Title: TRICYCLIC COMPOUND DERIVATIVES USEFUL IN THE TREATMENT OF NEOPLASTIC DISEASES, INFLAMMATORY DISORDERS AND IMMUNOMODULATORY DISORDERS

Abstract: Provided are compounds of formula (I) or a stereoisomer, tautomer, salt, hydrate or prodrug thereof, capable of modulating tyrosine kinases, compositions comprising the compounds and methods of their use.
Provided are compounds of formula (I):

Formula (1)

or a stereoisomer, tautomer, salt, hydrate or prodrug thereof, capable of modulating tyrosine kinases, compositions comprising the compounds and methods of their use.
TRICYCLIC COMPOUND DERIVATIVES USEFUL IN THE TREATMENT OF
NEOPLASTIC DISEASES, INFLAMMATORY DISORDERS AND
IMMUNOMODULATORY DISORDERS

1. FIELD

Provided are compounds that modulate tyrosine kinase activity, compositions that comprise the compounds and methods of using the compounds for the treatment or prevention of diseases or conditions that are characterized by tyrosine kinase activity or expression.

2. BACKGROUND

According to the latest American Cancer Society’s annual statistical report, released in January 2005, cancer has edged out heart disease as the leading cause of death in Americans under age 85. In 2002, the most recent year for which information is available, 476,009 Americans under 85 died of cancer compared with 450,637 who died of heart disease (those under 85 comprise 98.4 percent of the US population). Protein tyrosine kinases (PTK), which historically represented the majority of first discovered oncogenes, remain today one of the most important classes of oncology drug targets.

Protein kinases are enzymes which covalently modify proteins and peptides by the attachment of a phosphate group to one or more sites on the protein or peptide (for example, PTK phosphorylate tyrosine groups). The measurement of protein kinase activity is important since studies have shown that these enzymes are key regulators of many cell functions.

Over 500 protein kinases have been identified in the human genome ("kinome") (Manning et al. (2002) Science. 298:1912). Based on the recent advances in deciphering the human genome, the family of human PTK consists of approximately 90 members (Blume-Jensen and Hunter (2001) Nature, 411: 355-365; Robinson et al. (2000) Oncogene 19:5548-5557). This family can be divided in two major groups-receptor tyrosine kinases (RTK) and cytoplasmic (or non-receptor) tyrosine kinases (CTK)- and approximately 30 subfamilies based on structural similarity (see, e.g., Bolen et al. (1992) FASEB J. 6:3403-3409 (1992); Ullrich and Schlessinger (1990) Cell 61:203-212; Ihle (1995) Sem. Immunol. 7:247-254. PTKs are involved in regulation of many cellular processes, such as cell proliferation, survival and apoptosis. Enhanced activity of PTKs has been implicated in a variety of malignant and nonmalignant proliferative diseases. In addition, PTKs play a central role in the regulation of cells of the immune system. PTK inhibitors can thus impact a
wide variety of oncologic and immunologic disorders. Such disorders may be ameliorated by selective inhibition of a certain receptor or non-receptor PTK, such as LCK, or due to the homology among PTK classes, by inhibition of more than one PTK by an inhibitor.

In some forms of cancer, a PTK mutation or structural alteration can increase the ability to proliferate, and thus, provides an advantage over surrounding cells. PTK of growth factor receptors, for instance, have been shown to be involved in the transformation of normal to cancerous cells (see, e.g., Rao (1996) Curr. Opin. Oncol. 8:516-524). PTK also play a role in the regulation of apoptosis or programmed cell death (see, e.g., Anderson (1997) Microbiol. Rev. 61:33). By activation of PTK, apoptosis mechanisms can be shut off and the elimination of cancerous cells is prevented. Thus, PTK exert their oncogenic effects via a number of mechanisms such as driving proliferation and cell motility and invasion. These PTK include HER2, BCR-ABL, SRC, and IGFR.

There are many ways that a PTK can become oncogenic. For example, mutations (such as gain-of-function mutations) or small deletions in RTK and/or CTK are known to be associated with several malignancies (e.g., KIT/SCFR, EGFR/ERBB1, CSF-IR, FGFR1, FGFR3, HGFR, RET). Additionally, overexpression of certain types of PTK resulting, for example, from gene amplification has been shown to be associated with several common cancers in humans (e.g., EGFR/ERBB1, ERBB2/HER2/NEU, ERBB3/HER3, ERBB4/HER4, CSF-IR, PDGFR, FLK2/FLT3, FLT4/VEGFR3, FGFR1, FGFR2/K-SAM, FGFR4, HGFR, RON, EPHA2, PEHB2, EPHB4, AXL, TIE/TIE1). For a review of oncogenic kinase signaling, and mutated kinase genes that may be used in the systems and methods provided herein, see Blume-Jensen and Hunter (2001) Nature 411:355; Tibes et al (2005) Annu. Rev. Pharmacol. ToxicolA5:357; Gschwind (2004) Nature Reviews 4:361; Paul and Mukhopadhay (2004) Int. J. Med. Sci (2004) 1:101.

The majority of PTKs are believed to be important drug targets, especially for anti-cancer therapy. Indeed, a very large proportion of known PTKs have been shown to be hyperactivated in cancer cells due to overexpression or constitutively activating mutations and to directly drive tumor growth. In addition, a subset of RTKs, such as vascular endothelial growth factor receptors (VEGFR), fibroblast growth factor receptors (FGFR) and some ephrin receptor (EPH) family members, is involved in driving angiogenesis while others (e.g., Met and discoidin domain receptor (DDR)) promote cell motility and invasion (e.g., metastasis).

due to edema and hemorrhage (Sato, et al, Nature 376:70-74 (1995)). The TEK pathway seems to be involved in maturation steps and promotes interactions between the endothelium and surrounding vessel wall components (Suri et al, supra; and Vikkula et al, Cell 87:1 181-1190 (1996)).

The EPH tyrosine kinase subfamily appears to be the largest subfamily of transmembrane RTK (Pasquale et al, Curr. Opin. Cell Biol 9:608-615 (1997); and Orioli and Klein, Trends in Genetics 13:354-359 (1997)). Ephrins and their EPH receptors govern proper cell migration and positioning during neural development, presumably through modulating intercellular repulsion (Pasquale, supra; Orioli and Klein, supra). Bidirectional signaling has been observed for some Ephrin-B/EPHB ligand/receptor pairs (Holland et al, Nature 383:722-725 (1996); and Bruckner et al, Science 275:1640-1643 (1997)). For example, Ephrin-Al and Ephrin-B1 have been-proposed to have angiogenic properties (Pandey et al, Science 268:567-569 (1995); and Stein et al, Genes Dev. 12:667-678 (1998)). Ephrin-B2, a ligand for EPHB4 receptor, was recently reported to mark the arterial compartment during early angiogenesis, and mice that lack Ephrin-B2 showed severe anomalies in capillary bed formation (Wang et al, Cell 93: 741-753 (1998)).

It is known that some compounds possess an ability to inhibit a tyrosine kinase activity. In particular, WO 2004 discloses imidazole and pyridin derivatives as tyrosine kinase inhibitors.

Thus, modulating tyrosine kinase activity by chemical compounds represents a rational, targeted approach to cancer therapy. Additionally, because tyrosine kinases have a number of other diverse biological functions, such as regulation of metabolism, cell differentiation, inflammation, immune responses, and tissue morphogenesis, kinases are attractive for drug development outside oncology.

3. SUMMARY

Provided are compounds that modulate tyrosine kinase activity, compositions that comprise the compounds and methods of using the compounds for the treatment or prevention of diseases or conditions that are characterized by tyrosine kinase activity or expression including, for example, cancer, diabetes, restenosis, arteriosclerosis, psoriasis, angiogenic diseases and immunologic disorders, (see, e.g., Powis et al, 1994, Anti-Cancer Drugs Design 9: 263-277; Merenmies et al, 1997, Cell Growth Differ 8: 3-10; Shawver et al, 1997, Drug Discovery Today 2:50-63; the contents of each are hereby incorporated by reference in their entireties). The compounds provided herein are described below in detail.
Provided are compounds according to formula (1), or a stereoisomer, tautomer, salt, hydrate or prodrug thereof:

**Formula (1)**

wherein \( X^1, X^2, X^3, X^4, X^5, X^6, W^1, W^2, W^3, W^4, W^5, W^6, Y^1, Y^2 \) and \( R^1 \) are as defined below. In the description below, all combinations of the recitations for \( X^1, X^2, X^3, X^4, X^5, X^6, W^1, W^2, W^3, W^4, W^5, W^6, Y^1, Y^2 \) and \( R^1 \) are within the scope of this disclosure. Other embodiments are set forth below.

3.1. Definitions

When describing the compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms have the following meanings unless otherwise indicated. When two terms referring to chemical groups are combined, the combined term refers to the groups covalently linked in either orientation, unless specified otherwise. For instance, the term "acylamino" can refer to either "-C(O)-N(R)-" or to "-N(R)-C(O)-" unless specified otherwise and similarly sulfonamido or aminosulfonyl can refer to either -S(Oi)-N(R)- or -N(R)-S(O\(_2\))-.

"Acyl" refers to a radical -C(O)R, where \( R \) is hydrogen, alkyl, cycloalkyl, cycloheteroalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl as defined herein. Representative examples include, but are not limited to, formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl, benzylcarbonyl and the like.

"Aliphatic" refers to hydrocarbyl organic compounds or groups characterized by a straight, branched or cyclic arrangement of the constituent carbon atoms and an absence of aromatic unsaturation. Aliphatics include, without limitation, alkyl, alkylenle, alkenyl, alkenylene, alkynyl and alkynylene. Aliphatic groups typically have from 1 or 2 to about 12 carbon atoms.
"Alkyl" refers to monovalent saturated aliphatic hydrocarbyl groups, in one embodiment having up to about 11 carbon atoms, in another embodiment, as a lower alkyl, from 1 to 8 carbon atoms, and in yet another embodiment, from 1 to 6 carbon atoms. The hydrocarbon chain may be either straight-chained or branched. This term is exemplified by groups such as methyl, ethyl, t-propyl, isopropyl, n-butyl, wo-butyl, tert-butyl, 7-hexyl, n-octyl, tert-octyl and the like. The term "lower alkyl" refers to alkyl groups having 1 to 6 carbon atoms. The term "alkyl" also includes "cycloalkyl" as defined below.

"Substituted alkyl" includes those groups recited in the definition of "substituted" herein, and in one embodiment refers to an alkyl group having 1 or more substituents, in another embodiment, from 1 to 5 substituents, and yet in another embodiment, from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, substituted alkoxy, alkoxy carbonyl, alkoxy carbamylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarboxyloxy, aryl, arlyloxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, heteroaryl, keto, nitro, alklythio, substituted alklythio, arylthio, thioketo, thiol, alkyl-S(O)\(^{-}\), aryl-S(O)\(^{-}\), alkyl-S(O)\(_2\)\(^{-}\), and aryl-S(O)\(_2\)\(^{-}\).

"Alkylene" refers to divalent saturated aliphatic hydrocarbyl groups in one embodiment having up to about 11 carbon atoms and in another embodiment having 1 to 6 carbon atoms which can be straight-chained or branched. This term is exemplified by groups such as methylene (-CH\(_2\)-), ethylene (-CH\(_2\)CH\(_2\)-), the propylene isomers (e.g., -CH\(_2\)CH\(_2\)CH\(_2\)- and -CH(CH\(_3\))CH\(_2\)-) and the like.

"Substituted alkenylene" includes those groups recited in the definition of "substituted" herein, and particularly refers to an alkenylene group having in one embodiment 1 or more substituents, in another embodiment from 1 to 5 substituents, and in yet another embodiment from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, substituted alkoxy, alkoxy carbonyl, alkoxy carbamylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarboxyloxy, aryl, arlyloxy, azido, carboxyl, cyano, halogen, hydroxyl, keto, nitro, alklythio, substituted alklythio, arylthio, thioketo, thiol, alkyl-S(O)\(^{-}\), aryl-S(O)\(^{-}\), alkyl-S(O)\(_2\)\(^{-}\) and aryl-S(O)\(_2\)\(^{-}\).

"Alkenyl" refers to monovalent olefinically unsaturated hydrocarbyl groups having in one embodiment up to about 11 carbon atoms, in another embodiment from 2 to 8 carbon atoms, and in yet another embodiment from 2 to 6 carbon atoms, which can be straight-chained or branched and having at least 1 and particularly from 1 to 2 sites of olefinic
unsaturation. Particular alkenyl groups include ethenyl (–CH=CH₂), 1-propenyl (–CH₂CH=CH₂), isopropenyl (–C(CH₃)=CH₂), vinyl and substituted vinyl, and the like.

"Substituted alkenyl" includes those groups recited in the definition of "substituted" herein, and particularly refers to an alkenyl group having in one embodiment 1 or more substituents, in another embodiment from 1 to 5 substituents, and in yet another embodiment from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, substituted alkoxy, alkoxy carbonyl, alkoxy carbonylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarboxyloxy, aryl, aryloxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, keto, nitro, alkylthio, substituted alkylthio, arylthio, thioketo, thiol, alkyl-S(O)-, aryl-S(O)-, alkyl-S(O)₂⁻, and aryl-S(O)₂⁻.

"Alkenylene" refers to divalent olefinically unsaturated hydrocarbyl groups particularly having in one embodiment up to about 11 carbon atoms and in another embodiment 2 to 6 carbon atoms which can be straight-chained or branched and having at least 1 and particularly from 1 to 2 sites of olefinic unsaturation. This term is exemplified by groups such as ethenylene (-CH=CH-), the propylene isomers (e.g., -CH=CHCH₂- and -C(CH₃)=CH- and -CH=C(CH₃)-) and the like.

"Alkynyl" refers to acetylenically unsaturated hydrocarbyl groups particularly having in one embodiment up to about 11 carbon atoms and in another embodiment 2 to 6 carbon atoms which can be straight-chained or branched and having at least 1 and particularly from 1 to 2 sites of alkynyl unsaturation. Particular non-limiting examples of alkynyl groups include acetylenic, ethynyl (-C≡CH), propargyl (-CH₂C≡CH), and the like.

"Substituted alkynyl" includes those groups recited in the definition of "substituted" herein, and particularly refers to an alkynyl group having in one embodiment 1 or more substituents, in another embodiment from 1 to 5 substituents, and in yet another embodiment from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, substituted alkoxy, alkoxy carbonyl, alkoxy carbonylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarboxyloxy, aryl, aryloxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, keto, nitro, alkylthio, substituted alkylthio, arylthio, thioketo, thiol, alkyl-S(O)-, aryl-S(O)-, alkyl-S(O)₂⁻, and aryl-S(O)₂⁻.

"Alkanoyl" as used herein, which can include "acyl", refers to the group R-C(O)-, where R is hydrogen or alkyl as defined above.
"Alkoxy" refers to the group -OR where R is alkyl. Particular alkoxy groups include, by way of example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hексoxy, 1,2-dimethylbutoxy, and the like.

"Substituted alkoxy" includes those groups recited in the definition of "substituted" herein, and particularly refers to an alkoxy group having in one embodiment 1 or more substituents, in another embodiment from 1 to 5 substituents, and in yet another embodiment from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, substituted alkoxy, alkoxy carbonyl, alkoxy carbonylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarboxyloxy, aryl, arloxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, heteroaryl, hydroxyl, keto, nitro, alkylthio, substituted alkylthio, arylthio, thioketo, thiol, alkyl-S(O)-, aryl-S(O)-, alkyl-S(O)₂- and aryl-S(O)₂-.

"Heteroalkyl" refers to an alkyl chain as specified above, having one or more heteroatoms selected from O, S, or N.

"Aryl" refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, groups derived from acenaphthylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, 6-indacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene and the like. Particularly, an aryl group comprises from 6 to 14 carbon atoms.

"Substituted Aryl" includes those groups recited in the definition of "substituted" herein, and particularly refers to an aryl group that may optionally be substituted in one embodiment with 1 or more substituents, in another embodiment from 1 to 5 substituents, and in yet another embodiment from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkoxy carbonyl, alkyl, substituted alkyl, alkynyl, substituted alkynyl, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarboxyloxy, aryl, aryloxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, nitro, alkylthio, substituted alkylthio, arylthio, thiol, alkyl-S(O)-, aryl-S(O)-, alkyl-S(O)_2- and aryl-S(O)_2-.
"Fused Aryl" refers to an aryl having two of its ring carbon in common with a second aryl ring or with an aliphatic ring. In certain embodiments, a bicyclic compound of the invention comprises a fused aryl.

"Amino" refers to the radical -NH₂.

"Substituted amino" includes those groups recited in the definition of "substituted" herein, and particularly refers to the group -N(R)₂ where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted cycloalkyl, and where both R groups are joined to form an alkylene group. When both R groups are hydrogen, -N(R)₂ is an amino group.

"Azido" refers to the radical -N₃.

"Carbamoyl" refers to the radical -C(O)N(R)₂ where each R group is independently hydrogen, alkyl, cycloalkyl or aryl, as defined herein, which may be optionally substituted as defined herein.

"Carboxy" refers to the radical -C(O)OH.

"Cycloalkyl" refers to cyclic hydrocarbyl groups having from 3 to about 10 carbon atoms and having a single cyclic ring or multiple condensed rings, including fused and bridged ring systems, which optionally can be substituted with from 1 to 3 alkyl groups. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, 1-methylcyclopropyl, 2-methylcyclopentyl, 2-methylcyclooctyl, and the like, and multiple ring structures such as adamantanyl, and the like.

"Substituted cycloalkyl" includes those groups recited in the definition of "substituted" herein, and particularly refers to a cycloalkyl group having in one embodiment 1 or more substituents, in another embodiment from 1 to 5 substituents, and in yet another embodiment from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, substituted alkoxy, alkoxy carbonyl, alkoxy carbonylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, aryl, arlyloxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, keto, nitro, alkylthio, substituted alkylthio, arylthio, thioketo, thiol, alkyl-S(O)-, aryl-S(O)-, alkyl-S(O)₂- and aryl-S(O)₂-.

"Cycloalkoxy" refers to the group -OR where R is cycloalkyl. Such cycloalkoxy groups include, by way of example, cyclopentoxy, cyclohexoxy and the like.
"Cycloalkenyl" refers to cyclic hydrocarbyl groups having from 3 to 10 carbon atoms and having a single cyclic ring or multiple condensed rings, including fused and bridged ring systems and having at least one and particularly from 1 to 2 sites of olefinic unsaturation. Such cycloalkenyl groups include, by way of example, single ring structures such as cyclohexenyl, cyclopentenyl, cyclopropenyl, and the like.

"Substituted cycloalkenyl" includes those groups recited in the definition of "substituted" herein, and particularly refers to a cycloalkenyl group having in one embodiment 1 or more substituents, in another embodiment from 1 to 5 substituents, and in yet another embodiment from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, substituted alkoxy, alkoxy carbonyl, alkoxy carbonylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarboxyloxy, aryl, aryloxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, keto, nitro, alkylthio, substituted alkylthio, arylthio, thioketo, thiol, alkyl-S(O)-, aryl-S(O)-, alkyl-S(O)₂ and aryl-S(O)₂.

"Fused Cycloalkenyl" refers to a cycloalkenyl having two of its ring carbon atoms in common with a second aliphatic or aromatic ring and having its olefinic unsaturation located to impart aromaticity to the cycloalkenyl ring.

"Cyanato" refers to the radical -OCN.

"Cyano" refers to the radical -CN.

"Dialkylamino" means a radical -NRR' where R and R' independently represent an alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cyclo hetero alkyl, substituted cyclo hetero alkyl, hetero aryl, or substituted hetero aryl group as defined herein.

"Ethenyl" refers to substituted or unsubstituted -(C≡C)-.

"Ethylene" refers to substituted or unsubstituted -(C-C)-.

"Ethynyl" refers to -(C≡C)-.

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo. Particular halo groups are either fluoro or chloro.

"Hydroxy" refers to the radical -OH.

"Nitro" refers to the radical -NO₂.

"Hetero" when used to describe a compound or a group present on a compound means that one or more carbon atoms in the compound or group have been replaced by a nitrogen, oxygen, or sulfur heteroatom. Hetero may be applied to any of the
hydrocarbyl groups described above such as alkyl, e.g. heteroalkyl, cycloalkyl, e.g. 
cycloheteroalkyl, aryl, e.g. heteroaryl, cycloalkenyl, cycloheteroalkenyl, and the like having 
from 1 to 5, and especially from 1 to 3 heteroatoms.

"Heteroaryl" or "heteroaromatic" refers to a monovalent heteroaromatic group 
derived by the removal of one hydrogen atom from a single atom of a parent heteroaromatic 
ring system. Typical heteroaryl groups include, but are not limited to, groups derived from 
acridine, arsindole, carbazole, β-carboline, chromane, chromene, cinnoline, furan, imidazole, 
indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, 
isoquinoline, tetrahydroisoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, 
oxazole, perimidinide, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, 
purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, 
quinazoline, quinoline, tetrahydroquinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, 
thiazole, thiophene, triazole, xanthene, and the like. Particularly, heteroaryl can include other 
saturated ring systems, and can therefore be derived from indoline, indolizine, 
tetrahydroquinoline, and tetrahydroisoquinoline. In certain embodiments, the heteroaryl 
group is between 5-20 membered heteroaryl, with 5-10 membered heteroaryl being useful in 
certain embodiments. Particular heteroaryl groups are those derived from thiophene, pyrrole, 
benzothiophene, benzofuran, indole, pyridine, pyrimidine, quinoline, tetrahydroquinoline, 
isouquinoline, tetrahydroisoquinoline, imidazole, oxazole and pyrazine.

As used herein, the term "cycloheteroalkyl" refers to a stable heterocyclic non-
aromatic ring and fused rings containing one or more heteroatoms independently selected 
from N, O and S. A fused heterocyclic ring system may include carbocyclic rings and need 
only include one heterocyclic ring. Examples of heterocyclic rings include, but are not 
limited to, piperazinyl, homopiperazinyl, piperidinyl and morpholinyl.

"Sulfanyl" refers to the radical HS-. "Substituted sulfanyl" refers to a radical 
such as RS- wherein R is any substituent described herein. In certain embodiments, 
"substituted sulfanyl" refers to a radical -SR where R is an alkyl or cycloalkyl group as 
defined herein that may be optionally substituted as defined herein. Alkylthio or arylthio 
refer to the above sulfanyl group. Representative examples include, but are not limited to, 
methylthio, ethylthio, propylthio, butylthio, phenethylthio and the like.

"Sulfinyl" refers to the radical -S(O)H. "Substituted sulfinyl" refers to a radical 
such as S(O)-R wherein R is any substituent described herein.
"Sulfonyl" refers to the divalent radical -S(O)_2-. "Substituted sulfonyl" refers to a radical such as -S(O)_2-R wherein R is any substituent described herein. "Aminosulfonyl" or "Sulfonamide" refers to the radical H_2N(O)_2S-, and "substituted aminosulfonyl" or "substituted sulfonamide" refers to a radical such as R_2N(O)_2S- wherein each R is independently any substituent described herein. In particular embodiments, R is selected from H, lower alkyl, alkyl, aryl and heteroaryl.

One having ordinary skill in the art of organic synthesis will recognize that the maximum number of heteroatoms in a stable, chemically feasible heterocyclic ring, whether it is aromatic or non aromatic, is determined by the size of the ring, the degree of unsaturation and the valence of the heteroatoms. In general, a heterocyclic ring may have one to four heteroatoms as long as the heteroaromatic ring is chemically feasible and stable.

"Pharmaceutically acceptable salt" refers to any salt of a compound of this invention which retains its biological properties and which is not toxic or otherwise undesirable for pharmaceutical use. Such salts may be derived from a variety of organic and inorganic counter-ions well known in the art and include. Such salts include: (1) acid addition salts formed with organic or inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, sulfamic, acetic, trifluoroacetic, trichloroacetic, propionic, hexanoic, cyclopentylpropionic, glycolic, glutaric, pyruvic, lactic, malonic, succinic, sorbic, ascorbic, malic, maleic, fumaric, tartaric, citric, benzoic, 3-(4-hydroxybenzoyl)benzoic, picric, cinnamic, mandelic, phthalic, lauric, methanesulfonic, ethanesulfonic, 1,2-ethane-disulfonic, 2-hydroxyethanesulfonic, benzenesulfonic, 4-chlorobenzenesulfonic, 2-napthalenesulfonic, 4-toluencesulfonic, camphoric, camphorsulfonic, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic, glucoheptonic, 3-phenylpropionic, trimethylacetic, tert-butylacetic, lauryl sulfuric, gluconic, benzoic, glutamic, hydroxynaphthoic, salicylic, stearic, cyclohexylsulfamic, quinic, muconic acid and the like acids; or (2) salts formed when an acidic proton present in the parent compound either (a) is replaced by a metal ion, e.g.; an alkali metal ion, an alkaline earth ion or an aluminum ion, or alkali metal or alkaline earth metal hydroxides, such as sodium, potassium, calcium, magnesium, aluminum, lithium, zinc, and barium hydroxide, ammonia or (b) coordinates with an organic base, such as aliphatic, alicyclic, or aromatic organic amines, such as ammonia, methylamine, dimethylamine, diethylamine, picoline, ethanolamine, diethanolamine, triethanolamine, ethylenediamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylene-diamine, chlorprocaine,
diethanolamine, procaine, N-benzylphenethylamine, jV-methylglucamine piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, and the like.

Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium and the like, and when the compound contains a basic functionality, salts of non-toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, besylate, acetate, maleate, oxalate and the like. The term "physiologically acceptable cation" refers to a non-toxic, physiologically acceptable cationic counterion of an acidic functional group. Such cations are exemplified by sodium, potassium, calcium, magnesium, ammonium and tetraalkylammonium cations and the like.

"Solvate" refers to a compound of the present invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate.

It is to be understood that compounds having the same molecular formula but differing in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers".

Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, when it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is designated (R) or (S) according to the rules of Cahn and Prelog (Cahn et al. 1966, Angew. Chem. 78:413-447, Angew. Chem., Int. Ed. Engl. 5:385-414 (errata: Angew. Chem., Int. Ed. Engl. 5:51 1); Prelog and Helmchen , 1982, Angew. Chem. 94:614-631, Angew. Chem. Internal Ed. Eng. 21:567-583; Mata and Lobo, 1993, Tetrahedron: Asymmetry 4:657-668) or can be characterized by the manner in which the molecule rotates the plane of polarized light and is designated dextrorotatory or levorotatory (i.e., as (+)- or (-)-isomers, respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of enantiomers is called a "racemic mixture".

In certain embodiments, the compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as the individual (R)- or (S)-enantiomer or as a mixture thereof. Unless indicated otherwise, for example by designation of stereochemistry at any position of a formula, the description or naming of a
particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. Methods for determination of stereochemistry and separation of stereoisomers are well-known in the art. In particular embodiments, the present invention provides the stereoisomers of the compounds depicted herein upon use of stereoisomerically pure intermediates in their synthesis, such as pure enantiomers, or diastereomers as building blocks, prepared by chiral synthesis methodologies, or resolution by formation of diastereomeric salts with chiral acid or base and their separation, or separation by means of chromatography, including using chiral stationary phase. The racemic, or diastereomeric mixtures of embodiments (compounds) in this invention can also be separated by means of chromatography, including chiral stationary phase chromatography.

In certain embodiments, the compounds of the invention are "stereochemically pure." A stereochemically pure compound has a level of stereochemical purity that would be recognized as "pure" by those of skill in the art. Of course, this level of purity will be less than 100%. In certain embodiments, "stereochemically pure" designates a compound that is substantially free of alternate isomers. In particular embodiments, the compound is 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or 99.9% free of other isomers.

As used herein, the terms "disorder" and "disease" are used interchangeably to refer to a condition in a subject. Certain conditions may be characterized as more than one disorder. For example, certain conditions may be characterized as both non-cancerous proliferative disorders and inflammatory disorders.

As used herein, the term "effective amount" refers to the amount of a compound of the invention which is sufficient to reduce or ameliorate the severity, duration of a disorder, cause regression of a disorder, prevent the recurrence, development, or onset of one or more symptoms associated with a disorder, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy.

As used herein, the term "in combination" refers to the use of more than one therapies. The use of the term "in combination" does not restrict the order in which therapies (e.g., prophylactic and/or therapeutic agents) are administered to a subject with a disorder. A first therapy can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before),
concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy to a subject with a disorder.

As used herein, the terms "prophylactic agent" and "prophylactic agents" as used refer to any agent(s) which can be used in the prevention of a disorder or one or more symptoms thereof. In certain embodiments, the term "prophylactic agent" refers to a compound of the invention. In certain other embodiments, the term "prophylactic agent" does not refer a compound of the invention. In certain embodiments, a prophylactic agent is an agent which is known to be useful for, or has been or is currently being used to the prevent or impede the onset, development, progression and/or severity of a disorder. Prophylactic agents may be characterized as different agents based upon one or more effects that the agents have in vitro and/or in vivo. For example, an anti-angiogenic agent may also be characterized as an immunomodulatory agent.

As used herein, the terms "prevent," "preventing" and "prevention" refer to the prevention of the recurrence, onset, or development of one or more symptoms of a disorder in a subject resulting from the administration of a therapy, or the administration of a combination of therapies.

As used herein, the phrase "prophylactically effective amount" refers to the amount of a therapy which is sufficient to result in the prevention of the development, recurrence or onset of one or more symptoms associated with a disorder, or to enhance or improve the prophylactic effect(s) of another therapy.

As used herein, the terms "subject" and "patient" are used interchangeably herein. The terms "subject" and "subjects" refer to an animal, in certain embodiments a mammal including a non-primate (e.g., a cow, pig, horse, cat, dog, rat, and mouse) and a primate (e.g., a monkey such as a cynomolgous monkey, a chimpanzee and a human), and more particularly a human. In another embodiment, the subject is a farm animal (e.g., a horse, a cow, a pig, etc.) or a pet (e.g., a dog or a cat). In certain embodiments, the subject is a human.

As used herein, the term "synergistic" refers to a combination of a compound of the invention and another therapy which has been or is currently being used to prevent, manage or treat a disorder, which is more effective than the additive effects of the therapies. A synergistic effect of a combination of therapies permits the use of lower dosages of one or
more of the therapies and/or less frequent administration of said therapies to a subject with a disorder. The ability to utilize lower dosages of a therapy and/or to administer said therapy less frequently reduces the toxicity associated with the administration of said therapy to a subject without reducing the efficacy of said therapy in the prevention, management or treatment of a disorder. In addition, a synergistic effect can result in improved efficacy of agents in the prevention, management or treatment of a disorder. Finally, a synergistic effect of a combination of therapies may avoid or reduce adverse or unwanted side effects associated with the use of either therapy alone.

As used herein, the terms "therapeutic agent" and "therapeutic agents" refer to any agent(s) which can be used in the treatment, management, or amelioration of a disorder or one or more symptoms thereof. In certain embodiments, the term "therapeutic agent" refers to a compound of the invention. In certain other embodiments, the term "therapeutic agent" refers does not refer to a compound of the invention. In certain embodiments, a therapeutic agent is an agent which is known to be useful for, or has been or is currently being used for the treatment, management, prevention, or amelioration a disorder or one or more symptoms thereof. Therapeutic agents may be characterized as different agents based upon one or more effects the agents have in vivo and/or in vitro, for example, an anti-inflammatory agent may also be characterized as an immunomodulatory agent.

As used herein, the term "therapeutically effective amount" refers to that amount of a therapy sufficient to result in the amelioration of one or more symptoms of a disorder, prevent advancement of a disorder, cause regression of a disorder, or to enhance or improve the therapeutic effect(s) of another therapy. In a specific embodiment, with respect to the treatment of cancer, an effective amount refers to the amount of a therapy that inhibits or reduces the proliferation of cancerous cells, inhibits or reduces the spread of tumor cells (metastasis), inhibits or reduces the onset, development or progression of one or more symptoms associated with cancer, or reduces the size of a tumor. In certain embodiments, a therapeutically effective of a therapy reduces the proliferation of cancerous cells or the size of a tumor by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%, relative to a control or placebo such as phosphate buffered saline ("PBS").

As used herein, the terms "therapies" and "therapy" can refer to any protocol(s), method(s), and/or agent(s) that can be used in the prevention, treatment,
management, or amelioration of a disorder or one or more symptoms thereof. In certain embodiments, the terms "therapy" and "therapies" refer to chemotherapy, radiation therapy, hormonal therapy, biological therapy, and/or other therapies useful in the prevention, management, treatment or amelioration of a disorder or one or more symptoms thereof known to one of skill in the art (e.g., skilled medical personnel).

As used herein, the terms "treat", "treatment" and "treating" refer to the reduction or amelioration of the progression, severity and/or duration of a disorder, or the amelioration of one or more symptoms thereof resulting from the administration of one or more therapies.

As used herein, the term "modulation" or "modulating" refers to the alteration of the catalytic activity of a tyrosine kinase. In particular, modulating can refer to the activation or to the inhibition of the tyrosine kinase. The tyrosine kinase can be any tyrosine kinase known to those of skill in the art. In certain embodiments, the tyrosine kinase is a receptor tyrosine kinase or an intracellular tyrosine kinase.

The definitions used herein are according to those generally accepted in the art and those specified herein.

Abbreviations used herein are standard abbreviations used in the art of organic chemistry:

AcOH - acetic acid
TFA - trifluoroacetic acid
DMSO - dimethyl sulfoxide
DCM - dichlomethane
BOC - tert. Butyloxycarbonyl
THF - tetrahydrofuran
p-TOS - p-Toluenesulfonyl
TEA - triethylamine
ETOH - ethanol
MEOH - methanol
DIPEA - diisopropylethylamine

4. DETAILED DESCRIPTION

4.1. Compounds
In one aspect, provided are compounds according to formula (1), or a stereoisomer, tautomer, salt or hydrate thereof:

**Formula (1)**

In formula (1), each W¹ through W⁶ is independently a carbon atom or a nitrogen atom. When any W¹ through W⁶ is N, then the corresponding substituent(s) X¹ through X⁶ is (are) absent.

Compounds according to formula (1) can also be depicted in their respective "keto" form, which under certain conditions may predominate over the corresponding "enol" form. However, all possible tautomers and stereoisomers (such as for example, but not limited to: E and Z, (trans and cis) are incorporated herein. Examples of the tautomers of Formula (1) include, but are not limited to:

In formula (1), each X¹ through X⁵, X⁶ is independently selected from hydrogen, hydroxy, halogen, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted acylamino, optionally substituted sulfonamido, optionally...
substituted ureido, trifluoromethyl, trifluoromethoxy, nitro, cyano, optionally substituted aryl or heteroaryl, aryloxy or heteroaryloxy, arylamino or heteroarylamino (substituted by one or more groups selected from lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, carboxamide, sulfonamide, sulamido, ureido, methylenedioxy, ethylenedioxy, primary, secondary or tertiary amino, mono or dialkyl amido, heterocyclylamiido, optionally substituted heterocyclyl or cycloalkyl, optionally substituted heterocyclylalkyl, heteroalkyl), nitrogen-heterocyclyl, connected either by its nitrogen, or a carbon atom (such as piperazino, homopiperazino, morpholino, thiomorpholino, thiomorpholino-S-oxide, thiomorpholino-S,S-dioxide, pyrrolidino, piperidino, azetidino), nitrogen-heterocyclyl-alkyl, connected either by its nitrogen or a carbon atom (such as piperazinomethyl, piperazinoethyl, homopiperazinomethyl, morpholinomethyl, thiomorpholinomethyl, thiomorpholino-S-oxide-methyl, thiomorpholino-S,S-dioxide-methyl, pyrrolidinomethyl, piperidinoethyl, azetidinomethyl, all optionally substituted by groups selected from hydroxyalkyl, lower alkoxyalkyl, primary, secondary, or tertiary amino-alkyl, lower alkyl cycloalkyl or heterocycloalkyl). Such aryl and heteroaryl groups can be bicyclic in certain embodiments. In the above list, lower alkyl, lower alkoxy, aeyl amino, sulfonamide and ureido can be substituted, for example, with aryl, heteroaryl, cycloalkyl or cycloheteroalkyl.

In certain embodiments, any adjacent pair of X<sup>1</sup> through X<sup>3</sup> can be joined to form a cycloalkyl, cycloheteroalkyl, aryl or heteroaryl ring fused to the ring comprising W<sup>1</sup> through W<sup>3</sup>. Exemplary fused rings include naphthyl, benzidoxolyl, benzofuranyl, benzidoxinyl, dihydrobenzidoxinyl, quinolinyl, and others that will be recognized by those of skill in the art.

In formula (1), X<sup>4</sup> can be selected from hydrogen, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, optionally substituted (alkyl, alkenyl, alkynyl, alkoxy, cycloalkoxy, cycloalkyl, heterocycloalkyl), optionally substituted (aryl, heteroaryl, arylalkyl, heteroaryaryllalkyl, aryloxy, heteroaryloxy, aryalkoxy, heteroaryalkoxy, aeylthio, heteroarylythio, arylsulfonyl, heteroarylsulfonyl, arylsulfoxyl, heteroarylsulfoxyl, arylsulfonfonyl, heteroarylsulfonamido, arylaminosulfonfyl, heteroarylaminosulfonfyl, arylamino, heteroarylamino, aryalkylamino, heteroaryalkylamino), by substituents selected from hydrogen, halogen, hydroxy, amino, cyano, nitro, carboxamido, sulfonamido, alkoxy, amino, lower-alkylamino, di-lower-alkylamino, cycloalkyl, cycloalkylalkyl, cycloalkoxy, cycloalkylalkoxy, trifluoromethyl, trifluoromethoxy, methylenedioxy, ethylenedioxy,
methanesulfonyl, trifluoromethanesulfonyl, dialkylaminoalkyl, dialkylaminoalkoxy, heterocyclyl, heteroalkyl and heterocyclylalkyl.

X^4 is also selected from the following groups:

\[
\begin{array}{c}
\text{N-(CH}_2\text{)}_m\text{R}^2 \\
\text{N-(CH}_2\text{)}_n\text{R}^3
\end{array}
\]

wherein:

\[m = 1 \text{ to } 4, \quad n = 0 \text{ to } 4, \quad p = 1 \text{ to } 5; \quad \text{and } o = 0 \text{ to } 5.\]

R^2 is selected from optionally substituted aryl, or heteroaryl, -(CH_2)_o-aryl, -(CH_2)_o-heteroaryl, -(CH_2)_p-M^1-aryl, -(CH_2)_p-M^1-heteroaryl substituted by a substituent independently selected from a group consisting of hydrogen, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethanesulfonyl, 2,2,2-trifluoroethoxy, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, methylenedioxy, ethylenedioxy, trimethylene, dimethylenedioxy, cyano, nitro, primary, secondary or tertiary amino, such as dimethylamino, carboxamide, sulfonamide, lower alkylsulfonyl, lower alkylsulfanyl, lower alkylthio, lower alkylthioalkyl, lower alkylsulfonylalkyl, optionally substituted aryl or heteroaryl, wherein M^1 is a -(CH_2)- or a heteroatom O, S, or N-R^*; and R^* is selected from hydrogen, hydroxy, lower alkyl, lower alkoxy, acyl, optionally substituted aryl, heteroaryl, alkylsulfonyl or arylsulfonyl;

R^3 is selected from optionally substituted aryl, heteroaryl, -(CH_2)_o-aryl, -(CH_2)_o-heteroaryl, -(CH_2)_p-M^2-aryl, -(CH_2)_p-M^2-heteroaryl, substituted by a substituent independently selected from a group consisting of hydrogen, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethanesulfonyl, 2,2,2-trifluoroethoxy, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, methylenedioxy, ethylenedioxy, trimethylene, dimethylenedioxy, cyano, nitro, primary, secondary or tertiary amino, such as dimethylamino, carboxamide, sulfonamide, lower alkylsulfonyl, lower alkylsulfanyl, lower alkylthio, lower alkylthioalkyl, lower alkylsulfonylalkyl, optionally substituted aryl or heteroaryl, wherein M^2 is a heteroatom O, S, or N-R^**; and

R^** is selected from hydrogen, hydroxy, lower alkyl, lower alkoxy, acyl, optionally substituted aryl, heteroaryl, alkylsulfonyl or arylsulfonyl.

In formula (1), in certain embodiments, each (CH_2)_m or (CH_2)_n can be optionally substituted with one or more groups selected from hydrogen, halogen, hydroxy, carboxamido, lower alkylcarbonyl, hydroxy-lower alkyl, hydroxycycloalkyl, optionally
substituted (primary, secondary or tertiary amino, lower alkoxy, lower alkyl, lower heteroalkyl, cycloalkyl, heterocyclo, heterocycloalkyl, aryl, heteroaryl, aryloxy or heteroaryloxy), by groups selected from halogen, hydroxy, amino, lower alkyl, lower alkoxy, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethanesulfonyl, cyano, nitro, carboxamido, lower alkylthio, lower alkylsulfoxy, lower alkylsulfonyl, arylthio, arylsulfoxy, arylsulfonyl, lower alkylcarbonyl, arylcarbonyl) all groups optionally substituted by groups selected from hydrogen, halogen, lower alkyl, trifluoromethyl, trifluoromethoxy, lower alkoxy, lower alkylthio, hydroxy, sulfonamido, lower acylamino. In certain embodiments the \((\text{CH}_2)^m\) or \((\text{CH}_2)^n\) can form a cyclic structure. In addition, in certain embodiments, one or more methylene of \((\text{CH}_2)^m\) or \((\text{CH}_2)^n\) can be replaced by a heteroatom selected from O, NH or N-lower alkyl and S, where appropriate according to the judgment of one of skill in the art.

In certain embodiments according to formula (1), the substituent \(X^4\) is selected from the following groups:
wherein:

L is selected from O, S, N-R#9;

R#9 is selected from hydrogen, lower alkyl, cycloalkyl, alkenyl, alkynyl, heteroalkyl, heterocyclyl, optionally substituted aryl, heteroaryl, arylalkyl, heteroarylalkyl by groups selected from hydrogen, halogen, lower alkyl, lower alkoxy, trifluoromethyl,
trifluoromethoxy, lower alkylthio, nitro, azido, cyano, amido and ureido; and each X* is independently selected from hydrogen, lower alkyl, halogen, lower alkoxy, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, trifluoromethylthio, azido, cyano, nitro, methylenedioxy, trimethylene and dimethylenedioxy.

In another embodiment in formula (1), X* is selected from the following:

\[ \text{wherein:} \]

- \( X^A \) is hydrogen, halogen, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylsulfonyl, cycloalkylsulfonyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylthio, arylsulfonyl, heteroarythio, heteroarylsulfonyl; trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl, dialkylamino, mimoalkylamino, amino, nitro, cyano;

- \( X^B \) is hydrogen, halogen, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylsulfonyl, cycloalkylsulfonyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylthio, arylsulfonyl, heteroarythio, heteroarylsulfonyl; trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl, dialkylamino, mimoalkylamino, amino, nitro, cyano;

- \( X^C \) is hydrogen, halogen, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylsulfonyl, cycloalkylsulfonyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylthio, arylsulfonyl, heteroarythio, heteroarylsulfonyl; trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl, dialkylamino, mimoalkylamino, amino, nitro, cyano;

- \( X^D \) is hydrogen, halogen, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylsulfonyl, cycloalkylsulfonyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylthio, arylsulfonyl, heteroarythio, heteroarylsulfonyl; trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl, dialkylamino, mimoalkylamino, amino, nitro, cyano;

- \( X^E \) is hydrogen, halogen, optionally substituted alkyl, alkenyl, alkynyl,
cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkyloxysulfanyl, cycloalkylsulfanyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylthio, arylsulfanyl, heteroarylthio, heteroaryloxysulfanyl; trifluoromethyl, trifluoroethoxy, 2,2,2-trifluoroethoxy, heteroalkyl, dialkylamino, monoalkylamino, amino, nitro, cyano;

X*B and X*C or independently X*C and X*D or independently X*D and X*E can form a 5 to 7 membered ring, containing one or two heteroatoms such as oxygen, sulfur or nitrogen, (optionally substituted with a lower alkyl group), such as for example, but not limited to methylenedioxy, ethylenedioxy, propylenedioxy, dimethylenedioxy (dihydrobenzofuran ring), all optionally mono- or di-substituted and their partially, or fully fluorinated derivatives, including difluoromethylenedioxy; and

X*B and X*C or independently X*C and X*D or independently X*D and X*E can form an optionally substituted condensed aromatic or heteroaromatic ring, for example, but not limited to 1- or 2-naphthyl, 4-,5-,6- or 7-indolyl, 4-,5-,6- or 7-benzofuranyl, 4-,5-,6- or 7-thianaphthenyl, carbazolyl by groups selected from lower alkyl, lower alkoxy, halogen, trifluoromethyl, cyano, or nitro.

In another embodiment in formula (1), X⁴ is selected from the following:

![Diagram](attachment://diagram.png)

wherein:

X*A is lower alkyl, halogen, trifluoromethyl, trifluoroethoxy;
X*B is hydrogen, lower alkyl, halogen, lower alkoxy, trifluoromethyl, trifluoroethoxy, cyano, nitro, dimethylamino, diethylamino;
X*C is hydrogen, lower alkyl, halogen, lower alkoxy, trifluoromethyl, trifluoroethoxy, cyano, nitro, dimethylamino, diethylamino;
X*D is hydrogen, lower alkyl, halogen, lower alkoxy, trifluoromethyl, trifluoroethoxy, cyano, nitro, dimethylamino, diethylamino;
X*E is hydrogen, lower alkyl, halogen, lower alkoxy, trifluoromethyl, trifluoroethoxy, cyano, nitro, dimethylamino, diethylamino;
X*B and X*C or independently X*C and X*D or independently X*D and X*E can form a 5 to 7 membered ring, containing one or two heteroatoms such as oxygen, sulfur or nitrogen, (optionally substituted with a lower alkyl group), such as for example, but not limited to methylenedioxy, ethylenedioxy, propylenedioxy, dimethyleneoxy (dihydrobenzofuran ring), all optionally mono- or di-substituted and their partially, or fully fluorinated derivatives, including difluromethylenedioxy; and

X*B and X*C or independently X*C and X*D or independently X*D and X*E can form an optionally substituted condensed aromatic or heteroaromatic ring, for example, but not limited to 1- or 2-naphthyl, 4-,5,-6- or 7-indolyl, 4-,5,-6- or 7-benzofuranyl, 4-,5,-6- or 7-thianaphthenyl, carbazolyl by groups selected from lower alkyl, lower alkoxy, halogen, trifluoromethyl, cyano, or nitro.

In another embodiment in formula (1), each W\(^1\) through W\(^6\) is independently selected from carbon or nitrogen.

In another embodiment in formula (1), Y\(^1\) is independently selected from:

\[
\begin{align*}
\text{(CH}_2\text{)}_q & \quad \text{O} \quad \text{S} \quad \text{N}^{\text{R#10}} \quad \text{SO} \quad \text{F} \quad \text{F} \\
\end{align*}
\]

wherein:

- q is an integer from 0 to 4; and
- R#io is selected from hydrogen, lower alkyl, hydroxy and lower alkoxy.

In formula (1), in certain embodiments, each \((\text{CH}_2\text{)}_q\) can be optionally substituted with one or more groups selected from hydrogen, lower alkyl, heteroalkyl, heterocyclo, hydroxy-lower alkyl, cycloalkyl, hydroxycycloalkyl. In certain embodiments, such substituents can be joined to form a cyclic structure. In certain embodiments, one or more of the methylene groups of \((\text{CH}_2\text{)}_q\) can be replaced by a carbonyl group (C=O).

In yet another embodiment in formula (1), Y\(^1\) is independently selected from:

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\end{align*}
\]

In another embodiment in formula (1), Y\(^2\) is independently selected from:

\[
\begin{align*}
\text{(CH}_2\text{)}_r & \quad \text{O} \quad \text{S} \quad \text{N}^{\text{R#11}} \quad \text{SO} \quad \text{F} \quad \text{F} \\
\end{align*}
\]
wherein:

\[ r \] is an integer from 0 to 4; and

\[ R_{\#ii} \] is selected from hydrogen, lower alkyl, hydroxy and lower alkoxy.

In formula (1), in certain embodiments, each \((CH_2)_r\) can be optionally substituted with one or more groups selected from hydrogen, lower alkyl, heteroalkyl, heterocyclo, hydroxy-lower alkyl, cycloalkyl, hydroxycycloalkyl. In certain embodiments, such substituents can be joined to form a cyclic structure. In certain embodiments, one or more of the methylene groups of \((CH_2)_r\) can be replaced by a carbonyl group \((C=O)\).

In yet another embodiment in formula (1), \(Y^2\) is independently selected from:

\[
\begin{align*}
&\text{H} \\
&\text{O}
\end{align*}
\]

In another embodiment in formula (1), \(R^1\) is independently selected from optionally substituted heterocyclyl, heterocyclylalkyl, heteroaryllalkyl, heterocyclyloxyalkyl, heteroalkyl, heterocyclylaminoalkyl, aminoalkyl, lower alkylaminoalkyl, di-(lower alkyl)-aminoalkyl, aminocycloalkyl, alkylaminocycloalkyl, di- (lower alkyl)-aminocycloalkyl, di-(lower alkyl)-aminocycloalkylalkyl, by groups selected from hydrogen, lower alkyl, hydroxy, lower alkoxy, amino, amidino, carboxamido, sulfonamido, hydroxy, cyano, primary, secondary or tertiary amino, halo, azido, lower alkoxyalkyl, cyanoalkyl, azidalkyl, haloalkyl, hydroxyalkyl, methanesulfonylalkyl, primary, secondary or tertiary amino-alkyl, optionally substituted aryl, heteroaryl, heteroalkyl, heterocyclyl, cycloalkyl, alkenyl and alkynyl.

In another embodiment in formula (1), \(R^1\) is independently selected from optionally substituted heterocyclyl, heterocyclylalkyl, aminoalkyl, lower alkylaminoalkyl and di-(lower alkyl)-aminoalkyl.

