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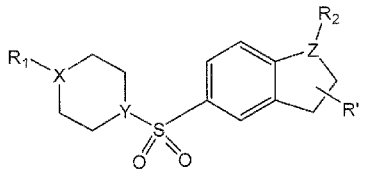
(54) Title: INDOLINE SCAFFOLD SHP-2 INHIBITORS AND CANCER TREATMENT METHOD



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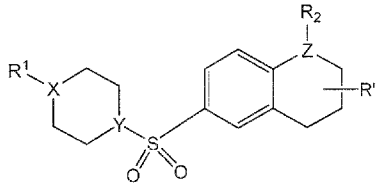

(II)

(57) Abstract: The subject invention concerns methods and compounds for inhibiting Shp2. In one embodiment, a compound of the invention has a chemical structure as shown in formula I or II: wherein X, Y, and Z are independently N or S; R_1 is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, any of which can be optionally substituted with one or more of halogen; alkyl; heteroalkyl; -COOH; $-C(R_3)_3$, wherein R_3 can independently be any of -H or halogen; or $-OR_4$, wherein R_4 can be any of H, alkyl. or heteroalkyl; R_2 is alkyl, alkylcarbonyl, heteroalkylcarbonyl, aryl, arylcarbonyl, heterocycloalkylcarbonyl, cycloalkylcarbonyl, or $-C(O)NR_6R_7$, any of which can be optionally substituted with one or more of halogen; alkyl; heteroalkyl; carbonyl; $-OR_4$, wherein R_4 can be -H, alkyl, or heteroalkyl; -OH; $-C(RO_3)_3$, wherein R_3 can independently be any of -H or halogen; aryl, which can be substituted with one or more of halogen or - OR_4; heterocycloalkyl; or $-C(O)OR_5$, wherein R_5 can be -H or alkyl; R_6 and R_7 are independently -H, alkyl, heteroalkyl, aryl, or heteroaryl; and R^1 is H or alkyl; or a pharmaceutically acceptable salt or hydrate thereof.

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DESCRIPTION

INDOLINE SCAFFOLD SHP-2 INHIBITORS AND CANCER TREATMENT METHOD

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims the benefit of U.S. Provisional Application Serial Nos. 61/082,382, filed July 21, 2008 and 61/170,354, filed April 17, 2009, each of which is hereby incorporated by reference herein in its entirety, including any figures, tables, nucleic acid sequences, amino acid sequences, and drawings.

GOVERNMENT SUPPORT

The subject matter of this application has been supported by a research grant from the National Institutes of Health under grant numbers CA118210 and CA077467. Accordingly, the government has certain rights in this invention.

BACKGROUND OF THE INVENTION

Tyrosyl phosphorylation is a mechanism involving in regulation of human cellular processes from cell differentiation and growth to apoptosis. The process of tyrosyl phosphorylation is regulated by protein-tyrosine phosphatases (PTP) and protein-tyrosine kinases (PTK). When this regulation is disrupted, diseases such as cancer can arise (Mohi and Neel, 2007). Although there is more research on PTKs since the first PTK was discovered about 10 years earlier than the first PTP, recent studies have found that PTPs have a prominent role in regulation of tyrosyl phosphorylation in the cells (Alonso *et al.*, 2004).

Shp2, encoded by the PTPN11 gene, is found to be mutated in several types of leukemias (Mohi and Neel, 2007). Futhermore, the wildtype Shp2 mediates cell signaling of many protein tyrosine kinase oncogenes such as ErbB and Met. Shp2 is necessary for embryonic development and for growth factor, cytokine, and extra-cellular matrix signaling (Salmond and Alexander, 2006) and is involved in regulation of cell

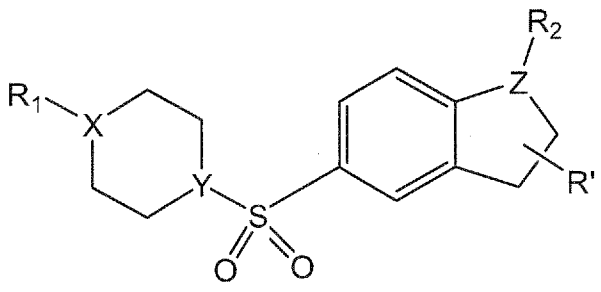
proliferation, differentiation, and migration. Shp2 mutations are linked to Noonan syndrome, juvenile myelomonocytic leukemia, acute myelogenous leukemia, and LEOPARD (lentigines, electrocardiogram abnormalities, ocular hypertelorism, pulmonic valvular stenosis, abnormalities of genitalia, retardation of growth, and deafness) syndrome.

Within these diseases, Shp2 is activated and interacts with the Gab family of docking proteins. This interaction activates a pathway leading to cell proliferation and tumorigenesis. The identification of Shp2's role in these diseases is very important for developing cancer therapy. Targeting and inhibiting Shp2 with small molecule inhibitors has become a major goal in developing a new cancer therapy.

Currently, there are a few known inhibitors of Shp2. Two of these compounds are CDL 4340-0580 (Hellmuth *et al.*, 2008) and NAT6-297775, seen in Figures 1A and 1B (Noren-Muller *et al.*, 2006). Although these compounds have the ability to inhibit Shp2, they also inhibit tumor suppressor Shp1, which is not the cause of these malignancies. Ultimately, a Shp2 inhibitor should only affect Shp2 and not other important cellular processes.

BRIEF SUMMARY OF THE INVENTION

The subject invention concerns methods and compounds for inhibiting Shp2. In one embodiment, a compound of the invention has a chemical structure as shown in formula I or II:



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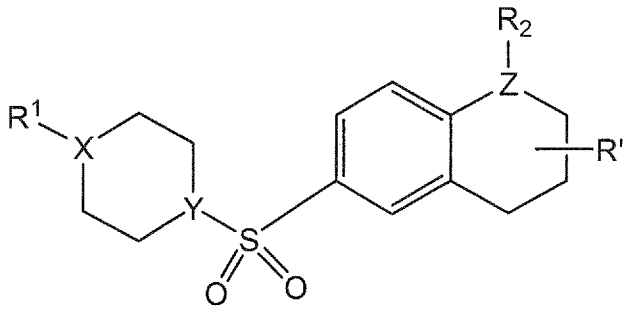


(II)

wherein

X, Y, and Z are independently N or S;

R_1 is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, any of which can be optionally substituted with one or more of halogen; alkyl; heteroalkyl; -COOH; $-C(R_3)_3$, wherein R_3 can independently be any of -H or halogen; or $-OR_4$, wherein R_4 can be any of H, alkyl, or heteroalkyl;

R_2 is alkyl, alkylcarbonyl, heteroalkylcarbonyl, aryl, arylcarbonyl, heterocycloalkylcarbonyl, cycloalkylcarbonyl, or $-C(O)NR_6R_7$, any of which can be optionally substituted with one or more of halogen; alkyl; heteroalkyl; carbonyl; $-OR_4$, wherein R_4 can be -H, alkyl, or heteroalkyl; -OH; $-C(R_3)_3$, wherein R_3 can independently be any of -H or halogen; aryl, which can be substituted with one or more of halogen or $-OR_4$; heterocycloalkyl; or $-C(O)OR_5$, wherein R_5 can be -H or alkyl;

R_6 and R_7 are independently -H, alkyl, heteroalkyl, aryl, or heteroaryl; and

R' is H or alkyl;

or a pharmaceutically acceptable salt or hydrate thereof.

The subject invention also concerns methods for treating oncological disorders in a patient. In one embodiment, an effective amount of one or more compounds or compositions of the present invention is administered to a patient having an oncological disorder and who is in need of treatment thereof.

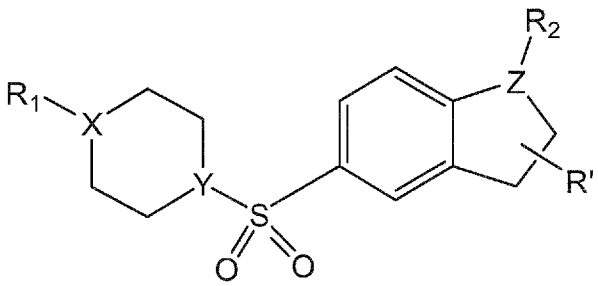
BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B are chemical diagrams of non-selective inhibitors of Shp2.

Figure 2 is a Shp2 inhibitor of the present invention identified through high throughput screening.

DETAILED DESCRIPTION OF THE INVENTION

The subject invention concerns methods and compounds for inhibiting Shp2. In one embodiment, a compound of the invention has a chemical structure as shown in formula I or II:



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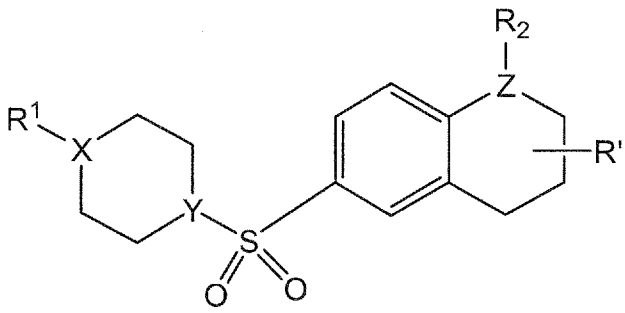


(II)

wherein

X, Y, and Z are independently N or S;

R_1 is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, any of which can be optionally substituted with one or more of halogen; alkyl; heteroalkyl; -COOH; $-C(R_3)_3$, wherein R_3 can independently be any of -H or halogen; or $-OR_4$, wherein R_4 can be any of H, alkyl, or heteroalkyl;

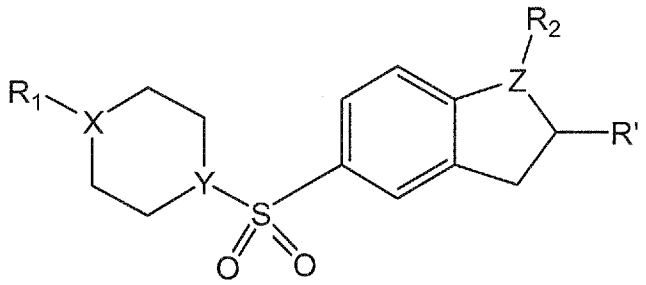
R_2 is alkyl, alkylcarbonyl, heteroalkylcarbonyl, aryl, arylcarbonyl, heterocycloalkylcarbonyl, cycloalkylcarbonyl, or $-C(O)NR_6R_7$, any of which can be optionally substituted with one or more of halogen; alkyl; heteroalkyl; carbonyl; $-OR_4$, wherein R_4 can be -H, alkyl, or heteroalkyl; -OH; $-C(R_3)_3$, wherein R_3 can independently be any of -H or halogen; aryl, which can be substituted with one or more of halogen or $-OR_4$; heterocycloalkyl; or $-C(O)OR_5$, wherein R_5 can be -H or alkyl;

R_6 and R_7 are independently -H, alkyl, heteroalkyl, aryl, or heteroaryl; and

R' is H or alkyl;

or a pharmaceutically acceptable salt or hydrate thereof.

In one embodiment, a compound of formula I has the structure:



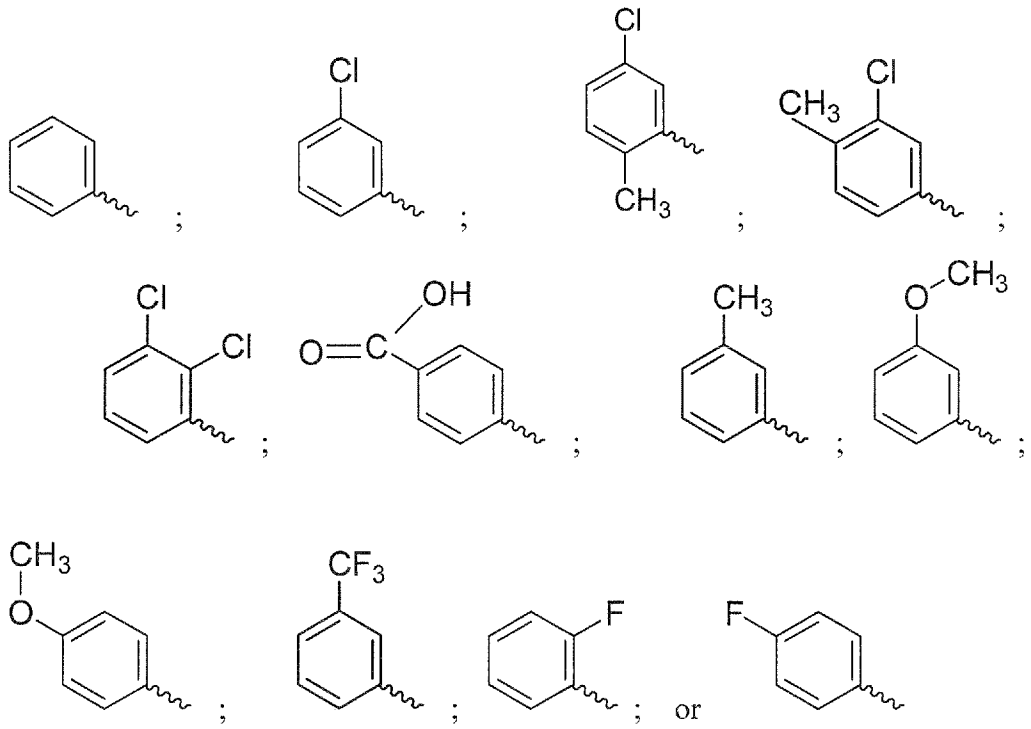
In an exemplified embodiment, X, Y, and Z are all N.

In one embodiment, R_1 is aryl optionally substituted with one or more of -Cl, -F, -COOH, $-CH_3$, CF_3, or $-OCH_3$.

In a further embodiment, R_1 is phenyl optionally substituted with one or more of -Cl, -F, -COOH, $-CH_3$, CF_3, or $-OCH_3$.

In one embodiment, $-OR_4$ is $-OCH_3$ or $-OCH_2CH_3$.

In a specific embodiment, R_1 has a structure selected from:

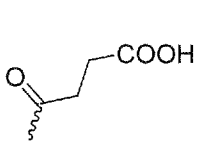


wherein ≋ indicates the point of attachment.

In one embodiment, R_2 is alkylcarbonyl optionally substituted with one or more of -OH, -COOH, aryl, or -OR, wherein R is -H or alkyl.

In one embodiment, R_2 is -C(O)NHR$_6$, wherein R_6 can be alkyl or aryl, any of which can be optionally substituted with one or more of halogen; carbonyl; -OR$_4$, wherein R_4 can be -H or alkyl; -OH; -C(R$_3$)$_3$, wherein R_3 can independently be any of -H or halogen; aryl, which can be substituted with one or more of halogen or -OR$_4$; or -C(O)OR$_5$, wherein R_5 can be -H or alkyl;

In a specific embodiment, R_2 has a structure selected from: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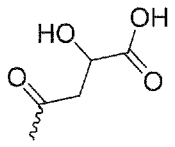
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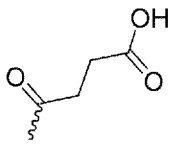
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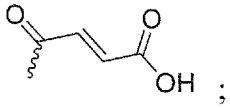
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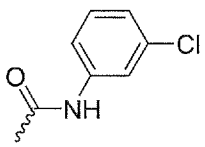
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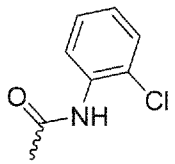
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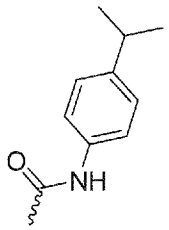
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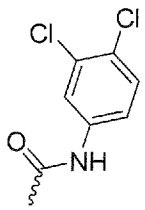
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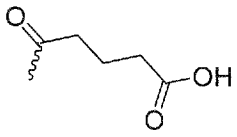
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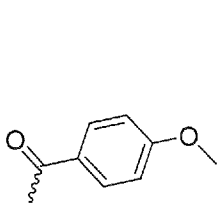
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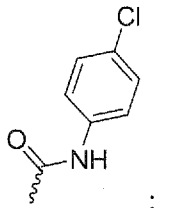
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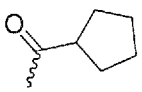
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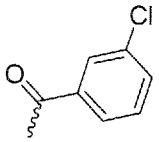
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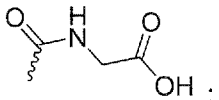
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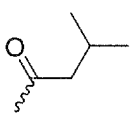
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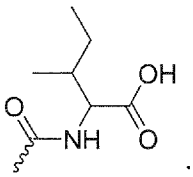
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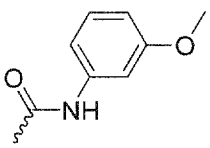
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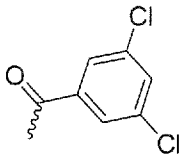
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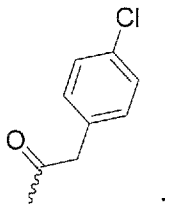
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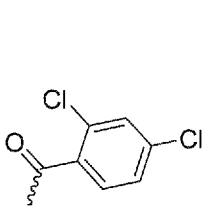
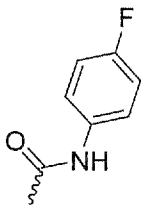
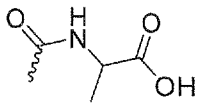
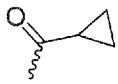
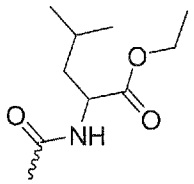
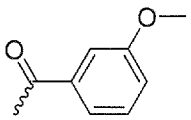
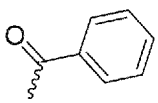
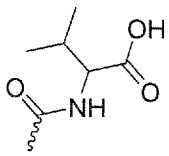
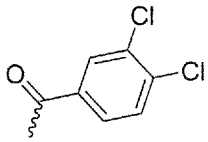
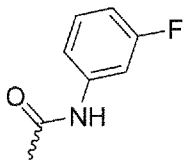
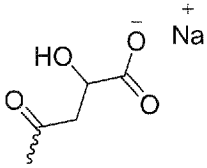
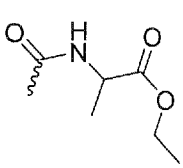
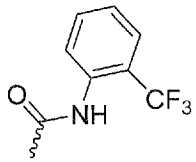
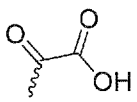
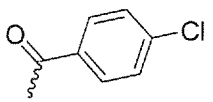
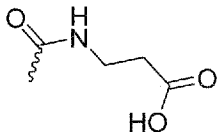
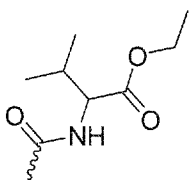
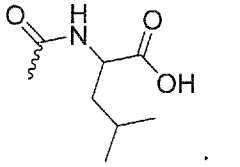
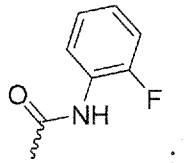
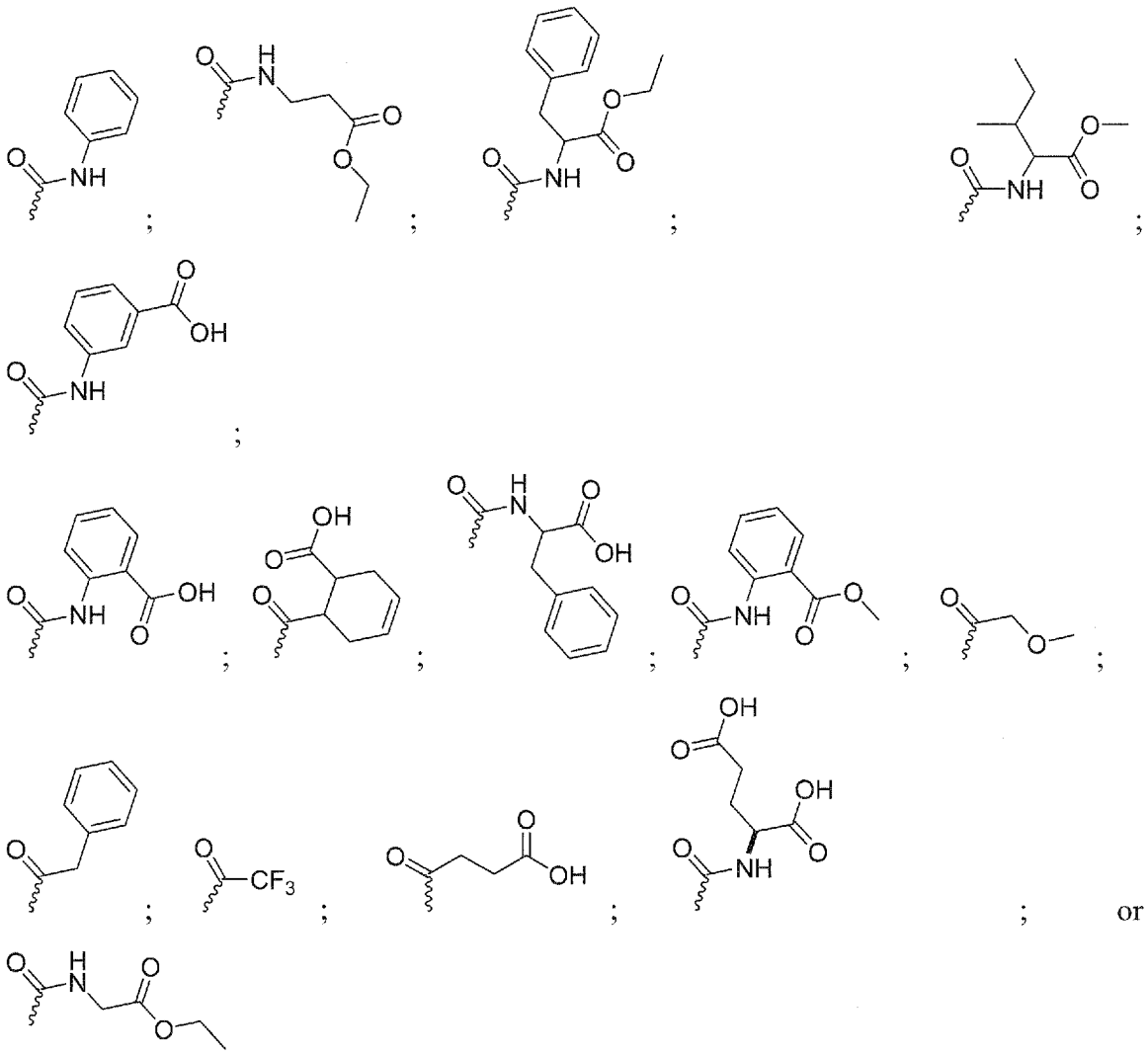






















wherein ≋ indicates the point of attachment.

Exemplified embodiments of compounds of the invention are shown in Table 3.

As used herein, alkyl means straight or branched chain, saturated or mono- or polyunsaturated hydrocarbon groups having from 1 to 20 carbon atoms and C_{1-X} alkyl means straight or branched chain alkyl groups containing from one up to X carbon atoms. For example, C_{1-6} alkyl means straight or branched chain alkyl groups containing from one up to 6 carbon atoms. Alkoxy means an alkyl-O- group in which the alkyl group is as previously described. Cycloalkyl includes a nonaromatic monocyclic or multicyclic ring system, including fused and spiro rings, of from about three to about 10 carbon atoms. A cyclic alkyl may optionally be partially unsaturated. Cycloalkoxy means a cycloalkyl-O- group in which cycloalkyl is as defined herein. Aryl means an aromatic monocyclic or

multicyclic carbocyclic ring system, including fused and spiro rings, containing from about six to about 14 carbon atoms. Aryloxy means an aryl-O- group in which the aryl group is as described herein. Alkylcarbonyl means a RC(O)- group where R is an alkyl group as previously described. Alkoxycarbonyl means an ROC(O)- group where R is an alkyl group as previously described. Cycloalkylcarbonyl means an RC(O)- group where R is a cycloalkyl group as previously described. Cycloalkoxycarbonyl means an ROC(O)- group where R is a cycloalkyl group as previously described.

Heteroalkyl means a straight or branched-chain having from one to 20 carbon atoms and one or more heteroatoms selected from nitrogen, oxygen, or sulphur, wherein the nitrogen and sulphur atoms may optionally be oxidized, *i.e.*, in the form of an N-oxide or an S-oxide. Heteroalkylcarbonyl means an RC(O)-group where R is a heteroalkyl group as previously described. Heterocycloalkyl means a monocyclic or multicyclic ring system (which may be saturated or partially unsaturated), including fused and spiro rings, of about five to about 10 elements wherein one or more of the elements in the ring system is an element other than carbon and is selected from nitrogen, oxygen, silicon, or sulphur atoms. Heteroaryl means a five to about a 14-membered aromatic monocyclic or multicyclic hydrocarbon ring system, including fused and spiro rings, in which one or more of the elements in the ring system is an element other than carbon and is selected from nitrogen, oxygen, silicon, or sulphur and wherein an N atom may be in the form of an N-oxide. Arylcarbonyl means an aryl-C(O)- group in which the aryl group is as described herein. Heteroarylcarbonyl means a heteroaryl-C(O)- group in which the heteroaryl group is as described herein and heterocycloalkylcarbonyl means a heterocycloalkyl-C(O)- group in which the heterocycloalkyl group is as described herein. Aryloxycarbonyl means an ROC(O)- group where R is an aryl group as previously described. Heteroaryloxycarbonyl means an ROC(O)- group where R is a heteroaryl group as previously described. Heteroaryloxy means a heteroaryl-O- group in which the heteroaryl group is as previously described. Heterocycloalkoxy means a heterocycloalkyl-O- group in which the heterocycloalkyl group is as previously described. Heterocycloalkoxycarbonyl means an ROC(O)- group where R is a heterocycloalkyl group as previously described.

Examples of saturated alkyl groups include, but are not limited to, methyl, ethyl, N-propyl, isopropyl, N-butyl, tert-butyl, isobutyl, sec-butyl, N-pentyl, N-hexyl, N-heptyl,

and N-octyl. An unsaturated alkyl group is one having one or more double or triple bonds. Unsaturated alkyl groups include, for example, ethenyl, propenyl, butenyl, hexenyl, vinyl, 2-propynyl, 2-isopentenyl, 2-butadienyl, ethynyl, 1-propynyl, 3-propynyl, and 3-butynyl. Cycloalkyl groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, and cycloheptyl. Heterocycloalkyl groups include, for example, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 3-morpholinyl, 4-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and 1,4-diazabicyclooctane. Aryl groups include, for example, phenyl, indenyl, biphenyl, 1-naphthyl, 2-naphthyl, anthracenyl, and phenanthracenyl. Heteroaryl groups include, for example, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyridyl, indolyl, quinolinyl, isoquinolinyl, benzoquinolinyl, carbazolyl, and diazaphenanthrenyl.

As used herein, halogen means the elements fluorine (F), chlorine (Cl), Bromine (Br), and iodine (I).

Compounds of the subject invention also include physiologically-acceptable salts and hydrates of the subject compounds. Physiologically-acceptable salts include salts of the compounds of the invention which are prepared with acids or bases, depending on the particular substituents found on the subject complexes described herein. Examples of physiologically-acceptable base addition salts include sodium, potassium, calcium, ammonium, or magnesium salt. Examples of physiologically-acceptable acid addition salts include hydrochloric, hydrobromic, nitric, phosphoric, carbonic, sulphuric, and organic acids like acetic, propionic, benzoic, succinic, fumaric, mandelic, oxalic, citric, tartaric, maleic, and the like. Physiologically-acceptable salts of compounds of the invention can be prepared using conventional techniques.

It will be appreciated by those skilled in the art that certain of the compounds of the invention may contain one or more asymmetrically substituted carbon atoms which can give rise to stereoisomers. It is understood that the invention extends to all such stereoisomers, including enantiomers, and diastereoisomers and mixtures, including racemic mixtures thereof.

In vivo application of the subject compounds, and compositions containing them, can be accomplished by any suitable method and technique presently or prospectively

known to those skilled in the art. The subject compounds can be formulated in a physiologically- or pharmaceutically-acceptable form and administered by any suitable route known in the art including, for example, oral, nasal, rectal, and parenteral routes of administration. As used herein, the term parenteral includes subcutaneous, intradermal, intravenous, intramuscular, intraperitoneal, and intrasternal administration, such as by injection. Administration of the subject compounds of the invention can be a single administration, or at continuous or distinct intervals as can be readily determined by a person skilled in the art.

The compounds of the subject invention, and compositions comprising them, can also be administered utilizing liposome technology, slow release capsules, implantable pumps, and biodegradable containers. These delivery methods can, advantageously, provide a uniform dosage over an extended period of time. The compounds of the invention can also be administered in their salt derivative forms or crystalline forms.

Compounds of the subject invention can be formulated according to known methods for preparing physiologically acceptable compositions. Formulations are described in detail in a number of sources which are well known and readily available to those skilled in the art. For example, *Remington's Pharmaceutical Science* by E.W. Martin describes formulations which can be used in connection with the subject invention. In general, the compositions of the subject invention will be formulated such that an effective amount of the compound is combined with a suitable carrier in order to facilitate effective administration of the composition. The compositions used in the present methods can also be in a variety of forms. These include, for example, solid, semi-solid, and liquid dosage forms, such as tablets, pills, powders, liquid solutions or suspension, suppositories, injectable and infusible solutions, and sprays. The preferred form depends on the intended mode of administration and therapeutic application. The compositions also preferably include conventional physiologically-acceptable carriers and diluents which are known to those skilled in the art. Examples of carriers or diluents for use with the subject compounds include ethanol, dimethyl sulfoxide, glycerol, alumina, starch, saline, and equivalent carriers and diluents. To provide for the administration of such dosages for the desired therapeutic treatment, compositions of the invention will advantageously comprise between about 0.1% and 99%, and especially, 1 and 15% by

weight of the total of one or more of the subject compounds based on the weight of the total composition including carrier or diluent.

The subject invention also concerns methods for treating a person or animal having a disorder or condition associated with aberrant or excessive Shp2 activity, or a mutation in Shp2, in a cell, wherein a therapeutically effective amount of one or more compounds or compositions of the invention is administered to the person or animal. In one embodiment, the disorder or condition is an oncological disorder or condition. In another embodiment, the disorder or condition is Noonan syndrome or LEOPARD syndrome. In one embodiment, the compound is a compound shown in Table 3. In a specific embodiment, the compound is the compound designated herein as JHE-02-032A or JHE-02-032B. In another embodiment, the compound is the compound designated herein as XW2-011B. In a further embodiment, the compound is the compound designated herein as JHE-02-035A.

The subject invention also concerns methods for inhibiting Shp2 enzymatic activity in a cell. In one embodiment, a cell is contacted with an effective amount of one or more inhibitor compounds or compositions of this invention. In one embodiment, the compound is a compound shown in Table 3. In a specific embodiment, the compound is the compound designated herein as JHE-02-032A or JHE-02-032B. In another embodiment, the compound is the compound designated herein as XW2-011B. In a further embodiment, the compound is the compound designated herein as JHE-02-035A. Cells can be any mammalian cell, such as a human cell, canine cell, feline cell, or equine cell. In one embodiment the cell is a tumor cell, a cancer cell or a transformed cell.

The subject invention also concerns a packaged dosage formulation comprising in one or more containers at least one inhibitor compound or composition of the invention. In one embodiment, the compound is a compound shown in Table 3. In one embodiment, a packaged dosage formulation comprises a compound designated herein as JHE-02-032A or JHE-02-032B. In another embodiment, the compound is the compound designated herein as XW2-011B. In a further embodiment, the compound is the compound designated herein as JHE-02-035A. A packaged dosage formulation can optionally comprise in one or more containers a pharmaceutically acceptable carrier or diluent.

Compounds of the invention, and compositions comprising them, can be delivered to a cell either through direct contact with the cell or via a carrier means. Carrier means for delivering compounds and compositions to cells are known in the art and include, for example, encapsulating the composition in a liposome moiety. Another means for delivery of compounds and compositions of the invention to a cell comprises attaching the compounds to a protein or nucleic acid that is targeted for delivery to the target cell. U.S. Patent No. 6,960,648 and Published U.S. Patent Application Nos. 20030032594 and 20020120100 disclose amino acid sequences that can be coupled to another composition and that allows the composition to be translocated across biological membranes. Published U.S. Patent Application No. 20020035243 also describes compositions for transporting biological moieties across cell membranes for intracellular delivery. Compounds can also be incorporated into polymers, examples of which include poly (D-L lactide-co-glycolide) polymer for intracranial tumors; poly[bis(p-carboxyphenoxy) propane:sebacic acid] in a 20:80 molar ratio (as used in GLIADEL); chondroitin; chitin; and chitosan.

