/021389 A2 (EXELIXIS INC [US]) 21 Feb 2008 (2008/02/21) Formula Ia, claim 1, page 318 and the compounds on page 330 lines 31-32.	11,12
X	MARTIN, Katie R., et al. Identification of small molecule inhibitors of PTPsigma through an integrative virtual and biochemical approach. PLoS One, (20 November 2012), Vol. 7, Issue 11: e50217. Retrieved from URL: >http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.796.4755&rep=rep1&type=pdf>. 20 Nov 2012 (2012/11/20) The whole document, especially compound 36, Figure 6B.	1,2,7,8,14,15,17,29, 31,32,36
Y		1-39
X	QUARMYNE, Mamle, et al. Protein tyrosine phosphatase–sigma regulates hematopoietic stem cell–repopulating capacity. The Journal of clinical investigation,(21.11 2014), 125.1, pages 177-182. Retrieved from URL:< file://main-jr-fs5/Users-Pt/nogab/My%20Documents/Downloads/Protein_tyrosine_phosphatase-s_regulates_hematopoi%20(1).pdf > 21 Nov 2014 (2014/11/21)	1-39
P,X	WO 2017/205795 A1 (UNIV CALIFORNIA [US]) 30 Nov 2017 (2017/11/30) The whole document, especially compounds DJ001-DJ016, DJ020, DJ024, DJ026-DJ027, DJ030, DJ033-DJ039, DJ043-DJ050, DJ059 and Formula (IIb).	1-39

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2018/063074

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
CN 104119285 A	29 Oct 2014	CN 104119285 A	29 Oct 2014
		CN 104119285 B	29 Jun 2016
CN 106279027 A	04 Jan 2017	CN 106279027 A	04 Jan 2017
JP S63239273 A	05 Oct 1988	JP S63239273 A	05 Oct 1988
		JP H0733374 B2	12 Apr 1995
WO 2013/082751 A1	13 Jun 2013	WO 2013082751 A1	13 Jun 2013
WO 2014/033122 A1	06 Mar 2014	WO 2014033122 A1	06 Mar 2014
		AU 2013307369 A1	19 Feb 2015
		AU 2013307369 B2	04 Jan 2018
		CA 2880374 A1	06 Mar 2014
		EP 2703384 A1	05 Mar 2014
		EP 2888228 A1	01 Jul 2015
		US 2015190370 A1	09 Jul 2015
		US 9408829 B2	09 Aug 2016
		US 2016228408 A1	11 Aug 2016
		US 9750717 B2	05 Sep 2017
CN 106631865 A	10 May 2017	CN 106631865 A	10 May 2017
CN 107325018 A	07 Nov 2017	CN 107325018 A	07 Nov 2017
WO 2013/096971 A1	27 Jun 2013	WO 2013096971 A1	27 Jun 2013
		US 2014350253 A1	27 Nov 2014
		US 9981977 B2	29 May 2018
EP 0779291 A1	18 Jun 1997	EP 0779291 A1	18 Jun 1997
		EP 0779291 B1	10 Oct 2001

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2018/063074

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
		AT 206709 T	15 Oct 2001
		CA 2192281 A1	12 Jun 1997
		DE 69615802 D1	15 Nov 2001
		DE 69615802 T2	04 Apr 2002
		DK 0779291 T3	21 Jan 2002
		ES 2161955 T3	16 Dec 2001
		GB 9525262 D0	07 Feb 1996
		JP H09202785 A	05 Aug 1997
		PT 779291 E	28 Feb 2002
		US 5922740 A	13 Jul 1999
WO 2008/021389 A2	21 Feb 2008	WO 2008021389 A2	21 Feb 2008
		WO 2008021389 A3	17 Jul 2008
		WO 2008021389 A8	12 Mar 2009
		AT 539752 T	15 Jan 2012
		AU 2007284562 A1	21 Feb 2008
		AU 2007284562 B2	02 May 2013
		CA 2658725 A1	21 Feb 2008
		CN 101528231 A	09 Sep 2009
		CN 104784695 A	22 Jul 2015
		EP 2056829 A2	13 May 2009
		EP 2056829 B1	04 Jan 2012
		EP 2056829 B9	26 Sep 2012
		HK 1130438 A1	05 Oct 2012
		JP 2010500994 A	14 Jan 2010
		JP 2013151570 A	08 Aug 2013
		JP 2014122243 A	03 Jul 2014
		JP 2016074743 A	12 May 2016
		JP 2017226702 A	28 Dec 2017
		US 2012302545 A1	29 Nov 2012
		US 8642584 B2	04 Feb 2014

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2018/063074

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
		US 2010075947 A1	25 Mar 2010
		US 2014100215 A1	10 Apr 2014
WO 2017/205795 A1	30 Nov 2017	WO 2017205795 A1	30 Nov 2017

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2018/063074

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (2019.01) C07C 225/22, C07C 233/11, C07C 233/36, C07D 207/333, C07D 213/50, C07D 213/74, C07D 231/56, C07D 333/36, C07D 249/06, C07D 401/06, A61K 135/00, A61K 31/166, A61K 31/167, A61K 31/381, A61K 31/402, A61K 31/416, A61K 31/44, A61P 7/00, A61P 43/00