In another embodiment in formula (1), exemplary \(R^1\) include, but are not limited to:
wherein:

- $R_{13}$ is selected from hydrogen, lower alkyl, heteroalkyl, heterocyclyl, cycloalkyl and heterocycloalkyl;
- $R_{14}$ is selected from hydrogen, hydroxy, lower alkoxy, di-(lower alkyl)amino, lower alkyl, heteroalkyl, heterocyclyl, cycloalkyl, heterocycloalkyl, lower alkoxyalkyl, cyanoalkyl, azidoalkyl, nitroalkyl, ketoalkyl, methanesulfonylalkyl, aminoalkyl, lower alkylaminoalkyl, di-(lower alkyl)aminoalkyl, optionally substituted aryl, heteroaryl, arylalkyl, heteroarylalkyl;
- $R_{15}$ is selected from hydrogen, amino, lower alkylamino, di-(lower alkyl)amino, hydroxy, lower alkoxy, heteroalkyl, lower alkoxyalkyl, aminoalkyl, lower alkylaminoalkyl and di-(lower alkyl)aminoalkyl;

- $a$ is an integer from 0 to 4; and
- $t, u, v$ are independent integers from 0 to 5.

It is understood that if any of the integers is (are) 0 (zero), it means a covalent chemical bond.

In another embodiment, $R_1$ is further selected from:
In $R^1$, in certain embodiments, the methylene chain between the connection and the heteroatom may be optionally substituted by one or more hydrogen, lower alkyl, hydroxy, hydroxy-lower alkyl, lower alkoxy, carboxamido or sulfonamido and one of the methylene groups can be substituted by a heteroatom, such as O, NR*** or S, S=O, or S(=0)$_2$, wherein R*** is selected from hydrogen, hydroxy, lower alkyl, lower alkoxy, heteroalkyl, hydroxyalkyl, aminoalkyl, lower alkylaminoalkyl and di-(lower alkyl)aminoalkyl. Any of the ring systems can also be optionally substituted by a lower alkyl or heteroalkyl group.

In another embodiment, the compounds have the following formula:

Formula Ia

$W^1$ is nitrogen or carbon.

The substituents are defined as described herein.

In another embodiment, the compounds have the following formulas:
The substituents are defined as described above.

In another embodiments, compounds correspond to the following formulas:
wherein

$X_{20}$ to $X_{24}$ are each independently selected from hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl, cycloalkyl, heterocycloalkyl, cyano, nitro, ureido, primary, secondary or tertiary amino, methylenedioxy, ethylenedioxy and difluoromethylenedioxy.

The other compounds include those corresponding to formulas II-1o, wherein:

$X_{20}=$methyl; $X_{21}=$chloro; $X_{22}=X_{23}=X_{24}=$hydrogen;
$X_{20}=$methyl; $X_{21}=$methyl; $X_{22}=X_{23}=X_{24}=$hydrogen;
$X_{20}=$methyl; $X_{21}=$methoxy; $X_{22}=X_{23}=X_{24}=$hydrogen;
$X_{20}=$chloro; $X_{21}=$methyl; $X_{22}=X_{23}=X_{24}=$hydrogen;
$X_{20}=$methyl; $X_{21}=$$X_{22}=X_{23}=X_{24}=$hydrogen;
$X_{20}=$ethyl; $X_{21}=$$X_{22}=X_{23}=X_{24}=$hydrogen;
$X_{20}=$isopropyl; $X_{21}=$$X_{22}=X_{23}=X_{24}=$hydrogen;
$X_{20}=$chloro; $X_{21}=$$X_{22}=X_{23}=X_{24}=$hydrogen;
$X_{20}=$bromo; $X_{21}=$$X_{22}=X_{23}=X_{24}=$hydrogen;
$X_{20}=$iodo; $X_{21}=$$X_{22}=X_{23}=X_{24}=$hydrogen;
$X_{20}=$bromo; $X_{21}=$fluoro; $X_{22}=X_{23}=X_{24}=$hydrogen;
$X_{20}=$methyl; $X_{21}=$methoxy; $X_{22}=$methyl; $X_{23}=X_{24}=$hydrogen;
$X_{20}=$methyl; $X_{21}=$hydrogen; $X_{22}=$methyl; $X_{23}=X_{24}=$hydrogen;
$X_{20}=$methyl; $X_{21}=$fluoro; $X_{22}=$methyl; $X_{23}=X_{24}=$hydrogen;
$X_{20}=$bromo; $X_{21}=$hydrogen; $X_{22}=$methyl; $X_{23}=X_{24}=$hydrogen;
$X_{20}=$chloro; $X_{21}=$$X_{22}=$methylenedioxy; $X_{23}=X_{24}=$hydrogen;
In another embodiment, the compounds correspond to the following formulas:

Formula 1p

Formula 1q
wherein

$X_{30}$ to $X_{34}$ are independently selected from hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl, cycloalkyl, heterocycloalkyl, cyano, nitro, ureido, primary, secondary or tertiary amino, methylenedioxy, ethylenedioxy and difluoromethylenedioxy.

Other compounds include those corresponding to formulas Ip to Is, wherein:

$X_{30}$= $X_{31}$= $X_{32}$= $X_{33}$= $X_{34}$=hydrogen;
$X_{30}$=methyl; $X_{31}$= $X_{32}$= $X_{33}$= $X_{34}$=hydrogen;
$X_{30}$= chloro; $X_{31}$= $X_{32}$= $X_{33}$= $X_{34}$=hydrogen;
$X_{30}$=hydrogen; $X_{31}$= chloro; $X_{32}$= $X_{33}$= $X_{34}$=hydrogen;
$X_{30}$= $X_{31}$=hydrogen; $X_{32}$= chloro; $X_{33}$= $X_{34}$=hydrogen;
$X_{30}$=hydrogen; $X_{31}$= methoxy; $X_{32}$= $X_{33}$= $X_{34}$=hydrogen;
$X_{30}$= $X_{31}$=hydrogen; $X_{32}$= methoxy; $X_{33}$= $X_{34}$=hydrogen;
$X_{30}$=methyl; $X_{31}$=hydrogen; $X_{32}$=methyl; $X_{33}$= $X_{34}$=hydrogen; and
$X_{30}$=methyl; $X_{31}$= $X_{32}$=hydrogen; $X_{33}$=fluoro; $X_{34}$=hydrogen.

In another embodiments, compounds correspond to the following formulas:
wherein

X\textsuperscript{40} to X\textsuperscript{44} are independently selected from hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoromethoxy, heteroalkyl, cycloalkyl, heterocycloalkyl, cyano, nitro, ureido, primary, secondary or tertiary amino, methylenedioxy, ethylenedioxy and difluoromethylenedioxy.

Such compounds include those corresponding to formulas It to Iw, wherein:

\begin{align*}
X^{40} & = \text{methyl}; \\
X^{41} & = \text{hydrogen}; \\
X^{42} & = \text{hydrogen; hydrogen; } \\
X^{43} & = \text{hydrogen; hydrogen; } \\
X^{44} & = \text{hydrogen; hydrogen.}
\end{align*}

In another embodiment, the compounds are:

(R)-2-(4-(3-(2,4-dimethylphenoxy)-2-hydroxypropylamino)-2-oxo-1,2-dihydropyridin-3-yl)-6-(1-methylpiperidin-4-yl)-6,7-dihydroimidazo[4,5-\text{i}]isoindol-5(1H)-one
(R)-2-(4-(3-(2,4-dimethylphenoxy)-2-hydroxypropylamino)-2-oxo-1,2-dihydropyridin-3-yl)-6-(1-(2-(methylsulfonyl)ethyl)piperidin-4-yl)-6,7-dihydroimidazo[4,5-\(\beta\)]isoindol-5(1\(\beta\))-one

(R)-2-(4-(3-(2-bromophenoxy)-2-hydroxypropylamino)-2-oxo-1,2-dihydropyridin-3-yl)-6-(1-methylpiperidin-4-yl)-6,7-dihydroimidazo[4,5-\(\beta\)]isoindol-5(1\(\beta\))-one
(R)-2-(4-(3-(6-ethylbenzo[d][1,3]dioxol-5-yloxy)-2-hydroxypropylamino)-2-oxo-1,2-dihydropyridin-3-yl)-6-(1-methylpiperidin-4-yl)-6,7-dihydroimidazo[4,5-\(\beta\)]isoindol-5(1/-\(\beta\))-one

(R)-2-(4-(3-(2-chloro-4-methoxyphenoxy)-2-hydroxypropylamino)-2-oxo-1,2-dihydropyridin-3-yl)-6-(1-methylpiperidin-4-yl)-6,7-dihydroimidazo[4,5-\(\beta\)]isoindol-5(1/-\(\beta\))-one

(R)-2-(4-(3-(2,4-dimethylphenoxy)-2-hydroxypropylamino)-2-oxo-1,2-dihydropyridin-3-yl)-6-(1-(3-oxobutyl)piperidin-4-yl)-6,7-dihydroimidazo[4,5-\(\beta\)]isoindol-5(1H)-one
4.2. Preparation of the compounds.

Compounds according to formula (1) can be prepared according to any method apparent to those of skill in the art. Provided below are exemplary methods for their preparation.

4.2.1 Procedure for the synthesis of substituted Imidazo[4,5-f]isoindole-5,7(1H,6H)-diones and substituted 6,7-dihydroimidazo[4,5-f]isoindol-5(3H)-one derivatives (C,C)

In certain embodiments, compounds of formula (1) are prepared according to the following procedures, according to scheme 1.

Scheme 1 describes the preparation of the tricycles. The starting diamino phthalimides and/or diaminolactams B (and/or their derivatives) are available by the synthetic methodologies described below. The method is general and is applicable to a variety of derivatives with different groups R\textsuperscript{1}Y\textsuperscript{1} and Y\textsuperscript{2}, as well as various X\textsuperscript{1} through X\textsuperscript{6} and W\textsuperscript{1} through W\textsuperscript{6}.

Condensations of the suitable aromatic, or heteroaromatic aldehydes (A, A') with the diamino-heterocycles (B) give in the presence of air, or a suitable oxidant the desired substituted aromatic heterotricycles (C, C). In the addition of exposure to air, use of palladium on charcoal, Raney nickel, or dehydrogenating agents, such as sulfur, Oxone\textsuperscript{R}, ferric chloride, sodium bisulfite, benzoquinone, or its derivatives and the like will also accomplish dehydrogenation of the initially formed dihydroderivatives to the aromatic heterotricycles (C, C). Other methods for cyclization of benzimidazole-type derivatives are
known in the art and can be utilized in the formation of the present heterotricyclic compounds, by way of example, but not limited to: acylation of the diamines (B) with an activated form of the carboxylic acids (D, D'), such as acid chlorides, fluorides, imidazolides, DCC, or DIC and related adducts with the diamine (B), followed by formation of the imidazole ring in acidic, or basic conditions (e.g.: heating in acetic acid, or in alcoholic potassium, or sodium methoxide, or use of PPA, or POC13 in the presence of pyridine, or diisopropylethylamine, to give (C,C). Alternatively, the 2-nitroamine (E) can be used for the acylation step, followed by reduction with titanium trichloride, or stannous chloride solution, followed by cyclization of the monoacyl diamine in acidic, or basic conditions (e.g.: heating in acetic acid, or in alcoholic potassium, or sodium methoxide, or use of PPA, or POC13 in the presence of pyridine, or diisopropylethylamine, to give (C,C). Carboxylic acids (D,D') are accessible by methods known in the art, including Kolbe synthesis, carboxylation of the corresponding lithium carbanions (preferably in a protected form, such as MOM ethers, or methoxy derivatives, followed by deprotection with HCl, or BBr3) with CO2, or oxidation of the corresponding aldehydes (A,A') with Ag2O, or sodium chlorite / isobutylene, under standard conditions.

In certain embodiments, compounds of formula (1) are prepared according to the following procedures, according to schemes 2-20.

Description of a substituent as R and R’ means that it may be any chemically feasible substituent, including hydrogen.

Synthesis of Tricyclic Derivatives (Imidazo[4,5-f]isoindole-5,7(1H,6H)-diones):

Scheme 2
Substituent $Q^1$ in Scheme 2 corresponds to the above reaction-compatible $X^s$ of formula (1), especially hydrogen, halogen or methyl. Substituent $Q^2$ in Scheme 2 corresponds to the above reaction-compatible $X^6$ of formula (1), especially hydrogen, halogen or methyl. Synthesis of halo-, nitro- and amino-substituted phthalimides can be also found in: E.H White and K. Matsuo, JOC, 1967, 1921 and S. Cherkez, J. Herzig, and H. Yellin J. Med. Chem. 1986, 29, 947-959.

Alternatively, 4-chloro-2-methoxy-3-pyridinecarboxaldehyde (A9) or 4-bromo-2-methoxy-3-pyridinecarboxaldehyde (A10) can be used in the cyclization of the diamine derivatives (A4) and (A15) to provide the corresponding tricyclic derivatives - (6,7-dihydroimidazo[4,5-f]isoindol-5(IH)-ones and imidazo[4,5-f]isoindole-5,7(IH,6H)-diones.
(A9) is a highly valuable precursor useful in the synthesis of biologically active compounds.

Synthesis of Lactam Derivatives (A14) (6,7-Dihydroimidazo[4,5-f]isoindol-5(1H)-ones):

The 6,7-Dihydroimidazo[4,5-f]isoindol-5(1H)-ones (A14) were synthesized according to two basic methods.

In method A, the fully constructed substituted [4,5-f]isoindole-5,7(1H,6H)-diones (A8) were reduced by zinc in acetic acid to the lactam derivatives.

Synthesis of (6,7-Dihydroimidazo[4,5-f]isoindol-5(1H)-ones) (A14)) shown in Scheme 3.

Method A
Synthesis of Lactam Derivatives (A14) (6,7-Dihydroimidazo[4,5-f]isoindol-5(1H)-ones):

Scheme 4

Method B

In the method B, the nitroamine imide (A3) was reduced by tin and hydrochloric acid to the corresponding diaminolactam (A5), which was converted to the iodo-derivative (A16), which was then hydrolyzed by HCl to the aminopyridone-lactam chloropyridone derivative (A17). Reaction of (A17) with amines in boiling ethanol and a base such as triethylamine gave the desired target (A14). The conditions are described below. (A17) is a highly valuable precursor useful in the production of biologically active compounds.
Synthesis of 4-chloro-2-methoxy-3-cyanopyridine (A20) and 4-chloro-2-methoxy-3-pyridinecarboxaldehyde (A9):

Scheme 5

![Chemical structures and reactions](image)


Preparation of 4-bromo-3-cyano-2-methoxypyridine and 4-iodo-3-cyano-2-methoxypyridine and the corresponding aldehydes

Scheme 6

![Chemical structures and reactions](image)

Thus, 2-chloro-3-cyanopyridine (Al 8) provided 2-methoxy-3-cyanopyridine (A19) upon treatment with sodium methoxide in methanol. Lithiation of the 2-methoxy-3-cyanopyridine (A19) with LDA gave the intermediate carbanion derivative 4-lithio-2-methoxy-3-cyanopyridine (A21), which upon treatment with hexachloroethane provided the 4-chloro-2-methoxy-3-cyanopyridine (A20). Analogously, reaction with bromine provides the 4-bromo-2-methoxy-3-cyanopyridine (A22) and reaction with iodine provides the 4-iodo-2-methoxy-3-cyanopyridine (A23). All 4-halo-2-methoxy-3-cyanopyridines are highly valuable intermediates, especially for the synthesis of kinase inhibitors. Reduction of the 4-halo-2-methoxy-3-cyanopyridines, for example with DIBAL (diisobutylaluminum hydride) in solvents such as toluene, dichloromethane, or tetrahydrofuran at temperatures ranging from -80°C to about 80°C, preferably at 20°C provides after standard workup the 4-halo-2-methoxypyridine-3-carboxaldehydes. The 4-halo-2-methoxypyridine-3-carboxaldehydes are
highly valuable synthetic intermediates. 4-chloro-2-methoxy-3-pyridinecarboxaldehyde (A9) was prepared in this manner.

4.2.1.1 Preparation of the 2-Methoxy-4-iodopyridine-3-carboxaldehyde

\[ \text{A5} \]


4.2.1.2 Preparation of the 4, 6-dichloropyrimidine-5-carbaldehyde

\[ \text{A24} \]

4.2.2 Synthesis of Sultam derivatives

**Scheme 7**

- **H<sub>2</sub>O<sub>2</sub>/TFA**
- **Na<sub>2</sub>SO<sub>3**
- **Cl<sub>2</sub> or tBu·OCl or NCS**
- **NH<sub>3**
- **HNO<sub>2</sub>/SO<sub>2</sub>/CuCl Or CuCl<sub>2</sub>**
- **NBS**
- **R·NH<sub>2</sub> or DIPEA**
- **KO-tBu / CCl<sub>3</sub>-CCl<sub>3</sub>**
- **KO-tBu / R·I**
- **H<sub>2</sub>/Pd/C**
4.2.3 General Procedure for the synthesis of difluorolactam derivatives

Scheme 8

4.2.4 General Procedure for the synthesis of dihydroisoindole derivatives

Scheme 9
4.2.5 General Procedure for the synthesis of gem-difluorodihydroisoindole derivatives

Scheme 10

4.2.6 General Procedure for the synthesis of substituted imino-dihydroisoindole derivatives

Scheme 11

4.2.7 General Procedure for the synthesis of substituted dihydroisoindole derivatives

Scheme 12
4.2.8 General Procedure for the synthesis of substituted dihydroisoindole and corresponding spirocompound derivative

Scheme 13
4.2.9 General Procedure for the synthesis of the intermediates for the synthesis of the compounds of the invention

Scheme 14

AR is an unsubstituted, mono-substituted or polysubstituted aryl or heteroaryl.
4.2.10 General procedure for the synthesis of the intermediates for the synthesis of the compounds of the invention

Scheme 15

1. EtMgBr or EtZnBr or BuLi*

2. or DBU or DIPEA

\[ A-\text{OH} \rightarrow \text{A-O-\text{NH}_2} \]

\[ A-\text{SH} \rightarrow \text{A-S-\text{NH}_2} \]

\[ A-\text{NH}_2 \rightarrow \text{A-N-\text{NH}_2} \]

* or DBU or DIPEA

xylene, DBU cat. heat

isopropanol heat

A is an unsubstituted, mono-substituted or polysubstituted alkyl, cycloalkyl, heteroalkyl, heterocycloalkyl, aryl or heretoaryl.
4.2.1 General Procedure for the synthesis of the intermediates of the compounds of the invention

Scheme 16

A is an unsubstituted, mono-substituted or polysubstituted alkyl, cycloalkyl, heteroalkyl, heterocycloalkyl, aryl, or heteroaryl.

4.2.12 General Procedure for the synthesis of the intermediates of the compounds of the invention

Scheme 17

\[ \text{H}_2\text{N}-(\text{CH}_2)^n*\text{--NHBOC} \xrightarrow{\text{RSO}_2\text{Cl}} \text{HN}-(\text{CH}_2)^n*\text{--NHBOC} \xrightarrow{\text{TFA}} \text{HN}-(\text{CH}_2)^n*\text{--NH}_2 \]

\( n^* \) is an integer from 2-6
4.2.13 General Procedure for the synthesis of the intermediates of the compounds of the invention

Scheme 18

A-(Cl, Br, I) → A-Mg(Cl, Br, I) or A-Li

Optional BF₃ or ZnCl₂ or CuCN

1. MsCl
2. NaN₃
3. H₂/Pd/C

For compounds containing hydrogenolyzable groups:

A-(Cl, Br, I) → A-Mg(Cl, Br, I) or A-Li

Optional BF₃ or ZnCl₂ or CuCN

1. MsCl
2. NaN₃
3. P(Bu)₃/H₃O⁺, then TBAF

A is an unsubstituted, mono-substituted or polysubstituted alkyl, cycloalkyl, heteroalkyl, heterocycloalkyl, aryl, or heteroaryl.

Both enantiomers of the epoxide starting material are available. The reaction proceeds with inversion at the chiral center.
4.2.14 General Procedure for the synthesis of the intermediates of the compounds of the invention

Scheme 19

A-(Cl,Br,I) → A-Mg(Cl,Br,I) → A-O-SO₂CF₃

or A-Li → H₂SO₄ / H₂O → A^-OH

Both enantiomers commercially available

A-CH₂-(Cl,Br,I) → A-CH₂-Mg(Cl,Br,I) → A-O-SO₂CF₃

1. NaN₃ → A-CH₂-OH

2. H₂/Pd/C or P(Bu)₃ / H₃O⁺ → A-CH₂-OH

A is an unsubstituted, mono-substituted or polysubstituted alkyl, cycloalkyl, heteroalkyl, heterocycloalkyl, aryl, or heteroaryl.
4.2.15 General Procedure for the synthesis of the phenol intermediates of the compounds of the invention

The phenols that are not commercial products were synthesized by application of methodology known in the art and routes outlined below.

Synthesis of Sesamol-derivatives

Scheme 20

4.2.16 Procedure for the synthesis of 3-aryloxy, 3-arythio and 3-arylamino-2-propanolamines (Method A).

Scheme 21

A 20 mL microwaveable vial was charged with N-(2,3-epoxypropyl)-2-phthalimide (677 mg, 3.0 mmole), the appropriate phenol, thiol or aniline (1.2 equiv, 3.6 mmole), chlorobenzene (10 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (100 uL). The vial was sealed and heated under microwaves to 220°C for 0.5 h. Upon cooling hydrazine (0.189
mL, 6.0 mmol) was added to the reaction vessel. The vial was re-sealed and heated to 150°C under microwaves for 12 min. Upon cooling the resulting suspension was poured onto ethyl acetate (100 mL) and extracted twice with 0.5 N NaOH (50 mL/extraction). The ethyl acetate fraction was isolated and extracted with saturated aqueous sodium chloride (25 mL). The ethyl acetate layer was isolated and dried over magnesium sulfate. The solid was removed by filtration and the volatiles were removed from the filtrate *in vacuo* to afford the product.

4.2. 16.1 Compounds prepared by Method A

Specific embodiments of compounds of formula (1) include, but are not limited to the following compounds that were prepared according to method A described above (Table I):

<table>
<thead>
<tr>
<th>Structure</th>
<th>Molecular Formula</th>
<th>[M+H]⁺</th>
<th>H NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure" /></td>
<td>C9H12FNO2</td>
<td>186.2</td>
<td><em>(CDCl₃): δ 7.10-7.30 (m, 1H, overlapped), 6.55-6.75 (m, 3H), 3.90-4.00. (m, 3H), 2.85-3.05 (m, 2H).</em></td>
</tr>
<tr>
<td><img src="image2" alt="Structure" /></td>
<td>C10H15NO2S</td>
<td>214.3</td>
<td><em>(DMSO-d₄): δ 7.18-7.23 (m, 1H), 6.87-6.89 (m, 2H), 6.71-6.74. (m, 1H), 4.98 (bs, 1H), 3.80 (s, 3H), 3.48-3.52 (m, 1H), 3.05-3.11 (m, 1H), 2.87-2.94 (m, 1H), 2.50-2.70 (m, 2H, overlapped), 1.48 (bs, 2H).</em></td>
</tr>
<tr>
<td><img src="image3" alt="Structure" /></td>
<td>C12H17ClN2O</td>
<td>241.7</td>
<td><em>(CD₃OD): δ 6.79-6.85 (m, 2H), 6.40-6.42 (m, 1H), 3.78-3.87 (m, 1H), 3.29-3.39 (m, 2H), 2.62-3.08 (m, 6H), 1.37 (s, 3H).</em></td>
</tr>
<tr>
<td>Chemical Structure</td>
<td>Formula</td>
<td>Molecular Weight</td>
<td></td>
</tr>
<tr>
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<td>-----------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td><img src="image1" alt="Structure 1" /></td>
<td>C10H12N2O2</td>
<td>193.2</td>
<td></td>
</tr>
<tr>
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<td>C12H17NO2</td>
<td>208.3</td>
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</tr>
<tr>
<td><img src="image3" alt="Structure 3" /></td>
<td>C9H12N2O4</td>
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<tr>
<td><img src="image4" alt="Structure 4" /></td>
<td>C9H8F5NO2</td>
<td>258.2</td>
<td></td>
</tr>
<tr>
<td><img src="image5" alt="Structure 5" /></td>
<td>C9H11Cl2NO2</td>
<td>237.1</td>
<td></td>
</tr>
<tr>
<td><img src="image6" alt="Structure 6" /></td>
<td>C10H14FNO2</td>
<td>200.2</td>
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<tr>
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<td>227.2</td>
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<td>227.2</td>
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<tr>
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<td>237.1</td>
<td></td>
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<tr>
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<td>Molecular Formula</td>
<td>Molecular Weight</td>
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<tr>
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<tr>
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<td>236.2</td>
<td></td>
</tr>
<tr>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>C10H15NO2S</td>
<td>214.3</td>
<td></td>
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<tr>
<td>Structure</td>
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<td><img src="image3.png" alt="Structure 3" /></td>
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<tr>
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</tr>
<tr>
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4.2.17 Procedure for synthesis of 2-\{4-[2-hydroxy-3-aryloxypropyl]amino]-2-oxo-1,2-dihydropyridin-3-yl\}-6-(methylpiperidin-4-yl)imidazo[4,5-/jisoindole-5,7(l//,6 H)-diones, 2-\{4-[2-hydroxy-3-arylthiopropyl]amino\]-2-oxo-1,2-dihydropyridin-3-yl\}-6-(methylpiperidin-4-yl)imidazo[4,5-/jisoindole-5,7(l H,6H)-diones, and 2-\{4-[2-hydroxy-3-arylaminopropyl]amino\]-2-oxo-1,2-dihydropyridin-3-yl\}-6-(methylpiperidin-4-yl)imidazo[4,5-/jisoindole-5,7(l//,6 H)-diones (Method B).