The subject invention also concerns methods for treating oncological disorders in a patient. In one embodiment, an effective amount of one or more compounds or compositions of the present invention is administered to a patient having an oncological disorder and who is in need of treatment thereof. Methods of the invention can optionally include identifying a patient who is or may be in need of treatment of an oncological disorder. The patient can be a human or other mammal, such as a primate (monkey, chimpanzee, ape, *etc.*), dog, cat, cow, pig, or horse, or other animals having an oncological disorder. Means for administering and formulating compounds for administration to a patient are known in the art, examples of which are described herein. Oncological disorders within the scope of the invention include, but are not limited to, cancer and/or tumors of the anus, bile duct, bladder, bone, bone marrow, bowel (including colon and rectum), breast, eye, gall bladder, kidney, mouth, larynx, esophagus, stomach, testis, cervix, head, neck, ovary, lung, mesothelioma, neuroendocrine, penis, skin, spinal cord, thyroid, vagina, vulva, uterus, liver, muscle, pancreas, prostate, blood cells (including lymphocytes and other immune system cells), and brain. Specific cancers contemplated for treatment with the present invention include carcinomas, Karposi's sarcoma, melanoma, mesothelioma, soft tissue sarcoma, pancreatic cancer, lung cancer,

leukemia (acute lymphoblastic, acute myeloid, chronic lymphocytic, chronic myeloid, myelomonocytic, and other), and lymphoma (Hodgkin's and non-Hodgkin's), and multiple myeloma.

Examples of cancers that can be treated according to the present invention are listed in Table 1.

Table 1. Examples of Cancer Types

Acute Lymphoblastic Leukemia, Adult Acute Lymphoblastic Leukemia, Childhood Acute Myeloid Leukemia, Adult Acute Myeloid Leukemia, Childhood Adrenocortical Carcinoma Adrenocortical Carcinoma, Childhood AIDS-Related Cancers AIDS-Related Lymphoma Anal Cancer Astrocytoma, Childhood Cerebellar Astrocytoma, Childhood Cerebral Basal Cell Carcinoma Bile Duct Cancer, Extrahepatic Bladder Cancer Bladder Cancer, Childhood Bone Cancer, Osteosarcoma/Malignant Fibrous Histiocytoma Brain Stem Glioma, Childhood Brain Tumor, Adult Brain Tumor, Brain Stem Glioma, Childhood Brain Tumor, Cerebellar Astrocytoma, Childhood Brain Tumor, Cerebral Astrocytoma/Malignant Glioma, Childhood Brain Tumor, Ependymoma, Childhood Brain Tumor, Medulloblastoma, Childhood Brain Tumor, Supratentorial Primitive Neuroectodermal Tumors, Childhood Brain Tumor, Visual Pathway and Hypothalamic Glioma, Childhood Brain Tumor, Childhood Breast Cancer Breast Cancer, Childhood	Hairy Cell Leukemia Head and Neck Cancer Hepatocellular (Liver) Cancer, Adult (Primary) Hepatocellular (Liver) Cancer, Childhood (Primary) Hodgkin's Lymphoma, Adult Hodgkin's Lymphoma, Childhood Hodgkin's Lymphoma During Pregnancy Hypopharyngeal Cancer Hypothalamic and Visual Pathway Glioma, Childhood Intraocular Melanoma Islet Cell Carcinoma (Endocrine Pancreas) Kaposi's Sarcoma Kidney (Renal Cell) Cancer Kidney Cancer, Childhood Laryngeal Cancer Laryngeal Cancer, Childhood Leukemia, Acute Lymphoblastic, Adult Leukemia, Acute Lymphoblastic, Childhood Leukemia, Acute Myeloid, Adult Leukemia, Acute Myeloid, Childhood Leukemia, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Hairy Cell Lip and Oral Cavity Cancer Liver Cancer, Adult (Primary) Liver Cancer, Childhood (Primary) Lung Cancer, Non-Small Cell Lung Cancer, Small Cell Lymphoma, AIDS-Related Lymphoma, Burkitt's Lymphoma, Cutaneous T-Cell, see Mycosis Fungoides and Sézary Syndrome Lymphoma, Hodgkin's, Adult

Breast Cancer, Male	Lymphoma, Hodgkin's, Childhood
Bronchial Adenomas/Carcinoids, Childhood	Lymphoma, Hodgkin's During Pregnancy
Burkitt's Lymphoma	Lymphoma, Non-Hodgkin's, Adult
	Lymphoma, Non-Hodgkin's, Childhood
Carcinoid Tumor, Childhood	Lymphoma, Non-Hodgkin's During Pregnancy
Carcinoid Tumor, Gastrointestinal	Lymphoma, Primary Central Nervous System
Carcinoma of Unknown Primary	Macroglobulinemia, Waldenström's
Central Nervous System Lymphoma, Primary	Malignant Fibrous Histiocytoma of Bone/Osteosarcoma
Cerebellar Astrocytoma, Childhood	Medulloblastoma, Childhood
Cerebral Astrocytoma/Malignant Glioma, Childhood	Melanoma
	Melanoma, Intraocular (Eye)
Cervical Cancer	Merkel Cell Carcinoma
Childhood Cancers	Mesothelioma, Adult Malignant
Chronic Lymphocytic Leukemia	Mesothelioma, Childhood
Chronic Myelogenous Leukemia	Metastatic Squamous Neck Cancer with Occult Primary
Chronic Myeloproliferative Disorders	Multiple Endocrine Neoplasia Syndrome, Childhood
Colon Cancer	Multiple Myeloma/Plasma Cell Neoplasm
Colorectal Cancer, Childhood	Mycosis Fungoides
Cutaneous T-Cell Lymphoma, see Mycosis Fungoides and Sézary Syndrome	Myelodysplastic Syndromes
	Myelodysplastic/Myeloproliferative Diseases
Endometrial Cancer	Myelogenous Leukemia, Chronic
Ependymoma, Childhood	Myeloid Leukemia, Adult Acute
Esophageal Cancer	Myeloid Leukemia, Childhood Acute
Esophageal Cancer, Childhood	Myeloma, Multiple
Ewing's Family of Tumors	Myeloproliferative Disorders, Chronic
Extracranial Germ Cell Tumor, Childhood	Nasal Cavity and Paranasal Sinus Cancer
Extragonadal Germ Cell Tumor	Nasopharyngeal Cancer
Extrahepatic Bile Duct Cancer	Nasopharyngeal Cancer, Childhood
Eye Cancer, Intraocular Melanoma	Neuroblastoma
Eye Cancer, Retinoblastoma	Non-Hodgkin's Lymphoma, Adult
	Non-Hodgkin's Lymphoma, Childhood
Gallbladder Cancer	Non-Hodgkin's Lymphoma During Pregnancy
Gastric (Stomach) Cancer	Non-Small Cell Lung Cancer
Gastric (Stomach) Cancer, Childhood	Oral Cancer, Childhood
Gastrointestinal Carcinoid Tumor	Oral Cavity Cancer, Lip and Oropharyngeal Cancer
Germ Cell Tumor, Extracranial, Childhood	Osteosarcoma/Malignant Fibrous Histiocytoma of Bone
Germ Cell Tumor, Extragonadal	Ovarian Cancer, Childhood
Germ Cell Tumor, Ovarian	Ovarian Epithelial Cancer
Gestational Trophoblastic Tumor	Ovarian Germ Cell Tumor
Glioma, Adult	Ovarian Low Malignant Potential Tumor
Glioma, Childhood Brain Stem	
Glioma, Childhood Cerebral	Pancreatic Cancer

Astrocytoma Glioma, Childhood Visual Pathway and Hypothalamic Skin Cancer (Melanoma) Skin Carcinoma, Merkel Cell Small Cell Lung Cancer Small Intestine Cancer Soft Tissue Sarcoma, Adult Soft Tissue Sarcoma, Childhood Squamous Cell Carcinoma, see Skin Cancer (non-Melanoma) Squamous Neck Cancer with Occult Primary, Metastatic Stomach (Gastric) Cancer Stomach (Gastric) Cancer, Childhood Supratentorial Primitive Neuroectodermal Tumors, Childhood T-Cell Lymphoma, Cutaneous, see Mycosis Fungoides and Sézary Syndrome Testicular Cancer Thymoma, Childhood Thymoma and Thymic Carcinoma Thyroid Cancer Thyroid Cancer, Childhood Transitional Cell Cancer of the Renal Pelvis and Ureter Trophoblastic Tumor, Gestational Unknown Primary Site, Carcinoma of, Adult Unknown Primary Site, Cancer of, Childhood Unusual Cancers of Childhood Ureter and Renal Pelvis, Transitional Cell Cancer Urethral Cancer Uterine Cancer, Endometrial Uterine Sarcoma Vaginal Cancer Visual Pathway and Hypothalamic Glioma, Childhood Vulvar Cancer Waldenström's Macroglobulinemia Wilms' Tumor	Pancreatic Cancer, Childhood Pancreatic Cancer, Islet Cell Paranasal Sinus and Nasal Cavity Cancer Parathyroid Cancer Penile Cancer Pheochromocytoma Pineoblastoma and Supratentorial Primitive Neuroectodermal Tumors, Childhood Pituitary Tumor Plasma Cell Neoplasm/Multiple Myeloma Pleuropulmonary Blastoma Pregnancy and Breast Cancer Pregnancy and Hodgkin's Lymphoma Pregnancy and Non-Hodgkin's Lymphoma Primary Central Nervous System Lymphoma Prostate Cancer Rectal Cancer Renal Cell (Kidney) Cancer Renal Cell (Kidney) Cancer, Childhood Renal Pelvis and Ureter, Transitional Cell Cancer Retinoblastoma Rhabdomyosarcoma, Childhood Salivary Gland Cancer Salivary Gland Cancer, Childhood Sarcoma, Ewing's Family of Tumors Sarcoma, Kaposi's Sarcoma, Soft Tissue, Adult Sarcoma, Soft Tissue, Childhood Sarcoma, Uterine Sezary Syndrome Skin Cancer (non-Melanoma) Skin Cancer, Childhood

In a specific embodiment, the oncological disorder is a leukemia.

For the treatment of oncological disorders, the compounds of this invention can be administered to a patient in need of treatment in combination with other antitumor or anticancer substances and/or with radiation and/or photodynamic therapy and/or with surgical treatment to remove a tumor. These other substances or treatments may be given at the same as or at different times from the compounds or compositions of this invention. For example, the compounds or compositions of the present invention can be used in combination with mitotic inhibitors such as taxol or vinblastine, alkylating agents such as cyclophosamide or ifosfamide, antimetabolites such as 5-fluorouracil or hydroxyurea, DNA intercalators such as adriamycin or bleomycin, topoisomerase inhibitors such as etoposide or camptothecin, antiangiogenic agents such as angiostatin, antiestrogens such as tamoxifen, and/or other anti-cancer drugs, antibodies, or interferons, such as, for example, GLEEVEC (Novartis Pharmaceuticals Corporation), HERCEPTIN (Genentech, Inc.), and INTRON A (Schering-Plough), respectively. In one embodiment, compounds and compositions of the invention can be used in combination with other Shp2 inhibitors, including, but not limited to, CDL 4340-0580 and NAT6-297775.

Many tumors and cancers have viral genome present in the tumor or cancer cells. For example, Epstein-Barr Virus (EBV) is associated with a number of mammalian malignancies. The compounds of the subject invention can also be used alone or in combination with anticancer or antiviral agents, such as ganciclovir, azidothymidine (AZT), lamivudine (3TC), *etc.*, to treat patients infected with a virus that can cause cellular transformation and/or to treat patients having a tumor or cancer that is associated with the presence of viral genome in the cells. The compounds of the subject invention can also be used in combination with viral based treatments of oncologic disease. For example, compounds of the invention can be used with mutant herpes simplex virus in the treatment of non-small cell lung cancer (Toyoizumi *et al.*, 1999).

While inhibitor compounds of the invention can be administered as isolated compounds, these compounds can also be administered as part of a pharmaceutical composition. The subject invention thus further provides compositions comprising one or more compounds in association with at least one pharmaceutically acceptable carrier. The pharmaceutical composition can be adapted for various routes of administration, such as enteral, parenteral, intravenous, intramuscular, topical, subcutaneous, and so forth.

Administration can be continuous or at distinct intervals, as can be determined by a person of ordinary skill in the art.

The inhibitor compounds of the invention can be formulated according to known methods for preparing pharmaceutically useful compositions. Formulations suitable for administration include, for example, aqueous sterile injection solutions, which may contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood or other physiological fluids of the intended recipient; and aqueous and nonaqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the condition of the sterile liquid carrier, for example, water for injections, prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powder, granules, tablets, *etc.* It should be understood that in addition to the ingredients particularly mentioned above, the compositions of the subject invention can include other agents conventional in the art having regard to the type of formulation in question.

The compounds of the present invention include all hydrates and salts that can be prepared by those of skill in the art. Under conditions where the compounds of the present invention are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids that form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, alpha-ketoglutarate, and alpha-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts of a compound may be obtained using standard procedures well known in the art, for example, by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

Therapeutic application of compounds and compositions containing them can be accomplished by any suitable therapeutic method and technique presently or

prospectively known to those skilled in the art. Further, compounds of the invention have use as starting materials or intermediates for the preparation of other useful compounds and compositions.

Compounds of the invention, and compositions thereof, may be locally administered at one or more anatomical sites, such as sites of unwanted cell growth (such as a tumor site or benign skin growth, *e.g.*, injected or topically applied to the tumor or skin growth) or sites of fungal infection, optionally in combination with a pharmaceutically acceptable carrier such as an inert diluent. Compounds of the invention, and compositions thereof, may be systemically administered, such as intravenously or orally, optionally in combination with a pharmaceutically acceptable carrier such as an inert diluent, or an assimilable edible carrier for oral delivery. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, aerosol sprays, and the like.

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

Compounds and compositions of the invention, including pharmaceutically acceptable salts or analogs thereof, can be administered intravenously, intramuscularly, or intraperitoneally by infusion or injection. Solutions of the active compound can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations can contain a preservative to prevent the growth of microorganisms.

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

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

For topical administration, compounds and compositions of the invention may be applied in as a liquid or solid. However, it will generally be desirable to administer them topically to the skin as compositions, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid. Compounds and compositions of the subject invention can be applied topically to a subject's skin to reduce the size (and may include complete removal) of malignant or benign growths, or to treat an infection site. Compounds and compositions of the invention can be applied directly to the growth or infection site. Preferably, the compounds and compositions are applied to the growth or infection site in a formulation such as an ointment, cream, lotion, solution, tincture, or the like. Drug delivery systems for delivery of pharmacological substances to dermal lesions can also be used, such as that described in U.S. Patent No. 5,167,649.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers, for example.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user. Examples of useful dermatological compositions which can be used to deliver a compound to the skin are disclosed in U.S. Patent No. 4,608,392; U.S. Patent No. 4,992,478; U.S. Patent No. 4,559,157; and U.S. Patent No. 4,820,508.

Useful dosages of the compounds and pharmaceutical compositions of the present invention can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Patent No. 4,938,949.

The present invention also concerns pharmaceutical compositions comprising a compound of the invention in combination with a pharmaceutically acceptable carrier.

Pharmaceutical compositions adapted for oral, topical or parenteral administration, comprising an amount of a compound constitute a preferred embodiment of the invention. The dose administered to a patient, particularly a human, in the context of the present invention should be sufficient to achieve a therapeutic response in the patient over a reasonable time frame, without lethal toxicity, and preferably causing no more than an acceptable level of side effects or morbidity. One skilled in the art will recognize that dosage will depend upon a variety of factors including the condition (health) of the subject, the body weight of the subject, kind of concurrent treatment, if any, frequency of treatment, therapeutic ratio, as well as the severity and stage of the pathological condition.

For the treatment of oncological disorders, compounds and compositions contemplated by the present invention can be administered to a patient in need of treatment prior to, subsequent to, or in combination with other antitumor or anticancer agents or substances (*e.g.*, chemotherapeutic agents, immunotherapeutic agents, radiotherapeutic agents, cytotoxic agents, *etc.*) and/or with radiation therapy and/or with surgical treatment to remove a tumor. For example, compounds and compositions of the present invention can be used in methods of treating cancer wherein the patient is to be treated or is or has been treated with mitotic inhibitors such as taxol or vinblastine, alkylating agents such as cyclophosamide or ifosfamide, antimetabolites such as 5-fluorouracil or hydroxyurea, DNA intercalators such as adriamycin or bleomycin, topoisomerase inhibitors such as etoposide or camptothecin, antiangiogenic agents such as angiostatin, antiestrogens such as tamoxifen, and/or other anti-cancer drugs or antibodies, such as, for example, GLEEVEC (Novartis Pharmaceuticals Corporation) and HERCEPTIN (Genentech, Inc.), respectively. These other substances or radiation treatments may be given at the same as or at different times from the compounds of this invention. Examples of other chemotherapeutic agents contemplated within the scope of the invention include, but are not limited to, altretamine, bleomycin, bortezomib (VELCADE), busulphan, calcium folinate, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, crisantaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, docetaxel, doxorubicin, epirubicin, etoposide, fludarabine, fluorouracil, gefitinib (IRESSA), gemcitabine, hydroxyurea, idarubicin, ifosfamide, imatinib (GLEEVEC), irinotecan, liposomal doxorubicin, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitoxantrone, oxaliplatin,

paclitaxel, pentostatin, procarbazine, raltitrexed, streptozocin, tegafur-uracil, temozolomide, thiotepa, tioguanine/thioguanine, topotecan, treosulfan, vinblastine, vincristine, vindesine, vinorelbine. In an exemplified embodiment, the chemotherapeutic agent is melphalan. Examples of immunotherapeutic agents contemplated within the scope of the invention include, but are not limited to, alemtuzumab, cetuximab (ERBITUX), gemtuzumab, iodine 131 tositumomab, rituximab, trastuzamab (HERCEPTIN). Cytotoxic agents include, for example, radioactive isotopes (*e.g.*, I^{131}, I^{125}, Y^{90}, P^{32}, *etc.*), and toxins of bacterial, fungal, plant, or animal origin (*e.g.*, ricin, botulinum toxin, anthrax toxin, aflatoxin, jellyfish venoms (*e.g.*, box jellyfish), *etc.*). The subject invention also concerns methods for treating an oncological disorder comprising administering an effective amount of a compound or composition of the invention prior to, subsequent to, and/or in combination with administration of a chemotherapeutic agent, an immunotherapeutic agent, a radiotherapeutic agent, or radiotherapy.

Examples of some chemotherapeutic agents that can be used according to the present invention are listed in Table 2.

Table 2. Examples of Chemotherapeutic Agents

- 13-cis-Retinoic Acid	- Mylocel
-2-Amino-6-Mercaptopurine	- Letrozole
	- Neosar
- 2-CdA	- Neulasta
- 2-Chlorodeoxyadenosine	- Neumega
- 5-fluorouracil	- Neupogen
- 5-FU	- Nilandron
- 6 - TG	- Nilutamide
- 6 - Thioguanine	- Nitrogen Mustard
- 6-Mercaptopurine	- Novaldex
- 6-MP	- Novantrone
- Accutane	- Octreotide
- Actinomycin-D	- Octreotide acetate
- Adriamycin	- Oncospar
- Adrucil	- Oncovin
- Agrylin	- Ontak
- Ala-Cort	- Onxal
- Aldesleukin	- Oprevelkin
- Alemtuzumab	- Orapred
- Alitretinoin	- Orasone

- Alkaban-AQ	- Oxaliplatin
- Alkeran	- Paclitaxel
- All-transretinoic acid	- Pamidronate
- Alpha interferon	- Panretin
- Altretamine	- Paraplatin
- Amethopterin	- Pediapred
- Amifostine	- PEG Interferon
- Aminoglutethimide	- Pegaspargase
- Anagrelide	- Pegfilgrastim
- Anandron	- PEG-INTRON
- Anastrozole	- PEG-L-asparaginase
- Arabinosylcytosine	- Phenylalanine Mustard
- Ara-C	- Platinol
- Aranesp	- Platinol-AQ
- Aredia	- Prednisolone
- Arimidex	- Prednisone
- Aromasin	- Prelone
- Arsenic trioxide	- Procarbazine
- Asparaginase	- PROCRIT
- ATRA	- Proleukin
- Avastin	- Prolifeprospan 20 with Carmustine implant
- BCG	- Purinethol
- BCNU	- Raloxifene
- Bevacizumab	- Rheumatrex
- Bexarotene	- Rituxan
- Bicalutamide	- Rituximab
- BiCNU	- Roveron-A (interferon alfa-2a)
- Blenoxane	- Rubex
- Bleomycin	- Rubidomycin hydrochloride
- Bortezomib	- Sandostatin
- Busulfan	- Sandostatin LAR
- Busulfex	- Sargramostim
- C225	- Solu-Cortef
- Calcium Leucovorin	- Solu-Medrol
- Campath	- STI-571
- Camptosar	- Streptozocin
- Camptothecin-11	- Tamoxifen
- Capecitabine	- Targretin
- Carac	- Taxol
- Carboplatin	- Taxotere
- Carmustine	- Temodar
- Carmustine wafer	- Temozolomide
- Casodex	- Teniposide
- CCNU	- TESPA
- CDDP	- Thalidomide

- CeeNU	- Thalomid
- Cerubidine	- TheraCys
- cetuximab	- Thioguanine
- Chlorambucil	- Thioguanine Tabloid
- Cisplatin	- Thiophosphoamide
- Citrovorum Factor	- Thioplex
- Cladribine	- Thiotepa
- Cortisone	- TICE
- Cosmegen	- Toposar
- CPT-11	- Topotecan
- Cyclophosphamide	- Toremifene
- Cytadren	- Trastuzumab
- Cytarabine	- Tretinoin
- Cytarabine liposomal	- Trexall
- Cytosar-U	- Trisenox
- Cytoxan	- TSPA
- Dacarbazine	- VCR
- Dactinomycin	- Velban
- Darbepoetin alfa	- Velcade
- Daunomycin	- VePesid
- Daunorubicin	- Vesanoid
- Daunorubicin hydrochloride	- Viadur
	- Vinblastine
- Daunorubicin liposomal	- Vinblastine Sulfate
- DaunoXome	- Vincasar Pfs
- Decadron	- Vincristine
- Delta-Cortef	- Vinorelbine
- Deltasone	- Vinorelbine tartrate
- Denileukin diftitox	- VLB
- DepoCyt	- VP-16
- Dexamethasone	- Vumon
- Dexamethasone acetate	- Xeloda
- dexamethasone sodium phosphate	- Zanosar
	- Zevalin
- Dexasone	- Zinecard
- Dexrazoxane	- Zoladex
- DHAD	- Zoledronic acid
- DIC	- Zometa
- Diodex	- Gliadel wafer
- Docetaxel	- Glivec
- Doxil	- GM-CSF
- Doxorubicin	- Goserelin
- Doxorubicin liposomal	- granulocyte - colony stimulating factor
- Droxia	- Granulocyte macrophage colony stimulating factor
- DTIC	

- DTIC-Dome	- Halotestin
- Duralone	- Herceptin
- Efudex	- Hexadrol
- Eligard	- Hexalen
- Ellence	- Hexamethylmelamine
- Eloxatin	- HMM
- Elspar	- Hycamtin
- Emcyt	- Hydrea
- Epirubicin	- Hydrocort Acetate
- Epoetin alfa	- Hydrocortisone
- Erbitux	- Hydrocortisone sodium phosphate
- Erwinia L-asparaginase	- Hydrocortisone sodium succinate
- Estramustine	- Hydrocortone phosphate
- Ethyol	- Hydroxyurea
- Etopophos	- Ibritumomab
- Etoposide	- Ibritumomab Tiuxetan
- Etoposide phosphate	- Idamycin
- Eulexin	- Idarubicin
- Evista	- Ifex
- Exemestane	- IFN-alpha
- Fareston	- Ifosfamide
- Faslodex	- IL - 2
- Femara	- IL-11
- Filgrastim	- Imatinib mesylate
- Floxuridine	- Imidazole Carboxamide
- Fludara	- Interferon alfa
- Fludarabine	- Interferon Alfa-2b (PEG conjugate)
- Fluoroplex	- Interleukin - 2
- Fluorouracil	- Interleukin-11
- Fluorouracil (cream)	- Intron A (interferon alfa-2b)
- Fluoxymesterone	- Leucovorin
- Flutamide	- Leukeran
- Folinic Acid	- Leukine
- FUDR	- Leuprolide
- Fulvestrant	- Leurocristine
- G-CSF	- Leustatin
- Gefitinib	- Liposomal Ara-C
- Gemcitabine	- Liquid Pred
- Gemtuzumab ozogamicin	- Lomustine
- Gemzar	- L-PAM
- Gleevec	- L-Sarcolysin
- Lupron	- Meticorten
- Lupron Depot	- Mitomycin
- Matulane	- Mitomycin-C
- Maxidex	- Mitoxantrone

- Mechlorethamine	- M-Prednisol
-Mechlorethamine Hydrochlorine	- MTC
	- MTX
- Medralone	- Mustargen
- Medrol	- Mustine
- Megace	- Mutamycin
- Megestrol	- Myleran
- Megestrol Acetate	- Iressa
- Melphalan	- Irinotecan
- Mercaptopurine	- Isotretinoin
- Mesna	- Kidrolase
- Mesnex	- Lanacort
- Methotrexate	- L-asparaginase
- Methotrexate Sodium	- LCR
- Methylprednisolone	

The subject invention also concerns methods for inhibiting Shp2 function in a cell by contacting the cell with an effective amount of a compound or composition of the invention. In one embodiment, the cell is a human or mammalian cell, and can be a cancer or tumor cell or other cell that exhibits abnormal proliferation, survival, migration or differentiation. In one embodiment, the cell constitutively expresses or expresses elevated or abnormal levels of a Shp2 or a mutated Shp2.

The subject invention also concerns methods for treating a person or animal having a disorder associated with constitutive, abnormal, or elevated expression of Shp2 in a cell, or a mutation in Shp2, wherein a therapeutically effective amount of a compound or composition of the invention is administered to the person or animal. The disorder can be one characterized, for example, by abnormal cell proliferation, cell survival, cell migration, and/or cell differentiation. In one embodiment, the disorder is Noonan syndrome or LEOPARD syndrome.

Depending upon the disorder or disease condition to be treated, a suitable dose(s) may be that amount that will reduce proliferation or growth of the target cell(s). In the context of cancer, a suitable dose(s) is that which will result in a concentration of the active agent in cancer tissue, such as a malignant tumor, which is known to achieve the desired response. The preferred dosage is the amount which results in maximum inhibition of cancer cell growth, without unmanageable side effects. Administration of a

compound or composition can be continuous or at distinct intervals, as can be determined by a person of ordinary skill in the art.

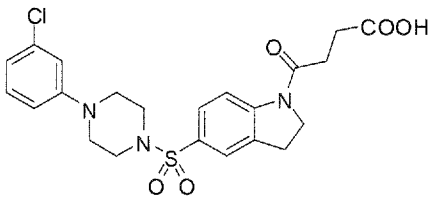
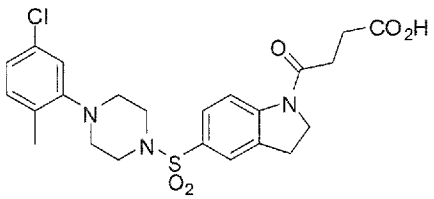
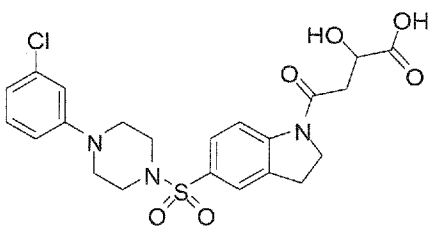
To provide for the administration of such dosages for the desired therapeutic treatment, in some embodiments, pharmaceutical compositions of the invention can comprise between about 0.1% and 45%, and especially, 1 and 15%, by weight of the total of one or more of the compounds based on the weight of the total composition including carrier or diluents. Illustratively, dosage levels of the administered active ingredients can be: intravenous, 0.01 to about 20 mg/kg; intraperitoneal, 0.01 to about 100 mg/kg; subcutaneous, 0.01 to about 100 mg/kg; intramuscular, 0.01 to about 100 mg/kg; orally 0.01 to about 200 mg/kg, and preferably about 1 to 100 mg/kg; intranasal instillation, 0.01 to about 20 mg/kg; and aerosol, 0.01 to about 20 mg/kg of animal (body) weight.

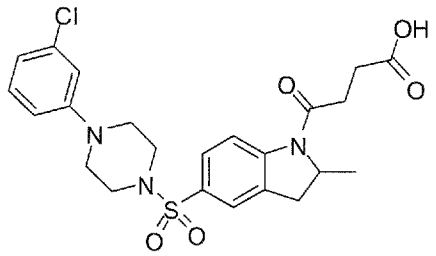
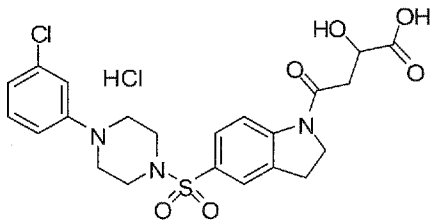
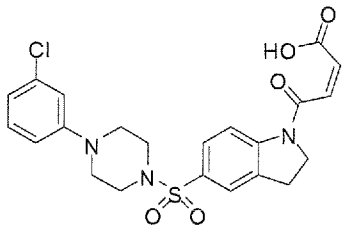
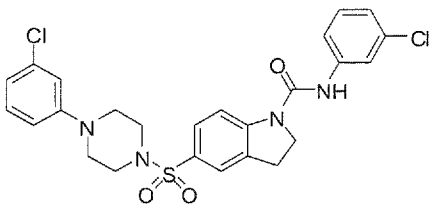
The subject invention also concerns kits comprising an inhibitor compound and/or composition of the invention in one or more containers. Kits of the invention can optionally include pharmaceutically acceptable carriers and/or diluents. In one embodiment, a kit of the invention includes one or more other components, adjuncts, or adjuvants as described herein. In another embodiment, a kit includes one or more anti-cancer agents, such as those agents described herein. In one embodiment, a kit of the invention includes instructions or packaging materials that describe how to administer a compound or composition of the kit. Containers of the kit can be of any suitable material, *e.g.*, glass, plastic, metal, *etc.*, and of any suitable size, shape, or configuration. In one embodiment, a compound and/or composition of the invention is provided in the kit as a solid, such as a tablet, pill, or powder form. In another embodiment, a compound and/or composition of the invention is provided in the kit as a liquid or solution. In one embodiment, the kit comprises an ampoule or syringe containing a compound and/or agent of the invention in liquid or solution form.

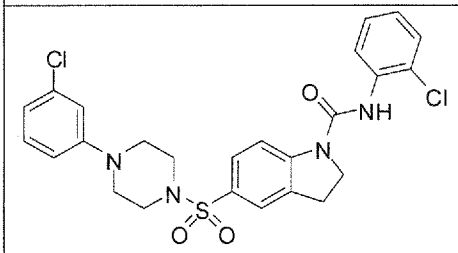
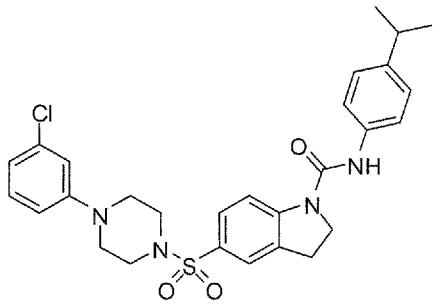
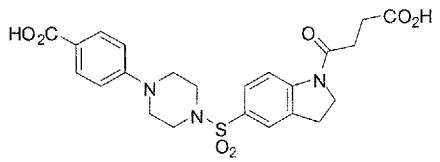
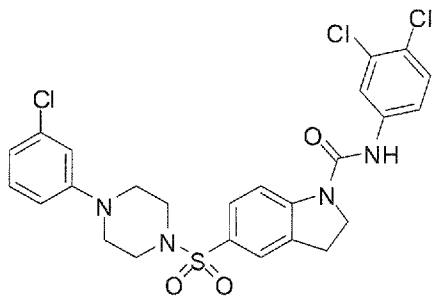
Mammalian species which benefit from the methods of the present invention include, but are not limited to, primates, such as apes, chimpanzees, orangutans, humans, monkeys; domesticated animals (*e.g.*, pets) such as dogs, cats, guinea pigs, hamsters, Vietnamese pot-bellied pigs, rabbits, and ferrets; domesticated farm animals such as cows, buffalo, bison, horses, donkey, swine, sheep, and goats; exotic animals typically found in zoos, such as bear, lions, tigers, panthers, elephants, hippopotamus, rhinoceros, giraffes, antelopes, sloth, gazelles, zebras, wildebeests, prairie dogs, koala bears,

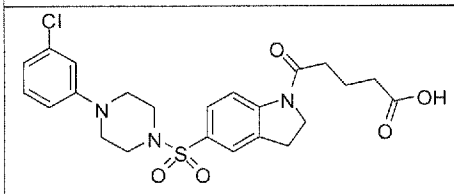
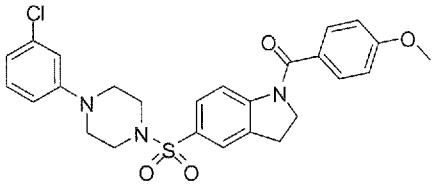
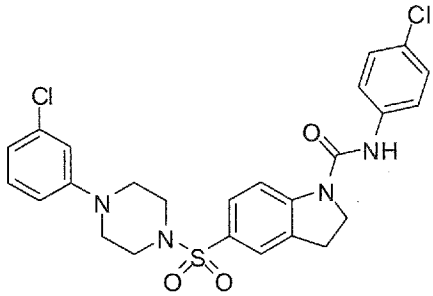
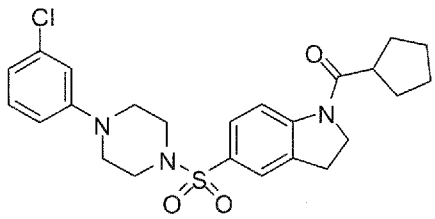
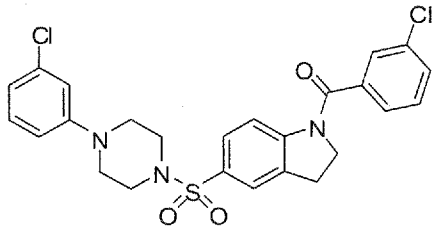
kangaroo, opossums, raccoons, pandas, hyena, seals, sea lions, elephant seals, otters, porpoises, dolphins, and whales. Other species that may benefit from the disclosed methods include fish, amphibians, avians, and reptiles. As used herein, the terms "patient" and "subject" are used interchangeably and are intended to include such human and non-human species. Likewise, *in vitro* methods of the present invention can be carried out on cells of such human and non-human species.

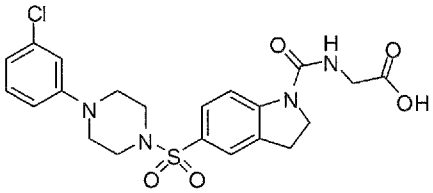
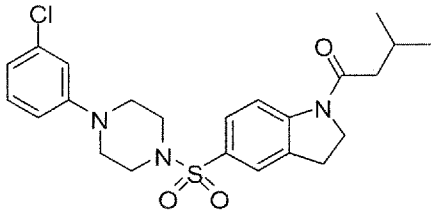
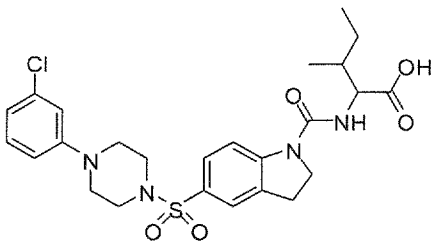
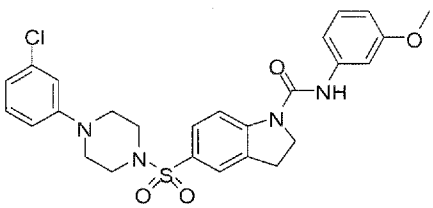
Table 3: IC_{50} values for indoline Shp2 inhibitors of the present invention, as determined by *in vitro* phosphotyrosine phosphatase activity (DiFMUP) assay. Numerous batches were tested, as indicated by the batch number in column 1.

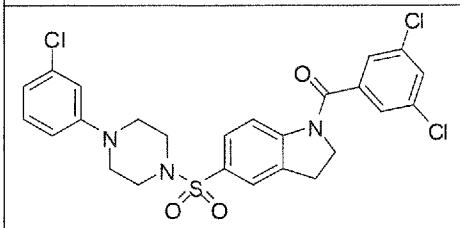
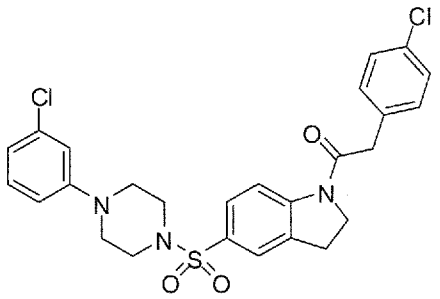
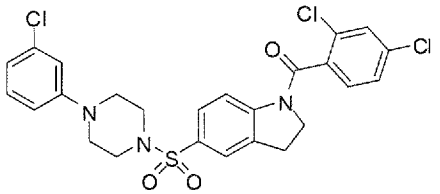
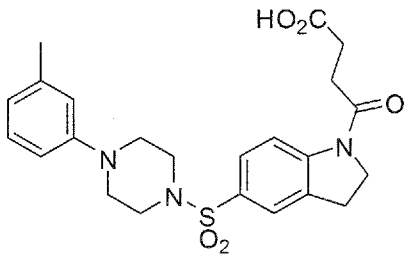
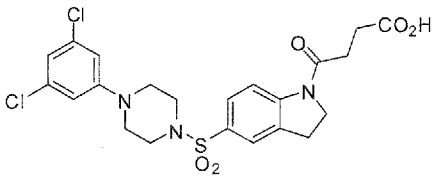
Name, Structure, Molecular Weight	IC_{50} (μM)
XW2-038H  **MW = 477.96**	0.7±0.3 n=44
XW2-125B  **MW = 491.99**	1.5±0 n=4
JHE-02-001  **MW = 493.96**	1.1±0.3 n=8

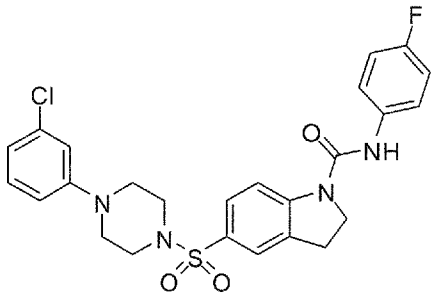
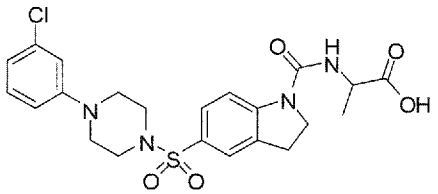
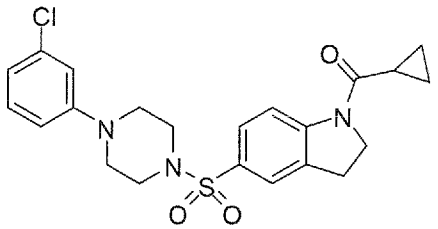
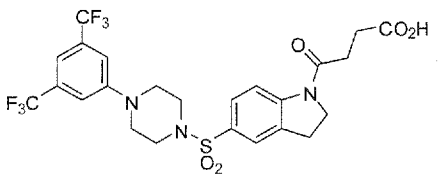
Name, Structure, Molecular Weight	IC_{50} (μM)
JHE-02-119  **MW = 491.99**	2.5±0.5 n=4
JHE-02-067  **MW = 530.42** **1.07 mg submitted on 06/30/08**	1.3±0.5 n=3
JHE-01-129A  **MW = 475.10**	2.8±0.7 n=3
JHE-02-032A  **MW = 531.45**	8.3±3.4 n=4
JHE-02-065B	3.2±0.5 n=4

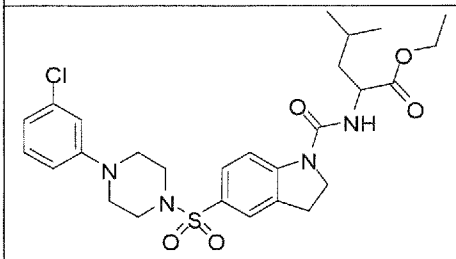
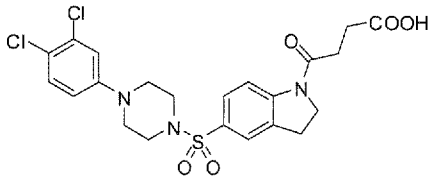
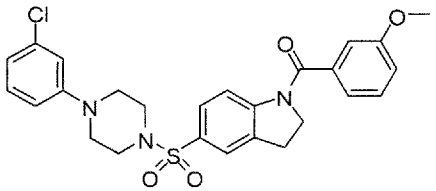
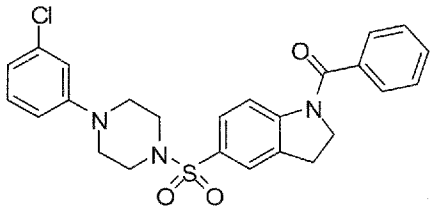
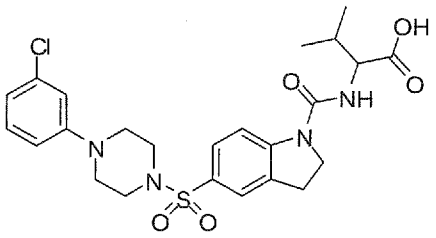
Name, Structure, Molecular Weight	IC_{50} (μM)
 **MW = 531.45**	
JHE-02-068B  **MW = 539.09**	4.1±1.0 n=4
XW3-002  **MW = 487.52**	6.1±1.8 n=4
JHE-02-068A  **MW = 565.90**	5.7±2.5 n=4
JHE-01-129B	2.8±0.7 n=3

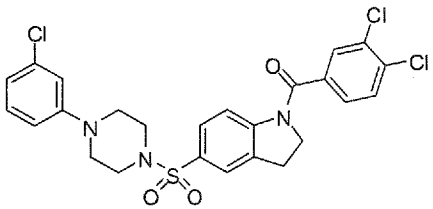
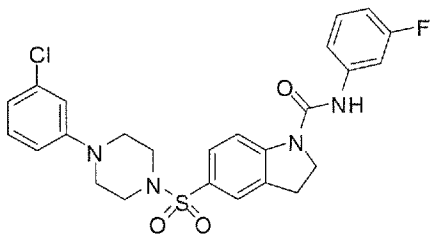
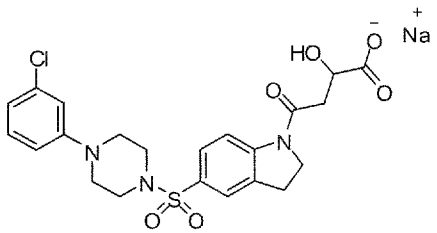
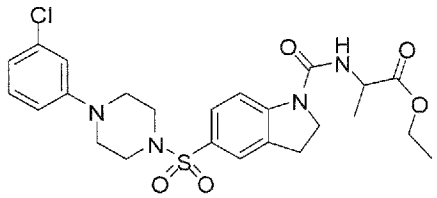
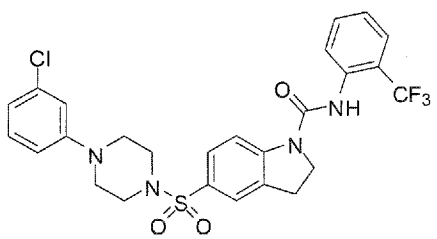
Name, Structure, Molecular Weight	IC_{50} (μM)
 **MW = 491.13**	
JF028  **MW = 512.02**	6.3±2.9 n=5
JHE-02-065A  **MW = 531.45**	19.1±5.1 n=5
JF026  **MW = 474.02**	6.9±2.2 n=5
JF020 	5.7±3.9 n=4

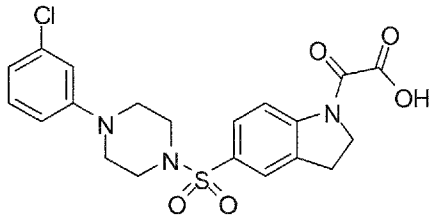
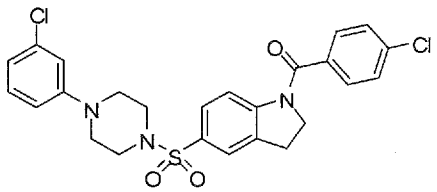
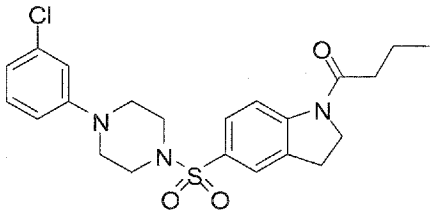
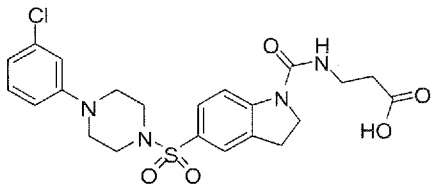
Name, Structure, Molecular Weight	IC_{50} (μM)
MW = 516.44	
JHE-01-137  **MW = 478.11**	4.6±0.3 n=3
JHE-02-033B  **MW = 462.00**	20.7±10.8 n=4
JHE-02-038  **MW = 535.06**	15.5±7.5 n=4
JHE-02-032B  **MW = 527.04**	9.9±3.5 n=4
JF025	8.2±2.6 n=5

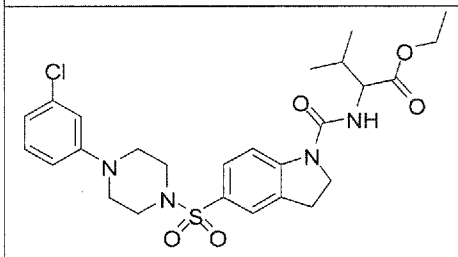
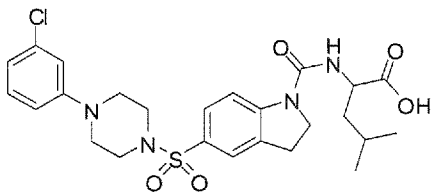
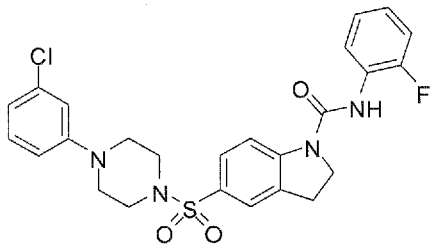
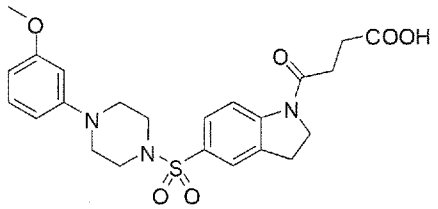
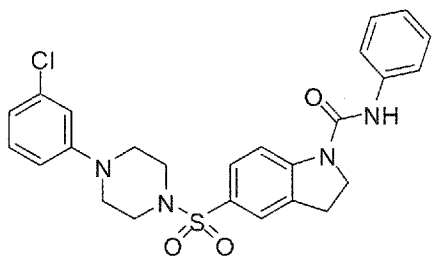
Name, Structure, Molecular Weight	IC_{50} (μM)
 **MW = 550.88**	
JHE-02-063B  **MW = 530.47**	8.0±1.9 n=4
JF024  **MW = 550.88**	7.6±1.3 n=5
XW2-057  **MW = 457.54**	3.4±2.3 n=5
XW2-124B 	4.5±1.2 n=4

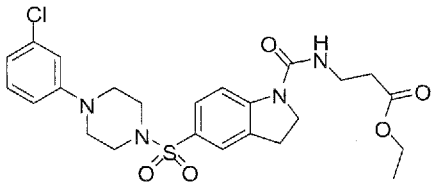
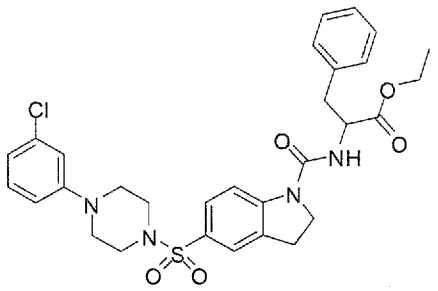
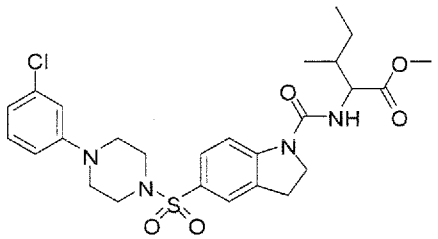
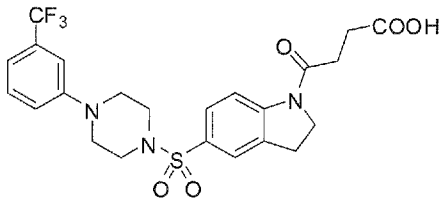
Name, Structure, Molecular Weight	IC_{50} (μM)
MW = 512.41	
JF038  **MW = 515.00**	12.6±5.4 n=5
JHE-02-017B  **MW = 492.98**	6.4±0.5 n=5
JF027  **MW = 445.96**	8.5±2.0 n=5
XW2-119  **MW = 579.51**	9.1±1.6 n=4
JHE-02-012	6.0±2.8 n=3

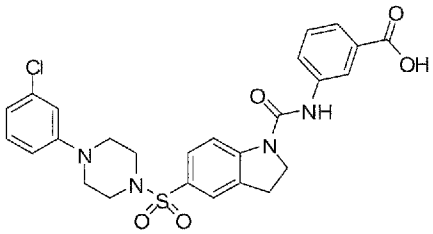
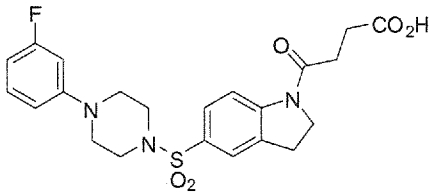
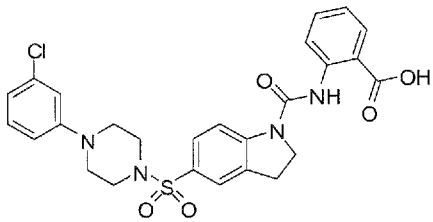
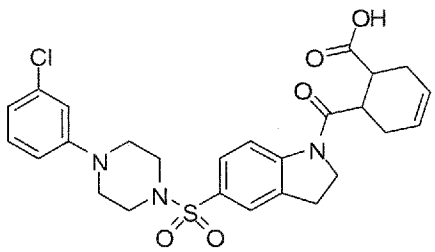
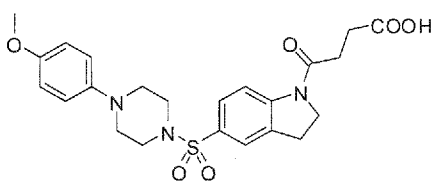
Name, Structure, Molecular Weight	IC_{50} (μM)
 **MW = 563.11**	
XW2-036  **MW = 512.41**	4.6±2.4 n=7
JHE-02-035A  **MW = 512.02**	8.1±0.8 n=4
JF022  **MW = 481.99**	8.4±2.3 n=7
JHE-02-017C  **MW = 521.03**	4.4±1.9 n=6

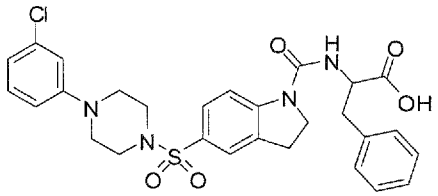
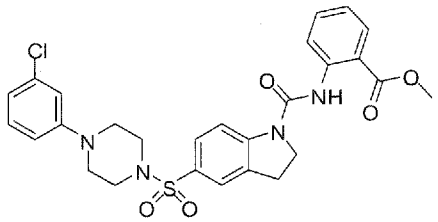
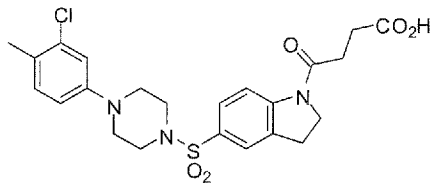
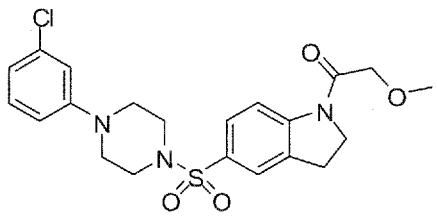
Name, Structure, Molecular Weight	IC_{50} (μM)
JF023  **MW = 550.88**	7.1±1.8 n=6
JF039  **MW = 515.00**	8.1±1.7 n=6
JHE-02-069  **MW = 515.94**	8.2±0.4 n=3
JHE-02-010B  **MW = 521.03**	5.1±2.7 n=6
JF040 	9.0±1.7 n=6

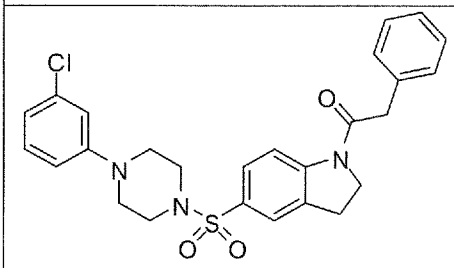
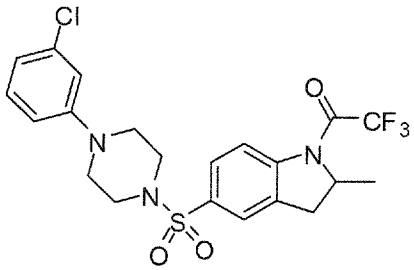
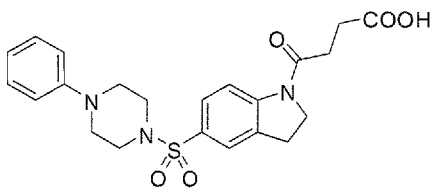
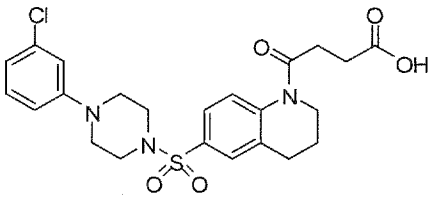
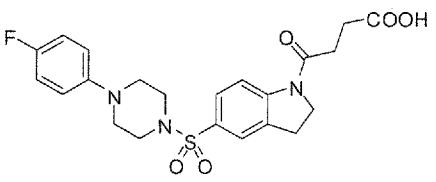
Name, Structure, Molecular Weight	IC_{50} (μM)
MW = 565.01	
JHE-01-155B  **MW = 449.08**	4.8±2.8
JF021  **MW = 516.44**	10.4±2.0 n=3
JHE-02-033A  **MW = 447.98**	7.8±2.1 n=4
JHE-02-017A  **MW = 492.98**	4.8±3.3 n=6
JHE-02-010C	7.7±2.4 n=5

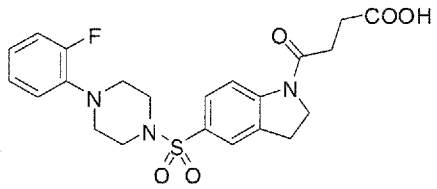
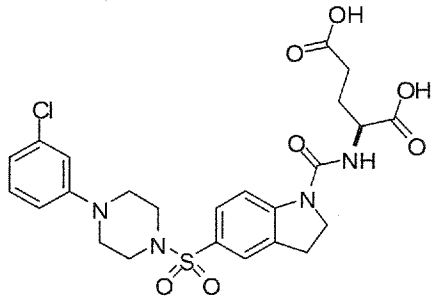
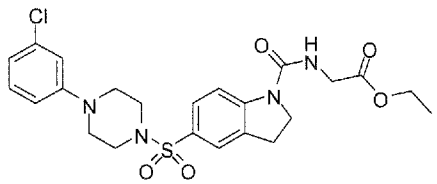
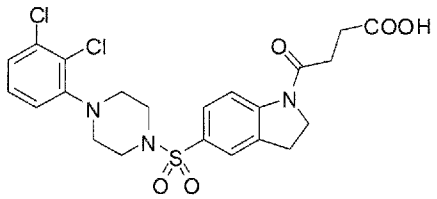
Name, Structure, Molecular Weight	IC_{50} (μM)
 **MW = 549.08**	
JHE-02-019A  **MW = 535.06**	4.5±3.5 n=3
JF035  **MW = 515.00**	12.2±2.0 n=5
XW2-038F  **MW = 473.54**	4.7±4.4 n=5
JF033 	11.7±1.4 n=5

Name, Structure, Molecular Weight	IC_{50} (μM)
MW = 497.01	
JHE-02-010A  **MW = 521.03**	9.3±2.2 n=5
JHE-02-014  **MW = 597.12**	6.9±4.2 n=6
JHE-02-029A  **MW = 549.08**	12.7±0.7 n=4
XW2-031B  **MW = 511.5**	11.3±3.1 n=5

Name, Structure, Molecular Weight	IC_{50} (μM)
JHE-02-020B  **MW = 541.02**	3.0±0.8 n=5
XW2-124A  **MW = 461.51**	13.2±3.6 n=4
JHE-02-020A  **MW = 541.02**	8.3±5.6 n=6
JHE-02-007  **MW = 530.04**	20.3±4.3 n=5
XW2-038E 	9.0±5.9 n=5

Name, Structure, Molecular Weight	IC_{50} (μM)
MW = 473.54	
JHE-02-019B  **MW = 569.07**	5.4±2.7 n=5
JHE-02-015A  **MW = 555.05**	14.3±4.1 n=5
XW3-006  **MW = 478.96**	16.6±3.6
JHE-01-169  **MW = 449.95**	9.6±2.4 n=5
JF031	22.8±4.5 n=5

Name, Structure, Molecular Weight	IC_{50} (μM)
 **MW = 496.02**	
JHE-02-117  **MW = 487.92**	47.0±17.7 n=4
XW2-038A  **MW =443.52**	14.8±7.3 n=5
JHE-02-023  **MW = 491.99**	37.3±5.3 n=3
XW2-011B  **MW = 461.5**	31.9±10.0 n=5

Name, Structure, Molecular Weight	IC_{50} (μM)
XW2-038D  **MW = 461.51**	34.6±12.6 n=4
JHE-02-052  **MW = 551.01**	37.6±13.8 n=6
JHE-01-134A  **MW = 506.14**	60.3
XW2-038G  **M.W.= 512.41**	143.6±89.5 n=5

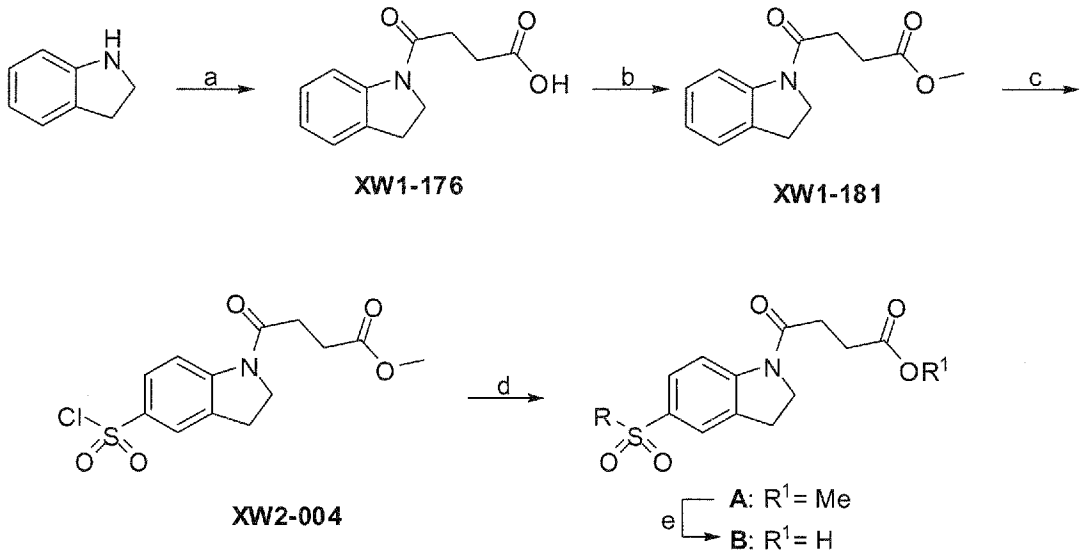
All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

Following are examples that illustrate procedures for practicing the invention. These examples should not be construed as limiting. All percentages are by weight and all solvent mixture proportions are by volume unless otherwise noted.

EXAMPLE 1

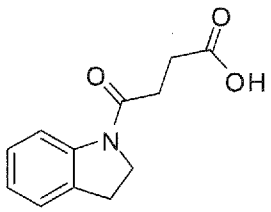
General. All reagents were purchased from commercial suppliers and used without further purification. Melting points were determined using a Barnstead international melting point apparatus and remain uncorrected. ^{1}H NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer with $CDCl_3$ or DMSO-d_6 as the solvent. ^{13}C NMR spectra are recorded at 100 MHz. All coupling constants are measured in Hertz (Hz) and the chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm) relative to TMS (δ 0), which was used as the internal standard. High resolution mass spectroscopy was carried out on an Agilent 6210 LC/MS (ESI-TOF). Microwave reactions were performed in CEM 908005 model and Biotage initiator 8 machines. HPLC analysis was performed using a JASCO HPLC system equipped with a PU-2089 Plus quaternary gradient pump and a UV-2075 Plus UV-VIS detector, using an Alltech Kromasil C-18 column (150 × 4.6 mm, 5 μm). Thin layer chromatography was performed using silica gel 60 F254 plates (Fisher), with observation under UV when necessary. Anhydrous solvents (acetonitrile, dimethyl formamide, ethanol, isopropanol, methanol and tetrahydrofuran) were used as purchased from Aldrich. HPLC grade solvents (methanol, acetontrile and water) were purchased from Burdick and Jackson for HPLC and mass analysis. Compounds were tested for IC_{50} by DiFMUP assay (results shown in Table 3).

Scheme 1.



Conditions and reagents: (a) succinic anhydride, pyridine, microwave, 90°C, 20 min; (b) H_2SO_4, MeOH, overnight; (c) chlorosulfonic acid, 0-70°C, 45 min; (d) substituted piperazines or substituted amines, pyridine, DCM, rt, 3 hr; (e) 1N LiOH, MeOH, microwave, 90°C, 10 min.

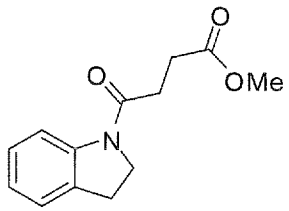
The library with modifications on the piperazine part was synthesized by coupling the sulfonyl chloride **XW2-004** with commercially available piperazines or amines. The coupling reaction of indoline with succinic anhydride afforded the free acid **XW1-176**, which was subsequently methylated to provide ester **XW1-181**. Sulfonation on the 5-position of **XW1-181** gave the key building block **XW2-004** in good yield, which was reacted with various piperazines or amines to provide the first generation library.



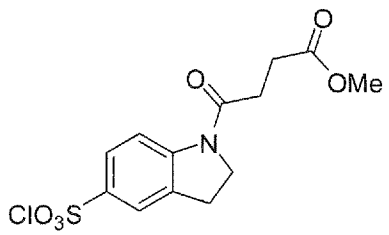
XW1-176: 4-(Indolin-1-yl)-4-oxobutanoic acid: *Tetrahedron letters, 46(2005), 1021-1022.*

The procedure was modified from the reported one. In a 20 mL microwave reaction tube equipped with a magnetic stirring bar, indoline (1.196 g, 10 mmol), succinic anhydride (1.004 g, 10mmol) and pyridine (8 mL) was mixed at room temperature. The tube was capped and irradiated in the microwave reactor (Biotage Initiator I) at 90 °C for 20 minutes. The reaction mixture was acidified to pH = 1 using 2 M HCl. The resulting

precipitate was filtered, washed with water and dried under high vacuum to afford light pink solid product (1.849 g, 92%). 1H NMR (400 MHz, $CDCl_3$) d 8.19 (d, 1H, J = 8.5 Hz), 7.18 (m, 2H), 7.03 (t, 1H, J = 7.4 Hz), 4.08 (t, 2H, J = 8.4 Hz), 3.22 (t, 2H, J = 8.4 Hz), 2.78 (m, 4H).