Scheme 22

An array of 8 mL vials, each containing one of the propanolamines prepared by Method A (100 umol), was prepared. A 0.1 M stock solution of 2-(4-chloro-2-oxo-1,2-dihydropyridin-3-yl)-6-(methylpiperidin-4-yl)imidazo[4,5-/jisoindole-5,7(l H,6H)-diones in 15% triethylamine in ethyl acetate (v/v) was prepared. To each of the vials was added the template stock solution (1000 uL, 1.0 equiv). The vials were capped and heated to 100°C for 16 h. Upon cooling the volatiles were removed \textit{in vacuo} and the resultant residue was purified by HPLC.

4.2.17.1 Compounds prepared by Method B

Specific embodiments of compounds of formula (1) include, but are not limited to the following compounds that were prepared according to method B described above (Table II):

Table II

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4.3 Methods of Use

In one aspect, provided are methods for modulating the activity of a tyrosine kinase. In general, the methods comprise the step of contacting the tyrosine kinase with a compound of the invention. The contacting can be in any environ known to those of skill in the art, for instance, in vitro, in vivo, ex vivo or otherwise. In certain embodiments, the present invention provides methods of modulating the activity of a tyrosine kinase in a mammal in need thereof comprising contacting the tyrosine kinase with a compound of the invention.

In another aspect, the protein tyrosine kinase, the catalytic activity of which is modulated by contact with a compound provided herein, or a stereoisomer, tautomer, salt, hydrate or prodrug thereof, is a receptor protein tyrosine kinase (RTK). Among the receptor protein tyrosine kinases whose catalytic activity can be modulated with a compound of this invention, are, without limitation, Alk, AxI, CSFR, DDR1, DDR2, EphB4, EphA2, EGFR, FIt-I, Flt3, Flt4, FGFR1, FGFR2, FGFR3, FGFR4, HER2, HER3, HER4, IR, IGFR, IRR, Kit, KDR/Flk-l,Met, Mer, PDGFR.alpha., PDGFR.beta., Ret, Ros, Ron, Tiel, Tie2, TrkA, TrkB, TrkC.

In yet another aspect, the protein tyrosine kinase whose catalytic activity is modulated by contact with a compound of this invention, or a stereoisomer, tautomer, salt, hydrate or prodrug thereof, can also be a non-receptor or cellular protein tyrosine kinase (CTK). Thus, the catalytic activity of CTKs such as, without limitation, AbI, Arg, Ack, Blk, Bmx, Brk, Btk, Csk, Fak, Fes, Fgr, Fps, Frk, Fyn, Hck, Itk, Jakl, Jak2, Jak3, Lck, Lyn, Src,
Syk, Tec, Yes, ZAP70, may be modulated by contact with a compound or a stereoisomer, tautomer, salt, hydrate or prodrug thereof provided herein.

In another aspect, provided are methods for treating or preventing a tyrosine kinase related disorder in a subject in need thereof. In general, the methods comprise administering to the subject an amount of a compound or a stereoisomer, tautomer, salt, hydrate or prodrug thereof effective to treat or prevent the disorder. The compound can be in the form of a pharmaceutical composition or a unit dose as described below.

A tyrosine kinase related disorder can be any disorder known to those of skill in the art to be related to tyrosine kinase activity. Such disorders include those related to excessive tyrosine kinase active, those related to reduced tyrosine kinase activity and to those that can be treated or prevented by modulation of tyrosine kinase activity. Excessive tyrosine kinase activity can arise as the result of, for example: (1) tyrosine kinase expression in cells which normally do not express tyrosine kinases; (2) increased tyrosine kinase expression leading to unwanted cell proliferation, differentiation and/or growth; or, (3) decreased tyrosine kinase expression leading to unwanted reductions in cell proliferation, differentiation and/or growth.

The tyrosine kinase related disorder can be a cancer selected from, but not limited to, astrocytoma, basal or squamous cell carcinoma, brain cancer, glioblastoma, bladder cancer, breast cancer, colorectal cancer, chondrosarcoma, cervical cancer, adrenal cancer, choriocarcinoma, esophageal cancer, endometrial carcinoma, erythroleukemia, Ewing's sarcoma, gastrointestinal cancer, head and neck cancer, hepatoma, glioma, hepatocellular carcinoma, leukemia, leiomyoma, melanoma, non-small cell lung cancer, neural cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, small cell lung cancer, thyoma, thyroid cancer, testicular cancer and osteosarcoma in a further aspect of this invention.

Other tyrosine kinase related disorder includes an IGFR-related disorder selected from diabetes, an autoimmune disorder, Alzheimer's and other cognitive disorders, a hyperproliferation disorder, aging, cancer, acromegaly, Crohn's disease, endometriosis, diabetic retinopathy, restenosis, fibrosis, psoriasis, osteoarthritis, rheumatoid arthritis, an inflammatory disorder and angiogenesis.

Other disorders which might be treated with compounds of this invention include, without limitation, immunological and cardiovascular disorders such as atherosclerosis.
4.4 Compositions and Method of Administration

In certain aspects, provided herein are compositions comprising a compound or a stereoisomer, tautomer, salt, hydrate or prodrug provided herein. The compositions can be used, for example, in the methods of use described herein.

In certain embodiments, a composition is a pharmaceutical composition or a single unit dosage form. Pharmaceutical compositions and single unit dosage forms comprise a prophylactically or therapeutically effective amount of one or more prophylactic or therapeutic agents (e.g., a compound of the invention, or other prophylactic or therapeutic agent), and a typically one or more pharmaceutically acceptable carriers or excipients or diluents. In one non-limiting embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant (e.g., Freund's adjuvant (complete and incomplete)), excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a particular carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin.

In one embodiment, pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well-known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient and the specific active ingredients in the dosage form. The composition or single unit dosage form, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.
Lactose-free compositions of the invention can comprise excipients that are well known in the art and are listed, for example, in the U.S. Pharmacopoeia (USP) SP (XXI)/NF (XVI). In general, lactose-free compositions comprise an active ingredient, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Exemplary lactose-free dosage forms comprise an active ingredient, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

Also provided are anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (e.g., 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, e.g., Jens T. Carstensen, Drug Stability: Principles & Practice, 2d Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are in certain embodiments anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

An anhydrous pharmaceutical composition can be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are in certain embodiments packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (e.g., vials), blister packs, and strip packs.

Further provided are pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.
The pharmaceutical compositions and single unit dosage forms can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Such compositions and dosage forms will contain a prophylactically or therapeutically effective amount of a prophylactic or therapeutic agent in certain embodiments in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration. In certain embodiments, the pharmaceutical compositions or single unit dosage forms are sterile and in suitable form for administration to a subject, in certain embodiments an animal subject, such as a mammalian subject, particularly a human subject.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include, but are not limited to, parenteral, e.g., intravenous, intradermal, subcutaneous, intramuscular, subcutaneous, oral, buccal, sublingual, inhalation, intranasal, transdermal, topical, transmucosal, intra-tumoral, intra-synovial and rectal administration. In a specific embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, intramuscular, oral, intranasal or topical administration to human beings. In an embodiment, a pharmaceutical composition is formulated in accordance with routine procedures for subcutaneous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocamne to ease pain at the site of the injection.

Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; ointments; cataplasms (poultices); pastes; powders; dressings; creams; plasters; solutions; patches; aerosols (e.g., nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; and sterile solids (e.g., crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.
The composition, shape, and type of dosage forms of the invention will typically vary depending on their use. For example, a dosage form used in the acute treatment of inflammation or a related disorder may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Also, the therapeutically effective dosage form may vary among different types of cancer. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease or disorder. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. See, e.g., Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton PA (1990).

Generally, the ingredients of compositions of the invention are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

Typical dosage forms of the invention comprise a compound of the invention, or a pharmaceutically acceptable salt, solvate or hydrate thereof lie within the range of from about 0.1 mg to about 1000 mg per day. Particular dosage forms of the invention have about 0.1, 0.2, 0.3, 0.4, 0.5, 1.0, 2.0, 2.5, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 100, 200, 250, 500 or 1000 mg of the compound.

4.4.1 Oral Dosage Forms

Pharmaceutical compositions that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally, Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton PA (1990).

In certain embodiments, the oral dosage forms are solid and prepared under anhydrous conditions with anhydrous ingredients, as described in detail in the sections above.
However, the scope of the invention extends beyond anhydrous, solid oral dosage forms. As such, further forms are described herein.

Typical oral dosage forms of the invention are prepared by combining the active ingredient(s) in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.
Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. An specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, specifically from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

Lubricants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, t alc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid.
silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Piano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

4.4.2 Controlled Release Dosage Forms

Active ingredients such as the compounds provided herein can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (e.g., adverse) effects.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this
constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

4.4.3 Parenteral Dosage Forms

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses patients’ natural defenses against contaminants, parenteral dosage forms are in certain embodiments sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms of the invention.

4.4.4 Transdermal, Topical & Mucosal Dosage Forms

Transdermal, topical, and mucosal dosage forms of the invention include, but are not limited to, ophthalmic solutions, sprays, aerosols, creams, lotions, ointments, gels, solutions, emulsions, suspensions, or other forms known to one of skill in the art. See, e.g., Remington's Pharmaceutical Sciences, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990); and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia (1985). Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or as oral gels. Further, transdermal dosage forms include
"reservoir type" or "matrix type" patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredients.

Suitable excipients (e.g., carriers and diluents) and other materials that can be used to provide transdermal, topical, and mucosal dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form lotions, tinctures, creams, emulsions, gels or ointments, which are non-toxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. See, e.g., Remington's Pharmaceutical Sciences, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990).

Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients of the invention. For example, penetration enhancers can be used to assist in delivering the active ingredients to the tissue. Suitable penetration enhancers include, but are not limited to: acetone; various alcohols such as ethanol, oleyl, and tetrahydrofurfuryl; alkyl suloxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.
4.4.5 Dosage & Frequency of Administration

The amount of the compound or composition provided herein which will be effective in the prevention, treatment, management, or amelioration of a disorder or one or more symptoms thereof will vary with the nature and severity of the disease or condition, and the route by which the active ingredient is administered. The frequency and dosage will also vary according to factors specific for each patient depending on the specific therapy (e.g., therapeutic or prophylactic agents) administered, the severity of the disorder, disease, or condition, the route of administration, as well as age, body, weight, response, and the past medical history of the patient. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

Exemplary doses of a compound include milligram or microgram amounts of the active peptide per kilogram of subject or sample weight (e.g., about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram). In general, the recommended daily dose range of a compound of the invention for the conditions described herein lie within the range of from about 0.01 mg to about 1000 mg per day, given as a single once-a-day dose in certain embodiments as divided doses throughout a day. It may be necessary to use dosages of the active ingredient outside the ranges disclosed herein in some cases, as will be apparent to those of ordinary skill in the art. Furthermore, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response.

Different therapeutically effective amounts may be applicable for different diseases and conditions, as will be readily known by those of ordinary skill in the art. Similarly, amounts sufficient to prevent, manage, treat or ameliorate such disorders, but insufficient to cause, or sufficient to reduce, adverse effects associated with the compounds of the invention are also encompassed by the above described dosage amounts and dose frequency schedules. Further, when a patient is administered multiple dosages of a compound of the invention, not all of the dosages need be the same. For example, the dosage administered to the patient may be increased to improve the prophylactic or therapeutic effect of the compound or it may be decreased to reduce one or more side effects that a particular patient is experiencing.

In certain embodiments, administration of the same compound may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days,
10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months. In other embodiments, administration of the same prophylactic or therapeutic agent may be repeated and the administration may be separated by at least at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months.

4.4.6 Biological Assays

The following assays can be employed in ascertaining the activity of a small-molecule compound as an inhibitor of the catalytic kinase activity of various tyrosine kinases.

4.4.6.1 Kinase Assays

To determine inhibition of several tyrosine kinases, such as IGF\textsubscript{1}R, InsR, A\textsubscript{tk}, TrkA and Jak2, kinase assays are conducted using either Kinase-Glo (Promega) or AlphaScreen (PerkinElmer) kinase assay platforms. The Kinase-Glo Luminescent Kinase Assay is a homogeneous method for measuring kinase activity by determining the amount of ATP remaining after a kinase reaction. The luminescent signal is proportional to the amount of ATP and inversely proportional to the amount of kinase activity. Tyrosine kinase PT66 AlphaScreen Assay is a high-sensitivity homogeneous, anti-phosphotyrosine antibody-mediated luminescent proximity method measuring incorporation of phosphate in synthetic poly(Glu-Tyr) substrate. The kinase preparations used consist of purified recombinant, 6xHis- or GST-tagged kinase domain fragments of the corresponding RTKs expressed in baculovirus system.

4.4.6.1.1 ELISA-based assay of IGF1 receptor autophosphorylation inhibition in cells

In another embodiment, compounds that interact with the IGF\textsubscript{1}R kinase domain are tested in a cell-based assay system. In accordance with this embodiment, cells expressing a full-length IGF\textsubscript{1} receptor or a fragment thereof containing the IGF\textsubscript{1}R kinase domain, are contacted with a candidate or a control compound and the ability of the compound to block tyrosine kinase activity of IGF\textsubscript{1}R within a cell is determined. This assay may be used to screen a single compound or a large library of candidate compounds. Typically, the cells or cell lines are of mammalian origin and they can express the IGF\textsubscript{1} receptor, or functional IGF\textsubscript{1}R kinase domain fragment, endogenously or be genetically engineered to express the IGF\textsubscript{1}R, or functional fragment thereof. The ability of the candidate compound to inhibit IGF\textsubscript{1}R kinase activity can be determined by methods known to those skilled in the art. For example, the inhibition can be determined by ELISA-type assay or
Western blot analysis with cell lysates or immunoprecipitated IGFlR receptor using various anti-IGFlR and anti-phosphotyrosine antibodies.

In general, cells expressing IGFlR are treated with modulators (i.e., inhibitors or activators) of IGFlR kinase activity and cell lysates are produced from these treated cells. IGFlRs are isolated from the lysate by immunoprecipitation and analyzed for phosphotyrosine content. Alternatively, or in addition, cellular protein substrates phosphorylated by IGFR may be immunoprecipitated from the lysates and their degree of tyrosine phosphorylation determined.

4.4.6.2 Cell Proliferation Inhibition Assay

IGFlR and other tyrosine kinase inhibitors can inhibit the proliferation of certain cancer cell lines indicating their possible therapeutic utility for treating the corresponding cancer types. Cancer cell lines of interest and control normal lines, including CHO, HEK293, BA/F3, MML, H929, COLO205, PC3, DU145, MCF7, Panel, ACHN, Hep G2, H460, K562, TT, U87-G, CAOV-3, SK-MEL5, Karpas 299, are plated in white, clear-bottomed 384-well cell culture plates at 2500-5000 cells per well and supplied with dilutions of tested compounds. After a desired period of time (typically 3 days), the number of viable cells is quantitated by using Cell Titer-Glo Luminescent Cell Viability Assay (Promega), a cell proliferation assay system based on detection of total amount of ATP present as a measure of cell metabolic activity. The plated cells are mixed with the Cell Titer-Glo developing reagent and counted in a luminescence multiwell plate reader according to the standard manufacturer's protocol to generate IC50 curves for cell proliferation inhibition.

4.4.6.3 Kinase Profiling

To determine inhibitory activity of the compounds against a panel of tyrosine and serine-threonine kinases, the commercial kinase panel profiling service (Kinase Profiler, Upstate Biotechnologies) is utilized. This kinase inhibition profiling platform consists of standard radiometric kinase assays in filter binding format based on direct measurements of radioactive phosphate incorporation in specific kinase substrates by scintillation counting.

The disclosure is further described by the way of non-limiting examples.

5. EXAMPLES

5.1 Example 1: Synthesis of the Compounds According To Formula (1)
Synthesis of 5-Amino-6-nitro-isoindole-1,3-dione (4-nitro-5-aminophthalimide) from 5-chloro-6-nitroisoindoline-1,3-dione (4-chloro-5-nitrophthalimide) is described in the following: Application No. CN 1314350 A20010926 and CN 2001-111559, 20010323.

The following procedure is our modification: A mixture of 5-chloro-6-nitroisoindoline-1,3-dione (28.0 g, 0.123 mol) and urea (73.8 g, 1.23 mol) was stirred at 150 °C for 6 h. Then the temperature was reduced to 90 °C, water (400 mL) was added, the mixture was stirred overnight at RT. Precipitate was collected by filtration, water (300 mL) was added and stirred for 4 h at 95 °C. The solid was collected by filtration and dried under vacuum. Yellow solid, 19.6 g (94.7 mmol, 77%). LCMS [M-H]⁻ 205.9. ¹H NMR (300 MHz, DMSO): δ 11.46 (s, 1H), 8.35 (s, 2H), 8.37 (s, 1H), 7.40 (s, 1H).

N-Substituted Phthalimides (2-substituted 5-chloro-6-nitroisoindoline-1,3-diones):

General Procedure A: A mixture of 5-amino-6-nitro-isoindole-1,3-dione (207 mg, 1.0 mmol), amine 2 (1.0 mmol) and diphenyl ether (3 mL) was stirred overnight under nitrogen at 210 °C, then cooled to 50 °C, diluted with hexane. Precipitate was collected by filtration.

General Procedure B: A mixture of 5-amino-6-nitro-isoindole-1,3-dione (12.84 g, 62.0 mmol), amine 2 (62.0 mmol), imidazole (4.22 g, 62.0 mmol) and diphenyl ether (50 mL) was stirred for 5 h under N₂ at 170 °C. Then the reaction mixture was cooled to
RT, ethanol (500 mL) was added, the mixture was refluxed for 1 h. After cooling to -20 °C yellow precipitate was collected by filtration, washed with cold ethanol and dried in vacuum at 100 °C overnight.

General Procedure C: A suspension of phthalimide 1 (292 mg, 1.41 mmol), diethylcarbonate (179 mg, 151 mmol) in 1,4-dioxane (3 mL), to which was then added DBU (0.217 mL, 1.45 mmol), was heated at 90-95 °C for 15 min. The amine 2 (1.44 mM) was then added and the reaction suspension was stirred at 100 °C for approximately 30 min at which point a dark solution had resulted. The reaction was cooled to room temperature and evaporated to redish foam under reduced pressure. Ethanol (3 mL) was then added and a yellow suspension formed. The yellow solid was isolated via filtration and washed with ethanol, then dried in vacuum overnight to afford the product 3.

General Procedure D: To a suspension of substituted phthalimide in dioxane (1-200-fold volume [mL] / weight [g] based on the phthalimide derivative, preferably 5-20 mL of 1,4-dioxane per g of the phthalimide derivative) is added equimolar amount of the amine R’-NH₂, imidazole (between 0.01% to 100% of the molar equivalent of the phthalimide [isoindoline-1,3-dione]) and heated to between 100 °C to 200 °C, preferably to between 110 °C to 150 °C, when necessary in a closed pressure vessel with efficient agitation. Then the reaction mixture is cooled to RT and diluted with hexane. The product is filtered by suction and washed with a small amount of cold ether or other suitable solvent. Alternatively, the mixture is concentrated in vacuo and the product may be further purified by washing with ether, hexane or ethyl acetate or their mixture. The product can also be purified by recrystallization from alcohol, or isopropanol. The product can also be purified by acid-base extraction, column chromatography, or HPLC.

5-Amino-2-(1-methyl-piperidin-4-yl)-6-nitro-isoindole-1,3-dione was prepared by General procedure B. Yield 74%. LCMS: [M+H]+ 305.4

$^1$H NMR: (300 MHz, DMSO) δ 8.38 (s, 2H), 8.28 (s, IH), 7.41 (s, IH), 3.89 (m, IH), 2.85 (d, J 11.3 Hz, 2H), 2.30 (m, 2H), 2.18 (s, 3H), 1.92 (t, J 11.3 Hz, 2H), 1.58 (d, J 10.9 Hz, 2H).
5-Amino-2-[2-(1H-imidazol-4-yl)-ethyl]-6-nitro-isoindole-1,3-dione was prepared by General procedure A. The product was additionally purified by chromatography on SiO₂ (CHCl₃-MeOH-NH₄OH 100:10:1). Yield 224 mg (0.74 mmol, 74%). LCMS [M+H]+ 302.4.

1H NMR (300 MHz, DMSO): δ 11.81 (s, 1H), 8.40 (s, 2H), 2.30 (s, 1H), 7.48 (s, 1H), 7.43 (s, 1H) 6.81 (s, 1H), 3.75 (m, 2H), 2.79 (m, 2H).

5-Amino-6-nitro-2-(3-pyrrolidin-1-yl-propyl)-isoindole-1,3-dione was prepared by General procedure A. The product was additionally purified by reverse phase chromatography (CH₃CN-H₂O-TFA). Yield 60 mg (0.19 mmol, 19%). LCMS [M+H]+ 319.4.

1H NMR (300 MHz, CDCl₃): δ 8.55 (s, 1H), 7.40 (s, 2H), 3.80 (m, 2H), 3.22 (m, 2H), 2.85 (m, 2H), 2.00-2.20 (6H), 1.60 (br.s., 4H).

5-Amino-2-(3-morpholin-4-yl-propyl)-6-nitro-isoindole-1,3-dione was prepared by General procedure A. The product was additionally purified by reverse phase
5-Amino-2- [3-(4-methyl-piperazin-1-yl)-propyl]-6-nitro-isoinole-1,3-dione was prepared by General procedure A. The product was additionally purified by RP chromatography (CH$_3$CN-H$_2$O-TFA). Yield 110 mg (0.32 mmol, 32%). LCMS: [M+H]$^+$ 348.3

$^1$H NMR (300 MHz, DMSO): $\delta$ 8.44 (s, 2H), 8.32 (s, IH), 7.47 (s, IH), 3.60 (m, 2H), 3.50-2.70 (13 H), 1.85 (m, 2H).

5-Amino-2- [1-(2-hydroxy-ethyl)-piperidin-4-ylmethyl]-6-nitro-isoinole-1,3-dione was prepared by General procedure A. Yield 270 mg (0.77 mmol, 77%). LCMS [M+H]$^+$ 349.3

$^1$H NMR (300 MHz, DMSO): $\delta$ 8.39 (s, 2H), 8.30 (s, IH), 7.45 (s, IH), 4.33 (m, IH), 3.43 (m, 4H), 2.81 (m, 2H), 2.35 (m, 2H), 1.87 (m, 2H), 1.55 (m, 3H), 1.15 (m, 2H).
5-Amino-2-[1-(2-methoxy-ethyl)-piperidin-4-ylmethyl]-6-nitro-isoindole-1,3-dione was prepared by General procedure B "Imidazole". Yield 267 mg (0.74 mmol, 74%).

LCMS [M+H]^+ 363.5

$^1$H NMR (300 MHz, DMSO): $\delta$ 8.41 (s, 2H), 8.31 (s, 1H), 7.45 (s, 1H), 3.38 (m, 4H), 3.21 (s, 3H), 2.80 (m, 2H), 2.40 (m, 2H), 1.85 (m, 2H), 1.60 (m, 1H), 1.54 (m, 2H), 1.24 (m, 2H).

5-Amino-2-(3-hydroxy-2,2-dimethyl-propyl)-6-nitro-isoindole-1,3-dione was prepared by General procedure B "Imidazole". Yield 168 mg (0.57 mmol, 57%).

LCMS [M-H]^− 292.3

$^1$H NMR (300 MHz, DMSO): $\delta$ 8.40 (s, 2H), 8.32 (s, 1H), 7.45 (s, 1H), 4.58 (t, J=5.5 Hz, 1H), 3.45 (s, 2H), 3.16 (d, J=5.5 Hz, 2H), 0.80 (s, 6H).

5-Amino-2-(2-hydroxy-1-hydroxymethyl-ethyl)-6-nitro-isoindole-1,3-dione was prepared by General procedure B "Imidazole". Yield 271 mg (0.96 mmol, 96%).

LCMS [M-H]^− 279.8
\[ ^1H \text{NMR (300 MHz, DMSO): } \delta 8.39 (s, 2H), 8.30 (s, IH), 7.44 (s, IH), 4.85 (m, 2H), 4.20 (m, IH), 3.78 (m, 2H), 3.63 (m, 2H). \]

5-Amino-2-[(2-(4-methyl-1-piperazin-1-yl)-ethyl]-6-nitro-isoindole-1,3-dione was prepared by General procedure C "diethylcarbonate". Yield 140 mg (0.42 mmol, 42%)

LCMS [M+H]^+ 334.5

\[ ^1H \text{NMR (300 MHz, DMSO): } \delta 8.59 (s, 2H), 8.40 (s, IH), 7.45 (s, IH), 3.65 (m, 2H), 2.20-2-10 (m, 10H), 2.10 (s, 3H). \]

Aminoalcohols

Scheme 23
Procedure for the synthesis of optically active aminoalcohol: (S)-2-(3-chlorophenyl)-2-hydroxy-ethylamine

(S)-1-(3-Chlorophenyl)-ethane-1,2-diol: AD mix alpha (86.0 g) was added to a stirred mixture of tert-BuOH (300 mL) and H₂O (300 mL), mixture was stirred for 15 min at RT, than cooled to 0 °C. 3-Chlorostyrene (8.51 g, 0.061 mol) was added over 15 min and the mixture was stirred at 0 °C for 48 h. The reaction mixture was quenched by adding 10% aq. sodium sulfite (120 mL) followed by addition of EtOAc (200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (200 mL). The combined organic layers were washed with 0.4 M H₂SO₄ in saturated Na₂SO₄ (100 mL), followed by drying over Na₂SO₄. The solvent was evaporated and the residue was separated on SiO₂ (70 g) (CHCl₃-MeOH 0 to 10%). Colorless oil, 9.83 g (0.057 mol, 93%).