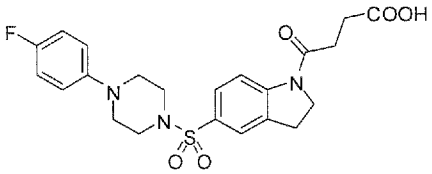
XW1-181: Methyl 4-(indolin-1-yl)-4-oxobutanoate: The acid **XW1-176** (500 mg, 2.28 mmol) was desolved in methanol (50 mL) and the solution was chilled in an ice –water bath. At 0°C, 20 drops of concentrated sulfuric acid was added. The solution was allowed to be warmed to room temperature and stirred for 15 hours. The reaction solution was concentrated to about 5 mL. The residue was carefully treated with saturated aq. sodium bicarbonate solution (100 mL). The resulting precipitate was filtered and washed with water. The product was obtained as light pink solid. (475 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) d 8.20 (d, 1H, J = 8.4 Hz), 7.17 (m, 2H), 7.01 (t, 1H, J = 7.3 Hz), 4.10 (t, 2H, J = 8.5 Hz), 3.72 (s, 3H), 3.22 (t, 2H, J = 8.4 Hz), 2.76 (s, 4H).



XW2-004: 1-(4-Methoxy-4-oxobutanoyl)indoline-5-sulfonyl chloride: At 0 °C, **XW1-181** (219 mg, 0.95 mmol) was added to chlorosulfonic acid (1.1 mL) slowly over a period of 20 min. The reaction mixture was then stirred at 0 °C for 3 hours. The clear reaction solution was carefully added to ice-water (70 mL) dropwise. A white precipitate formed and was filtered off and washed with water. The product was obtained as off-white solid. The water filtrate was extracted with ethyl acetate (3 × 10 mL). Combined ethyl acetate layers were dried over brine, sodium sulfate and the ethyl acetated was then removed

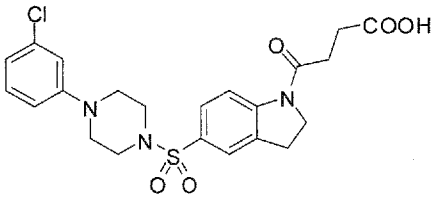
under vacuum to afford anther batch of solid product. The two batches of solid product were combined to give of **XW2-004** (217 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, 1H, J = 8.3 Hz), 7.88 (dd, 1H, J = 2.0, 8.7 Hz), 7.81 (d, 1H, J = 2.0 Hz), 4.25 (t, 2H, J = 8.0 Hz), 3.72 (s, 3H), 3.32 (t, 2H, J = 8.0 Hz), 2.78 (s, 4H).

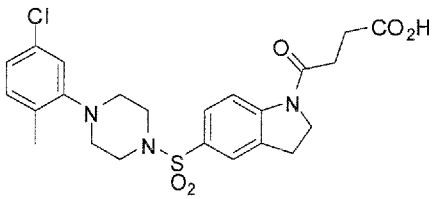


(XW2-011B): 4-(5-(4-(4-Fluorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-4-oxobutanoic acid: 1-(4-Fluorophenyl)piperazine (185 mg, 1.0 mmol) and pyridine (1 mL) were dissolved in dichloromethane (60 mL) under argon. The solution was chilled in ice-water bath and **XW2-004** 1-(4-methoxy-4-oxobutanoyl)indoline-5-sulfonyl chloride (333 mg, 1.0 mmol) was added. The reaction solution was then warmed to room temperature and stirred for 3 hours. After the reaction, water [(50 mL with 37% HCl (1 mL)] was added to the solution. The organic layer was separated and washed with water, brine and dried over magnesium sulfate. Removal of dichloromethane afforded light green solid product which was then triturated with methanol (10 mL). The white solid product was filtered off to give **methyl 4-(5-(4-(4-fluorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-4-oxobutanoate**, the methyl ester of **XW2-011B,** (320 mg, yield 67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, , J = 8.3 Hz, 1H), 7.62 (dd, 1H, J = 8.3, 2.0 Hz), 7.58 (d, 1H, J = 2.0 Hz), 6.95 (t, J = 9.0 Hz, 2H), 6.84 (m, 2H), 4.21 (t, J = 8.6 Hz, 2H), 3.72 (s, 3H), 3.30 (t, J = 8.6 Hz, 2H), 3.15 (s, 8H), 2.77 (s, 4 H). The white solid obtained from the above reaction (289mg, 0.63mmol) was mixed with methanol (10 mL) and lithium hydroxide (1 mL of a 1.0 M aq. solution) in a 20 mL microwave reaction tube. The tube was capped and irradiated in the microwave reactor (Biotage Initiator I) at 90°C for 10 minutes. The reaction solution was concentrated under vacuum and the residue was diluted with 20 mL of water treated with NaOH solution (1.0 M) till pH > 10. The aqueous solution was extracted with ethyl acetate (2 × 10 mL). Then the aqueous layer was acidified to pH~4, extracted with ethyl acetate (2 × 150 mL). The organic layer was dried over sodium sulfate and concentrated under vacuum. The resulted solid was

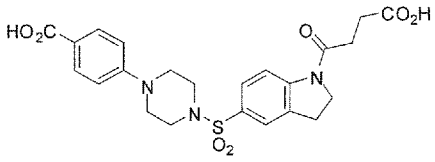
washed with dichloromethane to afford **XW2-011B** (180 mg, 69%) as a light orange solid product. Mp = 213-215 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, , J = 8.3 Hz, 1H), 7.58-7.65 (m, 2H), 6.95 (t, J = 9.0 Hz, 2H), 6.82 (dd, J = 4.5, 4.5 Hz, 2H), 4.20 (t, J = 8.6 Hz, 2H), 3.31 (t, J = 8.6 Hz, 2H), 3.15 (s, 8H), 2.80 (s, 4 H); HPLC 98% (R_t = 3.30, 90% methanol in acetonitrile); HRMS (ESI-ve) *m/z* calculated for $C_{22}H_{23}FN_3O_5S$ (M-H)- 460.13479, found 460.13475.



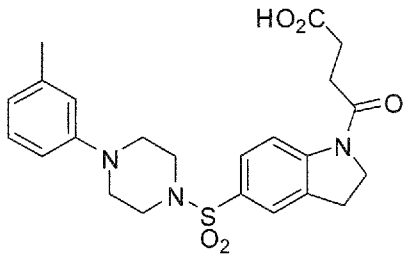
(XW2-038H) 4-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-4-oxobutanoic acid: **XW2-038H** was prepared using the same procedure as described for the preparation of **XW2-011B** as a white solid, (yield 64%). Mp = 228-230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 7.4 Hz, 1H), 7.55-7.60 (m, 2H), 7.19 (t, J = 8.1 Hz, 2H), 6.78-6.91 (m, 3H), 4.20 (bs, 2H), 3.25 (s, 8H), 2.96 (s, 4H), 2.70 (s, 2 H); HPLC 98% (R_t = 3.00, 30% water in acetonitrile with 0.1% TFA); HRMS (ESI-ve) *m/z* calculated for $C_{22}H_{23}ClN_3O_5S$ (M-H)- 476.10524, found 476.10541.



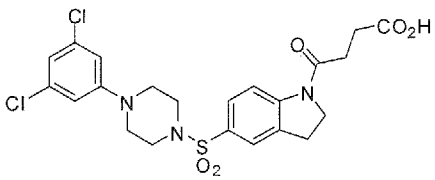
(XW2-125B) 4-(5-(4-(5-Chloro-2-methylphenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-4-oxobutanoic acid: **XW2-125B** was prepared using the same procedure as described for the preparation of **XW2-011B** as a white solid, (yield 34%). Mp = 255-256 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.0 Hz, 1H), 7.55-7.59 (m, 2H), 7.13 (d, J = 8.0 Hz, 1H), 6.99 (m, 2H), 4.20 (t, J = 8.5 Hz, 2H), 3.24 (t, J = 8.4 Hz, 2H), 2.98 (s, 4H), 2.90 (s, 4 H), 2.69 (bs, 2 H), 2.07 (s, 3 H); HRMS (ESI-ve) *m/z* calculated for $C_{23}H_{27}ClN_3O_5S$ (M+H)+ 492.13545, found 492.13568.



(XW3-002) 4-(4-(1-(3-Carboxypropanoyl)indolin-5-ylsulfonyl)piperazin-1-yl)benzoic acid: XW3-002 was prepared using the same procedure as described in the preparation of **XW2-011B** as a brown solid (yield 25%). Decomposed at 250 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 12.2 (bs, 2H), 8.20 (d, , J = 8.0 Hz, 1H), 7.74 (d, 2H, J = 8.2 Hz), 7.55-7.59 (m, 2H), 6.92 (d, J = 8.3 Hz, 1H), 4.18 (t, J = 8.5 Hz, 2H), 3.23 (t, J = 8.4 Hz, 2H), 2.96 (bs, 6H), 2.70 (s, 2 H); HRMS (ESI-ve) *m/z* calculated for $C_{23}H_{25}N_3O_7S$ (M-H)- 486.13404, found 486.13467.

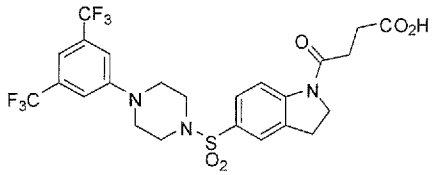


(XW2-057) 4-Oxo-4-(5-(4-m-tolylpiperazin-1-ylsulfonyl)indolin-1-yl)butanoic acid: XW2-057 was prepared using the same procedure as described for the preparation of **XW2-011B** as an off-white solid (yield 64%). Mp = 255-257 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.0 Hz, 1H), 7.58 (d, , J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.07 (t, 1H, J = 7.9 Hz), 6.63 (m, 3H), 4.13 (t, 2H, J = 8.6 Hz), 3.23 (t, 2H, J = 8.5 Hz), 3.15 (bs, 4H), 3.08 (bs, 4H), 2.73 (bs, 4H), 2.23 (s, 3H); HRMS (ESI-ve) *m/z* calculated for $C_{23}H_{26}N_3O_5S$ (M+H)+ 456.15987, found 456.16067.

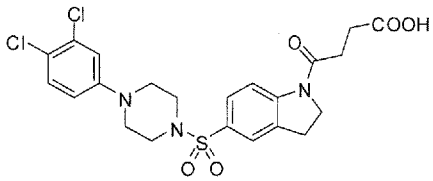


(XW2-124B) 4-(5-(4-(3,5-Dichlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-4-oxobutanoic acid: XW2-124B was prepared using the same procedure as described for the preparation of **XW2-011B** as a white solid (yield 88%). Decomposed at 250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.0 Hz, 1H), 7.53-7.55 (m, 2H), 6.90 (s, 2H), 6.85 (s, 1H), 4.19 (t, J = 8.5 Hz, 2H), 3.28 (bs, 4H), 3.20 (t, J = 8.4 Hz, 2H), 2.92 (bs, 4H),

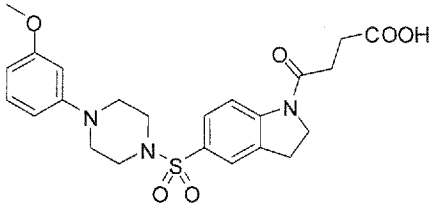
2.59 (t, J = 6.4 Hz4 H), 2.30 (t, J = 6.8 Hz, 2H); HRMS (ESI-ve) *m/z* calculated for $C_{22}H_{24}Cl_2N_3O_5S$ (M+H)+ 511.08082, found 511.08076.



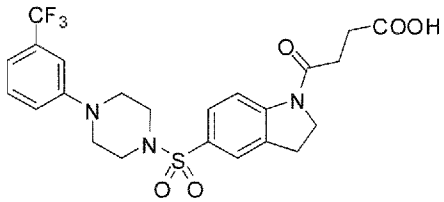
(XW2-119) 4-(5-(4-(3,5-Bis(trifluoromethyl)phenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-4-oxobutanoic acid: XW2-119 was prepared using the same procedure as described in the preparation of **XW2-011B** as a white solid (yield 84%). Mp = 206-207 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.19 (d, J = 8.0 Hz, 1H), 7.59 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.43 (s, 2H), 7.30 (s, 1H), 4.17 (t, J = 8.5 Hz, 2H), 3.42 (bs, 4H), 3.24 (t, J = 8.4 Hz, 2H), 2.97 (bs, 4H), 2.70 (s, 4 H), 2.69 (t, J = 6.8 Hz, 2 H), 2.49 (t, J = 6.4 Hz, 2 H); HRMS (ESI-ve) *m/z* calculated for $C_{24}H_{24}F_6N_3O_5S$ (M+H)+ 580.13354, found 580.13313.



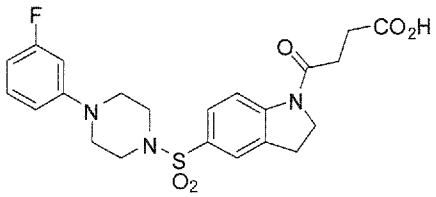
(XW2-036) 4-(5-(4-(3,4-Dichlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-4-oxobutanoic acid: XW2-036 was prepared using the same procedure as described for the preparation of **XW2-011B** as a white solid (yield 51%). Decomposed at 250 °C. ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.22 (d, J = 8.0 Hz, 1H), 7.60 (s, 1H), 7.57 (d , J = 8.0 Hz, 1H), 7.38 (d, J = 8.9 Hz, 1H), 7.11 (d, J = 2.6 Hz, 1H), 6.90 (dd, J = 2.6, 9.0 Hz, 1H), 4.19 (t, J = 8.5 Hz, 2H), 3.26 (bs, 8H), 2.96 (s, 4H), 2.71 (s, 2H); HRMS (ESI-ve) *m/z* calculated for $C_{22}H_{22}Cl_2N_3O_5S$ (M-H)- 510.06627, found 510.06782.



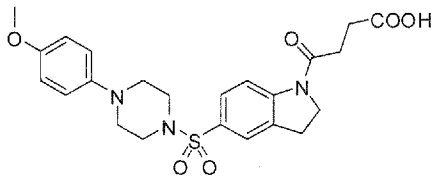
(XW2-038F) 4-(5-(4-(3-Methoxyphenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-4-oxobutanoic acid: XW2-038F was prepared using the same procedure as described for the preparation of **XW2-011B** as an off-white solid (yield 77%). Mp = 215-216 °C ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.22 (d, J = 8.0 Hz, 1H), 7.60 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.08 (t, J = 8.2, 1H), 6.47 (d, J = 8.6 Hz, 1H), 6.42 (s, 1H), 6.38 (d, J = 7.9 Hz, 1H), 4.20 (t, J = 8.4 Hz, 2H), 3.68 (s, 3H), 3.20 (bs, 6H), 2.96 (s, 4H), 2.71 (t, J = 6.0 Hz, 2H); HRMS (ESI-ve) *m/z* calculated for $C_{23}H_{28}N_3O_6S$ (M+H)+ 474.16933, found 474.16964.



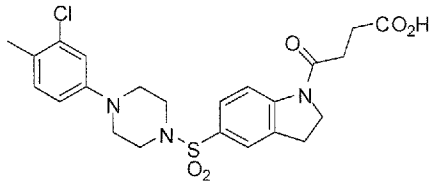
(XW2-031B) 4-Oxo-4-(5-(4-(3-(trifluoromethyl)phenyl)piperazin-1-ylsulfonyl)indolin-1-yl)butanoic acid: XW2-031B was prepared using the same procedure as described for the preparation of **XW2-011B** as a ink solid (yield 95%). Mp = 218-219 °C. ^{1}H NMR (400 MHz, DMSO-D_6) δ 12.14 (bs, 1H), 8.22 (d, J = 8.1 Hz, 1H), 7.61 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.18 (d, J = 8.5 Hz, 1H), 7.15 (s, 1H), 7.09 (d, J = 7.8, 1H), 4.20 (t, J = 8.6 Hz, 2H), 3.24 (t, J = 8.7 Hz, 2H), 2.99 (s, 4H), 2.71 (t, J = 5.9 Hz, 2H), 2.52 (t, J = 6.0 Hz, 2H); HRMS (ESI-ve) *m/z* calculated for $C_{23}H_{23}F_3ClN_3O_5S$ (M-H)- 510.13160, found 510.13180.



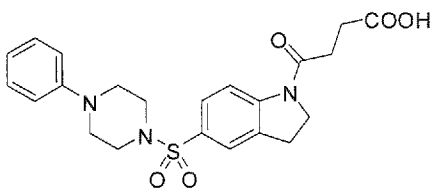
(XW2-124A) 4-(5-(4-(3-Fluorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-4-oxobutanoic acid: XW2-124A was prepared using the same procedure as described in the preparation of **XW2-011B** as a white solid (yield 55%). Mp = 274-276 °C. ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.20 (d, , J = 8.0 Hz, 1H), 7.52-7.55 (m, 2H), 7.17 (q, J = 8.4 Hz, 1H), 6.69 (m, 2H), 6.53 (m, 1H), 4.20 (t, J = 8.5 Hz, 2H), 3.17-3.24 (m, 6H), 2.94 (bs, 4H), 2.54 (t, J = 6.4 Hz, 2 H), 2.22 (t, J = 6.8 Hz, 2H); HRMS (ESI-ve) *m/z* calculated for $C_{22}H_{25}FN_3O_5S$ (M+H)+ 461.14935, found 461.14921.



(XW2-038E) 4-(5-(4-(4-Methoxyphenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-4-oxobutanoic acid: XW2-038E was prepared using the same procedure as described FOR the preparation of **XW2-011B** as a white solid (yield 82%). Decomposed at 250 °C. ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.23 (d, J = 7.1, 1H), 7.56 (m, 2H), 6.85 (d, J = 9.1, 2H), 6.79 (d, J = 9.1, 2H), 4.22 (t, J = 8.4, 2H), 3.66 (s, 3H), 3.23 (t, J = 8.3, 2H), 3.06 (s, 4H), 2.97 (s, 4H), 2.61 (t, J = 6.1, 2H), 2.31 (t, J = 6.7, 2H); HRMS (ESI-ve) *m/z* calculated for $C_{23}H_{28}N_3O_6S$ (M+H)+ 474.16933, found 474.17042.

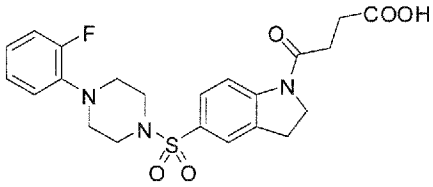


(XW3-006) 4-(5-(4-(3-Chloro-4-methylphenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-4-oxobutanoic acid: XW3-006 was prepared using the same procedure as described for the preparation of **XW2-011B** as an off-white solid (yield 86%). Decomposed at 250 °C. ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.20 (d, , J = 8.0 Hz, 1H), 7.53-7.56 (m, 2H), 7.12 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 2.4 Hz, 1H), 6.77 (dd, J = 2.4, 8.4 Hz, 1H), 4.20 (t, J = 8.5 Hz, 2H), 3.18 (bs, 6H), 2.93 (bs, 4H), 2.60 (bs, 2 H), 2.30 (t, J = 6.8 Hz, 2 H), 2.17 (s, 3H); HRMS (ESI-ve) *m/z* calculated for $C_{23}H_{27}ClN_3O_5S$ (M+H)+ 492.13545, found 492.13577.

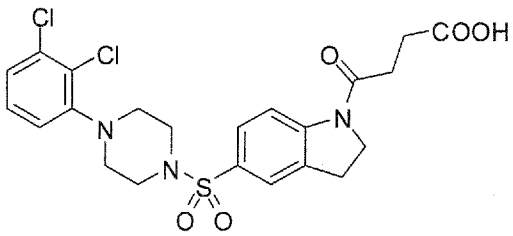


(XW2-038A) 4-oxo-4-(5-(4-Phenylpiperazin-1-ylsulfonyl)indolin-1-yl)butanoic acid: XW2-038A was prepared using the same procedure as described for the preparation of **XW2-011B** as a white solid (yield 64%). Mp = 221-223 °C. ^{1}H NMR (400 MHz, $CDCl_3$)

δ 8.34 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.58 (s, 1H), 7.26 (m, 2H), 6.87 (m, 3H), 4.19 (t, J = 8.5 Hz, 2H), 3.30 (t, J = 8.4 Hz, 2H), 3.24 (bs, 4H), 3.16 (bs, 4H), 2.79 (s, 4H); HRMS (ESI-ve) *m/z* calculated for $C_{22}H_{26}ClN_3O_5S$ (M+H)+ 444.15877, found 444.15878.

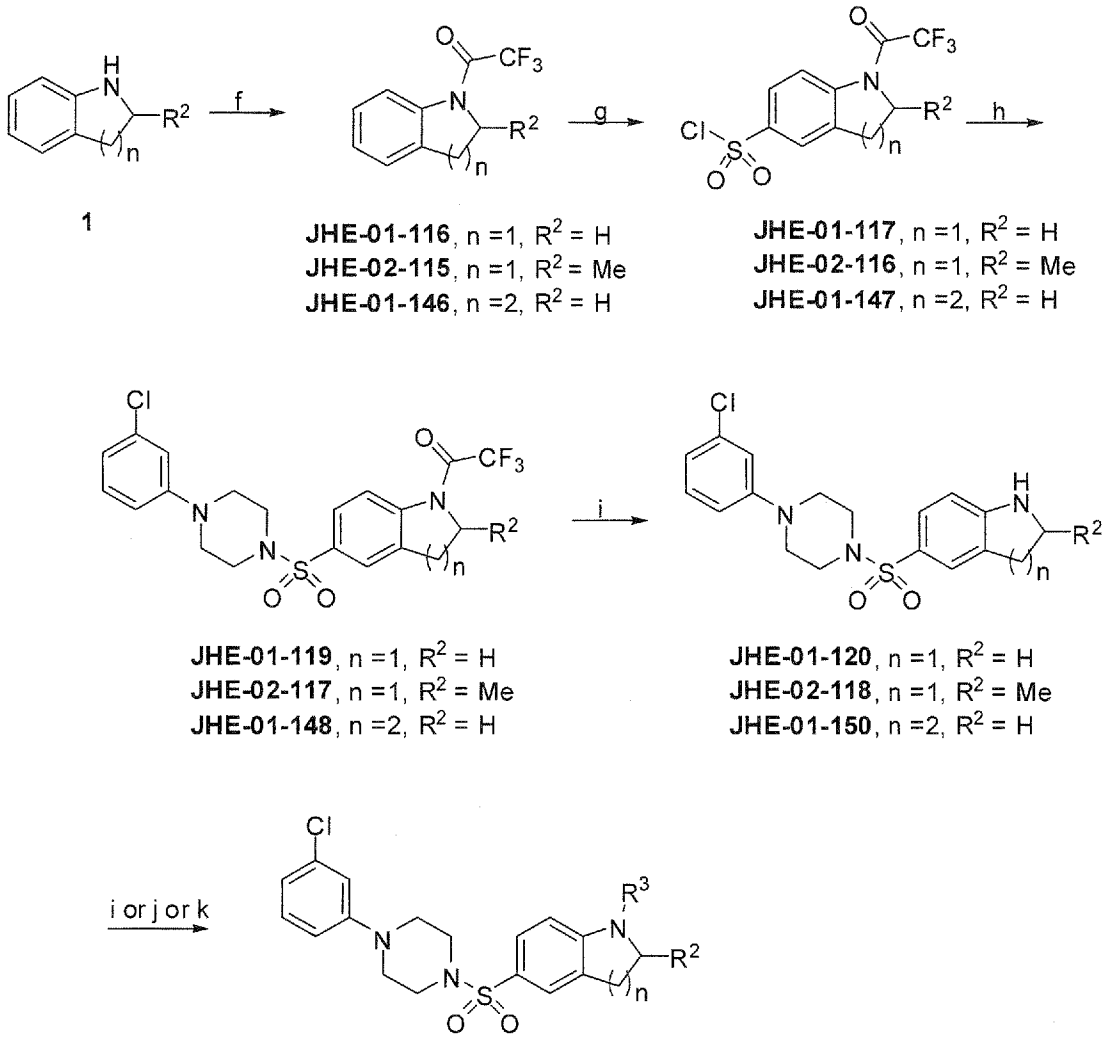


(XW2-038D) 4-(5-(4-(2-Fluorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-4-oxobutanoic acid: XW2-038D was prepared using the same procedure as described for the preparation of **XW2-011B** as a pink solid (yield 36%). Mp = 228-230 °C. ^{1}H NMR (400 MHz, DMSO-D_6) δ 12.13 (bs, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.61 (s, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.06 (m, 4H), 4.20 (d, J = 8.6 Hz, 2H), 3.27 (t, J = 8.5 Hz, 2H), 3.07 (s, 4H), 3.01 (s, 4H), 2.72 (s, 2H), 2.54 (t, J = 6.6 Hz, 2H); HRMS (ESI-ve) *m/z* calculated for $C_{22}H_{25}FN_3O_5S$ (M+H)+ 462.14935, found 462.14984.



(XW2-038G) 4-(5-(4-(2,3-Dichlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-4-oxobutanoic acid: XW2-038D was prepared using the same procedure as described for the preparation of **XW2-011B** as a white solid (yield 59%). Mp = 240-242. ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.24 (d, J = 8.2 Hz, 1H), 7.62 (s, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.32 (m, 2H), 7.17 (dd, J = 3.6, 6.1 Hz, 1H), 4.22 (t, J = 8.6, 2H), 3.27 (t, J = 8.0 Hz, 2H), 3.04 (bs, 8H), 2.73 (t, 2H, J = 6.1), 2.53 (t, J = 6.0 Hz, 2H); HRMS (ESI-ve) *m/z* calculated for $C_{22}H_{24}Cl_2N_3O_5S$ (M+H)+ 512.08082, found 512.08044.

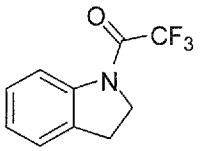
Scheme 2.



Reagents and conditions: (f) trifluoroacetic anhydride, DCM, 0 °C, 1 hr; (g) chlorosulfonic acid, 0-70 °C, 45 min; (h) 1-(3-chlorophenyl)piperazine, pyridine, DCE, microwave, 150 °C, 15 min; (d) 1N NaOH, THF, rt, 18 hr; (i) acid chloride, Et_3N, DCM, microwave, 80 °C; (j) isocyanates, THF, microwave, 100 °C, 20 min; (k) anhydrides,chloroform, 100 °C, 30 min.

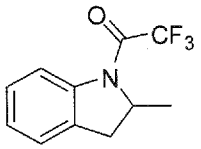
Starting from indoline (**1**), the NH group was first protected as its trifluoroacetamide. Following Carlier's procedure (*J. Org. Chem.* 1988, 2047-52), *N*-trifluoroacetylindoline **JHE-01-116** next underwent sulfonation at the *para*-5-position by treatment with chlorosulfonic acid. The resulting chlorosulfonylindoline **JHE-01-117** was coupled with 1-(3-chlorophenyl)piperazine to afford indoline **JHE-01-119**. After deprotection, indoline **JHE-01-120** was obtained, which could be used directly to next reaction without purification. **JHE-01-118** (when R^2 = Me) and **JHE-01-150** (when n =2) were

synthesized in a similar fashion. The following coupling reactions were carried with a variety of acid chlorides, isocyanates and anhydrides.



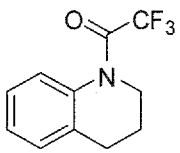
(JHE-01-116) 2,2,2-Trifluoro-1-(indolin-1-yl)ethanone WO 2005/123748

To a solution of indoline (2.0 mL, 17.7 mmol) in anhydrous dichloromethane (18 mL) at 0 °C, trifluoroacetic anhydride (5.0 mL, 35.3 mmol) was added drop-wise over 5 minutes. After stirring for another 1 hr, the reaction was quenched with water at 0 °C. The mixture was extracted with dichloromethane and the organic layer was washed with $NaHCO_3$ (sat. sol.) and brine. After concentration, the solid was washed with hexane to afford crude product (4.04 g, 100%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.8Hz, 1H), 7.28 (m, 2H), 7.16 (t, J = 7.1Hz, 1H), 4.29 (t, J = 8.3Hz, 2H), 3.27 (t, J = 8.3Hz, 2H)



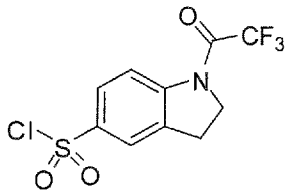
(JHE-02-115) 2,2,2-Trifluoro-1-(2-methylindolin-1-yl)ethanone

JHE-02-115 was prepared from 2-methylindoline using the same procedure as described for the preparation of **JHE-01-116.** Yield 100%; ^1H NMR (400 MHz, CD3CN) δ 8.05 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 7.4 Hz, 1H), 7.32 (t, J = 7.7 Hz, 1H), 7.23 (t, J = 7.4, 1H), 4.86 (t, J = 6.4 Hz, 1H), 3.47 (dd, J = 8.0, 15.7 Hz, 1H), 2.78 (d, J = 15.8 Hz, 1H), 1.30 (d, J = 6.4 Hz, 3H).



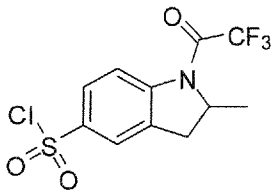
(JHE-01-146) 1-(3,4-Dihydroquinolin-1(2H)-yl)-2,2,2-trifluoroethanone

JHE-01-146 was prepared from 1,2,3,4-tetrahydroquinoline using the same procedure as described for the preparation of **JHE-01-116.** Yield 100%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (bs, 1H), 7.18-7.25 (m, 3H), 3.84 (t, J = 6.4 Hz, 2H), 2.88 (bs, 2H), 2.08(bs, 2H).



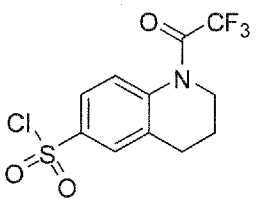
(JHE-01-117) 1-(2, 2, 2-trifluoroacetyl)indoline-5-sulfonyl chloride (*J. Org. Chem.* 1988, 2051)

The product **JHE-01-116** (5.07 g, 23.6 mmol) was added to chlorosulfonic acid (7.8 mL, 118.0 mmol) drop-wise at 0 °C over 15 minutes. After addition the reaction was slowly warmed to room temperature over 30 minutes and then heated to 70 °C for 2.5 hours. After cooling down, the solid was filtered and washed with water to afford crude product **JHE-01-117** (6.17 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 8.7 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.92 (s, 1H), 4.43 (t, J = 8.4 Hz, 1H), 3.40 (t, J = 8.3Hz, 2H).



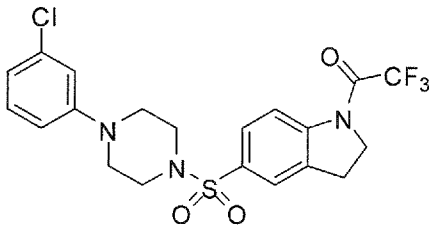
(JHE-02-116) 2-Methyl-1-(2,2,2-trifluoroacetyl)indoline-5-sulfonyl chloride

JHE-02-116 was prepared from **JHE-02-115** using the same procedure as described for the preparation of **JHE-01-117.** Yield 95%; ^{1}H NMR (400 MHz, CD3CN) δ 8.29 (d, J = 9.2 Hz, 1H), 8.06 (s, 1H), 8.04 (d, J = 8.7Hz, 1H), 4.99 (m, 1H), 3.55 (dd, J = 8.2, 16.4 Hz, 1H), 2.93 (d, J = 16.2 Hz, 1H), 1.34 (d, J = 6.4 Hz, 3H).



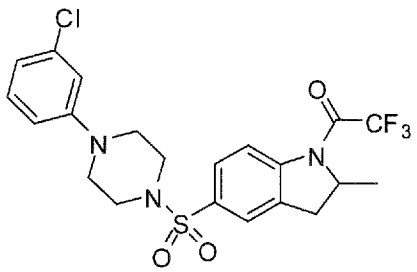
(JHE-01-147) 1-(2,2,2-Trifluoroacetyl)-1,2,3,4-tetrahydroquinoline-6-sulfonyl chloride

JHE-01-147 was prepared from **JHE-01-146** using the same procedure as described in the preparation of **JHE-01-117**. Yield 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.6Hz, 1H), 7.89 (m, 2H), 3.91 (t, J = 6.0 Hz, 2H), 3.02 (t, J = 6.8 Hz, 2H), 2.16 (m, 2H).



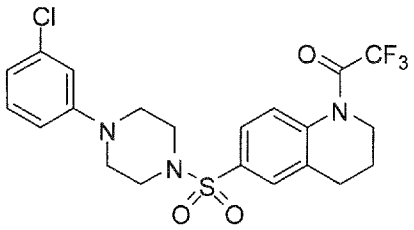
(JHE-01-119) 1-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-2,2,2-trifluoroethanone

To a solution of **JHE-01-117** (325 mg, 1.65 mmol) in dichloromethane (6 mL) was added 1-(3-chlorophenyl)piperazine (517 g, 1.65 mmol) and pyridine (0.4 mL, 4.96 mmol) at room temperature. The reaction mixture was iradiated in microwave reactor at 150 °C for 15 minutes and then the mixture was concentrated. The resulting solid was washed with water to afford **JHE-01-119** (678 mg, 86%). ^{1}H NMR (400 MHz, CD3CN) δ 8.30 (d, J = 8.2 Hz, 1H), 7.71 (m, 2H), 7.20 (t, J = 8.0 Hz, 1H), 6.91 (t, J = 2.0 Hz, 1H), 6.84 (m, 2H), 4.37 (t, J = 8.2 Hz, 2H), 3.35 (t, J = 8.2 Hz, 2H), 3.27 (t, J = 4.2 Hz, 4H), 3.09 (t, J = 4.0 Hz, 4H)



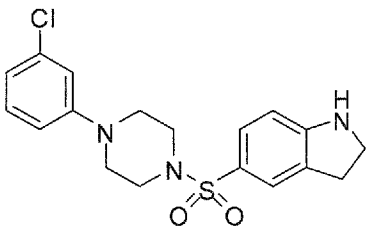
(JHE-02-117) 1-(5-(4-(3-chlorophenyl)piperazin-1-ylsulfonyl)-2-methylindolin-1-yl)-2,2,2-trifluoroethanone

JHE-02-117 was prepared from **JHE-02-116** using the same procedure as described for the preparation of **JHE-01-119** as an off-white solid (yield 86%). Mp = 174-175 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 8.22 (d, J = 8.4 Hz, 1H), 7.76 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.21 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.92 (dd, J = 2.2 Hz, 2.2 Hz, 1H), 6.86-6.82 (m, 2H), 4.98-4.91 (m, 1H), 3.52 (dd, J = 15.8 Hz, 8.0 Hz, 1H), 3.27 (t, J = 5.2 Hz, 3H), 3.11 (t, J = 5.2 Hz, 3H), 2.88 (d, J = 15.8 Hz, 1H), 1.32 (d, J = 6.4 Hz, 3H); HPLC 98% [t_R = 10.53, 70% acetonitrile in water (0.1% TFA)]; HPLC 98% (t_R = 29.53, 70% methanol in water (0.1% TFA)).



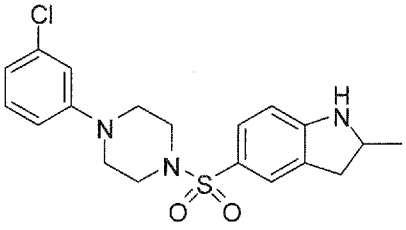
(JHE-01-148) 1-(6-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)-3,4-dihydroquinolin-1(2H)-yl)-2,2,2-trifluoroethanone

JHE-01-148 was prepared from **JHE-01-147** using the same procedure as described for the preparation of **JHE-01-119.** Yield 86%; ^{1}H NMR (400 MHz, CD3CN) δ 7.89 (d, J = 7.0 Hz, 1H), 7.67 (s, 1H), 7.63 (d, J = 9.0 Hz, 1H), 7.21 (t, J = 8.1 Hz, 1H), 6.92 (s, 1H), 6.85 (s, 2H), 3.87 (t, J = 6.0, 2H), 3.27 (t, J = 4.8 Hz, 4H), 3.10 (t, J = 4.8 Hz, 4H), 2.97 (t, J = 6.4 Hz, 2H), 2.09 (m, 2H)



(JHE-01-120) 5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indoline:

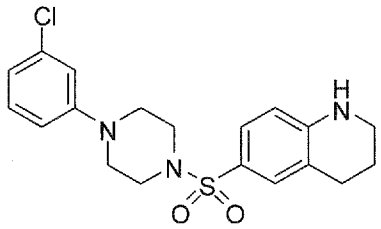
To a solution of **JHE-01-119** (265 mg, 0.56 mmol) in tetrahydrofuran (1 mL) was added NaOH (1.0 M in H_2O, 2 mL). The reaction was stirred overnight. After concentration, the solid was washed with water to afford the indoline **JHE-01-120** (204mg, 97%). ^{1}H NMR (400 MHz, CD3CN) δ 7.39 (m, 2H), 7.20 (t, J = 8.1 Hz, 1H), 6.91 (s, 1H), 6.84 (t, J = 7.1 Hz, 2H), 6.62 (d, J = 8.0 Hz, 1H), 5.05 (s, NH), 3.62 (t, J = 8.7 Hz, 2H), 3.25 (t, J = 4.8 Hz, 4H), 3.04 (m, 6H)



(JHE-02-118) 5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)-2-methylindoline

JHE-02-118 was prepared from **JHE-02-117** using the same procedure as described for the preparation of **JHE-01-120.** Yield 100%; ^{1}H NMR (400 MHz, CD3CN) δ 7.38 (m,

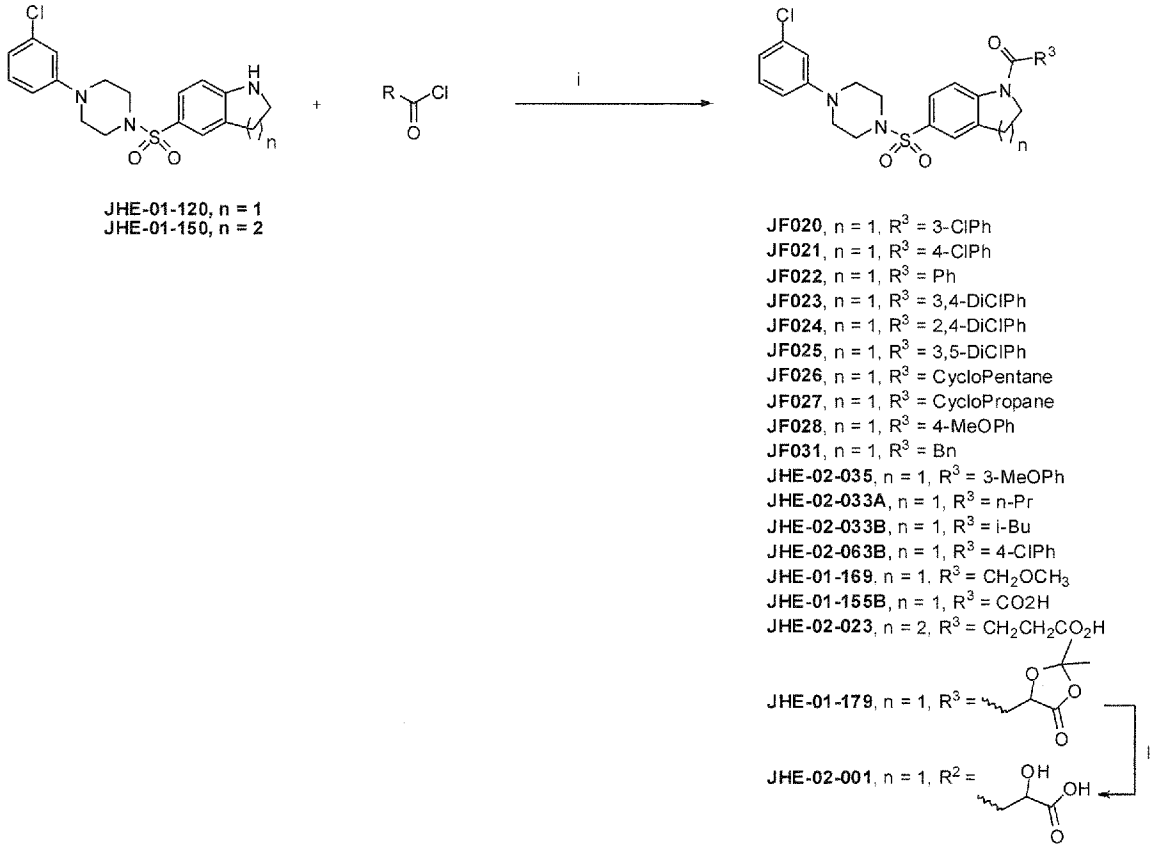
2H), 7.20 (t, J = 8.1 Hz, 1H), 6.91 (t, J = 2.1 Hz, 1H), 6.83 (ddd, J = 1.7, 3.7, 7.1 Hz, 2H), 6.58 (d, J = 8.6 Hz, 1H), 5.17 (s, NH), 4.07 (m, 1H), 3.25 (m, 4H), 3.19 (m, 1H), 3.01 (m, 4H), 2.64 (dd, J = 7.4, 16.1 Hz, 1H), 1.25 (d, J = 6.2 Hz, 3H)



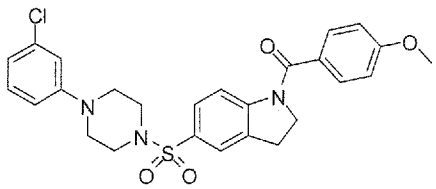
(JHE-01-150) 6-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)-1,2,3,4-tetrahydroquinoline

JHE-01-150 was prepared from **JHE-01-148** using the same procedure as described for the preparation of **JHE-01-120.** Yield 100%; ^{1}H NMR (400 MHz, CD3CN) δ 7.28 (m, 2H), 7.20 (t, 1H, J = 8.1 Hz), 6.91 (s, 1H), 6.84 (m, 2H), 6.54 (d, 1H, J = 9.1 Hz), 5.29 (s, NH), 3.30 (m, 2H), 3.25 (t, J = 4.8 Hz, 4H), 3.00 (t, J = 5.2 Hz, 4H), 2.77 (t, 2H, J = 6.2 Hz), 1.87 (m, 2H)

Scheme 3



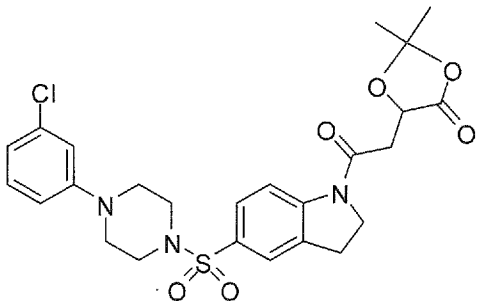
Reagents and conditions: (i) acid chloride, Et_3N, DCM, microwave, 80 °C; (l) AcOH, THF, H_2O 450°C, 7 hr.



(JF028) (5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)(4-methoxyphenyl)methanone

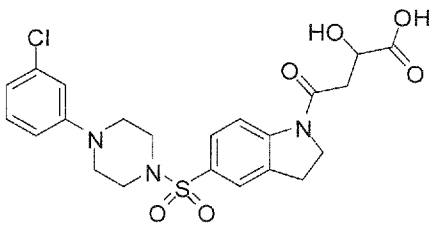
In a microwave reaction tube equipped with a magnetic stirring bar, **JHE-01-120** (54.0 mg, 0.143 mmol) was dissolved in dichloromethane (0.5 mL) at room temperature. To the solution was added triethylamine (18.3 µl, 0.143 mmol) and 4-methoxybenzyl chloride (24 mg, 0.143 mmol). The reaction tube was capped and iradiated in the microwave reactor (Biotage Initiator I) at 80 °C for 20 minutes. After concentration the solid product was purified by washing with water to provide **JF028** as an off-white solid yield 95%.

Mp = 193-194 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.92 (s, br, 1H), 7.63-7.58 (m, 2H), 7.18 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 2H), 6.91 (dd, J = 2.0 Hz, 2.0 Hz, 1H), 6.85 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.78 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 4.11 (t, J = 8.4 Hz, 2H), 3.81 (s, 3H), 3.27-3.24 (m, 4H), 3.16 (t, J = 8.4 Hz, 2H), 2.96-2.94 (m, 4H); HPLC 94% (t_R = 7.25, 70% acetonitrile in water (0.1% TFA)); HPLC 97% [t_R = 10.57, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{26}H_{27}ClN_3O_4S$ 512.1405 $(M+H)^+$; found 512.1410 $(M+H)^+$.



(JHE-01-179) 5-(2-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-2-oxoethyl)-2,2-dimethyl-1,3-dioxolan-4-one

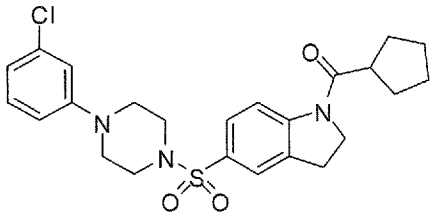
JHE-01-179 was prepared from **JHE-01-120** and 2-(2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetyl chloride (converted from the corresponding acid) using the same procedure as described for the preparation of **JF028**. The product was purified by column chromatography (ethyl acetate:hexane, 2:3)to give a dark brown solid, yield 85%. ^{1}H NMR (CD_3CN, 400 MHz) δ 8.29 (d, J = 8.3 Hz, 1H), 7.61 (d, J = 8.5 Hz, 2H), 7.20 (t, J = 8.1 Hz, 1H), 6.91 (t J = 2.1 Hz, 1H,), 6.83 (m, 2H), 4.85 (dd, J = 3.6, 5.6 Hz, 1H,), 4.18 (t, J = 8.4 Hz, 2H), 3.26 (m, 6H), 3.06 (m, 6H), 1.62 (s, 3H), 1.58 (s, 3H)



(JHE-02-001) 4-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-2-hydroxy-4-oxobutanoic acid

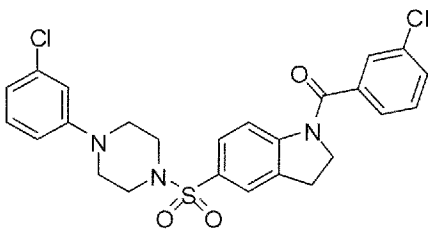
At room temperature, **JHE-01-179** (118 mg, 0.033 mmol) was mixed with acetic acid (4 mL), THF (1 mL) and water (2 mL) in a round bottom flask. The reaction mixture was heated to 45 °C for 7 hours. After concentration, the residue was triturated with water.

The precipitate was filtered and washed with dichloromethane, acetonitrile and methanol. **JHE-02-001:** Off white solid, yield 70%. Mp = 190-191 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.21 (d, J = 8.0 Hz, 1H), 7.58-7.55 (m, 2H), 7.17 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.90 (1H, s), 6.84 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.39 (t, J = 8.0 Hz, 1H), 4.18 (t, J = 8.0 Hz, 2H), 3.23 (m, 6H), 2.94 (m, 4H), 2.88-2.75 (m, 2H); HRMS (ESI-ve) m/z calcd. for $C_{22}H_{25}ClN_3O_6S$ 494.1147 $(M+H)^+$; found 494.1147 $(M+H)^+$.



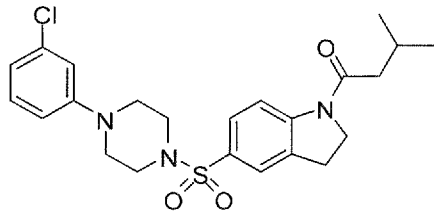
(JF026) (5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)(cyclopentyl)methanone

JF026 was prepared from **JHE-01-120** and cyclopentanecarbonyl chloride (converted from the corresponding acid) using the same procedure as described for the preparation of **JF028. JF026:** Off-white solid, yield 83%. Mp = 166-167 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.24 (d, J = 8.4 Hz, 1H), 7.57 (s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.17 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.90 (dd, J = 2.0 Hz, 2.0 Hz, 1H), 6.84 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.77 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 4.22 (t, J = 8.4 Hz, 2H), 3.27-3.19 (m, 6H), 3.05-2.92 (m, 5H), 1.90-1.82 (m, 2H), 1.77-1.52 (m, 6H); HPLC 98% (t_R = 10.05, 70% acetonitrile in water (0.1% TFA)); HPLC 99% [t_R = 12.61, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) m/z calcd. for $C_{24}H_{29}ClN_3O_3S$ 476.1613 $(M+H)^+$; found 476.1621 $(M+H)^+$.



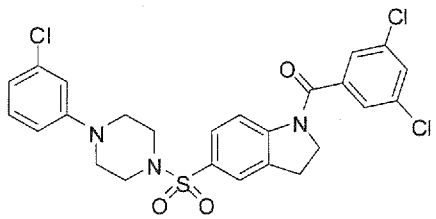
(JF020) (3-Chlorophenyl)(5-(4-(3-chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)methanone

JF020 was prepared from **JHE-01-120** and 3-chlorobenzoyl chloride (converted from the corresponding acid) using the same procedure as described in the preparation of **JF028.** **JF020:** Off-white solid, yield 92%. Mp = 221-222 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.14 (s, br, 1H), 7.67-7.50 (m, 6H), 7.18 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 2H), 6.91 (dd, J = 2.0 Hz, 2.0 Hz, 1H), 6.87 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.78 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 4.04 (t, J = 8.4 Hz, 2H), 3.29-3.24 (m, 4H), 3.16 (t, J = 8.4 Hz, 2H), 2.96-2.94 (m, 4H); HPLC 98% [t_R = 9.58, 70% acetonitrile in water (0.1% TFA)]; HRMS (ESI-ve) m/z calcd. for $C_{25}H_{24}Cl_2N_3O_3S$ 516.0910 $(M+H)^+$; found 516.0935 $(M+H)^+$.



(JHE-02-033B) 1-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-3-methylbutan-1-one

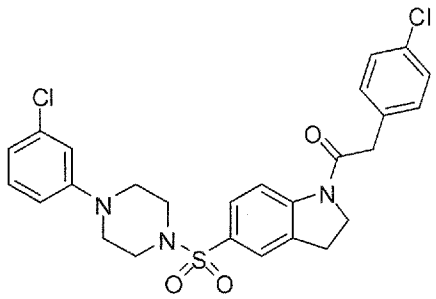
JHE-02-033B was prepared from **JHE-01-120** and 3-methylbutanoyl chloride (converted from the corresponding acid) using the same procedure as described for the preparation of **JF028. JHE-02-033B:** off-white solid, yield 86%. Mp = 162-163 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 8.30 (d, J = 8.8 Hz, 1H), 7.60-7.58 (m, 2H), 7.20 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.91 (dd, J = 2.0 Hz, 2.0 Hz, 1H), 6.85-6.82 (m, 2H), 4.16 (t, J = 8.4 Hz, 2H), 3.27-3.22 (m, 6H), 3.07 (t, J = 5.2 Hz, 4H), 2.37 (d, J = 6.8 Hz, 2H), 2.25-2.18 (m, 1H), 1.02 (s, 3H), 1.00 (s, 3H); HPLC 98% [t_R = 9.61, 70% acetonitrile in water (0.1% TFA)]; HPLC 98% [t_R = 23.81, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) m/z calcd. for $C_{23}H_{29}ClN_3O_3S$ 462.1613 $(M+H)^+$; found 462.1613 $(M+H)^+$.



(JF025) (5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)(3,5-dichlorophenyl)methanone

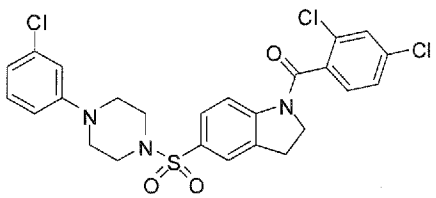
JF025 was prepared from **JHE-01-120** and 3,5-dichlorobenzoyl chloride (converted from the corresponding acid) using the same procedure as described for the preparation of

JF028. JF025: off-white solid, yield 90%. Mp = 262-263 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.20 (s, br, 1H), 7.92 (s, 1H), 7.69-7.62 (m, 4H), 7.18 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.91 (d, J = 2.0 Hz, 1H), 6.85 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.03 (t, J = 8.4 Hz, 2H), 3.29-3.23 (m, 4H), 3.17 (t, J = 8.4 Hz, 2H), 2.98-2.94 (m, 4H); HRMS (ESI-ve) *m/z* calcd. for $C_{25}H_{23}Cl_3N_3O_3S$ 550.0520 $(M+H)^+$; found 550.0518 $(M+H)^+$.



(JHE-02-063B) 2-(4-Chlorophenyl)-1-(5-(4-(3-chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)ethanone

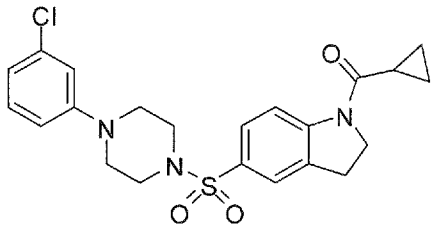
JHE-02-063B was prepared from **JHE-01-120** and 2-(4-chlorophenyl)acetyl chloride (converted from the corresponding acid) using the same procedure as described for the preparation of **JF028. JHE-02-063B:** off-white solid, yield 79%. Mp = 186-187 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.19 (d, J = 8.4 Hz, 1H), 7.59 (s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.17 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.90 (dd, J = 2.0 Hz, 2.0 Hz, 1H), 6.84 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.78 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 4.24 (t, J = 8.4 Hz, 2H), 3.88 (s, 2H), 3.25-3.21 (m, 6H), 2.95-2.92 (m, 4H); HPLC 99% [t_R = 11.43, 70% acetonitrile in water (0.1% TFA)].



(JF024) (5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)(2,4-dichlorophenyl)methanone

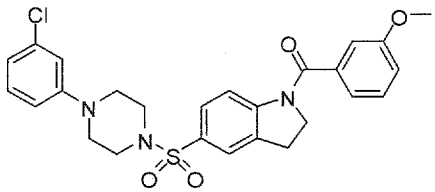
JF024 was prepared from **JHE-01-120** and 2,4-dichlorobenzoyl chloride (converted from the corresponding acid) using the same procedure as described for the preparation of **JF028. JF024:** yellow solid, yield 77%. Mp = 184-184.5 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.32 (d, J = 8.8 Hz, 1H), 7.81 (s, 1H), 7.68-7.57 (m, 4H), 7.18 (d, J = 8.0 Hz, 1H), 6.92 (s, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 3.81 (d, J = 8.0 Hz,

2H), 3.27-3.17 (m, 6H), 2.99-2.94 (m, 4H); HPLC 96% [t_R = 12.93, 70% acetonitrile in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{25}H_{23}Cl_3N_3O_3S$ 550.0520 $(M+H)^+$; found 550.0525 $(M+H)^+$.



(JF027) (5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)(cyclopropyl)methanone

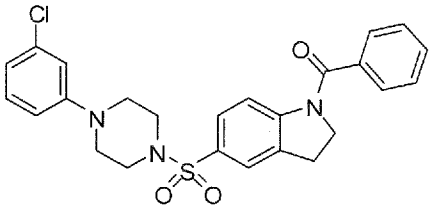
JF027 was prepared from **JHE-01-120** and cyclopropanecarbonyl chloride (converted from the corresponding acid) using the same procedure as described for the preparation of **JF028. JF027:** Off-white solid, yield 93%. Mp = 162.5-163 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.16 (d, J = 8.4 Hz, 1H), 7.58 (s, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.17 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.90 (dd, J = 2.0 Hz, 2.0 Hz, 1H), 6.84 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.77 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 4.22 (t, J = 8.4 Hz, 2H), 3.27-3.19 (m, 6H), 3.05-2.92 (m, 5H), 1.90-1.82 (m, 2H), 1.77-1.52 (m, 6H); HPLC 99% (t_R = 5.63, 70% acetonitrile in water (0.1% TFA)); HPLC 98% [t_R = 10.10, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{22}H_{25}ClN_3O_3S$ 446.1300 $(M+H)^+$; found 446.1310 $(M+H)^+$.



(JHE-02-035A) (5-(4-(3-chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)(3-methoxyphenyl)methanone

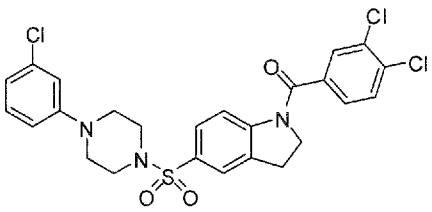
JHE-02-035A was prepared from **JHE-01-120** and 3-methoxybenzoyl chloride (converted from the corresponding acid) using the same procedure as described in the preparation of **JF028. JHE-02-035A**: Off-white solid, yield 90%. Mp = 155-156 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 7.65 (s, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.30 (dd, J = 7.6 Hz, 7.6 Hz, 1H), 7.21 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 7.14-7.09 (m, 4H), 6.92 (dd, J = 2.4 Hz, 2.4 Hz, 1H), 6.86-6.82 (m, 2H), 4.09 (t, J = 8.4 Hz, 2H), 3.84 (s, 3H), 3.27 (t, J = 5.2 Hz, 4H), 3.20 (t, J = 8.4 Hz, 2H), 3.08 (t, J = 5.2 Hz, 4H);); HPLC 98% (t_R = 7.51, 70% acetonitrile in water (0.1% TFA)); HPLC 98% (t_R = 19.45, 70% methanol in water (0.1%

TFA)); HRMS (ESI-ve) *m/z* calcd. for $C_{26}H_{27}ClN_3O_4S$ 512.1405 $(M+H)^+$; found 512.1406 $(M+H)^+$.



(JF022) (5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)(phenyl)methanone

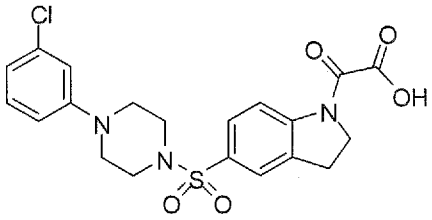
JF022 was prepared from **JHE-01-120** and benzoyl chloride (converted from the corresponding acid) using the same procedure as described for the preparation of **JF028.** **JF022:** Light brown solid, yield 87%. Mp = 200-201 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.64-7.46 (m, 8H), 7.18 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.92 (dd, J = 2.0 Hz, 2.0 Hz, 1H), 6.86 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.79 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 4.04 (t, J = 8.4 Hz, 2H), 3.27-3.24 (m, 4H), 3.16 (t, J = 8.4 Hz, 2H), 2.97-2.94 (m, 4H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 169.5, 152.2, 147.6, 137.1, 135.2, 134.5, 131.2, 129.6, 129.2, 128.4, 125.1, 119.5, 116.9, 115.9, 115.0, 51.6, 48.0, 46.3, 28.1;); HPLC 95% [t_R = 7.44, 70% acetonitrile in water (0.1% TFA)]; HPLC 95% [t_R = 16.75, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{25}H_{25}ClN_3O_3S$ 482.1300 $(M+H)^+$; found 482.1322 $(M+H)^+$.



(JF023) (5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)(3,4-dichlorophenyl)methanone

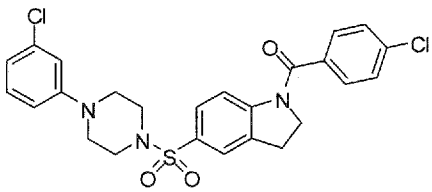
JF023 was prepared from **JHE-01-120** and 3,4-dichlorobenzoyl chloride (converted from the corresponding acid) using the same procedure as described for the preparation of **JF028.** **JF028:** Pale yellow solid, yield 27%. Mp = 174-175 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.90 (d, J = 2.0 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.65-7.59 (m, 3H), 7.18 (dd, J = 8.4 Hz, 8.4 Hz, 1H), 6.91 (dd, J = 2.0 Hz, 2.0 Hz, 1H), 6.85 (dd, J = 8.4 Hz, 2.0 Hz,

1H), 6.78 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 4.05 (t, J = 8.4 Hz, 2H), 3.26 (t, J = 4.8 Hz, 4H), 3.16 (t, J = 8.4 Hz, 2H), 2.95 (t, J = 4.8 Hz, 4H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 167.1, 152.2, 147.2, 137.5, 135.3, 134.5, 133.9, 132.1, 131.6, 131.2, 129.8, 128.5, 128.0, 125.2, 119.5, 117.0, 115.9, 115.0, 105.0, 51.5, 48.0, 46.3, 28.3;); HPLC 96% [t_R = 13.70, 70% acetonitrile in water (0.1% TFA)]; HRMS (ESI-ve) m/z calcd. for $C_{25}H_{23}Cl_2KN_3O_3S$ 554.0469 $(M+K)^+$; found 554.0470 $(M+K)^+$.



(JHE-01-155B) 2-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-2-oxoacetic acid

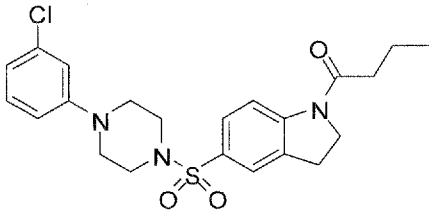
(JHE-01-155B) was hydrolyzed in the same fashion as **JHE-01-137** from the corresponding ethyl ester which was prepared from the corresponding acid chloride and **JHE-01-150** according the procedure described as for the preparation of **JF028. (JHE-01-155B):** off-white solid, yield 90%. Mp = 219-220 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.16 (d, J = 8.8 Hz, 1H), 7.67 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.91 (s, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 4.22 (t, J = 8.4 Hz, 2H), 3.27-3.22 (m, 6H), 2.97-2.94 (m, 4H); HPLC 97% [t_R = 3.47, 70% acetonitrile in water (0.1% TFA)]; HRMS (ESI-ve) m/z calcd. for $C_{20}H_{21}ClN_3O_5S$ 450.0885 $(M+H)^+$; found 450.0881 $(M+H)^+$.



(JF021) (4-Chlorophenyl)(5-(4-(3-chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)methanone

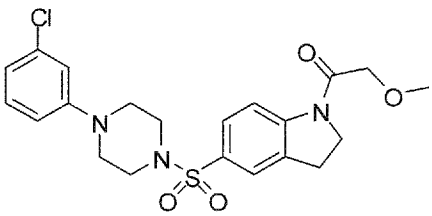
JF021 was prepared from **JHE-01-120** and 4-chlorobenzoyl chloride (converted from the corresponding acid) using the same procedure as described in the preparation of **JF028. JF021:** off-white solid, yield 91%. Mp = 191-192 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.07 (s, br, 1H), 7.64-7.55 (m, 6H), 7.18 (dd, J = 8.4 Hz, 8.4 Hz, 1H), 6.91 (dd, J = 2.0

Hz, 2.0 Hz, 1H), 6.85 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 6.78 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 4.05 (t, J = 8.4 Hz, 2H), 3.30-3.24 (m, 4H), 3.16 (t, J = 8.4 Hz, 2H), 2.96-2.94 (m, 4H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 168.5, 152.2, 147.4, 135.9, 135.8, 135.2, 134.5, 131.2, 129.8, 129.7, 129.3, 128.5, 125.1, 119.5, 117.0, 115.9, 115.0, 51.6, 48.0, 46.3, 28.1; HPLC 97% [t_R = 9.72, 70% acetonitrile in water (0.1% TFA)]; HRMS (ESI-ve) m/z calcd. for $C_{25}H_{24}Cl_2N_3O_3S$ 515.0910 $(M+H)^+$; found 515.0904 $(M+H)^+$.