¹H NMR (300 MHz, DMSO): δ 7.20-7.40 (m, 4H), 5.39 (d, J=4.6 Hz, IH), 4.76 (t, J=5.8 Hz, IH), 4.54 (q, J=4.9 Hz, IH), 3.43 (m, 2H).

![OtS](attachment:olefin_GS.png)

Toluene-4-sulfonic acid (S)-2-(3-chlorophenyl)-2-hydroxyethyl ester: To a mixture of (S)-1-(3-Chloro-phenyl)-ethane-1,2-diol (9.83 g, 0.057 mol) and triethylamine (11.8 ml, 0.086 mol) a solution of TsCl (10.87 g, 0.057 mol) in dichloromethane (50 mL) was added at 0 °C over 30 min. The mixture was stirred at 0 °C for 4 h. Precipitate formed was removed by filtration, the filtrate was washed with water (50 mL), dried over Na₂SO₄ and evaporated. The residue was dissolved in CH₂Cl₂ (200 mL), filtered through a SiO₂ pad and evaporated. Colorless oil, 16.34 g (0.050 mol, 88%).

¹H NMR (300 MHz, DMSO): δ 7.67 (d, J=8.5 Hz, 2H), 7.42 (d, J=8.5 Hz, 2H), 7.20-7.35 (m, 4H), 5.90 (d, J=4.9 Hz, IH), 4.79 (q, J=5.1 Hz, IH), 4.03 (m, 2H), 2.41 (s, 3H).

![azido](attachment:olefin_GS.png)
(S)-2-Azido-l-(3-chlorophenyl)-ethanol: A mixture of toluene-4-sulfonic acid (S)-2-(3-chlorophenyl)-2-hydroxyethyl ester (16.34 g, 0.050 mol), sodium azide (6.50 g, 0.10 mol) and DMSO (50 mL) was stirred for 2 h at 80 °C. Water (100 mL) was added, extracted with hexane-ether (1:1) mixture (2x150 mL). Combined extract was dried over Na₂SO₄, evaporated. The residue was separated on SiO₂ (100 g), hexane-EtOAc, 0 to 20%. Colorless oil, 7.0 g, (0.035 mol, 71%).

^1H NMR (300 MHz, DMSO): δ 7.46 (s, 1H), 7.36 (m, 3H), 5.95 (d, J=4.5 Hz, 1H), 4.82 (q, J=5.3 Hz, 1H), 3.35 (m, 2H).

(S)-2-Amino-l-(3-chloro-phenyl)-ethanol: A mixture of (S)-2-Azido-l-(3-chlorophenyl)-ethanol (5.14 g, 0.026 mol), NaBH₄ (1.97 g, 0.052 mol) and isopropyl alcohol (100 mL) was stirred at 80 °C for 24 h. The solvent was evaporated, the residue was separated on SiO₂ (15 g) CHCl₃ - MeOH (0 to 30%). Colorless oil, 3.70 g (0.021 mol, 83%). The material was reacted with BoC₂O in dichloromethane and NEt₃ and analyzed by chiral SFC using a CHIRALPAK AD-H column, 30% MeOH and determined to be 91% ee. LCMS [M+H]^+ 172.4

^1H NMR (300 MHz, DMSO): δ 7.24-7.39 (m, 4H), 4.46 (dd, J = 4.3, 7.5 Hz, 1H), 2.68 (dd, J = 4.3, 12.8 Hz, 1H), 2.57 (dd, J=7.5, 13.0 Hz, 1H).

Scheme 2 4

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- 120 -
(R)-l-Azido-3-(4-fluoro-phenoxy)-propan-2-ol. A mixture of (S)-l-Chloro-3-(4-fluoro-phenoxy)-propan-2-ol (5.0 g, 24.5 mmol), sodium azide (3.19 g, 49.0 mmol) and DMSO (25 mL) was stirred at 80 °C for 6h. Then the reaction mixture was poured into water (100 mL), extracted with hexane-Et₂O (1:1) mixture (2x100 mL). Extracts were washed with brine (100 mL), dried over Na₂SO₄ and evaporated. The residue was dried under vacuum at RT. Colorless oil, 4.83 g (22.9 mmol, 93%).

¹H NMR (300 MHz, CDCl₃): δ 6.98 (m, 2H), 6.84 (m, 2H), 4.15 (m, IH), 3.97 (m, 2H), 3.52 (m, 2H), 2.57 (d, J=5 Hz, IH).

(S)-l-Azido-3-(4-fluoro-phenoxy)-propan-2-ol was prepared by the same procedure.

(R)-l-Amino-3-(4-fluoro-phenoxy)-propan-2-ol. A mixture of (R)-l-azido-3-(4-fluoro-phenoxy)-propan-2-ol (4.83 g, 22.9 mmol) NaBH₄ (1.73 g, 45.8 mmol) in 'PrOH (100 mL) was stirred at 80 °C for 24 h. After cooling to RT, aq. HCl (200 mL, 0.25 M) was added, washed with CH₂Cl₂ (100 mL). Saturated aq. K₂CO₃ (150 mL) was added to the aqueous phase. The product was extracted with CH₂Cl₂ (2x100 mL), extracts were dried over Na₂SO₄ and evaporated. The residue was dried under vacuum. White solid, 2.20 g (11.9 mmol, 52%).

LCMS [M+H]⁺ 186.1
$^1$H NMR (300 MHz, DMSO): δ 7.00 (m, 2H), 6.86 (m, 2H), 3.93 (m, 3H), 2.96 (m, IH), 2.86 (m, IH), 1.71 (br. s, 3H).

(S)-l-Amino-3-(4-fluoro-phenoxy)-propan-2-ol was prepared by the same procedure.

Scheme 25

Procedure for the Preparation of l-Amino-3-aryloxypropan-2-ols, l-Amino-3-arylthiopropan-2-ols, and l-Amino-3-arylaminopropan-2-ols and their Heteroaryl analogs,

![Scheme 25](image)

General procedure for preparation of (R)-l-amino-3-aryloxy-propan-2-ols. A mixture of (R)-N-(2,3-epoxypropyl)-phthalimide (1.02 g, 5.0 mmol), phenol (5.0 mmol), p-xylene (2 mL) and DBU (0.05 mL) was stirred under N$_2$ at 120 0°C for 8 h. After cooling to 80 0°C PrOH (20 mL) and anhydrous hydrazine (1 mL) were added and the mixture was heated at 80 0°C for 4 h. The reaction mixture was cooled to RT, 0.5N aq. NaOH (50 mL) was added, extracted with EtOAc (100 mL). Extract was washed with 0.5N aq. NaOH (50 mL), brine (50 mL), dried over Na$_2$SO$_4$ and evaporated. The residue was triturated with cold Et$_2$O, the solid was collected by filtration, dried in vacuum.

The heteroaryloxy analogs and the thio and amino deivatives of are prepared analogously to the above procedure.

![Scheme 25](image)
(R)-1-Amino-3-(3-chloro-2-methyl-phenoxy)-propan-2-ol
Tan solid, 0.86 g. LCMS: [M+H]^+ 216.1

^1^H NMR: (300 MHz, DMSO): δ 7.16 (m, 1H), 6.97 (m, 2H), 3.93 (m, 2H), 3.73 (m, 1H), 2.66 (m, 2H).

(R)-1-Amino-3-(3-chloro-2,6-difluoro-phenoxy)-propan-2-ol. Tan solid, 1.01 g. LCMS [M+H]^+ 239.9

^1^H NMR (300 MHz, DMSO): δ 7.32 (m, 1H), 7.21 (m, 1H), 4.10 (m, 2H), 3.68 (m, 1H), 2.63 (m, 2H).

(R)-1-Amino-3-(3-chloro-2-fluoro-phenoxy)-propan-2-ol
Tan solid, 1.25 g. LCMS [M+H]^+ 219.8

^1^H NMR (300 MHz, DMSO): δ 7.15 (m, 3H), 4.02 (m, 2H), 3.77 (m, 1H), 2.64 (m, 2H).

(R)-I-Amino-3-(3-trifluoromethylsulfanyl-phenoxy)-propan-2-ol
Tan solid, 1.11 g. LCMS [M+H]^+ 267.6

^1^H NMR (300 MHz, DMSO): δ 7.46 (m, 1H), 7.24 (m, 3H), 4.04 (m, 1H), 3.90 (m, 1H), 3.72 (m, 1H), 2.62 (m, 2H).
(R)-1-Amino-3-(2,4,6-trimethyl-phenoxy)-propan-2-ol
Tan solid, 0.89 g. LCMS [M+H]^+ 210.1
\(^1H\) NMR (300 MHz, DMSO): δ 6.81 (s, 2H), 3.64 (m, 3H), 2.73 (m, IH), 2.60 (m, IH), 2.18 (s, 9H).

(R)-1-Amino-3-(3-chloro-4-methyl-phenoxy)-propan-2-ol
Tan solid, 0.99 g. LCMS [M+H]^+ 215.8
\(^1H\) NMR (300 MHz, DMSO): δ 7.23 (m, IH), 7.00 (s, IH), 6.81 (m, IH), 3.93 (m, IH, 3.82 (m, IH), 3.65 (m, IH), 2.61 (m, 2H), 2.23 (s, 3H).

(R)-1-Amino-3-(2,4-dimethyl-phenylsulfanyl)-propan-2-ol
Off white solid, 0.88 g. LCMS [M+H]^+ 212.1
\(^1H\) NMR (300 MHz, DMSO): δ 7.22 (d, J=8.3 Hz, IH), 7.01 (m, 2H), 4.95 (br. s., IH), 3.48 (m, IH), 2.97 (dd, J=5.8, 12.9 Hz, IH), 2.83 (dd, J=6.7, 12.9 Hz, IH), 2.58 (m, 2H), 2.25 (s, 3H), 2.22 (s, 3H).

(R)-1-Amino-3-(2-tert-butyl-4-methyl-phenoxy)-propan-2-ol
Brown solid, 0.94 g. LCMS [M+H]^+ 238.1
\( ^1H \text{NMR} \ (300 \text{ MHz, DMSO}) \): \( \delta \ 6.96 \ (s, 1H), \ 6.83 \ (m, 2H), \ 3.83 \ (m, 3H), \ 2.70 \ (m, 2H), \ 2.21 \ (s, 3H), \ 1.33 \ (s, 9H) \).

(R)-l-Amino-3-(2,2,3-trifluoro-2,3-dihydro-benzo[1,4]dioxin-5-yloxy)-propan-2-ol
White solid, 0.91 g. LCMS [M+H]\(^+\) 279.9

\( ^1H \text{NMR} \ (300 \text{ MHz, DMSO}) \): \( \delta \ 7.20-6.70 \ (m, 4H), \ 4.04 \ (m, 1H), \ 3.94 \ (m, 1H), \ 3.72 \ (m, 1H), \ 2.63 \ (m, 2H) \).

(R)-l-Amino-3-(3-chloro-2,6-dimethyl-phenoxy)-propan-2-ol
Brown solid, 1.06 g. LCMS [M+H]\(^+\) 279.9

\( ^1H \text{NMR} \ (300 \text{ MHz, DMSO}) \): \( \delta \ 7.13 \ (m, 1H), \ 7.04-6.78 \ (m, 3H), \ 4.00, \ (m, 2H), \ 3.74 \ (m, \IH), \ 2.63 \ (m, 2H) \).
Orange solid, 0.59 g (starting from 2.9 mmol of phenol). LCMS [M+H]+ 230.1

^1^H NMR (300 MHz, DMSO): δ 7.08 (m, 2H), 3.73 (m, 2H), 3.64 (m, 1H), 2.51 (m, 2H), 2.27 (s, 3H), 2.22 (s, 2H).

(R)-I -Amino-3-(3-chloro-2,4-dimethyl-phenoxy)-propan-2-ol

Brown solid, 0.59 g (starting from 2.9 mmol of phenol). LCMS [M+H]+ 230.4

^1^H NMR (300 MHz, CDCl\textsubscript{3}): δ 7.01 (d, J=8.6 Hz, 1H), 6.68 (d, J=8.4 Hz, 1H), 3.96 (m, 3H), 2.95 (m, 2H), 2.31 and 2.29 (two overlapped singlets, 6H), 2.20 (br. s, 3H).

(R)-I -Amino-3-(3-methoxy-2-methyl-phenoxy)-propan-2-ol

Tan solid, 0.51 g (starting from 3.0 mmol of phenol).
LCMS [M+H]+ 246.1.

^1^H NMR (300 MHz, CDCl\textsubscript{3}): δ 6.73 (s, 2H), 3.95 (m, 3H), 3.86 (s, 3H), 2.95 (m, 2H), 2.31 (s, 3H).

(R)-I -Amino-3-(3-methoxy-2-methyl-phenoxy)-propan-2-ol

Beige solid, 0.40 g. LCMS [M+H]+ 212.3.
(R)-l-Amino-3-(2,3-difluoro-4-methyl-phenoxy)-propan-2-ol
White solid, 0.49 g. LCMS [M+H] + 218.1.

(R)-l-Amino-3-(3-fluoro-2-methyl-phenoxy)-propan-2-ol
Brown solid, 0.81 g. LCMS [M+H] + 200.4.

(R)-l-Amino-3-(3-methoxy-2,4-dimethyl-phenoxy)-propan-2-ol
Yellow solid, 0.82 g. LCMS [M+H] + 226.4.

(R)-l-Amino-3-(2-trifluoromethoxy-phenoxy)-propan-2-ol
LCMS [M+H] + 251.9.

(R)-l-Amino-3-(2-methylsulfanyl-phenoxy)-propan-2-ol
LCMS [M+H] + 213.9.
(R)-l-Amino-3-o-tolyloxy-propan-2-ol

LCMS [M+H]+ 181.9.

(R)-l-Amino-3-(2-ethyl-phenoxy)-propan-2-ol

LCMS [M+H]+ 196.1.

Preparation of (R)-l-Amino-3-(2,4-dimethylphenoxy)propan-2-ol:

1. To a solution of (i?-N-(2,3-epoxypropyl)-phthalimide (3.0 g, 14.8 mmol) and 2,4-dimethylphenol (1.6 g, 13.0 mmol) in toluene (30 mL) was added DBU (1.3 mmol) and the resulting mixture was heated at 120 °C for 18 h. The reaction mixture was cooled to 75 °C, diluted with isopropanol (50 mL) and treated with hydrazine (4 mL). After stirring the mixture at 80 °C for 4 h, cooled to room temperature and solvents were evaporated in vacuo.

2. The residue was dissolved in aq. NaOH (100 mL, 5 N) and extracted with chloroform (2x100 mL). The combined organic layer was washed with brine (100 mL) and dried over Na₂SO₄. The solvent was filtered and evaporated in vacuo to afford the desired product as an off-white solid. Yield: 1.7 g, 59% LCMS [M+H]+ 196.1 The product can be recrystallized from isopropyl alcohol.

According to this methodology, many derivatives of the above can be prepared from phenols, their heteroaryl analogs, thiols, amines, alcohols and sulfonamides.
Nitration of 3-Methylphthalic anhydride

Scheme 26

Methyl-phthalic anhydride (100.0 g) was placed in 1 L-3-neck flask equipped with thermometer, addition funnel and long reflux condenser and was added cone. H$_2$SO$_4$ (130 mL). The suspension was heated to 70 °C using oil bath. The oil bath was removed and the fuming nitric acid (43 mL) was added dropwise while the temperature was maintained between 90-110 °C. Once addition was completed, cone. HNO$_3$ (180 mL) was added at a rate the temperature of the reaction mixture don't exceed 110 °C. After the addition was complete, the reaction mixture was heated at 90 °C for 2 h. The reaction mixture was cooled to room temperature and let stand overnight. The suspension was poured into ice-water (1 L) and extracted with EtOAc (2 x 750 mL). The combined organic layer was washed with water (1 L), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to afford light yellow solid. The obtained solid was triturated with hexanes (1 L), filtered and dried in vacuo to afford the mixture of nitro-methyl-phthalic acids as a light yellow solid. Yield: 128.0 g, 93%.

Esterification of mixture of nitro-3-methylphthalic acids

Scheme 27

To a stirred solution of mixture of nitro-3-methylphthalic acids (124.0 g) in anhydrous MeOH (650 mL) was added cone. H$_2$SO$_4$ (40 mL) slowly and the resulting mixture was heated at reflux for 24 h. The reaction mixture was cooled to room temperature, solvent was evaporated in vacuo. The residue was dissolved in EtOAc (1.2 L), washed with water (1 L), sat. aq. NaHCO$_3$ (2 x 600 mL) and water (600 mL). The organic layer was dried over Na$_2$SO$_4$, filtered and evaporated in vacuo to afford the mixture of methyl-esters (3) (40.0 g, 29%) as a light yellow syrup which solidify on standing. The NaHCO$_3$ wash acidified with
cone. HCl to pH = 2, and extracted with EtOAc (1 L). The organic layer was dried over 
Na₂SO₄, filtered and concentrated in vacuo to afford the by-product mono-ester (3a) (90.0 g, 
69%) as an off-white solid.

Hydrogenation of mixture of nitro-esters

Scheme 28

\[
\begin{array}{c}
\text{H₂/Pd-C} \\
\text{MeOH, RT}
\end{array}
\quad
\begin{array}{c}
\text{H₂N} \\
\text{NH₂}
\end{array}
\]

To a suspension of niro-methylphthalic esters (40.0 g) and 10% Pd/C (4.0 g) was added 
MeOH (400 mL) carefully and evacuated under vacuum. The flask was filled with hydrogen 
under balloon pressure and stirred at room temperature for overnight. If the reaction is 
incomplete, add HCl/ether and continue the reaction. After the reaction was completed, the 
mixture was filtered through Celite bed, washed with MeOH (2 x 200 mL). The combined 
filtrate was concentrated in vacuo and the residue was basified aq. NaHCO₃ solution. The 
mixture was extracted with EtOAc (2 x 500 mL), dried over Na₂SO₄, filtered and 
concentrated in vacuo to afford the mixture of aminomethylphthalic esters in quantitative 
yield.

Acetylation of amino-methylphthalic esters

Scheme 29

\[
\begin{array}{c}
\text{Ac₂O, THF} \\
\text{50 C}
\end{array}
\quad
\begin{array}{c}
\text{AcH₂N} \\
\text{NHAc}
\end{array}
\]

To a solution of amino-methylphthalic esters (34.3 g) in THF was added 1.2 eq OfAc₂O (19.0 
ml) and the mixture was heated at 50 °C for 6 h. The reaction mixture was evaporated in 
vacuo and the residue was neutralized with aq. NaHCO₃ solution. The mixture was extracted 
with EtOAc (2 x 400 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to afford a 
mixture of isomers. The mixture was triturated with ether (300 mL), filtered the precipitated 
solid, washed with cold ether (2 x 50 mL) and dried to afford 4-acetamido-3-methylphthalic 
acid dimethyl ester (17.1 g, 40%) as a white solid. The ether layer contains above 90% of 6-
acetamido-3-methylphthalic acid dimethyl ester.
\( ^1H \) NMR (CDCl\(_3\), 300 MHz) for compound 6: \( \delta \) 2.16 (s, 3H); 2.22 (s, 3H); 3.88 (s, 3H); 3.97 (s, 3H); 7.37 (br.s, IH); 7.83 (d, \( J = 6.0 \) Hz, IH); 8.03 (d, \( J = 6.0 \) Hz, IH). ESI-MS (m/z): 266 (M+H\(^+\)); 234 (M-32).

Synthesis of 4-Acetylamido-3-methyl-5-nitro-phthalic acid dimethyl ester:

Scheme 30

To a cold solution of fuming HNO\(_3\) was added compound 6 (2.44 g, 9.20 mmol) in portions at 0 \(^\circ\)C and the mixture was kept standing at 4 \(^\circ\)C for overnight. The reaction mixture was poured into ice-water (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layer was washed with aq. NaHCO\(_3\) solution, dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo to afford 4-acetylamido-3-methyl-5-nitro-phthalic acid dimethyl ester (2.0 g, 71%) as a yellow solid.

Alternative work up for large scale reaction: Reaction mixture was poured into ice-water, the precipitated solid was isolated by filtration, washed with water, aq. NaHCO\(_3\) solution, water and dried in vacuo to afford the desired product as a light yellow solid.

\( ^1H \) NMR (CDCl\(_3\), 300 MHz): \( \delta \) 2.12, 2.40 (2s, 6H); 3.89, 3.90 (2s, 6H); 8.25 (s, IH); 10.27 (s, IH). ESI-MS (m/z): 311 (M+H\(^+\)).

Synthesis of 4-Amino-3-methyl-5-nitro-phthalic acid dimethyl ester

Scheme 31

A solution of 4-acetamido-3-methyl-5-nitro-phthalic acid dimethyl ester (2.8 g, 9.03 mmol) in cone. H\(_2\)SO\(_4\) was stirred at room temperature for 2 h. The reaction mixture was poured into ice-water (200 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with water (200 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo to afford the product 8 (1.8 g, 74%) as a yellow solid.
Synthesis of 4-Amino-3-methyl-5-nitro-phthalic acid 2-methyl ester

Scheme 32

To a solution of 4-Amino-3-methyl-5-nitro-phthalic acid dimethyl ester (1.8 g, 6.72 mmol) in THF (10 mL) and water (20 mL) was added 5 N NaOH (4.0 mL) and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was acidified with cone. HCl (pH = 2.0) and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the 4-Amino-3-methyl-5-nitrophthalic acid 2-methyl ester (1.3 g, 76%) as a yellow solid.

Synthesis of 5-Amino-4-methyl-2-(1-methyl-piperidin-4-yl)-6-nitro-isoiindole-1,3-dione

Scheme 33

To a solution of 4-Amino-3-methyl-5-nitro-phthalic acid 2-methyl ester (1.3 g, 5.12 mmol), EDCI.HCl (1.07 g, 5.63 mmol) and HOBt (0.69 g, 5.12 mmol) was added Et$_3$N (3.64 mL, 25.6 mL) and stirred at room temperature for 10 min. 4-Amino-1-methylpiperidine dihydrochloride (1.04 g, 5.63 mmol) was added and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was evaporated in vacuo, the residue was dissolved in CHCl$_3$ (200 mL), washed with water (2 x 100 mL). The organic layer was filtered over Na$_2$SO$_4$ and concentrated in vacuo to afford 5-Amino-4-methyl-2-(1-methyl-piperidin-4-yl)-6-nitro-isoiindole-1,3-dione (1.7 g, quant), which was used as such for further reaction.
Synthesis of 5,6-Diamino-4-methyl-2-(1-methyl-piperidin-4-yl)-isoindole-1,3-dione

Scheme 34

To a suspension of 5-Amino-4-methyl-2-(1-methyl-piperidin-4-yl)-6-nitro-isoindole-1,3-dione (1.7 g, 5.34 mmol) and 10% Pd/C (250 mg) was added MeOH (100 mL) carefully and evacuated in vacuo. The flask was filled with hydrogen under balloon pressure and stirred for 1 h. The reaction mixture was filtered and evaporated in vacuo to afford the crude 5,6-diamino-4-methyl-2-(1-methyl-piperidin-4-yl)-isoindole-1,3-dione (1.5 g, quant.), which was used as such for further reaction.

Synthesis of 2-(4-Iodo-2-methoxy-pyridin-3-yl)-4-methyl-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione

Scheme 35

To a solution of 5,6-Diamino-4-methyl-2-(1-methyl-piperidin-4-yl)-isoindole-1,3-dione (1.7 g, 5.90 mmol) in MeOH (50 mL) were added AcOH (3 mL) and 4-iodo-2-methoxynicotinaldehyde (1.55 g, 5.90 mmol) and the resulting mixture was heated at 60 °C for overnight. The reaction mixture was evaporated in vacuo and the residue was purified by flash chromatography (5-10%(6% NH₃ in MeOH)/CHCl₃) to afford 2-(4-Iodo-2-methoxy-pyridin-3-yl)-4-methyl-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione (1.48 g, 47%) as a yellow solid.
Synthesis of 2-(4-Iodo-2-oxo-1,2-dihydro-pyridin-3-yl)-4-methyl-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione Hydrochloride

Scheme 36

To a solution of 2-(4-Iodo-2-methoxy-pyridin-3-yl)-4-methyl-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione (1.48 g, 2.78 mmol) in 1,4-dioxane (30 mL) was added conc. HCl (3 mL) and the resulting solution was stirred at room temperature for overnight. The solid precipitated was isolated by filtration, washed with THF (10 mL) and dried in vacuo to afford 2-(4-Chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-4-methyl-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione Hydrochloride and 2-(4-Iodo-2-oxo-1,2-dihydro-pyridin-3-yl)-4-methyl-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione Hydrochloride (1.5 g, quant.) as a yellow solid.