(JHE-02-033A) 1-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)butan-1-one

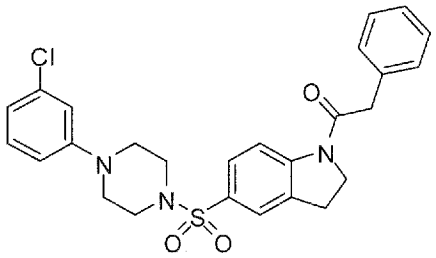
JHE-02-033A was prepared from **JHE-01-120** and butyryl chloride (converted from the corresponding acid) using the same procedure as described for the preparation of **JF028.** **JHE-02-033A**: Pale yellow solid, yield 84%. Mp = 267-268 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 8.32 (d, J = 8.0 Hz, 1H), 7.60-7.58 (m, 2H), 7.20 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.91 (dd, J = 2.0 Hz, 2.0 Hz, 1H), 6.85-6.81 (m, 2H), 4.16 (t, J = 8.4 Hz, 2H), 3.27-3.22 (m, 6H), 3.07 (t, J = 5.2 Hz, 4H), 2.46 (t, J = 6.8 Hz, 2H), 1.74-1.65 (m, 2H), 1.00 (t, J = 7.6 Hz, 3H); HPLC 99% (t_R = 7.29, 70% acetonitrile in water (0.1% TFA)); HPLC 98% (t_R = 16.01, 70% methanol in water (0.1% TFA));HRMS (ESI-ve) m/z calcd. for $C_{22}H_{27}ClN_3O_3S$ 448.1456 $(M+H)^+$; found 448.1456 $(M+H)^+$.



(JHE-01-169) 1-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-2-methoxyethanone

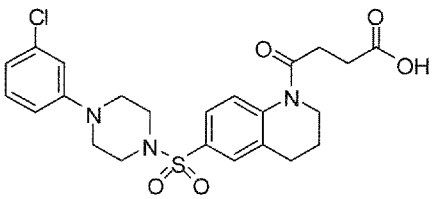
JHE-01-169 was prepared from **JHE-01-120** and 2-methoxyacetyl chloride (converted from the corresponding acid) using the same procedure as described for the preparation of **JF028.** **JHE-01-169:** Off-white solid, yield 89%. Mp = 229.5-230 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 8.29 (s, 1H), 8.63-8.62 (m, 2H), 7.20 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.91 (dd, J = 2.4 Hz, 2.4 Hz, 1H), 6.85-6.82 (m, 2H), 4.18 (s, 2H), 4.09 (t, J = 8.4 Hz, 2H), 3.44 (s,

3H), 3.30-3.25 (m, 6H), 3.07 (t, J = 5.2 Hz, 4H), 3.08 (t, J = 5.6 Hz, 4H); HPLC 99% (t_R = 3.81, 70% acetonitrile in water (0.1% TFA)); HPLC 98% [t_R = 7.13, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{27}H_{28}ClN_4O_5S$ 555.1463 $(M+H)^+$; found 555.1454 $(M+H)^+$.



(JF031) 1-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-2-phenylethanone

JF031 was prepared from **JHE-01-120** and 2-phenylacetyl chloride (converted from the corresponding acid) using the same procedure as described for the preparation of **JF028.** **JF031:** Off-white solid, yield 84%. Mp = 213-214 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) 8.20 (d, J = 8.4 Hz, 1H), 7.58-7.55 (m, 2H), 7.33-7.21 (m, 5H), 7.17 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.90 (dd, J = 1.6 Hz, 1.6 Hz, 1H), 6.84 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 6.78 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 4.24 (t, J = 8.4 Hz, 2H), 3.87 (s, 2H), 3.25-3.21 (m, 6H), 2.96-2.92 (m, 4H); HPLC 97% (t_R = 7.77, 70% acetonitrile in water (0.1% TFA)); HPLC 98% [t_R = 14.33, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{26}H_{27}ClN_3O_3S$ 496.1456 $(M+H)^+$; found 496.1457 $(M+H)^+$.



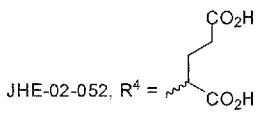
(JHE-02-023) 4-(6-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)-3,4-dihydroquinolin-1(2H)-yl)-4-oxobutanoic acid

(JHE-02-023) was hydrolyzed in the same fashion as **JHE-01-137** from the corresponding ethyl ester (not reported here) which was prepared from the corresponding acid chloride and **JHE-01-150** according the procedure described as for the preparation of **JF028. JHE-02-023:** Off-white solid, yield 53%. Mp = 135-136 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 7.85 (d, J = 8.4 Hz, 1H), 7.59 (s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.20 (dd, J =

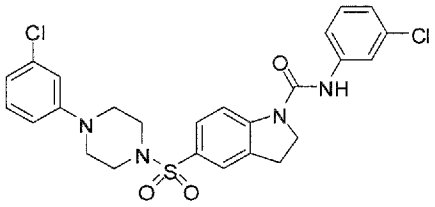
8.0 Hz, 8.0 Hz, 1H), 6.92 (s, 1H), 6.86-6.82 (m, 2H), 3.78 (t, J = 6.4 Hz, 2H), 3.27 (t, J = 5.2 Hz, 4H), 3.09 (t, J = 5.2 Hz, 4H), 2.85 (t, J = 6.4 Hz, 2H), 2.81-2.78 (m, 2H), 2.62-2.59 (m, 2H), 2.01-1.98 (m, 2H); HPLC 95% [t_R = 3.16, 70% acetonitrile in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{23}H_{27}ClN_3O_5S$ 492.1355 $(M+H)^+$; found 492.1356 $(M+H)^+$.

Scheme 4.

JF033, R^4 = Ph
JF035, R^4 = 2-FPh
JF038, R^4 = 4-FPh
JF039, R^4 = 3-FPh
JF040, R^4 = 3-CF_3Ph
JHE-02-032A, R^4 = 3-ClPh
JHE-02-032B, R^4 = 3-MeOPh
JHE-02-065A, R^4 = 4-ClPh
JHE-02-065B, R^4 = 2-ClPh
JHE-02-068A, R^4 = 3,4-DiClPh
JHE-02-068B, R^4 = 4-i-PrPh
JHE-02-010A, R^4 = $(CH_2)_3CO_2Et$ ⇄ $(CH_2)_3CO_2H$]m
JHE-02-017A, R^4 = $(CH_2)_3CO_2H$
JHE-02-010B, R^4 = $(CH_3)CHCO_2Et$ ⇄ $(CH_3)CHCO_2H$]m
JHE-02-017B, R^4 = $(CH_3)CHCO_2H$
JHE-02-010C, R^4 = (i-Pr)$CHCO_2Et$ ⇄ (i-Pr)$CHCO_2H$]m
JHE-02-017C, R^4 = (i-Pr)$CHCO_2H$
JHE-02-012, R^4 = (i-Bu)$CHCO_2Et$ ⇄ (i-Bu)$CHCO_2H$]m
JHE-02-019A, R^4 = (i-Bu)$CHCO_2H$
JHE-01-134A, R^4 = CH_2CO_2Et ⇄ CH_2CO_2H]m
JHE-01-137, R^4 = CH_2CO_2H
JHE-02-029A, R^4 = (2-Bu)$CHCO_2Me$ ⇄ (2-Bu)$CHCO_2H$]m
JHE-02-038, R^4 = (2-Bu)$CHCO_2H$
JHE-02-015A, R^4 = 2-CO_2MePh ⇄ 2-CO_2HPh]m
JHE-02-020A, R^4 = 2-CO_2HPh
JHE-02-014, R^4 = (Bn)$CHCO_2Et$ ⇄ (Bn)$CHCO_2H$]m
JHE-02-019B, R^4 = (Bn)$CHCO_2H$
JHE-02-015B, R^4 = 3-CO_2EtPh ⇄ 3-CO_2HPh]m
JHE-02-020B, R^4 = 3-CO_2HPh

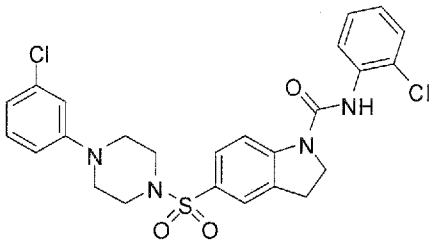


Reagents and conditions: (j) isocyanate, THF, microwave, 100 °C, 30 min. (m) 6N NaOH, THF, EtOH, microwave, 80 °C, 10 min.



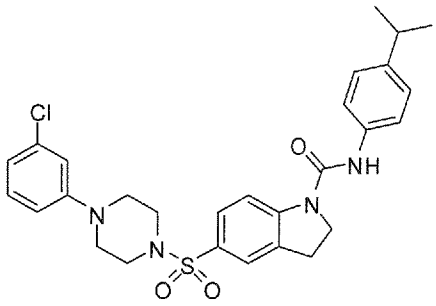
(JHE-02-032A) ***N*-(3-Chlorophenyl)-5-(4-(3-chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamide**

In a microwave reaction tube equipped with a magnetic stirring bar, **JHE-01-120** (54.0 mg, 0.143 mmol) was dissolved in THF (0.5 mL) at room temperature. To the solution was added 3-chlorophenylisocyanate (23 mg, 0.143 mmol). The reaction tube was capped and irradiated in the microwave reactor (Biotage Initiator I) at 100 °C for 20 minutes. The product that precipitated from the reaction was filtered to afford pure **JHE-02-032A** as a pale yellow solid, yield 74%. Mp = 189.5-190 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 8.13 (d, J = 8.0 Hz, 1H), 7.72 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.59 (s, 1H), 7.48-7.43 (m, 2H), 7.33 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 7.20 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 7.13-7.10 (m, 2H), 6.91 (s, 1H), 6.86-6.82 (m, 2H), 4.20 (t, J = 8.0 Hz, 2H), 3.32 (t, J = 8.0 Hz, 2H), 3.27 (d, J = 4.0 Hz, 4H), 3.07 (d, J = 4.0 Hz, 4H); HPLC 98% [t_R = 10.91, 70% acetonitrile in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{25}H_{25}Cl_2N_4O_3S$ 531.1019 $(M+H)^+$; found 531.1001 $(M+H)^+$.



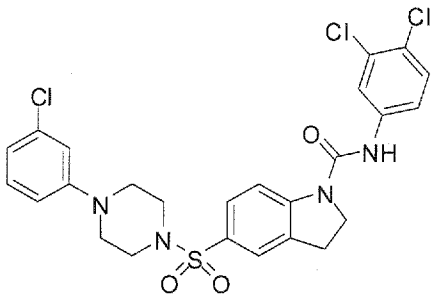
(JHE-02-065B) ***N*-(2-Chlorophenyl)-5-(4-(3-chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamide**

JHE-02-065B was prepared using the same procedure as described for the preparation of **JHE-02-032A**. **JHE-02-065B:** Off-white solid, yield 83%. Mp = 205-206 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.55 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.56-7.50 (m, 4H), 7.34 (ddd, J = 8.0 Hz, 8.0 Hz, 1.2 Hz, 1H), 7.23 (ddd, J = 8.0 Hz, 8.0 Hz, 1.2 Hz, 1H), 7.18 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.91 (s, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.21 (t, J = 8.8 Hz, 2H), 3.31-3.23 (m, 6H), 2.96-2.93 (m, 4H); HPLC 99% [t_R = 10.32, 70% acetonitrile in water (0.1% TFA)]; HPLC 98% [t_R = 27.85, 70% acetonitrile in water (0.1% TFA)].



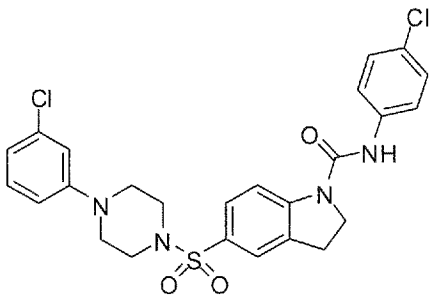
(JHE-02-068B) 5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)-*N*-(4-isopropylphenyl)indoline-1-carboxamide

JHE-02-068B was prepared using the same procedure as described for the preparation of **JHE-02-032A. JHE-02-068B**: Off-white solid, yield 83%. Mp = 182-182.5 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.63 (s, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.54-7.51 (m, 2H), 7.43 (d, J = 8.4 Hz, 1H), 7.20-7.14 (m, 3H), 6.91 (s, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.19 (t, J = 8.8 Hz, 2H), 3.27-3.22 (m, 6H), 2.96-2.93 (m, 4H), 2.86-2.79 (m, 1H), 1.17 (d, J = 7.2 Hz, 6H); HPLC 98% [t_R = 15.00, 70% acetonitrile in water (0.1% TFA)].



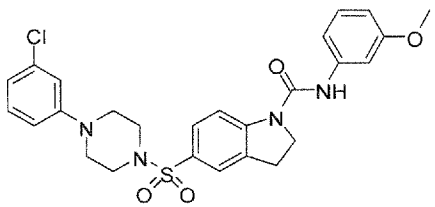
(JHE-02-068A) 5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)-*N*-(3,4-dichlorophenyl)indoline-1-carboxamide

JHE-02-068A was prepared using the same procedure as described in the preparation of **JHE-02-032A. JHE-02-068A**: Off-white solid, yield 92%. Mp = 195-196 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.96 (s, 1H), 8.03 (d, J = 9.2 Hz, 1H), 7.92 (d, J = 2.0 Hz, 1H), 7.59-7.53 (m, 4H), 7.17 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.91 (dd, J = 2.0 Hz, 2.0 Hz, 1H), 6.85 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.78 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 4.19 (t, J = 8.8 Hz, 2H), 3.29-3.23 (m, 6H), 2.96-2.93 (m, 4H); HPLC 98% [t_R = 16.65, 70% acetonitrile in water (0.1% TFA)].



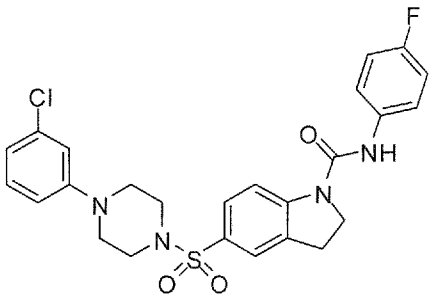
(JHE-02-065A) ***N*-(4-Chlorophenyl)-5-(4-(3-chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamide**

JHE-02-065A was prepared using the same procedure as described for the preparation of **JHE-02-032A. JHE-02-065A**: off-white solid, yield 81%; Mp = 188-188.5 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.82 (s, 1H), 8.03 (d, J = 9.2 Hz, 1H), 7.61-7.53 (m, 4H), 7.35-7.33 (m, 2H), 7.18 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.91 (dd, J = 2.0 Hz, 2.0 Hz, 1H), 6.85 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.78 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 4.20 (t, J = 8.8 Hz, 2H), 3.27-3.23 (m, 6H), 2.96-2.93 (m, 4H); HPLC 98% [t_R = 10.45, 70% acetonitrile in water (0.1% TFA)].



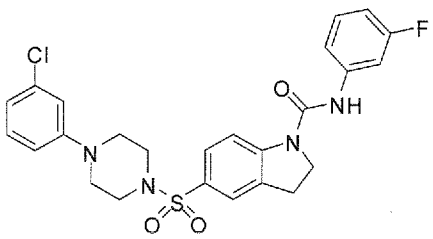
(JHE-02-032B) **5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)-*N*-(3-methoxyphenyl)indoline-1-carboxamide**

JHE-02-032B was prepared using the same procedure as described for the preparation of **JHE-02-032A. JHE-02-032B**: pale yellow solid, yield 79%. Mp = 199-199.5 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 8.13 (d, J = 8.0 Hz, 1H), 7.60-7.58 (m, 2H), 7.31 (s, br, 1H, N*H*), 7.27-7.13 (m, 4H), 6.91 (dd, J = 2.0 Hz, 2.0 Hz, 2H), 6.86-6.82 (m, 2H), 6.68 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 4.20 (t, J = 8.8 Hz, 2H), 3.80 (s, 3H), 3.34-3.25 (m, 6H), 3.07 (t, J = 5.2 Hz, 4H); HPLC 98% [t_R = 6.88, 70% acetonitrile in water (0.1% TFA)]; HPLC 97% [t_R = 21.43, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{26}H_{28}ClN_4O_4S$ 527.1514 $(M+H)^+$; found 527.1515 $(M+H)^+$.



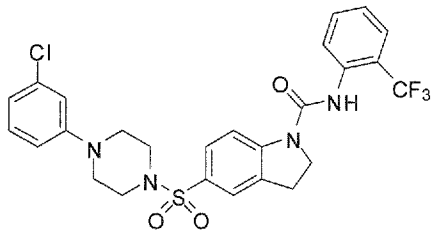
(JF038) 5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)-*N*-(4-fluorophenyl)indoline-1-carboxamide

JF038 was prepared using the same procedure as described for the preparation of **JHE-02-032A. JF038:** off-white solid, yield 62%. Mp = 192.5-193.5 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.76 (s, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.56-7.52 (m, 4H), 7.20-7.11 (m, 3H), 6.91 (dd, J = 2.0 Hz, 2.0 Hz, 1H), 6.84 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.78 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 4.19 (t, J = 8.4 Hz, 2H), 3.27-3.23 (m, 6H), 2.97-2.93 (m, 4H); HPLC 97% [t_R = 7.13, 70% acetonitrile in water (0.1% TFA)]; HPLC 97% [t_R = 14.63, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{25}H_{25}ClFN_4O_3S$ 515.1314 $(M+H)^+$; found 515.1310 $(M+H)^+$.



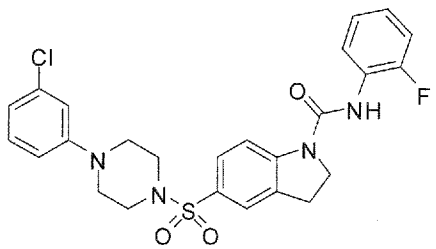
(JF039) 5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)-*N*-(3-fluorophenyl)indoline-1-carboxamide

JF039 was prepared using the same procedure as described for the preparation of **JHE-02-032A. JF039:** white solid, 84%. Mp = 208.5-209.5 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.88 (s, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.55-7.49 (m, 3H), 7.38-7.28 (m, 2H), 7.18 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.91, (s, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.21 (t, J = 8.4 Hz, 2H), 3.29-3.23 (m, 6H), 2.96-2.93 (m, 4H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 163.9, 161.6, 153.0, 148.7, 142.0, 134.5, 133.5, 131.2, 130.7, 128.7, 127.5, 124.8, 119.5, 116.7, 115.9, 115.0, 109.7, 107.8, 48.7, 48.0, 46.3, 27.6; HPLC 96% [t_R = 8.19, 70% acetonitrile in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{25}H_{25}ClFN_4O_3S$ 515.1314 $(M+H)^+$; found 515.1313 $(M+H)^+$.



(JF040) 5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)-*N*-(2-(trifluoromethyl)phenyl)indoline-1-carboxamide

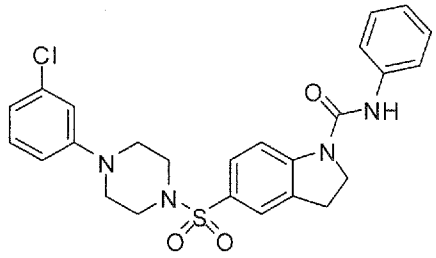
JF040 was prepared using the same procedure as described for the preparation of **JHE-02-032A. JF040:** White solid, yield 68%. Mp = 204-205 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.63 (s, br, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.97 (dd, J = 7.6 Hz, 7.6 Hz, 1H), 7.56-7.45 (m, 4H), 7.18 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.91, (s, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 4.17 (t, J = 8.8 Hz, 2H), 3.30-3.24 (m, 6H), 2.95-2.93 (m, 4H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 154.1, 152.3, 148.9, 134.5, 133.6, 133.2, 131.5, 131.2, 128.8, 127.1, 124.8, 119.5, 115.9, 115.0, 114.6, 48.6, 48.0, 46.4, 27.6; ^{19}F NMR (DMSO-d_6, 100.6 MHz) δ -59.4; HPLC 97% [t_R = 8.63, 70% acetonitrile in water (0.1% TFA)]; HRMS (ESI-ve) m/z calcd. for $C_{26}H_{25}ClF_3N_4O_3S$ 565.1283 $(M+H)^+$; found 565.1283 $(M+H)^+$.



(JF035) 5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)-*N*-(2-fluorophenyl)indoline-1-carboxamide

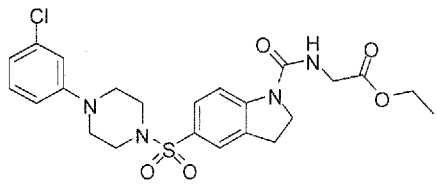
JF035 was prepared using the same procedure as described for the preparation of **JHE-02-032A. JF035:** White solid, yield 62%. Mp = 174-175 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.62 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.54 (s, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.27-7.15 (m, 4H), 6.91 (s, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.20 (t, J = 8.8 Hz, 2H), 3.29-3.24 (m, 6H), 2.96-2.93 (m, 4H); HPLC 100% [t_R = 6.38, 70% acetonitrile in water (0.1% TFA)]; HPLC 99% [t_R = 12.52, 70% methanol in water (0.1%

TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{25}H_{25}ClFN_4O_3S$ 515.1314 $(M+H)^+$; found 515.1320 $(M+H)^+$.



(JF033) 5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)-*N*-phenylindoline-1-carboxamide

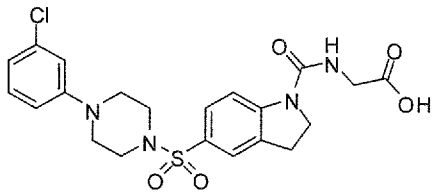
JF033 was prepared using the same procedure as described for the preparation of **JHE-02-032A. JF033:** White solid, yield 85%. Mp = 177-178 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.70 (s, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.55-7.53 (m, 4H), 7.31-7.27 (m, 2H), 7.18 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 7.03 (dd, J = 7.2 Hz, 7.2 Hz, 1H), 6.91 (dd, J = 2.0 Hz, 1H), 6.85 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 6.78 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 4.21 (t, J = 8.8 Hz, 2H), 3.37-3.23 (m, 6H), 2.97-2.93 (m, 4H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 153.2, 152.3, 149.0, 139.8, 134.5, 133.3, 131.2, 129.1, 128.7, 127.2, 124.7, 123.7, 121.4, 119.5, 115.9, 115.0, 114.9, 48.7, 48.0, 46.4, 27.6; HPLC 99% [t_R = 6.52, 70% acetonitrile in water (0.1% TFA)]; HPLC 99% [t_R = 13.22, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{25}H_{26}ClN_4O_3S$ 497.1409 $(M+H)^+$; found 497.1416 $(M+H)^+$.



(JHE-01-134A) ethyl 2-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)acetate

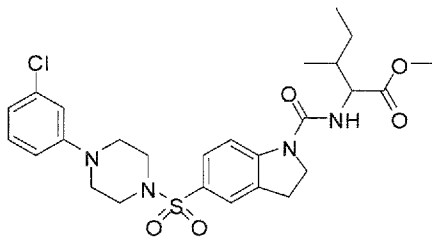
JHE-01-134A was prepared using the same procedure as described for the preparation of **JHE-02-032A. JHE-01-134A**: light brown solid, yield 100%. Mp = 149.5-150.5 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 8.05 (d, J = 9.2 Hz, 1H), 7.56-7.53 (m, 2H), 7.20 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.91 (dd, J = 2.0 Hz, 2.0 Hz, 1H), 6.85-6.82 (m, 2H), 5.92 (t, J = 6.0 Hz, 1H, N*H*), 4.18 (q, J = 7.2 Hz, 2H), 4.03 (t, J = 8.8 Hz, 2H), 3.93 (d, J = 6.0 Hz, 2H), 3.30-3.24 (m, 6H), 3.06 (t, J = 5.2 Hz, 4H), 1.26 (t, J = 7.2 Hz, 3H); HPLC 96% [t_R =

4.13, 70% acetonitrile in water (0.1% TFA)]; HPLC 98% [t_R = 9.37, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{22}H_{25}ClN_3O_6S$ 494.1147 $(M+H)^+$; found 494.1147 $(M+H)^+$.



(JHE-01-137) 2-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)acetic acid

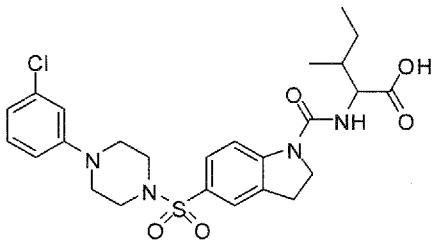
JHE-01-134A (50 mg, 0.01 mmol) was mixed with NaOH (6.0M, 0.1mL), ethanol (0.2 mL) and THF (0.4mL) at room temperature in a microwave reaction tube equipped with a magnetic stirring bar. The reaction tube was capped and irradiated in the microwave reactor (Biotage Initiator I) at 80 °C for 10 minutes. After concentration, the reaction mixture was acidified to pH~4 and diluted with water. The product was filtered and washed with water. **JHE-01-137:** gray solid, yield 97%. Mp = 214-214.5 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.97 (d, *J* = 8.8 Hz, 1H), 7.50-7.48 (m, 2H), 7.27 (t, *J* = 5.6 Hz, 1H, N*H*), 7.17 (dd, *J* = 8.0 Hz, 8.0 Hz, 1H), 6.90 (1H, s), 6.84 (d, *J* = 8.8 Hz, 1H), 6.77 (d, *J* = 7.2 Hz, 1H), 3.98 (t, *J* = 8.8 Hz, 2H), 3.74 (d, *J* = 5.6 Hz, 2H), 3.26-3.19 (m, 6H), 2.94-2.91 (m, 4H); HPLC 94% [t_R = 2.60, 70% acetonitrile in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{21}H_{24}ClN_4O_5S$ 479.1150 $(M+H)^+$; found 479.1141 $(M+H)^+$.



(JHE-02-029A) Methyl 2-(5-(4-(3-chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)-3-methylpentanoate

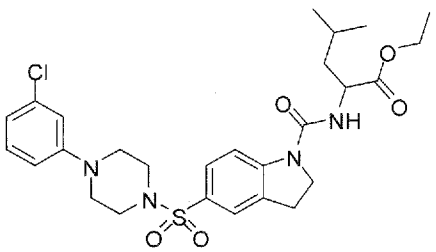
JHE-02-029A was prepared using the same procedure as described for the preparation of **JHE-02-032A. JHE-02-029A**: white solid, yield 87%. Mp = 145-146 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 8.03 (d, *J* = 9.2 Hz, 1H), 7.55-7.53 (m, 2H), 7.20 (dd, *J* = 8.0 Hz, 8.0 Hz, 1H), 6.91 (dd, *J* = 2.0, Hz, 2.0 Hz, 1H), 6.85-6.82 (m, 2H), 5.55 (t, *J* = 8.0 Hz,

1H, N*H*), 4.34 (dd, *J* = 8.0 Hz, 6.4 Hz, 1H), 4.07 (t, *J* = 8.8 Hz, 2H), 3.71 (s, 3H), 3.30-3.24 (m, 6H), 3.06 (t, *J* = 5.2 Hz, 4H), 1.81-1.78 (m, 1H), 1.59-1.51 (m, 1H), 1.33-1.21 (m, 1H), 0.96-0.89 (m, 6H); HPLC 98% (t_R = 8.44, 70% acetonitrile in water (0.1% TFA)); HPLC 99% [t_R = 26.23, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{26}H_{34}ClN_4O_5S$ 549.1933 $(M+H)^+$; found 549.1937 $(M+H)^+$.



(JHE-02-038) 2-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)-3-methylpentanoic acid

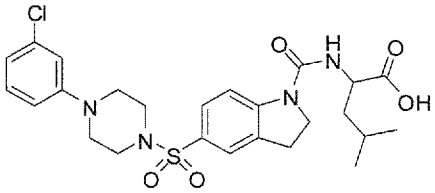
JHE-02-038 was prepared from **JHE-02-029A** using the same procedure as described for the preparation of **JHE-02-137. JHE-02-038:** light pink solid, yield 93%. Mp = 163-164 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 8.04 (d, *J* = 8.4 Hz, 1H), 7.56-7.54 (m, 2H), 7.20 (dd, *J* = 8.0 Hz, 8.0 Hz, 1H), 6.91 (dd, *J* = 2.0 Hz, 2.0 Hz, 1H), 6.85-6.82 (m, 2H), 5.55 (d, *J* = 7.6 Hz, 1H, N*H*), 4.28 (dd, *J* = 7.6 Hz, 6.4 Hz, 2H), 4.07 (t, *J* = 8.0 Hz, 2H), 3.29-3.24 (m, 6H), 3.06 (t, *J* = 5.2 Hz, 4H), 1.63-1.53 (m, 1H), 1.34-1.21 (m, 1H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.95 (t, *J* = 8.0 Hz, 3H); HPLC 99% [t_R = 4.53, 70% acetonitrile in water (0.1% TFA)]; HPLC 99.5% [t_R = 18.53, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{25}H_{32}ClN_4O_5S$ 535.1776 $(M+H)^+$; found 535.1780 $(M+H)^+$.



(JHE-02-012) Ethyl 2-(5-(4-(3-chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)-4-methylpentanoate

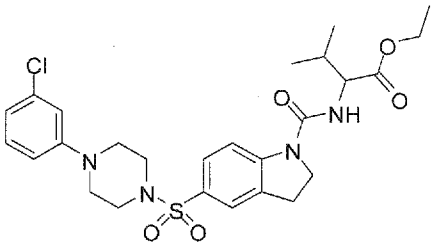
JHE-01-12 was prepared using the same procedure as described for the preparation of **JHE-02-032A. JHE-02-012:** light orange foam-like solid, yield 100%. Mp = 76-77 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 8.03 (d, *J* = 6.8 Hz, 1H), 7.55 (s, 1H), 7.54 (d, *J* = 6.8 Hz,

1H), 7.20 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.91 (d, J = 2.0 Hz, 1H), 6.85-6.81 (m, 2H), 5.67 (d, J = 8.0 Hz, 1H, N*H*), 4.43-4.37 (m, 1H), 4.19-4.12 (m, 2H), 4.09-3.99 (m, 2H), 3.29-3.24 (m, 6H), 3.05 (t, J = 5.2 Hz, 4H), 1.82-1.58 (m, 3H), 1.25 (t, J = 8.4 Hz, 3H), 0.98 (d, J = 6.4 Hz, 3H), 0.95 (t, J = 6.4 Hz, 3H); HPLC 95% [t_R = 10.47, 70% acetonitrile in water (0.1% TFA)]; HPLC 96% [t_R = 9.77, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{27}H_{36}ClN_4O_5S$ 563.2090 $(M+H)^+$; found 563.2090 $(M+H)^+$.



(JHE-02-019A) 2-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)-4-methylpentanoic acid

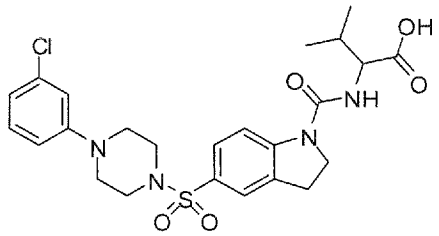
JHE-02-019A was prepared from **JHE-02-012** using the same procedure as described for the preparation of **JHE-02-137. JHE-02-019A**: pink solid, yield 87%. Mp = 138.5-140 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 8.03 (d, J = 9.2 Hz, 1H), 7.55-7.53 (m, 2H), 7.20 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.91 (t, J = 2.0 Hz, 1H), 6.85-6.81 (m, 2H), 5.71 (d, J = 8.0 Hz, 1H, N*H*), 4.39-4.34 (m, 1H), 4.10-3.99 (m, 2H), 3.29-3.24 (m, 6H), 3.05 (t, J = 5.2 Hz, 2H), 1.80-1.72 (m, 2H), 1.68-1.63 (m, 1H), 0.98 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H); HPLC 96% [t_R = 4.56, 70% acetonitrile in water (0.1% TFA)]; HPLC 96% [t_R = 19.05, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{25}H_{32}ClN_4O_5S$ 535.1776 $(M+H)^+$; found 535.1773 $(M+H)^+$.



(JHE-02-010C) Ethyl 2-(5-(4-(3-chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)-3-methylbutanoate

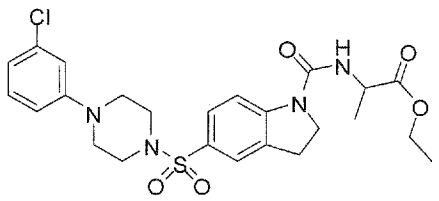
JHE-02-010C was prepared using the same procedure as described for the preparation of **JHE-02-032A. JHE-02-010C**: off-white solid, yield 95%. Mp = 143-143.5 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 8.03 (d, J = 9.2 Hz, 1H), 7.55-7.53 (m, 2H), 7.20 (dd, J = 8.0 Hz,

8.0 Hz, 1H), 6.91 (t, J = 2.0 Hz, 1H), 6.85-6.81 (m, 2H), 5.52 (d, J = 8.0 Hz, 1H, N*H*), 4.27 (dd, J = 8.0 Hz, 6.4 Hz, 1H), 4.23-4.14 (m, 2H), 4.09 (t, J = 8.8 Hz, 2H), 3.29-3.24 (m, 6H), 3.05 (t, J = 5.2 Hz, 4H), 1.27 (t, J = 7.2 Hz, 3H), 1.00 (d, J = 7.2 Hz, 3H), 0.99 (d, J = 7.2 Hz, 3H), 0.96-0.87 (m, 1H); HPLC 95% [t_R = 8.57, 70% acetonitrile in water (0.1% TFA)]; HPLC 96% [t_R = 25.36, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{26}H_{34}ClN_4O_5S$ 549.1933 $(M+H)^+$; found 549.1936 $(M+H)^+$.



(JHE-02-017C) 2-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)-3-methylbutanoic acid

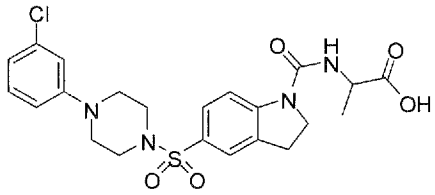
JHE-02-017C was prepared from **JHE-02-010C** using the same procedure as described for the preparation of **JHE-02-137. JHE-02-017C**: gray solid, yield 49%. Mp = 185-186 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.04 (d, J = 8.4 Hz, 1H), 7.56-7.54 (m, 2H), 7.20 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.91 (d, J = 2.0 Hz, 1H), 6.85-6.82 (m, 2H), 5.54 (d, J = 8.0 Hz, 1H, N*H*), 4.24 (dd, J = 8.0 Hz, 6.4 Hz, 1H), 4.08 (d, J = 8.8 Hz, 1H), 3.29-3.24 (m, 6H), 3.05 (t, J = 5.2 Hz, 4H), 1.01 (d, J = 6.4 Hz, 3H), 1.00 (d, J = 6.4 Hz, 3H);); HPLC 96% [t_R = 3.81, 70% acetonitrile in water (0.1% TFA)]; HPLC 96% [t_R = 12.69, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{24}H_{30}ClN_4O_5S$ 521.1620 $(M+H)^+$; found 526.1618 $(M+H)^+$.



(JHE-02-010B) Ethyl 2-(5-(4-(3-chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)propanoate

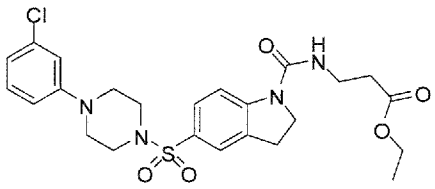
JHE-02-010B was prepared using the same procedure as described for the preparation of **JHE-02-032A. JHE-02-010B**: off-white solid, yield 94%. Mp = 167-168.5 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 8.04 (d, J = 8.4 Hz, 1H), 7.55-7.53 (m, 2H), 7.20 (dd, J = 8.4 Hz,

8.4 Hz, 1H), 6.91 (dd, J = 2.0 Hz, 2.0 Hz, 1H), 6.85-6.82 (m, 2H), 5.77 (d, J = 7.2 Hz, 1H, N*H*), 4.38 (dq, J = 7.2 Hz, 7.2 Hz, 1H), 4.20-4.12 (m, 2H), 4.09-3.99 (m, 2H), 3.29-3.24 (m, 6H), 3.07-3.04 (m, 4H), 1.43 (d, J = 7.2 Hz, 1H), 1.29-1.22 (m, 3H); HPLC 93% [t_R = 5.13, 70% acetonitrile in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{24}H_{30}ClN_4O_5S$ 521.1620 $(M+H)^+$; found 521.1630 $(M+H)^+$.



(JHE-02-017B) 2-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)propanoic acid

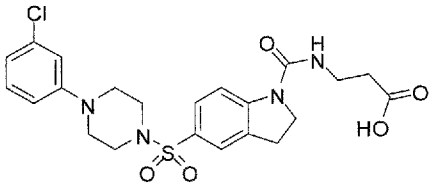
JHE-02-017B was prepared from **JHE-02-010B** using the same procedure as described for the preparation of **JHE-02-137. JHE-02-017B**: off-white solid, yield 95%. Mp = 175-176 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.95 (d, J = 8.4 Hz, 1H), 7.49 (s, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.17 (dd, J = 8.4 Hz, 8.4 Hz, 1H), 7.13 (d, J = 6.8 Hz, 1H, N*H*), 6.90 (s, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 4.35 (t, J = 8.4 Hz, 2H), 3.27-3.23 (m, 6H), 2.95-2.93 (m, 4H), 1.99-1.93 (m, 1H), 0.88 (d, J = 6.0 Hz, 4H); HPLC 95% [t_R = 2.89, 70% acetonitrile in water (0.1% TFA)]; HPLC 94% [t_R = 7.16, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{22}H_{26}ClN_4O_5S$ 493.1307 $(M+H)^+$; found 493.1306 $(M+H)^+$.



(JHE-02-010A) Ethyl 3-(5-(4-(3-chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)propanoate

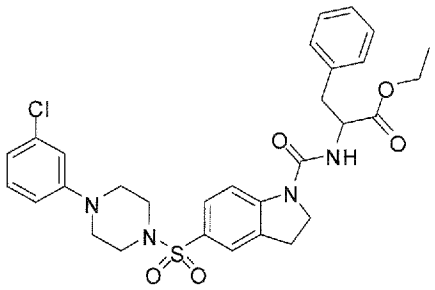
JHE-02-010A was prepared using the same procedure as described for the preparation of **JHE-02-032A. JHE-02-010A**: light orange solid, yield 92%. Mp = 161.5-162.5 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 8.07 (d, J = 9.2 Hz, 1H), 7.56-7.53 (m, 2H), 7.20 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.91 (dd, J = 2.0, Hz, 2.0 Hz, 1H), 6.85-6.81 (m, 2H), 5.71 (t, J = 6.8 Hz, 1H, N*H*), 4.12 (q, J = 7.2 Hz, 2H), 3.94 (q, J = 8.4 Hz, 2H), 3.48 (dt, J = 6.8 Hz, 6.8

Hz, 2H), 3.27-3.12 (m, 6H), 3.05 (t, J = 5.2 Hz, 4H), 2.55 (t, J = 6.8 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H); HPLC 98% [t_R = 4.47, 70% acetonitrile in water (0.1% TFA)]; HPLC 98% [t_R = 11.67, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{24}H_{30}ClN_4O_5S$ 521.1620 $(M+H)^+$; found 521.1631 $(M+H)^+$.



(JHE-02-017A) 3-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)propanoic acid

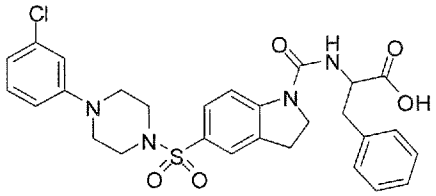
JHE-02-017A was prepared from **JHE-02-010A** using the same procedure as described for the preparation of **JHE-02-137. JHE-02-017A**: off-white solid, yield 81%. Mp = 199-199.5 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.98 (d, J = 8.8 Hz, 1H), 7.49-7.47 (m, 2H), 7.17 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.96 (t, J = 5.6 Hz, 1H, NH), 6.90 (s, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 3.91 (t, J = 8.8 Hz, 2H), 3.29-3.17 (m, 8H), 2.93-2.90 (m, 4H), 2.43 (t, J = 7.2 Hz, 2H); HPLC 97% [t_R = 2.65, 70% acetonitrile in water (0.1% TFA)]; HPLC 97% [t_R = 6.49, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{22}H_{26}ClN_4O_5S$ 493.1307 $(M+H)^+$; found 493.1304 $(M+H)^+$.



(JHE-02-014) Ethyl 2-(5-(4-(3-chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)-3-phenylpropanoate

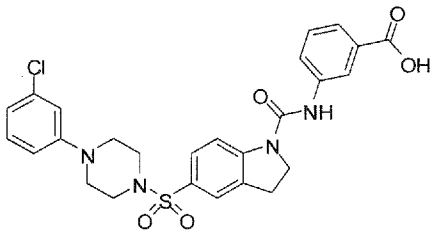
JHE-02-014 was prepared using the same procedure as described for the preparation of **JHE-02-032A. JHE-02-014:** pale yellow solid, yield 100%. Mp = 123-124 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 7.98 (d, J = 9.2 Hz, 1H), 7.54-7.51 (m, 2H), 7.35-7.26 (m, 5H), 7.20 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.91 (dd, J = 2.0, Hz, 2.0 Hz, 1H), 6.84-6.81 (m, 2H), 5.90 (t, J = 8.0 Hz, 1H, N*H*), 4.65-4.60 (m, 1H), 4.15 (q, J = 7.2 Hz, 2H), 4.03-3.88 (m,

2H), 3.26-3.21 (m, 7H), 3.11-3.03 (m, 5H), 1.22 (t, J = 7.2 Hz, 3H); HPLC 97% [t_R = 9.40, 70% acetonitrile in water (0.1% TFA)]; HPLC 97% [t_R = 8.73, 70% methanol in water (0.1% TFA)].



(JHE-02-019B) 2-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)-3-phenylpropanoic acid

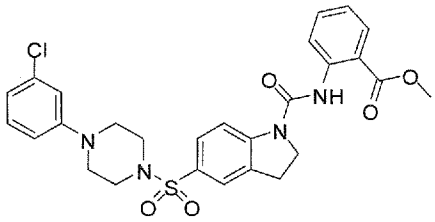
JHE-02-019B was prepared from **JHE-02-014** using the same procedure as described for the preparation of **JHE-02-137. JHE-02-019B:** light pink solid, yield 74%. Mp = 134-135 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 7.98 (d, J = 9.2 Hz, 1H), 7.54-7.52 (m, 2H), 7.35-7.19 (m, 6H), 6.93 (s, 1H), 6.87-6.83 (m, 2H), 5.72 (d, J = 8.4 Hz, 1H), 4.63-4.57 (m, 1H), 3.99-3.87 (m, 2H), 3.27-3.20 (m, 7H), 3.11-3.05 (m, 5H); HPLC 97% [t_R = 4.33, 70% acetonitrile in water (0.1% TFA)]; HPLC 98% [t_R = 18.15, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{28}H_{30}ClN_4O_5S$ 569.1620 $(M+H)^+$; found 569.1627 $(M+H)^+$.



(JHE-02-020B) 3-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)benzoic acid

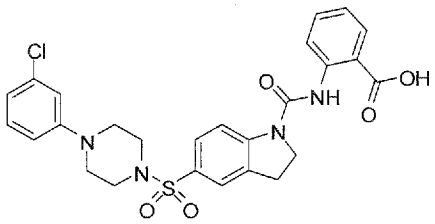
(JHE-02-015B) Ethyl 3-(5-(4-(3-chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)benzoate was prepared from the indoline **JHE-01-120** and the corresponding acid chloride using the same procedure as described for the preparation of **JHE-02-32A.** Then **JHE-02-020B** was hydrolyzed from **JHE-02-015B** using the same procedure as described for the preparation of **JHE-02-137. JHE-02-020B**: white solid, yield 100%. Mp = 250 °C decomposed; ^{1}H NMR (CD_3CN, 400 MHz) δ 8.24 (s, 1H), 8.15 (d, J = 9.2 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.61-7.59 (m, 2H),

7.50-7.44 (m, 2H), 7.21 (dd, *J* = 8.0 Hz, 8.0 Hz, 1H), 6.92 (s, 1H), 6.86-6.82 (m, 2H), 4.21 (t, *J* = 8.8 Hz, 2H), 3.33 (t, *J* = 8.8 Hz, 2H), 3.27 (t, *J* = 5.2 Hz, 4H), 3.07 (t, *J* = 5.2 Hz, 4H); HRMS (ESI-ve) *m/z* calcd. for $C_{26}H_{26}ClN_4O_5S$ 541.1307 $(M+H)^+$; found 541.1303 $(M+H)^+$.



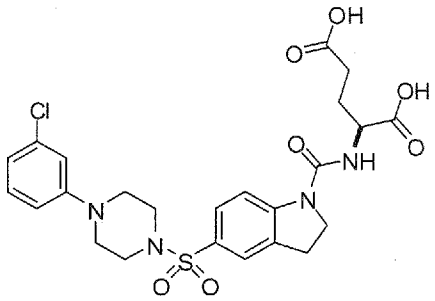
(JHE-02-015A) Methyl 2-(5-(4-(3-chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)benzoate

JHE-02-015A was prepared using the same procedure as described for the preparation of **JHE-02-032A. JHE-02-015A**: off-white solid. Mp = 229.5-230 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 10.85 (s, 1H, N*H*), 8.65 (d, *J* = 8.8 Hz, 1H), 8.20 (d, *J* = 9.2 Hz, 1H), 8.08 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.65-7.61 (m, 3H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.91 (s, 1H), 6.86-6.82 (m, 2H), 4.29 (t, *J* = 8.8 Hz, 2H), 3.94 (s, 3H), 3.67 (t, *J* = 8.8 Hz, 2H), 3.27 (t, *J* = 5.6 Hz, 4H), 3.08 (t, *J* = 5.6 Hz, 4H); HPLC 98% [t_R = 17.68, 70% acetonitrile in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{22}H_{25}ClN_3O_6S$ 494.1147 $(M+H)^+$; found 494.1147 $(M+H)^+$.



(JHE-02-020A) 2-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)benzoic acid

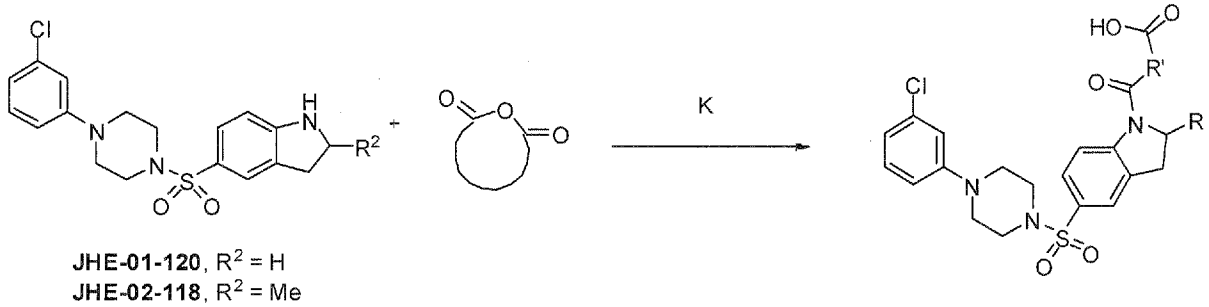
JHE-02-020A was prepared from **JHE-02-015A** using the same procedure as described for the preparation of **JHE-02-137. JHE-02-020A**: pink solid, yield 88%. Mp = 240.5-241 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.53 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 9.2 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.61-7.56 (m, 3H), 7.17 (dd, *J* = 8.4 Hz, 8.4 Hz, 1H), 7.09 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 6.91 (s, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 4.23 (t, *J* = 8.8 Hz, 2H), 3.29-3.24 (m, 6H), 2.96-2.94 (m, 4H).



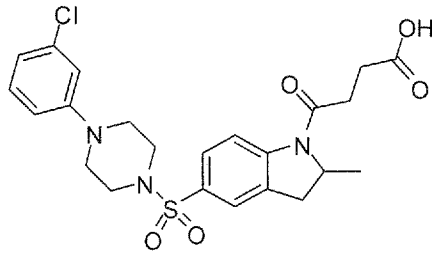
(JHE-02-052) (*S*)-2-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carboxamido)pentanedioic acid

(JHE-02-052) was hydrolyzed in the same fashion as **JHE-01-137** from the corresponding ester (not reported here) which was prepared according the procedure described as for the preparation of **JHE-02-32A. JHE-02-052:** pale yellow solid, yield 81%. Mp = 181-181.5 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.95 (d, J = 8.4 Hz, 1H), 7.49 (s, 2H), 7.48 (d, J = 8.4 Hz, 1H), 7.17 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.90 (s, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.13-4.19 (m, 1H), 4.08-3.96 (m, 2H), 3.24-3.18 (m, 6H), 2.94-2.90 (m, 4H), 2.33 (t, J = 7.6 Hz, 2H), 2.08-1.99 (m, 1H), 1.96-1.84 (m, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 174.7, 174.5, 155.2, 152.3, 149.1, 134.5, 133.0, 131.2, 128.7, 126.8, 124.7, 119.5, 115.9, 115.0, 114.4, 53.2, 48.2, 48.0, 46.4, 31.1, 27.5, 26.5; HPLC 98% [t_R = 2.31, 70% acetonitrile in water (0.1% TFA)]; HPLC 96% [t_R = 5.41, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) m/z calcd. for $C_{24}H_{28}ClN_4O_7S$ 551.1362 $(M+H)^+$; found 551.1362 $(M+H)^+$.

Scheme 5

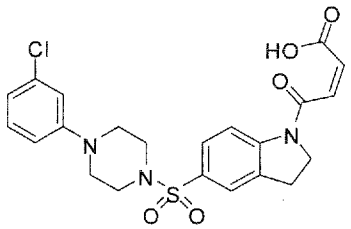


Reagents and conditions: (k) Anhydrides, $CHCl_3$, microwave, 100°C, 30 min.



(JHE-02-119) 4-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)-2-methylindolin-1-yl)-4-oxobutanoic acid

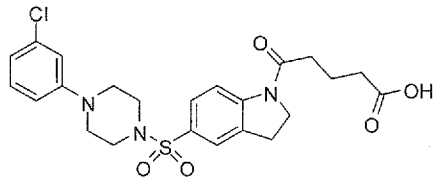
In a microwave reaction tube equipped with a magnetic stirring bar, **JHE-02-118** (77.0 mg, 0.197 mmol) was dissolved in chloroform (0.5 mL) at room temperature. To the solution was added succinic anhydride (20 mg, 0.200 mmol). The reaction tube was capped and irradiated in the microwave reactor (Biotage Initiator I) at 100 °C for 30 minutes. The product was filtered and washed with dichloromethane and then with ethyl acetate/hexane (3:7) to afford the pure **JHE-02-119** as pale pink solid, (81 mg, 84%). Mp = 209.5-210 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.14 (s, 1H), 7.63 (s, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.18 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.90 (d, J = 2.0 Hz, 1H), 6.85 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.78 (dd, J = 8.0 Hz, 2.0Hz, 1H), 4.78-4.71 (m, 1H), 3.44-3.35 (m, 1H), 3.25-3.22 (m, 4H), 2.98-2.95 (m, 4H), 2.89-2.65 (m, 3H), 2.57-2.52 (m, 2H); HPLC 99% [t_R = 3.32, 70% acetonitrile in water (0.1% TFA)]; HPLC 99% [t_R = 7.36, 70% methanol in water (0.1% TFA)].



(JHE-01-129A) (*Z*)-4-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-4-oxobut-2-enoic acid

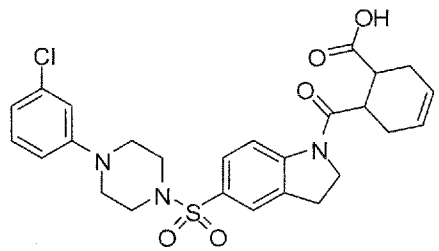
JHE-01-129A was prepared from **JHE-01-120** and maleic anhydride using the same procedure as described for the preparation of **JHE-02-119. JHE-01-129A**: pale yellow solid, yield 68%. Mp = 191-192 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.19 (d, J = 8.0 Hz, 1H), 7.61 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.15 (dd, J = 8.0 Hz, 8.0 Hz, 1H), 6.91 (s, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.80-6.77 (m, 2H), 6.13 (d, J = 12.0 Hz, 1H), 4.03 (t, J = 8.0 Hz, 2H), 3.28-3.19 (m, 6H), 2.98-2.93 (m, 4H); HPLC 98% [t_R = 3.04, 70%

acetonitrile in water (0.1% TFA)]; HPLC 94% [t_R = 5.63, 70% methanol in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{22}H_{23}ClN_3O_5S$ 476.1041 $(M+H)^+$; found 476.1044 $(M+H)^+$.



(JHE-01-129B) 5-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indolin-1-yl)-5-oxopentanoic acid

JHE-01-129B was prepared from **JHE-01-120** and glutaric anhydride using the same procedure as described for the preparation of **JHE-02-119. JHE-01-129B**: white solid, yield 80%. Mp = 220-220.5 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.24 (d, *J* = 7.6 Hz, 1H), 7.57 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.17 (dd, *J* = 8.0 Hz, 8.0 Hz, 1H), 7.20 (dd, *J* = 8.0 Hz, 8.0 Hz, 1H), 6.90 (s, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 4.12 (t, *J* = 8.4 Hz, 2H), 3.27-3.18 (m, 6H), 2.93 (m, 4H), 2.48 (m, 2H), 2.28 (t, *J* = 7.6 Hz, 2H), 1.78 (tt, *J* = 7.6 Hz, 2H); HPLC 97% [t_R = 3.11, 70% acetonitrile in water (0.1% TFA)]; HPLC 96% [t_R = 7.53, 70% acetonitrile in water (0.1% TFA)]; HRMS (ESI-ve) *m/z* calcd. for $C_{23}H_{27}ClN_3O_5S$ 492.1355 $(M+H)^+$; found 492.1359 $(M+H)^+$.



(JHE-02-007) 6-(5-(4-(3-Chlorophenyl)piperazin-1-ylsulfonyl)indoline-1-carbonyl)cyclohex-3-enecarboxylic acid

JHE-02-007B was prepared from **JHE-01-120** and 1,2,3,6- tetrahydrophthalic anhydride using the same procedure as described in the preparation of **JHE-02-119. JHE-02-00:** off-white solid, yield 49%. Mp = 146.5-147.5 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 8.28 (s, 1H), 7.62 (s, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.20 (dd, *J* = 8.4 Hz, 8.4 Hz, 1H), 6.91 (s, 1H), 6.85-6.82 (m, 2H), 5.78 (d, *J* = 10.0 Hz, 1H), 5.66 (d, *J* = 10.0 Hz, 1H), 4.33-4.21 (m, 2H), 3.39-3.33 (m, 1H), 3.30-3.25 (m, 6H), 3.07 (t, *J* = 5.2 Hz, 4H), 2.97-2.93 (m,

1H), 2.77-2.72 (m, 1H), 2.50-2.11 (m, 3H); HRMS (ESI-ve) *m/z* calcd. for $C_{26}H_{29}ClN_3O_5S$ 530.1511 $(M+H)^+$; found 530.1505 $(M+H)^+$.

Based on the high throughput screening, **XW2-011B** from HePTP screens, seen in Figure 2, was synthesized, exhibiting an IC_{50} of 47.8 μM. Focused libraries based on these hits have been prepared and assessed for Shp2 inhibitory activity. As an initial step, building block molecules were synthesized. An indoline skeleton molecule was then constructed, which was used to couple with the individual building blocks to afford the target molecules. Additional target molecules were also produced by coupling different acid chlorides and isocyanates with the indoline core. Finally, a chemical probe was also synthesized as a subunit for potential small molecules to develop another biologically active, small molecule skeleton like the indoline.

It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims. In addition, any elements or limitations of any invention or embodiment thereof disclosed herein can be combined with any and/or all other elements or limitations (individually or in any combination) or any other invention or embodiment thereof disclosed herein, and all such combinations are contemplated with the scope of the invention without limitation thereto.

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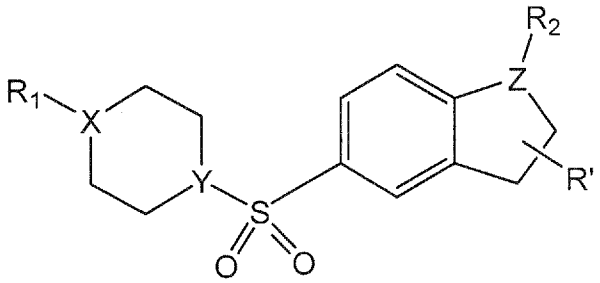
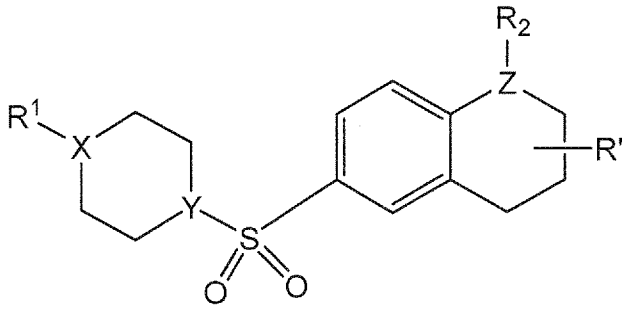
CLAIMS

We claim:

1. A Shp2 inhibitor compound having the chemical structure shown in formula I or II:



(I)



(II)

wherein

X, Y, and Z are independently N or S;

R_1 is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, any of which can be optionally substituted with one or more of halogen; alkyl; heteroalkyl; -COOH; $-C(R_3)_3$, wherein R_3 can independently be any of -H or halogen; or $-OR_4$, wherein R_4 can be any of H, alkyl, or heteroalkyl;

R_2 is alkyl, alkylcarbonyl, heteroalkylcarbonyl, aryl, arylcarbonyl, heterocycloalkylcarbonyl, cycloalkylcarbonyl, or $-C(O)NR_6R_7$, any of which can be optionally substituted with one or more of halogen; alkyl; heteroalkyl; carbonyl; $-OR_4$, wherein R_4 can be -H, alkyl, or heteroalkyl; -OH; $-C(R_3)_3$, wherein R_3 can independently be any of -H or halogen; aryl, which can be substituted with one or more of halogen or $-OR_4$; heterocycloalkyl; or $-C(O)OR_5$, wherein R_5 can be -H or alkyl;

R_6 and R_7 are independently -H, alkyl, heteroalkyl, aryl, or heteroaryl; and

R' is H or alkyl;

or a pharmaceutically acceptable salt or hydrate thereof.

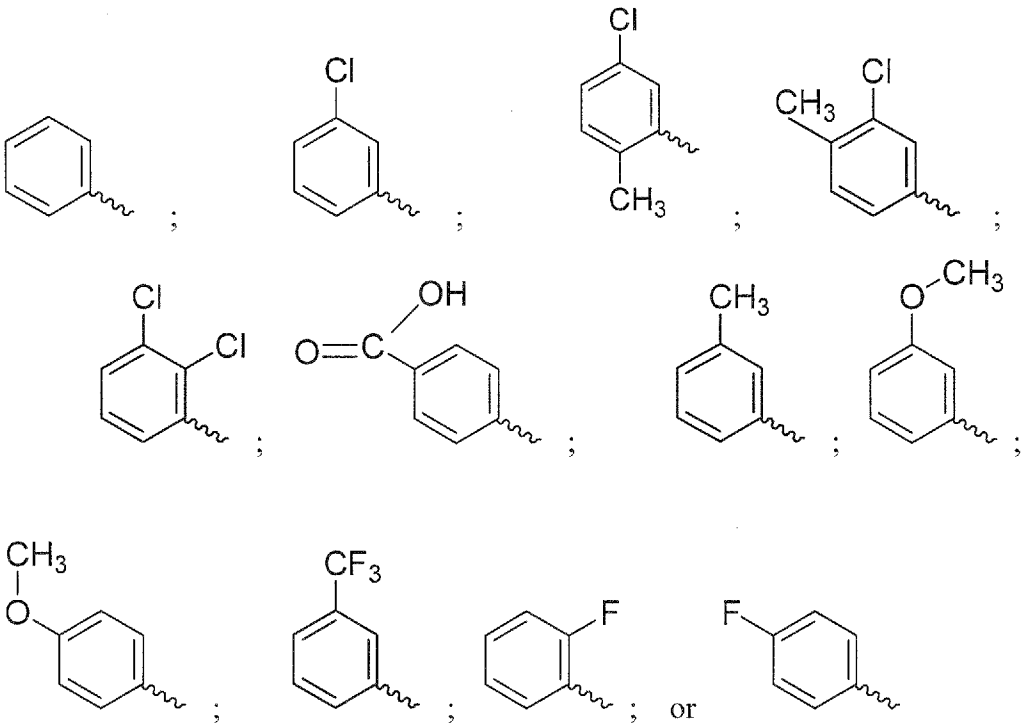
2. The compound of claim 1, wherein X, Y, and Z are all N.

3. The compound of claim 1, wherein R_1 is aryl optionally substituted with one or more of -Cl, -F, -COOH, $-CH_3$, CF_3, or $-OCH_3$.

4. The compound of claim 1, wherein R_1 is phenyl optionally substituted with one or more of -Cl, -F, -COOH, $-CH_3$, CF_3, or $-OCH_3$.

5. The compound of claim 1, wherein $-OR_4$ is $-OCH_3$ or $-OCH_2CH_3$.

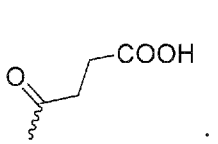
6. The compound of claim 1, wherein R_1 has a structure selected from:



wherein ≈ indicates the point of attachment.

7. The compound of claim 1, wherein R_2 is alkylcarbonyl optionally substituted with one or more of -OH, -COOH, aryl, or -OR, wherein R is -H or alkyl.