Synthesis of 2-{(R)-3-(2,4-dimethyl-phenoxy)-2-hydroy-propylamino}-2-oxo-1,2-dihydro-pyridin-3 -yl }-4-methyl-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione

Scheme 37

To a suspension of 2-(4-Iodo-2-oxo-1,2-dihydro-pyridin-3-yl)-4-methyl-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione Hydrochloride and 2-(4-Chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-4-methyl-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-
5,7-dione Hydrochloride (0.75 g, 1.45 mmol), (R)-3-amino-l-(2,4-dimethylphenoxy)-2-propanol (0.34 g, 1.73 mmol) in EtOH (20 mL) was added Et₃N (0.61 mL, 4.35 mmol) and the resulting mixture was heated at reflux for overnight. The reaction mixture was evaporated in vacuo and the residue was purified by flash chromatography (10%/6% NH₃/MeOH/CHCl₃) to afford 2-{{4-[(R)-3-[(2,4-dimethylphenoxy)-2-hydroxypropylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-4-methyl-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione (0.45 g, 57%) as a yellow solid.

1H NMR (DMSO-d⁶, 300 MHz): δ 1.58 (d, J = 10.8 Hz, 2H); 1.93 (t, J = 11.5 Hz, 2H); 2.15, 2.19 (2s, 9H); 2.32-2.40 (m, 2H); 2.77-2.88 (m, 6H); 3.34-3.70 (m, 2H); 3.91-4.23 (m, 5H), 5.55 (d, J = 4.7 Hz, IH); 6.20 (d, J = 7.5 Hz, IH); 6.78-6.97 (m, 3H); 7.38 (d, J = 6.7 Hz, IH); 7.94 (s, IH), 11.13 (s, IH), 11.29 (br.s, IH); 13.32 (s, IH). ESI-MS mlz 585.5 (MH⁺). Elemental analysis calcd. for C₃₂H₃₆N₆O₅H₂O: C, 63.77; H, 6.36; N, 13.94. Found: C, 63.68; H, 6.24; N, 14.07.

Synthesis of 2-{{4-[(R)-3-[(3-Chloro-2-methyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-4-methyl-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione

Scheme 38

Compound was prepared following the general procedure as described above.

1H NMR (DMSO-d⁶, 300 MHz): δ 1.59 (d, J = 12.0 Hz, 2H); 1.91-1.99 (m, 3H); 2.20 (s, 3H); 2.25 (s, 3H); 2.33-2.44 (m, 2H); 2.75 (s, 3H); 2.82-2.89 (m, 3H); 3.34 (br.s, 2H); 3.55-3.74 (m, 2H); 3.90-4.20 (m, 4H); 5.62 (d, J = 6.0 Hz, IH); 6.21 (d, J = 6.0 Hz, IH); 6.94-7.17
(m, 4H); 7.40 (br.s, IH); 7.95 (s, IH); 11.13 (br.s, IH); 11.29 (br.s, IH), 13.42 (s, IH). ESI-MS (m/z): 605.3 and 607.5.

Synthesis of 2-{4-[(R)-3-(3-Chloro-2,6-difluoro-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl }-4-methyl-6-( 1-methyl-piperidin-4-yl)- IH-1,3,6-triaza-s-indacene-5,7-dione

Scheme 39

Compound was prepared following the general procedure as described above.

IH NMR (DMSO-d$_6$, 300 MHz): $\delta$ 1.59 (d, J = 12.0 Hz, 2H); 1.91-1-99 (m, 3H); 2.20 (s, 3H); 2.34-2.46 (m, 2H); 2.81 (s, 3H); 2.87-2.90 (m, 3H); 3.34 (br.s, 2H); 3.55-3.72 (m, 2H); 3.91-4.10 (m, 4H); 4.28 (d, J = 3.0 Hz, 2H); 5.62 (d, J = 6.0 Hz, IH); 6.21 (d, J = 6.0 Hz, IH); 7.18-7.41 (m, 4H); 7.95 (s, IH); 11.09 (br.s, IH); 11.31 (br.s, IH), 13.42 (s, IH). ESI-MS (m/z): 627.5.

Synthesis of 2-{4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl }-6-((S)- 1-methyl-piperidin-3 -yl)- IH-1,3,6-triaza-s-indacene-5,7-dione

Scheme 40
Compound was prepared following the general procedure as described above.

IH NMR (DMSO-d$_6$, 300 MHz): $\delta$ 1.53-1.61 (m, 1H); 1.72-1.90 (m, 3H); 1.99-2.21 (m, 8H); 2.74 (br.s, 2H); 3.35 (s, 3H); 3.47-3.59 (m, 2H); 3.94-4.16 (m, 4H); 5.56 (d, $J = 6.0$ Hz, 1H); 6.23 (d, $J = 6.0$ Hz, 1H); 6.82-6.97 (m, 3H); 7.40-7.42 (m, 1H); 7.66 (s, 1H); 8.10 (s, 1H); 10.98 (br.s, 1H), 11.32 (br.s, 1H); 13.42 (s, 1H). ESI-MS (m/z): 571.3.

Synthesis of 2-{(4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1, 2-dihydro-pyridin-3 -yl]-6-((R)- 1-methyl-piperidin-3 -yl)-1H-1,3,6-triaza-s-indacene-5 ,7-dione

Scheme 41

Compound was prepared following the general procedure as described above.

IH NMR (DMSO-d$_6$, 300 MHz): $\delta$ 1.53-1.61 (m, 1H); 1.72-1.90 (m, 3H); 1.99-2.21 (m, 8H); 2.74 (br.s, 2H); 3.35 (s, 3H); 3.47-3.59 (m, 2H); 3.94-4.16 (m, 4H); 5.56 (d, $J = 6.0$ Hz, 1H);
6.23 (d, J = 6.0 Hz, IH); 6.82-6.97 (m, 3H); 7.40-7.42 (m, IH); 7.66 (s, IH), 8.10 (s, IH); 10.98 (br.s, IH), 11.32 (br.s, IH); 13.42 (s, IH). ESI-MS (m/z): 571.3.

Synthesis of 2-[[4-[(R)-3-(5-Chloro-2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione

Scheme 42

Compound was prepared following the general procedure as described above.

IH NMR (DMSO-d$_6$, 300 MHz): δ 1.62 (d, J = 12.0 Hz, 2H); 1.95 (t, J = 12.0 Hz, 2H); 1.21, 1.23 (2s, 6H); 2.33-2.44 (m, 2H); 2.87 (d, J = 9.0 Hz, 2H); 3.56-3.74 (m, 2H); 3.88-4.17 (m, 4H); 5.62 (d, J = 3.0 Hz, IH); 6.23 (d, J = 6.0 Hz, IH); 6.84 (d, J = 12.0 Hz, 2H); 7.40 (d, J = 9.0 Hz, IH); 7.69 (s, IH); 8.08 (s, IH); 8.33 (s, IH); 10.96 (br.s, IH); 11.32 (br.s, IH); 13.40 (s, IH). ESI-MS (m/z): 605.3.

Preparation of 1-Amino-3-heteroaryl-2-propanols

Scheme 43

General Procedure for the Preparation of (R)-1-Amino-3-indol-1-yl-propan-2-ols: A mixture of (R)-N-(2,3-epoxypropyl)-phthalimide (1.02 g, 5.0 mmol), substituted indole (5.0 mmol), p-xylene (5 mL) and NaH (80 mg of 60% in mineral oil) was stirred under N$_2$ at 120 °C for 8 h. After cooling to 80 °C EtOH (10 mL) and anhydrous hydrazine (1 mL) were added, the mixture was heated at 80 °C for 2 h. Then the reaction mixture was cooled to RT, diluted with EtOAc (100 mL), washed with 0.5N NaOH (2x50 mL), brine (50 mL). Organic
phase was dried over Na₂SO₄, evaporated. The residue was triturated with Et₂O, the precipitate was collected by filtration, dried in vacuum.

![Structural formula of 1-((R)-3-Amino-2-hydroxy-propyl)-1H-indole-4-carbonitrile]

Tan solid, 0.56 g. LCMS [M+H]⁺ 216.3.

¹H NMR (300 MHz, CDCl₃): δ 7.63 (d, J = 8.3 Hz, IH), 7.47 (d, J = 7.5 Hz, IH), 7.34 (d, J = 3.6 Hz, IH), 7.24 (t, J = 7.9 Hz, IH), 6.73 (d, J = 3.6 Hz, IH), 4.22 (m, 2H), 3.90 (m, IH), 2.89 (m, IH), 2.55 (m, IH).

![Structural formula of (R)-1-Amino-3-(5-methoxy-indol-1-yl)-propan-2-ol]

Tan solid, 0.27 g. LCMS [M+H]⁺ 221.1.

¹H NMR (300 MHz, CDCl₃): δ 7.25 (d, J = 8.5 Hz, IH), 7.12-7.08 (m, 2H), 6.85 (dd, J = 2.5, 8.8 Hz, IH), 6.43 (d, J = 3.4 Hz, IH), 4.12 (m, 2H), 3.94-3.80 (m, 4H), 2.82 (dd, J = 3.9, 13.1 Hz, IH), 2.55 (dd, J = 7.7, 12.7 Hz, IH).
Synthesis of (R)-2-(4-3-substituted-2-hydroxypropylamino)-2-oxo-1,2-dihydropyridin-3-yl)-
6-(1-methylpiperidin-4-yl)imidazo[4,5-f]isoindole-5,7(lH,6H)-dione

Scheme 44

\[
\text{R}^1 = \text{SAr}, \text{OA}r, \text{NHA}r, \text{N(lower alkyl)Ar}', \\
\text{R}^2 = \text{H, CH}_3 \\
\text{R}^3 = \text{O, H}_2 \\
\text{Ar}=\text{aryl or heteroaryl}
\]

General procedure

A mixture of chloropyridone [2-(4-chloro-2-oxo-1,2-dihydropyridin-3-yl)-6-
substituted-imidazo[4,5-f]isoindole-5,7(IH,6H)-dione] or 2-(4-chloro-2-oxo-1,2-
dihydropyridin-3-yl)-6-substituted-6,7-dihydroimidazo[4,5-f]isoindol-5(IH)-one (0.25
mmol), aminoalcohol (0.35 mmol), ethanol (5 mL) and triethylamine (0.35 ml) was stirred at
100 °C overnight. Then reaction was cooled to RT, the solvent was removed in vacuum, the
residue was purified by HPLC on a C18 column (acetonitrile-0.1% aq. TFA from 5:95% to
95:5%).
2-{4-[(R)-3-(3-Chloro-2-methyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-2,3-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione.

LCMS [M+H]+ 591.3.

^1H NMR (300 MHz, DMSO): δ 13.45 (br.s., IH), 11.33 (d, J= 6.2 Hz, IH), 10.96 (t, J= 5.2 Hz, IH), 9.85 (br.s., IH), 7.60-8.20 (br.s., 2H), 7.41 (t, J= 7.1 Hz, IH), 7.17 (t, J= 8.1 Hz, IH), 7.04-6.98 (2d, 2H), 6.24 (d, J= 8.1 Hz, IH), 4.40-4.20 (m, IH), 4.20-4.10 (m, IH), 4.10-4.00 (m, 2H), 3.80-3.70 (m, IH), 3.60-3.45 (m, 3H), 3.25-3.05 (m, 3H), 2.76 (d, J= 4.17 Hz, 3H), 2.70-2.50 (m, 2H), 2.30-2.20 (s and m, 4H), 2.00-2.85 (m, 2H).

2-{4-[(R)-3-(3-Chloro-2,6-difluoro-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione.

LCMS [M+H]+ 613.3.
$^1$H NMR (300 MHz, DMSO): $\delta$ 11.35 (d, $J$= 6.2 Hz, IH), 10.94 (t, $J$= 4.4 Hz, IH), 9.88 (br.s., IH), 7.99 (br.s., 2H), 7.50-7.15 (m, 3H), 6.22 (d, $J$= 7.1 Hz, IH), 4.40-4.05 (m, 5H), 3.75-3.60 (m, IH), 3.60-3.40 (m, 3H), 3.25-3.07 (m, 2H), 2.76 (d, $J$= 4.29 Hz, 3H), 2.70-2.50 (m, 2H), 1.94 (m, 2H).

2-{$\text{[(R)-3-(3-Chloro-2-fluoro-phenoxy)-2-hydroxy-propylamino]-2-oxo-2,3-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione.}$

LCMS [M+H]$^+$ 595.3.

$^1$H NMR (300 MHz, DMSO): $\delta$ 13.46 (s, IH), 11.33 (d, $J$= 6.0 Hz, IH), 10.96 (m, IH), 9.37 (br.s., 1H), 8.12 (s, IH), 7.75 (s, IH), 7.40 (m, IH), 7.30-7.10 (m, 4H), 6.22 (d, $J$= 7.0 Hz, IH), 5.73 (br.s., IH), 4.40-4.10 (m, 5H), 3.80-3.60 (m, IH), 3.60-3.40 (m, 3H), 3.30-3.10 (m, 2H), 2.78 (d, $J$= 4.20 Hz, 3H), 2.70-2.50 (m, 2H), 2.00 (m, 2H).
2-{4-[(R)-2-Hydroxy-3-(3-trifluoromethylsulfanyl-phenoxy)-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione. LCMS [M+H]+ 643.3.

$^1$H NMR (300 MHz, DMSO): δ 13.45 (br.s., 1H), 11.33 (d, J= 6.3 Hz, IH), 10.99 (m, IH), 9.75 (br.s., IH), 8.20-7.60 (2H), 7.50-7.20 (m, 5H), 6.25 (d, J= 7.1 Hz, IH), 4.40-4.25 (m, IH), 4.20-4.00 (m, 3H), 3.80-3.65 (m, IH), 3.60-3.45 (m, 4H), 3.23-3.10 (m, 2H), 2.80-2.70 (d, J= 4.2 Hz, 3H), 2.70-2.50 (m, 2H), 2.00-2.85 (m, 2H).

2-{4-[(R)-2-Hydroxy-3-(2,4,6-trimethyl-phenoxy)-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione. LCMS [M+H]+ 585.3.

$^1$H NMR (300 MHz, DMSO): δ 13.50 (br.s., 0.5H), 11.34 (d, J= 6.2 Hz, IH), 10.98 (m, IH), 9.91 (br.s., IH), 7.95 (br.s., 2H), 7.42 (t, J= 6.9 Hz, IH), 6.81 (s, 2H), 6.25 (d, J= 7.9 Hz, IH), 4.40-4.25 (m, IH), 4.20-4.10 (m, IH), 3.85-3.65 (m, 4H), 3.60-3.45 (m, 3H), 3.20-3.05 (m, 2H), 2.80-2.70 (m, 3H), 2.70-2.50 (m, 2H), 2.20, 2.17 (two s, 9H), 2.00-1.85 (m, 2H).
2- {4-[(R)-3-(3-Chloro-4-methyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione.

LCMS [M+H]+ 591.2.

\(^1\)H NMR (300 MHz, DMSO): \(\delta\) 13.50 (br.s., 0.5 H), 11.33 (d, J= 6.1 Hz, IH), 10.94 (m, IH), 9.90 (br.s., IH), 8.10-7.80 (2H), 7.42 (t, J= 6.9 Hz, IH), 7.25 (d, J= 8.4 Hz, IH), 7.05 (d, J= 2.4 Hz, IH), 6.90 (dd, J= 8.4, 2.4 Hz, IH), 6.23 (d, J= 7.5 Hz, IH), 4.40-4.25 (m, IH), 4.15-4.00 (m, 3H), 3.75-3.60 (m, IH), 3.55-3.43 (m, 3H), 3.22-3.08 (m, 2H), 2.80-2.70 m, 3H), 2.70-2.50 (m, 2H), 2.25 (s, 3H), 2.00-1.85 (m, 2H).
2-{4-[(R)-3-(2,4-Dimethyl-phenylsulfanyl)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3 -yl} -6-( 1-methyl-piperidin-4-yl)- IH- 1,3,6-triaza-s-indacene-5 ,7-dione.

LCMS [M+H]^+ 587.2.

\[
\text{\textsuperscript{\textit{1}}}H \text{ NMR (300 MHz, DMSO): } \delta 13.43 (\text{br.s., IH}), 11.32 (d, J= 6.2 Hz, IH), 10.92 (m, IH), 9.43 (\text{br.s., IH}), 8.13 (\text{br.s., IH}), 7.87 (\text{br.s., IH}), 7.39 (t, J= 6.5 Hz, IH), 7.26 (d, J= 7.9 Hz, IH), 7.02 (s, IH), 6.93 (d, J= 7.7 Hz, IH), 6.14 (d, J= 7.5 Hz, IH), 5.6 (\text{br.s., IH}), 4.32 (m, IH), 3.90 (m, IH), 3.30-2.90 (m, 5H), 2.80 (s, 3H), 2.70-2.50 (m, 2H), 2.30-2.20 (8H), 2.00-1.90 (m, 2H).
\]

2-{4-[(R)-3-(2-tert-Butyl-4-methyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3 -yl} -6-(1-methyl-piperidin-4-yl)- IH- 1,3,6-triaza-s-indacene-5 ,7-dione (free base). LCMS [M+H]^+ 613.2.

\[
\text{\textsuperscript{\textit{1}}}H \text{ NMR (300 MHz, DMSO): } \delta 13.41 (\text{br.s., IH}), 11.32 (d, J= 6.1 Hz, IH), 11.01 (m, IH), 8.09 (s, IH), 7.59 (s, IH), 7.41 (t, J= 6.8 Hz, IH), 7.06 (s, IH), 6.95-6.85 (m, 2H), 6.21 (d, J= 7.5 Hz, IH), 5.56 (d, J= 4.6Hz, IH), 4.20 (m, IH), 4.10-3.90 (3H), 3.80-3.70 (m, IH), 3.65-3.50 (m, IH), 2.95-2.85 (m, 2H), 2.50- 2.30 (m, 2H), 2.30-2.20 (7H), 2.10-1.90 m, 2H), 1.70-1.60 (m, 2H), 1.38 (s, 9H).
2-{4-[((R)-2-Hydroxy-3-(2,2,3-trifluoro-2,3-dihydro-benzo[1,4]dioxin-5-
yloxy)-propylamino] -2-oxo- 1,2-dihydro-pyridin-3 -yl] -6-(1-methyl-piperidin-4-yl)- 1H-1,3,6-
triaza-s-indacene-5,7-dione. LCMS [M+H]^+ 655.3.

\[ \delta 13.44 \text{ (br.s., IH), 11.34 (d, J= 5.4 Hz, IH), 10.99 (m, IH),}
9.49 (br.s, IH), 8.12 (br.s., IH), 7.84 (m, IH), 7.40 (t, J=6.1 Hz, IH), 7.20-7.00n (m, 3H),
6.95-6.85 (m, 2H), 6.23 (d, J= 7.9 Hz, IH), 5.69 (br.s., IH), 4.32 (m, IH), 4.10-3.90 (3H),
3.60-3.40 (2H), 3.30-3.05 (m, 2H), 2.79 (s, 3H), 2.70-2.50 (m, 2H), 2.00-1.85 (m, 2H). \]
2-\{4-[(R)-2-Hydroxy-3-(2,3,3-trifluoro-2,3-dihydro-benzo[1,4]dioxin-5-yloxy)-propylamino] -2-oxo- 1,2-dihydro-pyridin-3 -yl}\} -6-( 1-methyl-piperidin-4-yl)- 1H-1,3,6-triaza-s-indacene-5,7-dione.  LCMS [M+H]+= 655.7.

\[\text{\textsuperscript{1}H NMR (300 MHz, DMSO): } \delta 13.44 \text{ (br.s., IH), } \ \ 11.33 \text{ (d, J= 5.4 Hz, IH), } \ \ 10.99 \text{ (m, IH),} \ \ 9.44 \text{ (br.s, IH), } \ \ 8.13 \text{ (br.s, IH), } \ \ 7.80 \text{ (m, IH), } \ \ 7.38 \text{ (t, J=6.1 Hz, IH), } \ \ 7.20-6.95 \text{ (m, 3H), } \ \ 6.95-6.80 \text{ (m, 2H), } \ \ 6.23 \text{ (d, J= 7.9 Hz, IH), } \ \ 5.72 \text{ (br.s., IH), } \ \ 4.32 \text{ (m, IH), } \ \ 4.25-4.15 \text{ (3H), } \ \ 3.30-3.05 \text{ (m, 2H), } \ \ 2.79 \text{ (m, 3H), } \ \ 2.70-2.50 \text{ (m, 2H), } \ \ 1.99-1.85 \text{ (m, 2H).} \]

\[
\begin{align*}
\text{\textsuperscript{1}H NMR (300 MHz, DMSO): } \delta 13.47 \text{ (br.s., IH), } \ \ 11.34 \text{ (d, J= 5.8 Hz, IH), } \ \ 10.95 \text{ (m, IH),} \ \ 9.54 \text{ (br.s, IH), } \ \ 8.13 \text{ (br.s, IH), } \ \ 7.85 \text{ (m, IH), } \ \ 7.42 \text{ (t, J=6.8 Hz, IH), } \ \ 7.05-7.00 \text{ (m, 2H), } \ \ 6.24 \text{ (d, J 8.0 Hz, IH), } \ \ 4.55-4.45 \text{ (m, 2H), } \ \ 4.35-4.27 \text{ (m, IH), } \ \ 4.20-4.10 \text{ (m, IH), } \ \ 3.95-03.85 \text{ (m, 3H), } \ \ 3.25-3.10 \text{ (m, 2H), } \ \ 2.90 \text{ (s, 3H), } \ \ 2.80-2.75 \text{ (m, 3H), } \ \ 2.70-2.50 \text{ (m, 2H), } \ \ 2.30-2.20 \text{ (8H), } \ \ 1.99-1.85 \text{ (m, 2H).}
\end{align*}
\]
2-{4-[(R)-3-(3-Chloro-2,6-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione. LCMS [M+H]^+ 605.3.

^1H NMR (300 MHz, DMSO): δ 13.45 (br.s., 0.5H), 11.34 (d, J= 5.7 Hz, IH), 10.98 (m, IH), 9.86 (br.s, IH), 7.99 (br.s., IH), 7.43 (t, J=6.7 Hz, IH), 7.14-7.05 (m, 2H), 6.24 (d, J= 7.7 Hz, IH), 4.35-4.27 (m, IH), 4.20-4.10 (m, IH), 3.90-3.80 (m, 3H), 3.22-3.10 (m, 2H), 2.90 (m, 3H), 2.70-2.50 (m, 2H), 2.29 (s, 3H), 2.23 (s, 3H), 2.00-1.85 (m, 2H).

1-((R)-2-Hydroxy-3-[3-{6-(1-methyl-piperidin-4-yl)-5,7-dioxo-1,5,6,7-tetrahydro-1,3,6-triaza-s-indacen-2-yl]-2-oxo-1,2-dihydro-pyridin-4-ylamino }-propyl)-1H-indole-4-carbonitrile. LCMS [M+H]^+ 591.3.
$^1$H NMR (300 MHz, DMSO): $\delta$ 11.34 (d, $J=6.1$ Hz, IH), 10.97 (m, IH), 9.91 (br.s, IH), 8.03 (br.s., 2H), 7.99 (d, $J=8.3$ Hz, IH), 7.72 (d, $J=3.6$ Hz, IH), 7.55 (d, $J=6.7$ Hz, IH), 7.41 (t, $J=7.3$ Hz, IH), 7.29-7.22 (m, IH), 6.62 (d, $J=3.1$ Hz, IH), 6.16 (d, $J=7.2$ Hz, IH), 4.50 (dd, $J=13.9, 4.1$ Hz, 2H), 4.40-4.20 (m, 2H), 3.80-3.60 (m, 2H), 3.57 (s, IH), 3.55-3.42 (m, 3H), 3.22-3.05 (m, 2H), 2.85 (m, 3H), 2.70-2.50 (m, 2H), 2.00-1.85 (m, 2H).

2-{4-[(R)-2-Hydroxy-3-(5-methoxy-indol-1-yl)-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione.

LCMS [M+H]$^+$ 596.3.
2-{4-[(R)-3-(3-Chloro-2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl} -8-methyl-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione. LCMS [M+H]+ 619.5.

$^1$H NMR (300 MHz, DMSO): $\delta$ 13.35 (s, IH), 11.30 (d, J = 6.6 Hz, IH), 11.11 (m, IH), 9.39 (br.s, IH), 7.96 (s, IH), 7.40 (t, J = 6.6 Hz, IH), 7.08 (d, J = 8.8 Hz, IH), 6.86 (d, J = 8.8 Hz, IH), 6.22 (d, J = 8.8 Hz, IH), 5.59 (br.s., IH), 4.35-4.25 (m, IH), 4.23-4.15 (m, IH), 4.12-4.00 (m, 2H), 3.80-3.70 (m, IH), 3.30-3.05 (m, 2H), 2.90-2.70 (7H), 2.24 (s, 7H), 2.00-1.85 (m, 2H).