8. The compound of claim 1, wherein R_2 has a structure selected from:



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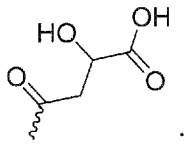

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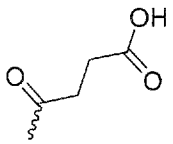

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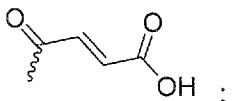

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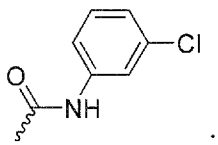

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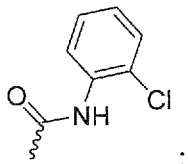

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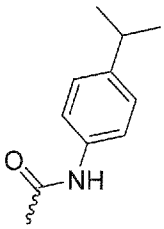

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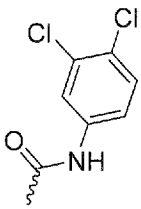

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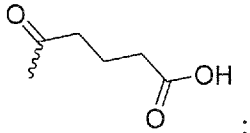

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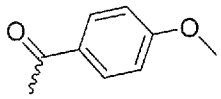

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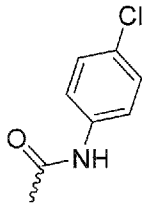

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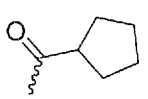

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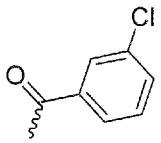

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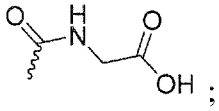

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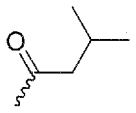

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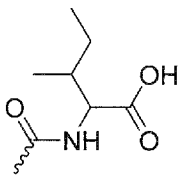

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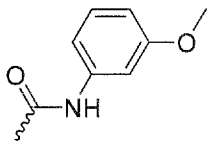

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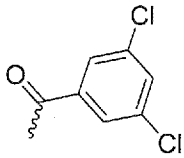

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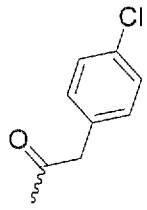

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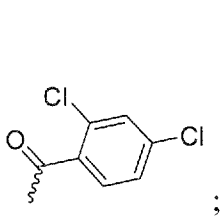

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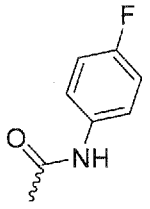

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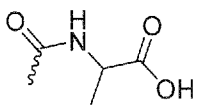

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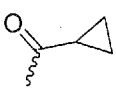

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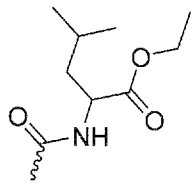

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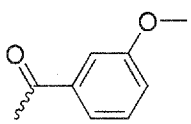

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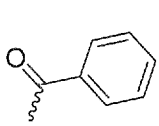

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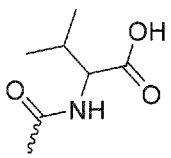

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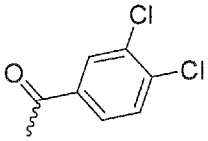

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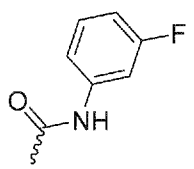

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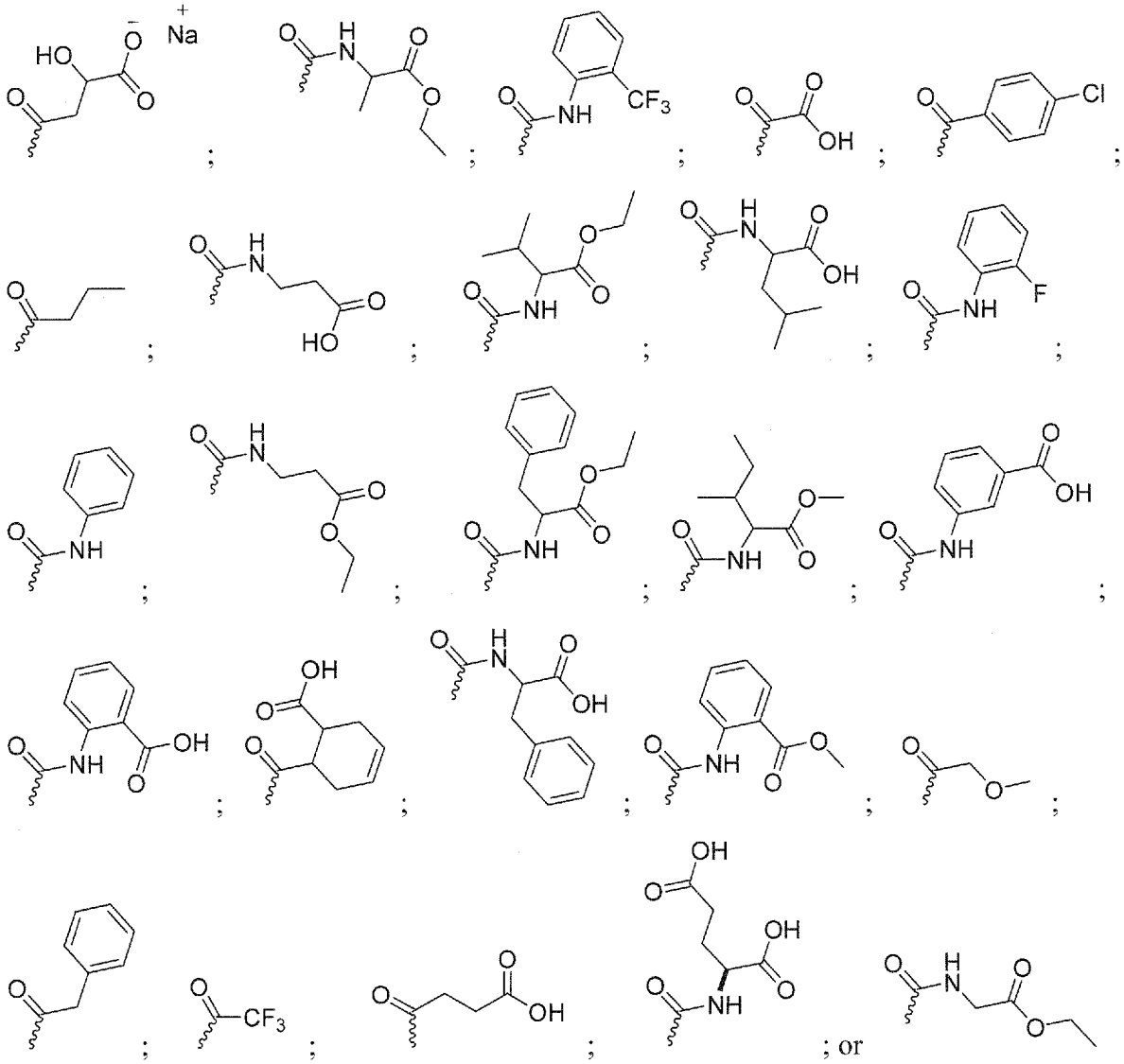
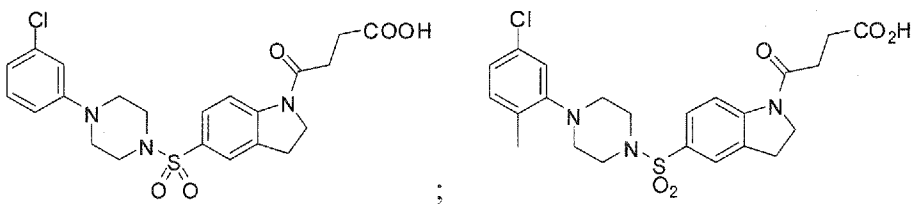
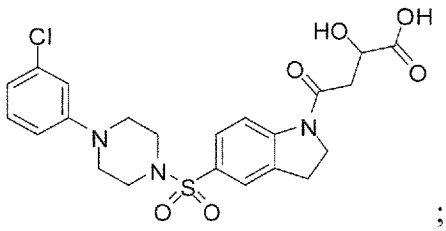


wherein ~ indicates the point of attachment.

9. The compound of claim 1, wherein the compound has the structure:

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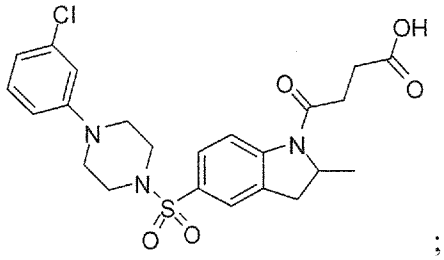
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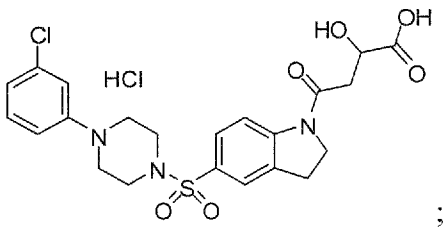
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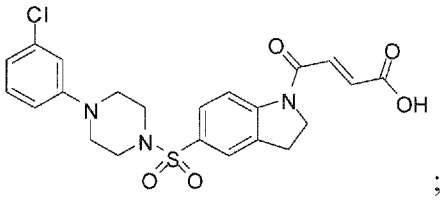
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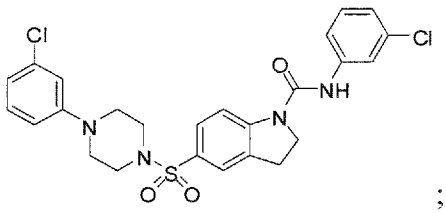
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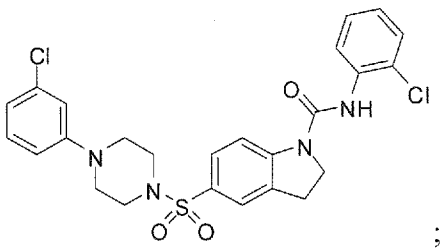
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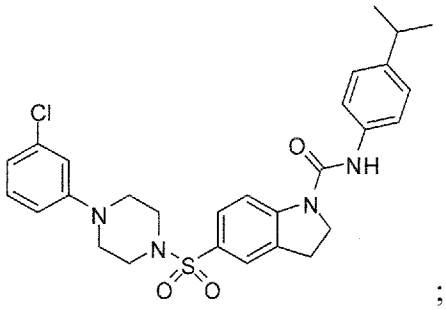
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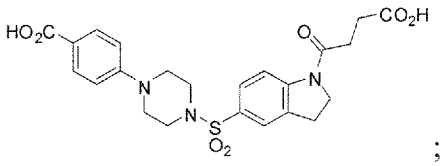
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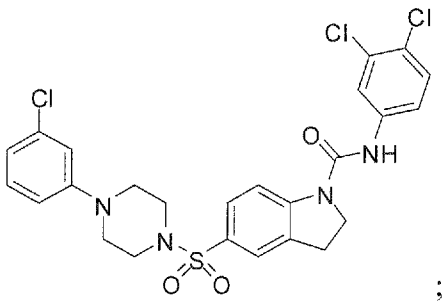
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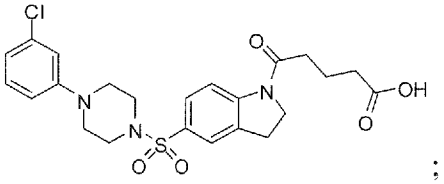
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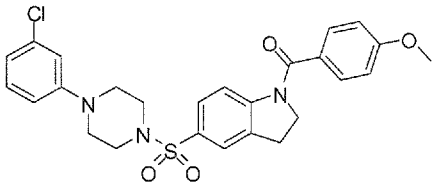
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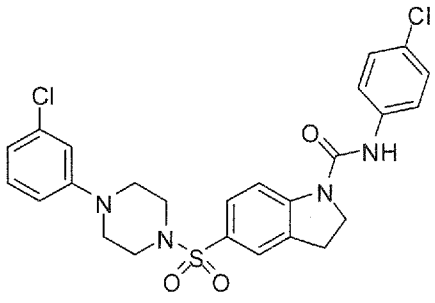
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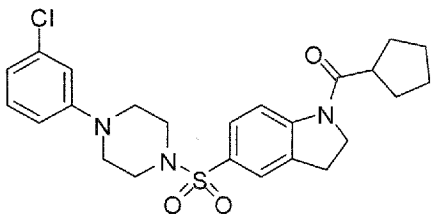
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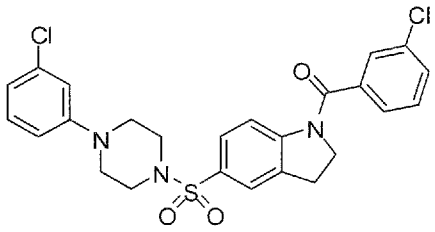
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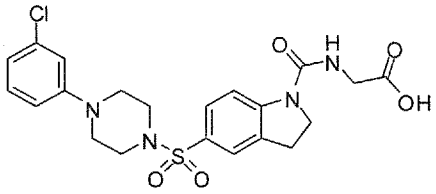
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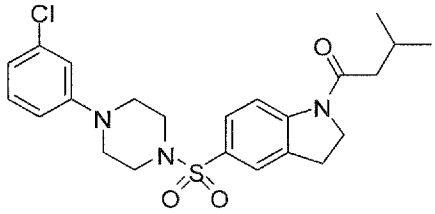
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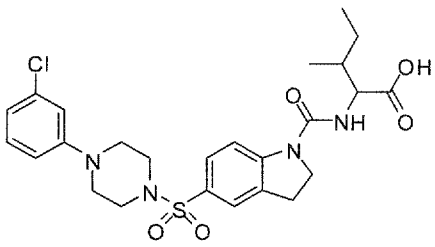
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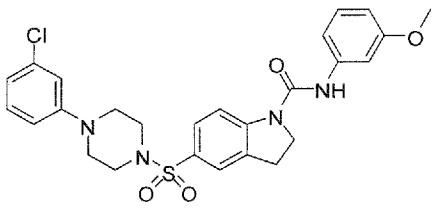
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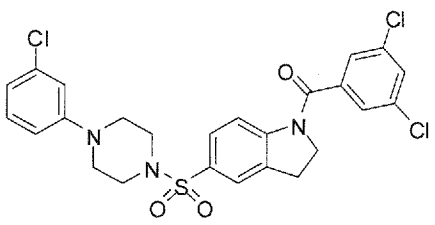
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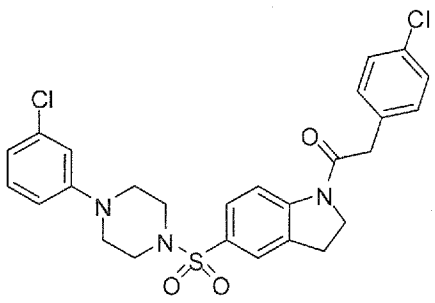
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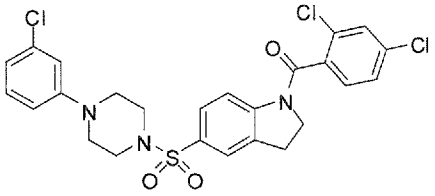
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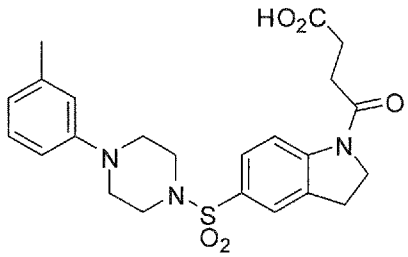
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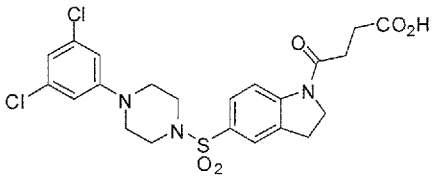
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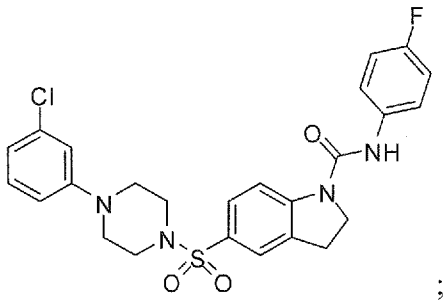
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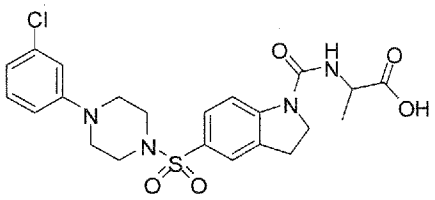
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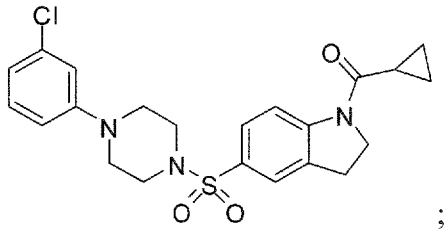
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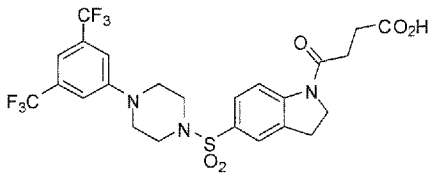
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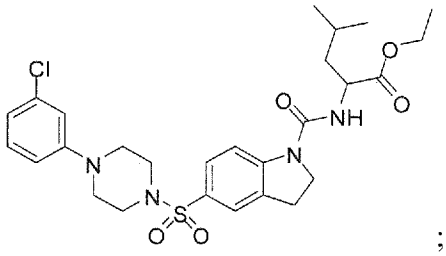
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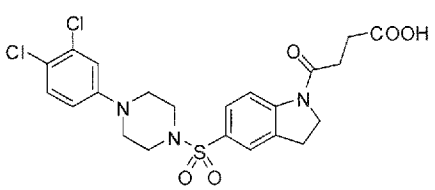
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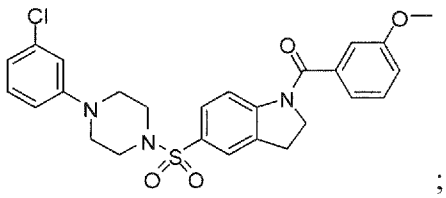
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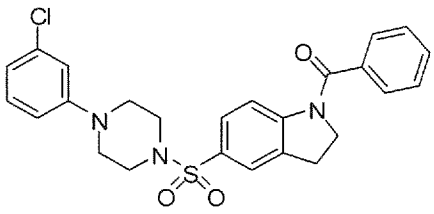
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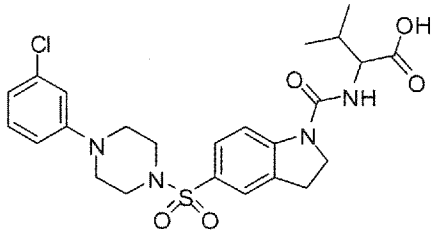
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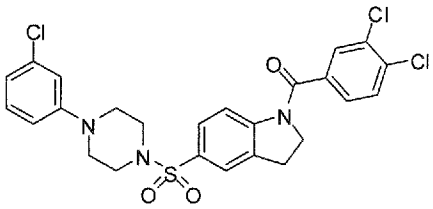
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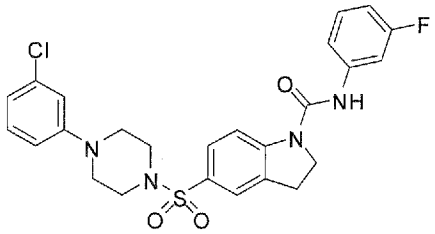
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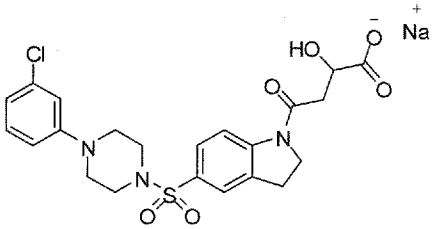
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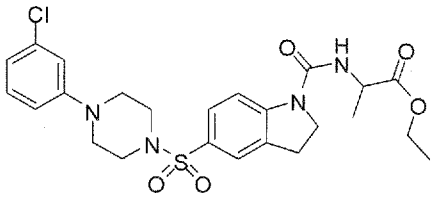
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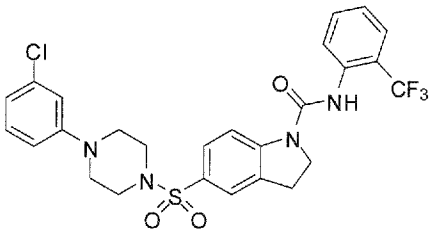
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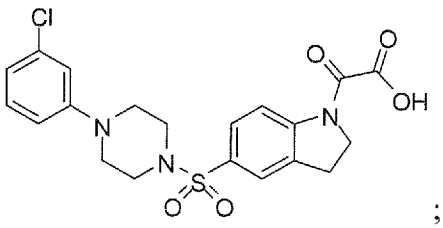
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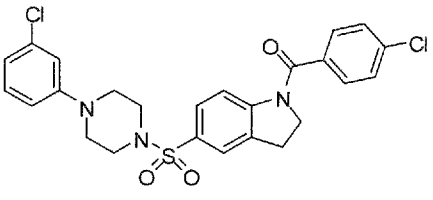
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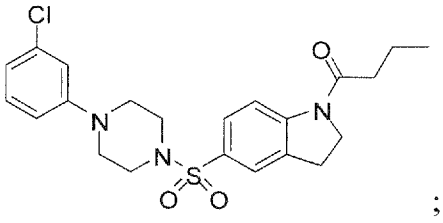
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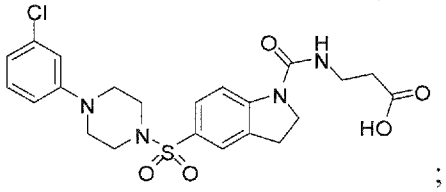
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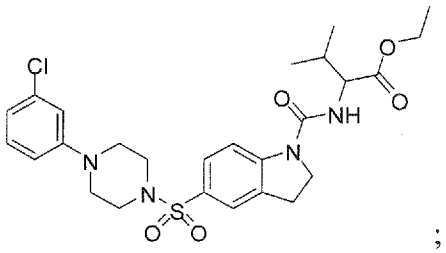
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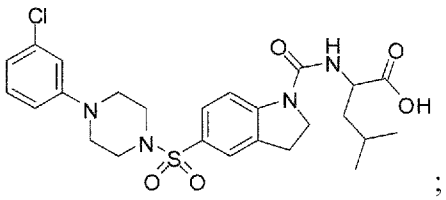
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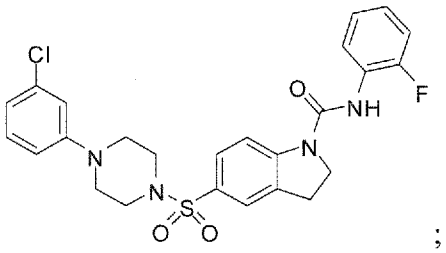
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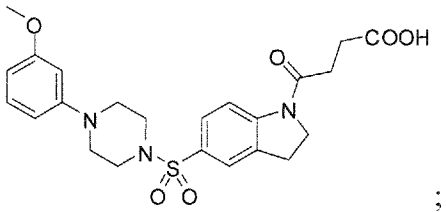
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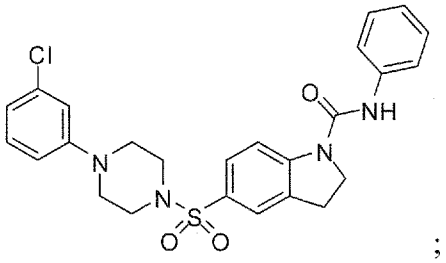
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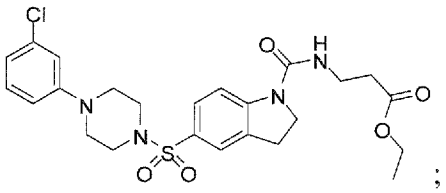
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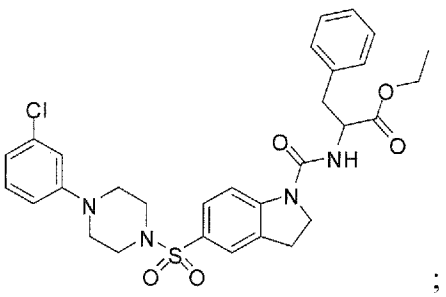
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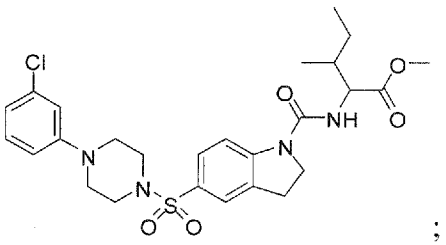
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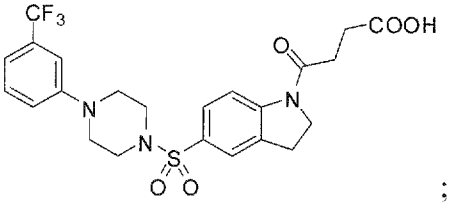
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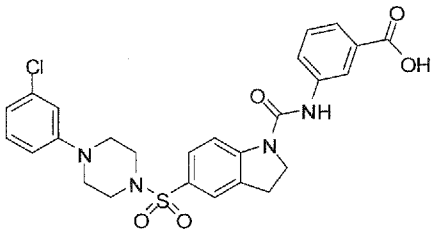
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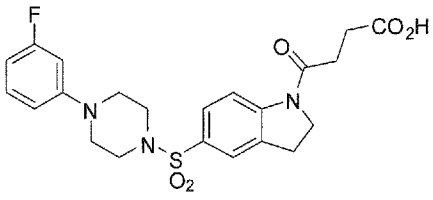
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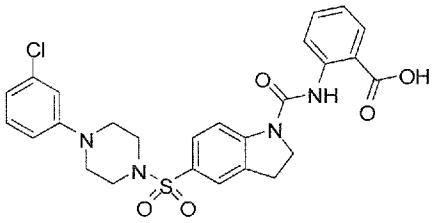
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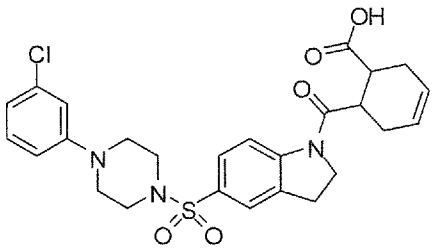
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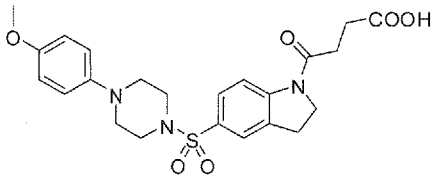
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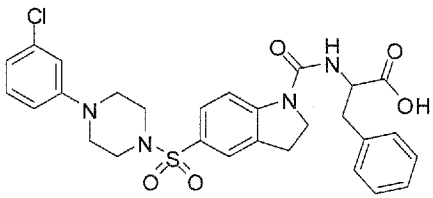
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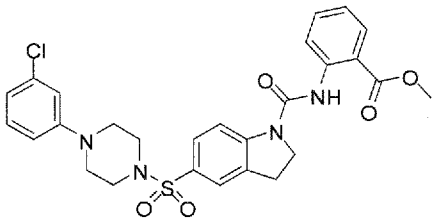
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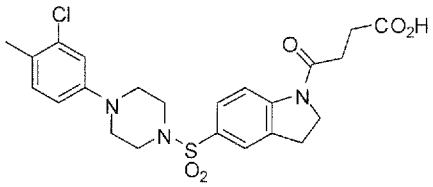
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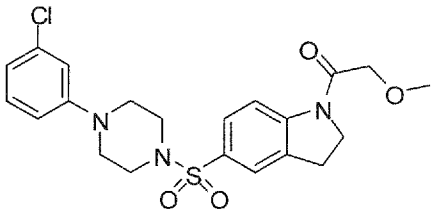
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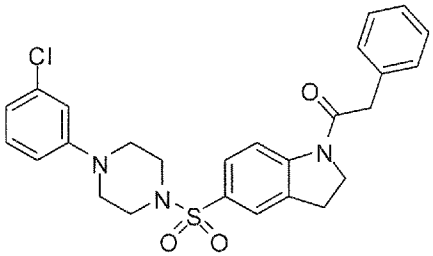
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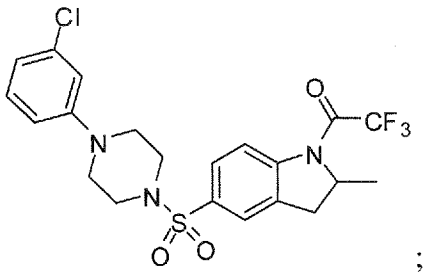

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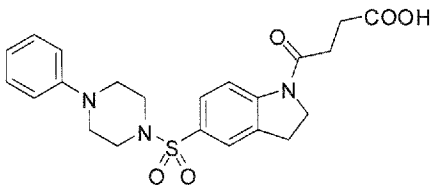

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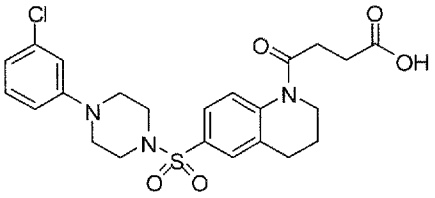

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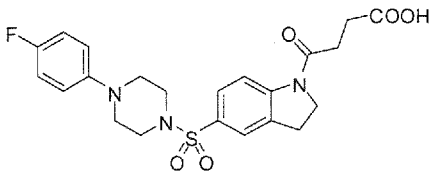

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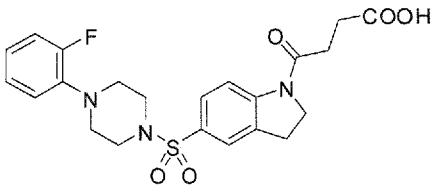

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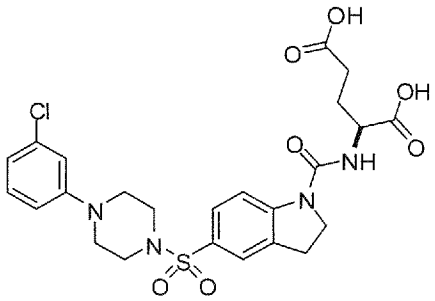

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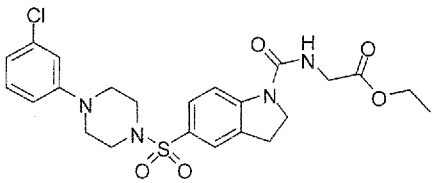

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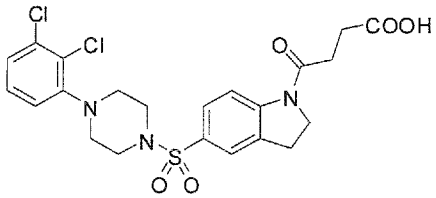


.

10. A composition comprising a compound of any preceding claim and a pharmaceutically acceptable carrier or diluent.

11. A method of treating an oncological disorder in a person or animal, said method comprising administering an effective amount of a compound and/or composition of any preceding claim to the person or animal.

12. The method according to claim 11, wherein the oncological disorder is cancer and/or tumors of the anus, bile duct, bladder, bone, bone marrow, bowel (including colon and

rectum), breast, eye, gall bladder, kidney, mouth, larynx, esophagus, stomach, testis, cervix, head, neck, ovary, lung, mesothelioma, neuroendocrine, penis, skin, spinal cord, thyroid, vagina, vulva, uterus, liver, muscle, pancreas, prostate, blood cells (including lymphocytes and other immune system cells), or brain, or a carcinoma, Karposi's sarcoma, melanoma, mesothelioma, soft tissue sarcoma, pancreatic cancer, lung cancer, leukemia (acute lymphoblastic, acute myeloid, chronic lymphocytic, chronic myeloid, myelomonocytic, and other), lymphoma (Hodgkin's and non-Hodgkin's), or multiple myeloma.

13. A method of treating a person or animal having a condition or disorder associated with aberrant or excessive Shp2 activity, or a mutation in Shp2, in a cell, said method comprising administering an effective amount or a compound of any of claims 1 to 9 and/or a composition of claim 10 to the person or animal.

14. The method of claim 13, wherein the condition or disorder is Noonan syndrome or LEOPARD syndrome.

15. A method of inhibiting Shp2 enzymatic activity in a cell, said method comprising contacting a cell with an effective amount of a compound of any of claims 1 to 9 and/or a composition of claim 10.

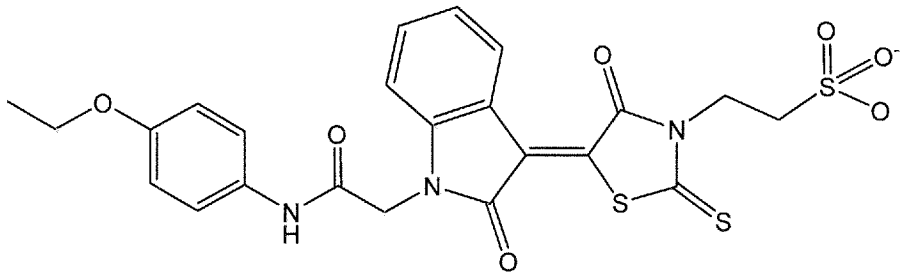
16. The method according to claim 15, wherein the cell is human or mammalian cell.

17. The method according to claim 15, wherein the cell is a cancer cell or tumor cell.

18. The method according to claim 15, wherein the cell exhibits abnormal proliferation, survival, migration, or differentiation.

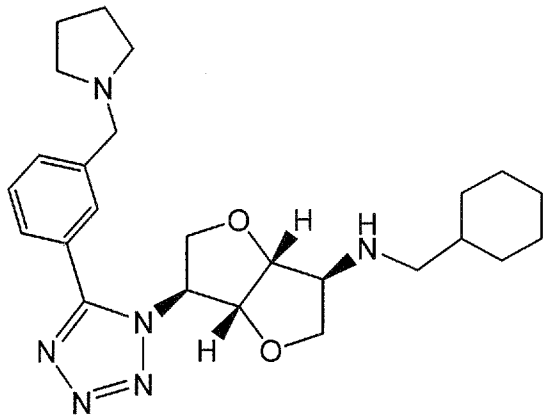
19. The method according to claim 15, wherein the cell constitutively expresses or expresses elevated or abnormal levels of a Shp2 or a mutated Shp2.

20. A kit comprising in one or more containers a compound of any of claims 1 to 9 and/or a composition of claim 10.



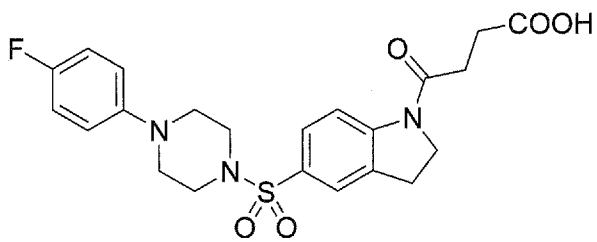
CDL 4340-0580
IC_{50} (Shp2) : 2.2 μM

FIG. 1A



NAT6-297775
IC_{50} (Shp2) : 2.5 μM

FIG. 1B



XW2-011B: IC_{50} 47.8 μM

FIG. 2