2-{4-[(R)-3-(3-Chloro-4-methoxy-2-methyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl} -8-methyl-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione. LCMS [M+H]+ 635.5.

$^1$H NMR (300 MHz, DMSO): $\delta$ 13.35 (s, IH), 11.30 (d, J = 5.6 Hz, IH), 11.11 (m, IH), 9.38 (br.s, IH), 7.96 (s, IH), 7.40 (t, J = 6.4 Hz, IH), 6.90 (m, 2H), 6.22 (d, J = 8.2 Hz, IH), 5.58 (br.s., IH), 4.37-4.23 (m, IH), 4.22-4.13 (m, IH), 4.12-4.00 (m, 3H), 3.85-3.65 (m, 7H), 3.65-3.50 (m, 2H), 3.25-3.08 (m, 2H), 2.90-2.70 (m, 7H), 2.35-2.20 (m, 8H), 2.15-2.05 (m, 3H), 2.00-1.85 (m, 2H).

- 150 -
Synthesis of lactam derivatives
Scheme 45

Ar=aryl or heteroaryl

General procedure.

A mixture of phthalimide-type compound [2-(4-(substituted-amino)-2-oxo-1,2-dihydropyridin-3-yl)-6-({Rl-substituted}imidazo[4,5-f]isoindole-5,7(HH,6H)-dione] (20 mg), AcOH (1.0 mL), Zn (dust) (100 mg) was stirred at 70°C for 10 h. Then the reaction mixture was cooled to RT, filtered, evaporated. The residue was purified by preparative HPLC on C18 column (acetonitrile-0.1% TFA) (5:95% to 95:5%).
2-[(R)-2-Hydroxy-3-(3-methoxy-2-methyl-phenoxo)-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1H-1,3,6-triaza-s-indacen-5-one. LCMS [M+H]+ 573.3.

2-[(R)-2-Hydroxy-3-(5-methoxy-indol-1-yl)-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1H-1,3,6-triaza-s-indacen-5-one. LCMS [M+H]+ 583.0.
2-[(R)-2-Hydroxy-1-(1H-imidazol-4-ylmethyl)-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1H-1,3,6-triaza-s-indacen-5-one. LCMS [M+H]^+ 503.5.

2-{4-[(R)-3-(2,3-Difluoro-4-methyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1H-1,3,6-triaza-s-indacen-5-one. LCMS [M+H]^+ 579.5.
2-\{(R)\}-2-Hydroxy-3-(2-fluoromethoxy-phenoxy)-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-IH-1,3,6-triaza-s-indacen-5-one. LCMS [M+H]^+ 613.3.

2-\{(R)\}-2-Hydroxy-3-(2-methylsulfanyl-phenoxy)-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-IH-1,3,6-triaza-s-indacen-5-one. LCMS [M+H]^+ 575.5.
\[ \text{LCMS } [M+H]^+ \text{ 543.5.} \]

\[ \text{LCMS } [M+H]^+ \text{ 557.5} \]
2-\{4-[(R)-3-(3-Fluoro-2-methyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}\}-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1H-1,3,6-triaza-s-indacen-5-one. LCMS [M+H]^+ 561.3.

2-\{4-[(R)-2-Hydroxy-3-(3-methoxy-2,4-dimethyl-phenoxy)-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl\}-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1H-1,3,6-triaza-s-indacen-5-one. LCMS [M+H]^+ 587.3.
2-[(R)-3-(3-Chloro-2,6-difluoro-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1H-1,3,6-triaza-s-indacen-5-one. LCMS [M+H]+ 599.5.

1H NMR (300 MHz, DMSO): δ 13.08 (br.s., IH), 11.24 (d, J = 5.9 Hz, IH), 11.14 (m, IH), 9.43 (br.s, IH), 8.02-7.70 (m, 2H), 7.37 (t, J = 6.4 Hz, IH), 7.29-6.94 (m, 3H), 6.22 (d, J = 7.5 Hz, IH), 5.58 (br.s., IH), 4.46 (s, 2H), 4.37-4.24 (m, IH), 4.20-4.11 (m, IH), 4.08 (s, 2H), 3.77-3.62 (m, IH), 3.25-3.16 (m, 2H), 2.81 (d, J = 4.3 Hz, 3H), 2.28 (s, 3H), 2.28-2.24 (m, IH), 2.08 (s, 2H), 2.03-1.96 (m, 3H).
\[ ^1H \text{NMR (300 MHz, DMSO): } \delta \ 13.08 \text{ (br.s., IH), } 11.26 \text{ (d, J= 6.7 Hz, IH), } 11.11 \text{ (m, IH), } 9.47 \text{ (br.s., IH), } 8.05-7.60 \text{ (m, 2H), } 7.40-6.95 \text{ (m, 3H), } 6.20 \text{ (d, J= 7.3 Hz, IH), } 5.56 \text{ (br.s., IH), } 4.48 \text{ (s, 2H), } 4.42-4.28 \text{ (m, IH), } 4.18-4.05 \text{ (m, 2H), } 3.77-3.62 \text{ (m, IH), } 3.60-3.35 \text{ (m, 4H), } 3.30-3.10 \text{ (m, 2H).} \]

Synthesis of 5,6-diamino-2-(1-methylpiperidin-4-yl)isoindolin-1-one

\[
\text{5,6-Diamino-2-(1-methylpiperidin-4-yl)isoindoline-1-one. A mixture of 5-amino-2-(1-methyl-piperidin-4-yl)-6-nitro-isoindole-1,3-dione (10.0 g, 32.9 mmol), tin powder (39.7 g, 329 mmol), EtOH (300 mL) and cone. HCl (100 mL) was stirred at 75 °C for 4 h. After cooling to RT excess of Tin was removed by filtration, the filtrate was evaporated. The residue was dissolved in CH}_2Cl_2-MeOH (1:1) mixture, basified with NH}_4OH. Precipitate formed was removed by filtration, SiO}_2 was added to the filtrate, stirred for 1 h, the solvent was evaporated, the residue was loaded onto SiO}_2 (500 g) column. Eluted with CH}_2Cl_2-MeOH-NH4OH (gradient from 100:0:0 to 100:10:1 v/v). Yield 7.86 g (30.2 mmol, 92%) as beige solid. LCMS [M+H]^+ 261.4.} \]
Nitration of 2-chloro-m-xylene. Nitric acid (90%, 50mL) was cooled to -35 °C (ethanol-dry ice bath). 2-Chloro-m-xylene (10 mL) was added dropwise over 1h keeping the temperature between -30 °C and -35 °C. The reaction mixture was poured onto ice, stirred for 10 min, precipitate formed was collected by filtration, washed with water, dried. The crude product was purified on SiO₂ (50 g), hexane -EtOAc (0 to 2% v/v). The product - yellow solid, 12.8 g, as a mixture of 2-chloro-1,3-dimethyl-4-nitro-benzene and chloro-1,3-dimethyl-5-nitro-benzene (4:1).

¹H NMR (300 MHz, CDCl₃): δ 7.95 (s, 0.5H) (II), 7.63 (d, J = 8.3 Hz, 1.0H) (I), 7.21 (d, J = 8.3 Hz, IH) (I), 2.55 (s, 3H) (I), 2.47 (s, 1.5H) (II), 2.45 (s, 3H) (I).
3-Chloro-2,4-dimethyl-aniline. To a solution of a mixture 2-chloro-1,3-dimethyl-4-nitro-benzene and chloro-1,3-dimethyl-5-nitro-benzene (12.8 g, 69 mmol) in EtOH (75 mL), cone. HCl (75 niL) was added. Than SnCl₂ (51.0 g) was added in two portions. The mixture was stirred overnight at RT, then heated at 60°C for 30 min, cooled to 0-5°C (ice bath). Neutralized with NaOH (70 g) in H₂O (500 ml). The product was extracted with Et₂O (500 ml). Extract was dried over Na₂SO₄, evaporated. The residue was crystallized two times from hexane providing 3.66 g 3-chloro-2,4-dimethyl-phenylamine as white crystals. The filtrates were evaporated in vacuo and the residue was separated on SiO₂ column (200 g), hexane -EtOAc (0 to 10% v/v), providing additionally 3.11 g of the product. Yield 6.77 g (43.5 mmol, 63%).

¹H NMR (300 MHz, CDCl₃): δ 6.89 (d, J= 8.3 Hz, IH), 6.52 (d, J= 8.0 Hz, IH), 3.57 (br.s., 2H), 2.27 (s, 3H), 2.24 (s, 3H).

3-Chloro-2,4-dimethylphenol. To a suspension of 3-chloro-2,4-dimethyl-aniline (0.47 g, 3.0 mmol), in a mixture of water (3 mL) and cone. H₂SO₄ (2 ml), a solution ofNa₂NO₂ (0.22 g) in H₂O (5 ml) was added dropwise at 0 °C. The mixture was stirred 1 h at 0 °C, than treated with urea (0.2 g), stirred for 10 min at 0 °C. A solution of CuSO₄ (1.0 g) in water (6 mL) was added and the mixture was stirred for 60 h at RT. The reaction mixture was extracted with CH₂Cl₂ (2x20 ml), extracts were dried over Na₂SO₄ and evaporated. The residue was separated on SiO₂ (4.0 g) column, hexane -EtOAc (0 to 10%). Brown crystals, 45 mg (0.29 mmol, 10%).

¹H NMR (300 MHz, CDCl₃): δ 6.92 (d, J= 8.3 Hz, IH), 6.59 (d, J= 8.1 Hz, IH), 4.96 (br.s., IH), 2.29 (s, 6H).
Preparation of 3-methoxy-2,4-dimethyl-phenol

Scheme 47

2,4-Dihydroxy-3-methyl-benzaldehyde. Phosphorus oxychloride (8.0 mL, 86 mmol) was added dropwise with stirring to DMF (26 mL, 0.336 mol) the temperature being kept at 10-20 °C. This reagent was slowly added to a solution of 2-methylresorcinol (4.84 g, 39 mmol) in 26 mL DMF at 20-30 °C. After 30 min the reaction mixture was poured in 2 M aq. NaOH (200 ml), extracted with Et₂O (2x100 mL), aqueous phase was neutralized with 5N aq. HCl, the product was extracted with Et₂O (2x200 mL), dried and evaporated. The residue was separated on SiO₂ (100g) column, hexane-EtOAc (0 to 20% v/v). Yield 4.1 g (27 mmol, 69%) as white solid. ¹H NMR (300 MHz, DMSO): δ 11.61 (s, IH), 10.79 (s, IH), 9.71 (s, IH), 7.43 (d, J= 8.4 Hz, IH), 6.55 (d, J= 8.5 Hz, IH), 1.97 (s, 3H).
4-Benzylloxy-2-hydroxy-3-methyl-benzaldehyde. A mixture of 2,4-dihydroxy-3-methyl-benzaldehyde (3.31 g, 21.8 mmol), benzylbromide (4.09 g, 23.9 mmol), NaHCO$_3$ (5.49 g, 65.4 mmol), 1,4-dioxane (30 mL) and water (12 mL) was stirred at 60 °C for overnight. Then the reaction mixture was cooled to RT, water (100 mL) was added, extracted with EtOAc (2x200 mL). The extract was dried over Na$_2$SO$_4$, evaporated. The residue was purified on SiO$_2$ (25 g) column, hexane-EtOAc (0 to 5%). Yield 1.57 g (6.48 mmol, 29%) as off-white solid.

$^1$H NMR (300 MHz, DMSO): δ 11.38 (s, 1H), 9.82 (s, 1H), 7.62 (d, J= 8.7 Hz, 1H), 7.84-7.32 (m, 5H), 6.85 (d, J= 8.6 Hz, 1H), 5.27 (s, 2H), 2.05 (s, 3H).

4-Benzylloxy-2-methoxy-3-methyl-benzaldehyde. A mixture of 4-benzylloxy-2-hydroxy-3-methyl-benzaldehyde (1.57 g, 6.49 mmol), dimethylsulfate (1.04 ml, 10.9 mmol), NaOH (1.02 g, 25.5 mmol), 1,4-dioxane (20 mL) and water (10 mL) was stirred at 90 °C for 6 h. The reaction mixture was cooled to RT, water (100 mL) was added, extracted with EtOAc (150 mL). The extract was washed with brine (100 mL), dried over Na$_2$SO$_4$ and
evaporated. The residue was purified on SiO₂ (25 g) column, hexane to toluene. Yield 1.20 g (4.68 mmol, 72%), white solid. ¹H NMR (300 MHz, DMSO):  δ 10.11 (s, 1H), 7.64 (d, J = 8.9 Hz, 1H), 7.49-7.32 (m, 5H), 7.05 (d, J = 8.9 Hz, 1H), 5.24 (s, 2H), 3.81 (s, 3H), 2.14 (s, 3H).

3-Methoxy-2,4-dimethyl-phenol. A mixture of 4-benzyloxy-2-methoxy-3-methyl-benzaldehyde (1.1 g, 4.68 mmol), 10% Pd/C (0.150 g), MeOH (20 mL) and cone. HCl was stirred under H₂ at RT for 1 h. Pd/C was removed by filtration, the filtrate was evaporated, the residue was purified on SiO₂ column (12 g), hexane - CH₂Cl₂ (100:0 to 50:50). Yield 0.67 g (4.40 mmol, 94%), brown oil. ¹H NMR (300 MHz, CDC13): δ 6.88 (d, J = 8.1 Hz, 1H), 6.49 (d, J = 8.2 Hz, 1H), 4.73 (s, 1H), 3.70 (s, 3H), 2.21 (s, 2H), 2.18 (s, 3H).

3-Methoxy-2-methyl-phenol was prepared according to published procedure: J.Org. Chem. 55, 5, 1990, 1469. To a solution of 2.0 g (50 mmol) NaOH and 2-methylresorcinol (6.2 g, 50 mmol) in water (50 mL), dimethylsulfate (4.8 mL, 50 mmol) was added at 95 °C over 30 min, then reaction was stirred for 2 h at 95 °C. After cooling to RT, the reaction mixture was poured into aqueous NaOH (8.0 g in 200 mL H₂O). Extracted with Et₂O (2x100 mL). The aqueous phase was acidified with 5 N aq. HCl, extracted with Et₂O (2x100 mL), extracts were dried over Na₂SO₄ and evaporated. The residue was purified on SiO₂ (200 g) column, hexane - EtOAc (0 to 20%). Yield 3.37 g (24.0 mmol, 49%), colorless oil. ¹H NMR (300 MHz, DMSO): δ 9.21 (s, 1H), 6.93 (t, J = 8.4 Hz, 1H), 6.48-6.38 (m, 2H), 3.72 (s, 3H), 1.98 (s, 3H).
Synthesis of lactams with 2-hydroxyamine side chains

Scheme 48

Synthesis of the compounds illustrated in Scheme 48
4-(5-Amino-6-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester: A mixture of 5-amino-6-nitro-isoindole-1,3-dione (2.07 g, 10 mmol), tert-butyl 4-amino-piperidine-1-carboxylate (2.5 g, 12 mmol), imidazole (1.63 g, 24 mmol) in dioxane (100 mL) was sealed in a ChemGlass heavy wall pressure flask. After it was heated at 140 °C for 72 h, the reaction mixture was evaporated to dryness at 95 °C (the bath temperature) under reduced pressure. The residue was mixed with (R)-l-amino-3-(2,4-dimethyl-phenoxy)-propan-2-ol (2.5 g, 12.8 mmol) in 1,4-dioxane (3.37 mL) and then 4-amino-piperidine-l-carboxylate (3.35 mL) at 50 °C for 1 h was added 2-propanol (20 mL), and then MeOH (230 mL). After it was stirred under atmospheric hydrogen pressure for 4 h, the reaction mixture was filtered through Celite. The filtrate was mixed with 4-iodo-2-methoxynicotinic aldehyde (3.37 g, 12.8 mmol) and AcOH (13 mL), stirred at the room temperature for 16 h, and evaporated under reduced pressure to afford a crude, which was mixed with HCl in 1,4-dioxane (4 M, 60 mL) and H2O (5 mL), heated at 70 °C for 1.5 h and evaporated at 95 °C (the bath temperature) to dryness. Et3N (5.35 mL, 38.4 mmol) was added to the solution of the residue in CH2Cl2 (250 mL) at 0 °C under N2, followed by the addition of the solution of BoC2O (3.35 g, 15.4 mmol). After it was stirred at 0 °C for 1 h and at the room temperature for 19 h, the reaction mixture was mixed slowly with MeOH (200 mL) at 0 °C and then evaporated at 70 °C (the bath temperature) to dryness under reduced pressure. The residue was mixed with (R)-l-amino-3-(2,4-dimethyl-phenoxy)-propan-2-ol (2.5 g, 12.8 mmol) in MeOH/28% aqueous NH4OH (320:10:1) afforded the title compound (2.09 g, 54 %). 1H NMR (CDCl3) δ 1.49 (s, 9H), 1.73 (m, 2H), 2.38 (m, 2H), 2.80 (m, 2H), 4.20-4.31 (3H), 7.03 (br s, 2H, NH), 7.34 (s, IH), 8.61 (s, IH); ESI-MS mlz 391.5 (MH+).
mmol) and Et$_3$N (5.35 mL, 38.4 mmol) in EtOH (200 mL) resulting a mixture, which was heated at 100 °C for 5 h and then concentrated. Chromatography of the residual mixture with CH$_2$Cl$_2$/MeOH/28% aqueous NH$_4$OH (250:10:1) furnished a fluorescent product which was mixed with zinc dust (5.5 g, 84 mmol) and AcOH (200 mL). After it was heated at 90 °C for 2 h, the reaction mixture was filtered and the filtrate was concentrated at 70 °C (the bath temperature) under reduced pressure. The residue was mixed with HCl in dioxane (4 M, 60 mL) and H$_2$O (5 mL), heated at 70 °C for 2.5 h and evaporated at 95 °C (the bath temperature) to dryness. The residue was basified with NH$_3$ in EtOH (2 M) and concentrated. Chromatography of the crude with CH$_2$Cl$_2$/MeOH/28% aqueous NH$_4$OH (40:10:1) afforded a fluorescent product (6.5 g). 50 mg of this product was subjected to HPLC purification to furnish the title compound in TFA salt form (37 mg). $^1$H NMR (DMSO-$d_6$) $\delta$ 1.90-2.05 (4H), 2.19 (s, 3H, CH$_3$), 2.22 (s, 3H, CH$_3$), 3.13 (m, 2H), 3.42 (m, 2H), 3.55 (m, IH), 3.69 (m, IH), 4.03 (m, 2H), 4.13 (m, IH), 4.39 (m, IH), 4.46 (s, 2H), 6.22 (d, $J = 7$ Hz, IH), 6.84 (d, $J = 7$ Hz, IH), 6.94 (d, $J = 7$ Hz, IH), 6.98 (s, IH), 7.39 (d, $J = 7$ Hz, IH), 7.55 (br s, IH), 7.85 (br s, IH), 11.14 (br s, IH, NH), 11.23 (br d, $J = 6$ Hz, IH, NH); ESI-MS mlz 543.5 (MH$^+$).

![Chemical Structure](image.png)

3-[4-{2-[(R)-3-[(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-7-oxo-5,7-dihydro-1H-1,3,6-triaza-s-indacen-6-yl]-piperidin-l-yl]-propionitrile: To a solution of the TFA salt of 2-[(R)-3-[(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-piperidin-4-yl-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one (40 mg, 0.061 mmol) in MeOH (2.4 mL) was added DIEA (600 µL, 3.4 mmol) at 0 °C under N$_2$ resulting a mixture which was stirred under N$_2$ at 0 °C for 20 min and followed by addition of acrylonitrile (197 µL, 3.0 mmol) via a syringe. The reaction mixture was stirred under N$_2$ at 0 °C for 1 h and at the room temperature for 1 h and then evaporated. The residue was subjected to HPLC purification to afford the title compound in
TFA salt form. 1H NMR (DMSO-δ6) δ 1.99-2.13 (4H), 2.19 (s, 3H, CH3), 2.22 (s, 3H, CH3), 3.12 (m, 2H), 3.22 (m, 2H), 3.47 (m, 2H), 3.51-3.75 (4H), 4.01 (m, 2H), 4.13 (m, 2H), 4.34 (m, 2H), 4.47 (s, 2H), 6.22 (d, J = 7 Hz, IH), 6.84 (d, J = 7 Hz, IH), 6.94 (d, J = 7 Hz, IH), 6.96 (s, IH), 7.36 (d, J = 7 Hz, IH), 7.59 (br s, IH), 7.86 (br s, IH), 11.13 (br s, IH, NH), 11.23 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 596.5 (MH+).

2-{4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-[(2-methanesulfonyl-ethyl)-piperidin-4-yl]-3H-1,3,6-triaza-s-indacen-5-one: A mixture of the TFA salt of 2-{4-[(R)-3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-piperidin-4-yl-3H-1,3,6-triaza-s-indacen-5-one (40 mg, 0.061 mmol) and methyl'vinyl sulfone (318.4 mg, 3.0 mmol) in EtOH (2.0 mL) was heated at 90 °C for 22 h and then evaporated. Chromatography of the residue with CH2Cl2/MeOH/28% aqueous NH4OH (125:10:1) afforded a fluorescent product which was subjected to HPLC purification to afford the title compound in TFA salt form. 1H NMR (DMSO-δ6) δ 2.01-2.17 (4H), 2.19 (s, 3H, CH3), 2.21 (s, 3H, CH3), 3.15 (s, 3H, CH3), 3.23 (m, 2H), 3.51-3.75 (8H), 4.01 (m, 2H), 4.15 (m, IH), 4.34 (m, IH), 4.47 (s, 2H), 6.22 (d, J = 7 Hz, IH), 6.84 (d, J = 7 Hz, IH), 6.94 (d, J = 7 Hz, IH), 6.98 (s, IH), 7.36 (dd, J = 7 Hz and 6Hz, IH), 7.59 (br s, IH), 7.83 (br s, IH), 11.14 (br s, IH, NH), 11.23 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 649.5 (MH+).
6-(1-Cyclopropylmethyl-piperidin-4-yl)-2-{4-[(R)-3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one: To a solution of the TFA salt of 2-{4-[(R)-3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-piperidin-4-yl-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one (40 mg, 0.061 mmol) and cyclopropanecarbaldehyde (150 µL, 2.0 mmol) in a mixed solvent of CH₃CN (6 nL) and H₂O (2 mL) was added AcOH (500 µL) at 0 °C and the resulting reaction mixture was stirred at 0 °C for 20 min and followed by addition of Na(OAc)₂BH (254 mg, 1.2 mmol). The reaction mixture was stirred at 0 °C for 1 h and at the room temperature for 1 h and then evaporated. The residue was subjected to HPLC purification to afford the title compound in TFA salt form. ¹H NMR (DMSO-ᵈ) δ 0.39 (m, 2H), 0.67 (m, 2H), 1.10 (m, IH), 2.03 (m, 2H), 2.12 (m, 2H), 2.19 (s, 3H, CH₃), 2.21 (s, 3H, CH₃), 3.01 (m, 2H), 3.18 (m, 2H), 3.50-4.15 (7H), 4.32 (m, IH), 4.47 (s, 2H), 6.22 (d, J = 7 Hz, IH), 6.80 (d, J = 7 Hz, IH), 6.91 (d, J = 7 Hz, IH), 6.97 (s, IH), 7.38 (d, J = 7 Hz, IH), 7.57 (br s, IH), 7.82 (br s, IH), 11.13 (br s, IH, NH), 11.22 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 597.3 (MH⁺).
2-{4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-ethyl-piperidin-4-yl)-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one: $^1$H NMR (DMSO$_d_6$) $\delta$ 1.00 (t, $J = 6$Hz, 3H), 1.70 (m, 2H), 1.80 (m, 2H), 2.02 (m, 2H), 2.18 (s, 3H, CH$_3$), 2.22 (s, 3H, CH$_3$), 2.33 (m, 2H), 2.98 (m, 2H), 3.55 (m, IH), 3.70 (m, IH), 3.97-4.08 (3H), 4.12 (m, IH), 4.42 (s, IHO, 4.46 (s, IH), 5.47 (d, $J = 4$ Hz, 0.5H, NH), 5.53 (d, $J = 4$ Hz, 0.5H, NH), 6.20 (d, $J = 7$ Hz, 0.5H), 6.21 (d, $J = 7$ Hz, 0.5H), 6.81 (d, $J = 7$ Hz, IH), 6.90 (s, IH), 6.95 (d, $J = 7$ Hz, IH), 7.37 (s, 0.5H), 7.31 (d, $J = 7$ Hz, IH), 7.68 (s, 0.5H), 7.80 (s, 0.5H), 7.94 (s, 0.5H), 11.15 (br d, $J = 7$ Hz, IH, NH), 11.19 (br s, $J = 7$ Hz, IH, NH); ESI-MS $mlz$ 571.3 (MH$^+$).

Scheme 49

Synthesis of the compounds illustrated by Scheme 49

2- {4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one: 2-{4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione (3.0 g, 5.26 mmol) was mixed with zinc dust (6.88g, 10.52 mmol) in AcOH (150 mL). After it was heated at 90 °C for 2 h, the reaction mixture was filtered and the filtrate was evaporated at 95 °C (the bath temperature) under reduced pressure to dryness. The residue was basified with 28%
aqueous NH₄OH solution and concentrated. Chromatography of the residual crude with CH₂Cl₂/MeOH/28% aqueous NH₄OH (90:10:1) afforded the title compound (2.45 g, 84%). ¹H NMR (DMSO-^δ) δ 1.70 (m, 2H), 1.80 (m, 2H), 2.05 (m, 2H), 2.20 (s, 3H, CH₃), 2.22 (s, 3H, CH₃), 2.28 (s, 3H, CH₃), 2.89 (m, 2H), 3.57 (m, IH), 3.79 (m, IH), 3.95-4.09 (3H), 4.11 (m, IH), 4.40 (s, IH), 4.45 (s, IH), 5.47 (d, J = 3 Hz, 0.5H, NH), 5.54 (d, J = 3 Hz, 0.5H, NH), 6.21 (m, IH), 6.80-7.00 (3H), 7.30-7.39 (1.5H), 7.69 (s, 0.5H), 7.79 (s, 0.5H), 7.93 (s, 0.5H), 11.12 (br d, J = 6 Hz, IH, NH), 11.22 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 557.7 (MH⁺).

2-{4-{[R]-3-(2,4-Dimethyl-phenox)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3 -yl }-8-methyl-6-( 1-methyl-piperidin-4-yl)-6,7-dihydro-3 H-1,3,6-triazas-indacen-5-one: ¹H NMR (DMSO-^δ) δ 1.70 (m, 2H), 1.82 (m, 2H), 2.01 (m, 2H), 2.16 (s, 3H, CH₃), 2.18 (s, 3H, CH₃), 2.20 (s, 3H, CH₃), 2.25 (s, 2H, CH₃ on the benzoimidazole), 2.50 (s, 2H, CH₃ on the benzoimidazole), 2.89 (m, 2H), 3.53 (m, IH), 3.69 (m, IH), 3.98-4.11 (3H), 4.18 (m, IH), 4.41 (s, 2H), 5.53 (br s, 1H, NH), 6.19 (d, J = 7Hz, IH), 6.79 (d, J = 7Hz, IH), 6.90 (d, J = 7Hz, IH), 6.95 (s, IH), 7.35 (d, J = 7Hz, IH), 7.79 (s, IH), 11.35 (br s, IH₃NH); ¹H NMR (MeOH-^δ) δ 1.78 (m, 2H), 1.87 (m, 2H), 2.12 (s, 3H, CH₃), 2.13 (m, 2H), 2.14 (s, 3H, CH₃), 2.25 (s, 3H, CH₃), 2.42 (s, 2H, CH₃ on the benzoimidazole), 2.89 (m, 2H), 3.58 (m, IH), 3.72 (m, IH), 4.01 (m, 2H), 4.11 (m, IH), 4.20 (m, 2H), 4.18 (m, IH), 4.38 (s, 2H), 6.12 (d, J = 7Hz, IH), 6.69 (d, J = 7Hz, IH), 6.79 (d, J = 7Hz, IH), 6.85 (s, IH), 7.20 (d, J = 7Hz, IH), 7.65 (s, IH); ESI-MS mlz 571.7 (MH⁺).
2-{4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-4-methyl-6-(l-methyl-piperidin-4-yl)-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one:  

$^1$H NMR (DMSO-$^6$) $\delta$ 1.67 (m, 2H), 1.82 (m, 2H), 2.00 (m, 2H), 2.16 (s, 3H, CH$_3$), 2.20 (s, 3H, CH$_3$), 2.22 (s, 3H, CH$_3$), 2.80 (s, 2H, CH$_3$ on the benzoimidazole), 2.85 (m, 2H), 3.56 (m, 2H), 3.68 (m, 2H), 3.96-4.11 (3H), 4.17 (m, 2H), 4.39 (br s, 2H), 5.50 (br s, 2H, NH), 6.19 (d, $J$ = 7Hz, IH), 6.79 (d, $J$ = 7Hz, IH), 6.90 (d, $J$ = 7Hz, IH), 6.95 (s, IH), 7.35 (d, $J$ = 7Hz, IH), 7.60 (s, IH), 11.20 (br s, IH, NH); 11.30 (br s, IH, NH); ESI-MS mlz 571.7 (MH$^+$).

2-{4-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-di hydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one:  

2-{4-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one (36.1 mg, 0.066 mmol) was mixed with zinc dust (100 mg) in AcOH (4 mL) and the reaction mixture was heated at 90 °C for 2 h. After it was cooled to the room temperature, the upper clear layer of the reaction mixture was evaporated and the residue was subjected to HPLC purification to afford the title
compound in TFA salt form (9.2 mg, 22%)

\[ ^1H \text{NMR (DMSO-}{^6}\text{)} \delta 1.90-2.15 (4H), 2.75 (s, 3H, CH\textsubscript{3}), 3.21 (m, 2H), 3.42-3.60 (2H), 3.65 (m, IH), 4.31 (m, IH), 4.50 (s, 2H), 4.98 (m, IH), 6.19 (d, J = 6 Hz, IH), 7.31-7.41 (3H), 7.51 (d, J = 6 Hz, IH), 7.63 (s, IH), 7.78 (s, IH), 7.90 (s, IH), 9.60 (br s, IH), 11.06 (br s, IH, NH), 11.23 (br d, J = 6 Hz, IH, NH); ESI-MS \text{mlz} 533.5 (MH^+) \]

Lactams with sulfonamide side chains

Scheme 50

\[ \text{iV-(2-Amino-ethyl)-2-bromo-benzenesulfonamide: To solution of (2-amino-ethyl)-carbamic acid tert-butyl ester (208 mg, 1.3 mmol) in CH}_2\textsubscript{2}Cl\textsubscript{2} (20 mL) was added DIEA (300 \mu L, 1.72 mmol) at 0 \degree C, followed by the addition of 2-bromo-benzenesulfonyl chloride (383 mg, 1.5 mmol). After it was stirred at 0 \degree C for 1 h and at the room temperature for another 16 h, the reaction mixture was evaporated thoroughly. The residue was diluted with 20\% TFA in CH}_2\textsubscript{2}Cl\textsubscript{2} (10 mL), stirred for 3 h at the room temperature, and evaporated. Chromatography of the residual crude with CH}_2\textsubscript{2}Cl\textsubscript{2}/MeOH/28\% aqueous NH}_4\textsubscript{OH (90:10:1) afforded the title compound (313 mg, 86\%). ^1H NMR (DMSO-}{^6}\text{)} \delta 2.86 (t, J = 8 Hz, 2H), 3.04 (t, J = 8 Hz, 2H), 7.55-7.65 (2H), 7.89 (d, J = 8 Hz, IH), 8.01 (d, J = 8 Hz, IH); ESI-MS \text{mlz} 279.1 (MH^+) \]
2-Bromo-N-(2- {3-[6-(1-methyl-piperidin-4-yl)-7-oxo-1,5,6,7-tetrahydro-1,3,6-triaza-s-indacen-2-yl]-2-oxo-1,2-dihydro-pyridin-4-ylamino}-ethyl)-benzenesulfonamide: To a solution of 2-(4-chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one (40 mg, 0.1 mmol) and 7N-(2-amino-ethyl)-2-bromo-benzenesulfonamide (56 mg, 0.20 mmol) in EtOH (4 mL) was added Et$_3$N (500 µL, 3.6 mmol) and the reaction was heated at 95 °C for 16 h. The solvent was evaporated in vacuo and the residue was purified by flash chromatography with CH$_2$Cl$_2$/MeOH/28% aqueous NH$_4$OH (100:10:1) afforded the title compound (7.3 mg, 11%). $^1$H NMR (DMSO-$_d_6$) $\delta$ 1.70 (m, 2H), 1.85 (m, 2H), 2.15 (m, 2H), 2.29 (s, 3H, CH$_3$), 2.96 (m, 2H), 3.19 (m, IH), 3.50 (m, 2H), 4.05 (m, IH), 4.48 (s, IH), 6.05 (d, $J = 7$ Hz, IH), 7.32 (br s, IH), 7.38-7.50(1.5H), 7.62-7.70 (1.5H), 7.82 (s, 0.5H), 7.87 (s, 0.5H), 7.96-7.99 (2H), 8.20 (br S, IH, NH), 11.02 (br s, IH, NH), 11.26 (br s, IH, NH); ESI-MS $mlz$ 640.5 (MH$^+$).
Synthesis of phenol and pyrimidinone derivatives

Scheme 51

3-Bromo-2-(5,5-dimethyl-[1,3]dioxan-2-yl)-6-methoxy-phenol: A mixture of 6-bromo-2-hydroxy-3-methoxy-benzaldehyde (2.31 g, 10.0 mmol), neopentyl glycol (1.14 g, 11.0 mmol), TsOH (9.5 mg) and triethyl orthoformate (1.93 g, 13.0 mmol) were heated at 110 °C for 30 min and then partitioned between NaHCO₃ (300 mL) solution and EtOAc (200 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined extracts were washed with brine and dried through Na₂SO₄. Evaporation of solvent afforded the title
2-(6-Bromo-3-methoxy-2-methoxymethoxy-phenyl)-5,5-dimethyl-[1,3]dioxane:

To the solution of 3-bromo-2-(5,5-dimethyl-[1,3]dioxan-2-yl)-6-methoxy-phenol in DCM (20 mL) was added DIEA (697 µL, 4 mmol), followed by addition of chloromethoxymethane (228 µL, 3 mmol). After it was stirred at the room temperature for 72 h, the reaction mixture was evaporated and the residue was partitioned between NaHCO$_3$ (50 mL) solution and EtOAc (40 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined extracts were washed with brine and dried through Na$_2$SO$_4$. Evaporation of solvent afforded the title compound. $^1$H NMR (CDCl$_3$) $\delta$ 0.80 (s, 3H), 1.45 (s, 3H), 3.57 (s, 3H), 3.65 (d, $J$ = 12 Hz, 2H), 3.79 (s, 3H), 3.80 (d, $J$ = 12 Hz, 2H), 5.11 (s, 2H), 6.00 (s, IH), 6.76 (d, $J$ = 8 Hz, IH), 7.32 (d, $J$ = 8 Hz, IH).

(R)-I-[2-(5,5-Dimethyl-[1,3]dioxan-2-yl)-4-methoxy-3-methoxymethoxy-phenylamino]-3-(2,4-dimethyl-phenoxy)-propan-2-ol:

A mixture of 2-(6-bromo-3-methoxy-2-methoxymethoxy-phenyl)-5,5-dimethyl-[1,3]dioxane (36 mg, 0.1 mmol), (R)-l-amino-3-(2,4-dimethyl-phenoxy)-propan-2-ol (30 mg, 0.15 mmol), CuI (51.4 mg, 0.27 mmol), ethylene glycol (168 mg, 2.7 mmol), and K$_3$PO$_4$ (573 mg, 2.7 mmol) in 2-propanol (8 mL) was heated at 90°C in a sealed vial for 14 h and evaporated. Chromatography of the residue with hexanes and EtOAc afforded the title compound (305 mg, 71%). $^1$H NMR (CDCl$_3$) $\delta$ 0.79 (s, 3H, CH$_3$), 1.29 (s, 3H, CH$_3$), 2.21 (s, 3H, CH$_3$), 2.25 (s, 3H, CH$_3$), 2.95 (br s, IH,
OH), 3.30 (m, IH), 3.49 (s, 3H, OCH₃), 3.51 (m, IH), 3.65 (m, 2H), 3.75 (s, 3H, OCH₃), 3.77 (m, 2H), 4.00 (m, 2H), 4.25 (m, IH), 5.09 (s, 2H), 6.05 (s, IH), 6.48 (d, J = 8 Hz, IH), 6.69 (d, J = 8 Hz, H), 6.82 (d, J = 8 Hz, IH), 6.92 (d, J = 8 Hz, IH), 6.95 (s, IH). ESI-MS mlz 476.8 (MH⁺).

2-{6-{(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino}-2-hydroxy-3-methoxy-phenyl}-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one:
To a solution of (R)-1-[2-(5,5-dimethyl-[1,3]dioxan-2-yl)-4-methoxy-3-methoxymethoxy-phenylamino]-3-(2,4-dimethyl-phenoxy)-propan-2-ol (102 mg, 0.21 mmol) in THF (5.0 mL) was added 36% aqueous HCl (1.0 mL). After it was heated at 50 °C for 1.5 h, the reaction mixture was evaporated and the residue was mixed with 5,6-diamino-2-(1-methyl-piperidin-4-yl)-2,3-dihydro-isindol-1-one (76 mg, 0.21 mmol) and AcOH (0.4 mL) in EtOH (8 mL). The mixture was stirred at the room temperature for 30 min, heated at 80 °C for 1.5 h, and evaporated to dryness. Chromatography of the residual crude with CH₂Cl₂/MeOH/2 8% aqueous NH₄OH (40:10:1) afforded the title compound (13 mg, 10%). ESI-MS mlz 586.5 (MH⁺).
Synthesis of pyrimidinone derivatives

Scheme 51

2-{4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-6-oxo-1,6-dihydro-pyrimidin-5-yl}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione:

To a solution of 4,6-dichloro-pyrimidine-5-carbaldehyde (177 mg, 1.0 mmol) and (R)-I-amino-3-(2,4-dimethyl-phenoxy)-propan-2-ol (195.3 mg, 1.0 mmol) in chloroform (8 mL) was added Et₃N (348 µL, 2.5 mmol). After it was stirred at the room temperature for 8 h, the reaction mixture was evaporated under reduced pressure thoroughly. The remaining residue was mixed with 5,6-diamino-2-(1-methyl-piperidin-4-yl)-isoindole-1,3-dione (274 mg, 1.0 mmol) in DMA (10 mL). After it was heated at 110 °C for 14 h, the reaction mixture was cooled to the room temperature and mixed with aqueous HCl solution (12 N, 1 mL). The resulting mixture was heated in a sealed vial at 110 °C for 3 h and evaporated to dryness. The residue was basified with NH₃ in EtOH (2 M) and concentrated. Chromatography of the
crude afforded the title compound (93 mg, 17% yield for 3 steps). \(^1\)H NMR (DMSO-\(\text{c/_6}\)) \(\delta\) 1.62 (m, 2H), 1.97 (m, 2H), 2.14 (s, 3H, \(\text{CH}_3\)), 2.17 (s, 3H, \(\text{CH}_3\)), 2.17 (s, 3H, \(\text{CH}_3\)), 2.38 (m, 2H), 2.89 (m, 2H), 3.80 (m, 2H), 3.90-4.02 (4H), 4.11 (m, 1H), 5.47 (br s, 1H, NH), 6.82 (d, \(J = 6\) Hz, 1H), 6.93 (d, \(J = 6\) Hz, 1H), 6.97 (s, 1H), 8.06 (s, 1H), 8.12 (s, 1H), 10.83 (br s, 1H, NH); ESI-MS \(\text{mlz}\) 572.3 (MH\(^+\)).

\[
\begin{array}{c}
\text{O} \\
\text{H} \\
\text{N} \\
\text{N} \\
\text{H} \\
\text{NH} \\
\text{OH} \\
\text{O} \\
\end{array}
\]

\[
\text{2-\{6-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-4-oxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-yl\}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione}
\]

was mixed with zinc dust (300 mg) in AcOH (12 mL) resulting a mixture which was heated at 90 °C for 1 h, then cooled to the room temperature and filtered. The filtrate was evaporated, the residue was basified with \(\text{NH}_3\) in EtOH (2 M) and purified by chromatography with \(\text{CH}_2\text{Cl}_2/\text{MeOH/28\% aqueous NH}_3\text{OH (60:10:1)}\) to furnish a fluorescent product which was subjected to HPLC purification to afford the title compound in TFA salt form (42 mg, 60%). \(^1\)H NMR (DMSO-cfe) \(\delta\) 1.90-2.15 (4H), 2.13 (s, 3H, \(\text{CH}_3\)), 2.20 (s, 3H, \(\text{CH}_3\)), 2.81 (s, 3H, \(\text{CH}_3\)), 3.20 (m, 2H), 3.40-3.60 (4H), 3.97 (m, 2H), 4.13 (m, 1H), 4.31 (m, 1H), 4.40 (s, 2H), 4.46 (s, 2H), 6.83 (d, \(J = 6\) Hz, 1H), 6.93 (d, \(J = 6\) Hz, 1H), 6.96 (s, 1H), 7.53 (br s, 1H), 7.75 (s, 1H), 9.75 (br s, 1H); ESI-MS \(\text{mlz}\) 560.5 (MH\(^+\)).
Synthesis of additional phthalimide derivatives

Scheme 53

Synthesis of the compound illustrated by Scheme 53

2-{4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-piperidin-4-yl-1,3,6-triaza-s-indacene-5,7-dione: To a mixture of 4-(5-amino-6-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester (203 mg, 0.52 mmol) and 10% Pd/C (20 mg) was added 2-propanol (2 mL), and then MeOH (50 mL). After it was stirred under atmospheric hydrogen pressure for 3 h, the reaction mixture was filtered through Celite. The filtrate was mixed with 4-iodo-2-methoxynicotinic aldehyde (137 mg, 0.52 mmol) and AcOH (3 mL), stirred at the room temperature for 14 h, and evaporated under reduced pressure to afford a crude, which was mixed with HCl in dioxane (4 M, 15 mL) and H₂O (1 mL), heated at 70 °C for 4 h and evaporated at 95 °C (the bath temperature) to dryness. The residue was mixed with (R)-I-amino-3-(2,4-dimethyl-phenoxy)-propan-2-ol (117 mg, 0.6 mmol) and Et₃N (418 µL, 3 mmol) in EtOH (8 mL) resulting a mixture, which was heated at 95 °C for 18 h and then concentrated. Chromatography of the residual mixture with CH₂Cl₂/MeOH/28% aqueous
NH₃OH (100:10:1) furnished a fluorescent product that was subjected to HPLC purification to furnish the title compound in TFA salt form (6.23 mg, 1.9%). ¹H NMR (DMSO- d₆) δ 1.90 (m, 2H), 2.19 (s, 3H, CH₃), 2.22 (s, 3H, CH₃), 3.10 (m, 2H), 3.30-3.42 (4H), 3.49 (m, IH), 3.72 (m, IH), 4.01 (m, 2H), 4.15 (m, IH), 5.58 (br s, IH, NH), 6.24 (d, J = 7 Hz, IH), 6.84 (d, J = 7 Hz, IH), 6.93 (d, J = 7 Hz, IH), 6.98 (s, IH), 7.40 (d, J = 7 Hz, IH), 7.66 (br s, IH), 8.11 (br s, IH), 10.96 (br s, IH, NH), 11.31 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 557.7 (MH⁺).

Scheme 54

Synthesis of the compounds illustrated by Scheme 54:

2-(4-Chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(1-ethyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione: To a mixture of 4-(5-amino-6-nitro-1,3-dioxo-1,3-dihydroisoindol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester (203 mg, 0.52 mmol) and 10% Pd/C (20 mg) was added 2-propanol (2 mL), and then MeOH (50 mL). After it was stirred under atmospheric hydrogen pressure for 3 h, the reaction mixture was filtered through Celite. The filtrate was mixed with 4-iodo-2-methoxynicotinic aldehyde (137 mg, 0.52 mmol) and AcOH (3 mL), stirred at the room temperature for 14 h, and evaporated under reduced pressure to afford a crude, which was mixed with HCl in dioxane (4 M, 15 mL) and H₂O (1...
mL), heated at 70 °C for 4 h and evaporated at 95 °C (the bath temperature) to dryness. To the residue and acetaldehyde (150 µL, 2.6 mmol) in a mixture of CH₃CN (6 mL) and H₂O (2 mL) at 0 °C, was added AcOH (500 µL) and the resulting mixture was stirred at 0 °C for 20 min, followed by addition of Na(OAc)₃BH (762 mg, 3.6 mmol). The reaction mixture was stirred at 0 °C for 1 h and at the room temperature for 1 h and then evaporated. The chromatography of the residue with CH₂Cl₂/MeOH/28% aqueous NH₄OH (70:10:1) afforded the title compound (143 mg, 67%). ESI-MS mlz 426.0 (MH⁺).

2-{4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3 -yl]-6-(1-ethyl-piperidin-4-yl)- 1H-1,3,6-triaza-s-indacene-5,7-dione: To a solution of 2-(4-chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(1-ethyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione (143 mg, 0.336 mmol) and (R)-l-amino-3-(2,4-dimethyl-phenoxy)-propan-2-ol (78 mg, 0.403 mmol) in EtOH (200 mL) was added Et₃N (5.35 mL, 38.4 mmol) and the mixture was heated at 95 °C for 16.5 h and then concentrated. Chromatography of the crude with CH₂Cl₂/MeOH/28% aqueous NH₄OH (160:10:1) (65 mg, 33%). ¹H NMR (DMSO-δ) 6 1.02 (t, J = 6 Hz, 3H), 1.63 (m, 2H), 1.83 (m, 2H), 2.19 (s, 3H, CH₃), 2.21 (s, 3H, CH₃), 2.29-2.40 (4H), 2.98 (m, 2H), 3.53 (m, IH), 3.70 (m, IH), 3.91-4.08 (3H), 4.18 (m, IH), 5.52 (d, J = 4 Hz, IH, NH), 6.23 (d, J = 7 Hz, IH), 6.83 (d, J = 7 Hz, IH), 6.91 (d, J = 7 Hz, IH), 6.97 (s, IH), 7.38 (d, J = 7 Hz, IH), 7.65 (s, IH), 8.09 (br s, IH), 10.95 (br s, IH, NH), 11.08 (br s, IH, NH); ESI-MS mlz 585.5 (MH⁺).
Synthesis of the compound illustrated by Scheme 55:

\[
\begin{align*}
2\{-4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-
dihydro-pyridin-3\text{-yl}\}6-\{1-(1-imino-ethyl)-piperidin-4-y1\} - 1\text{H} - 1,3,6\text{-triaza-s-indacene-5,7-dione: A mixture of 2-\{4-[(R)-3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-
dihydro-pyridin-3-y1\}-6-piperidin-4-yl-IH-1,3,6-triaza-s-indacene-5,7-dione (109 mg, 0.2 mmol) and ethyl acetimidate (3 g) in Et$_3$N (8 mL) was stirred at the room temperature for 110 h. After it was concentrated at 35 °C (the bath temperature) under reduced pressure, the mixture was subjected to chromatography [CH$_2$Cl$_2$/MeOH/28% aqueous NH$_4$OH (90:10:1)] to furnish a fluorescent product which was purified again with HPLC to afford the title compound in TFA salt form (5.06 mg, 3.6%). \text{\textsuperscript{1}H NMR (DMSCW$_6$) } \delta 1.93 (m, 2H), 2.19 (s, 3H, CH$_3$), 2.21 (s, 3H, CH$_3$), 2.35 (s, 3H, CH$_3$), 3.26 (m, IH), 3.40 (m, IH), 3.58 (m, IH), 3.86 (m, IH), 3.91-4.26 (7H), 4.43 (m, IH), 6.23 (d, $J = 7$ Hz, IH), 6.86 (d, $J = 7$ Hz, IH), 6.92 (d, $J = 7$ Hz, IH), 7.00 (s, IH), 7.41 (d, $J = 7$ Hz, IH), 7.71 (s, IH), 8.10 (s, IH), 8.68 (br s, IH, NH), 9.21 (br s, IH, NH), 10.97 (br s, IH, NH), 11.30 (br s, IH, NH); ESI-MS m/z 598.7 (MH$^+$).
\end{align*}
\]
Synthesis of additional phthalimide derivatives

Scheme 56

2-{4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-[1-(2-hydroxy-ethyl)-piperidin-4-ylmethyl]-1H-1,3,6-triaza-s-indacene-5,7-dione: To a solution of 5-amino-2-[1-(2-hydroxy-ethyl)-piperidin-4-ylmethyl]-6-nitro-isouindole-1,3-dione (90.0 mg, 0.258 mmol) in MeOH (30 mL) was added 10 mg of Pd/C (10%) and AcOH (1.5 mL) (the solution was purged with N₂ before adding Pd/C). After it was stirred under H₂ for 2 h, the reaction mixture was filtered through Celite. To the filtrate was added 4-ido-2-methoxynicotinic aldehyde (100.0 mg, 0.38 mmol) and the resulting mixture was stirred at the room temperature for 1 h and heated at 80 °C for 3 h, and then evaporated to dryness under reduced pressure. The residue was mixed with 4 M HCl/dioxane (8 mL) and H₂O (0.6 mL), heated at 70 °C for 1 h and evaporated to dryness under reduced pressure. The chromatography of the crude residue (50:10:1 CH₂Cl₂/MeOH/28% aqueous NH₄OH) afforded the corresponding chloropyridone intermediate (73 mg, 62 % for 3 steps),
which was then mixed with (S)-2-amino-l-(3-chloro-phenyl)-ethanol (12 mg, 0.06 mmol) and Et$_3$N (18 mg, 0.18 mmol) in EtOH (1.5 mL). After it was heated at 95 °C for 23 h, the reaction mixture was concentrated and subjected to HPLC purification to furnish the title compound (40.3 mg, 34% for the last step). $^1$H NMR (DMSO-$d_6$) δ 1.50 (m, 2H), 1.83 (2H), 1.98 (m, IH), 2.19 (s, 3H, CH$_3$), 2.21 (s, 3H, CH$_3$), 2.90 (m, 2H), 3.11 (m, 2H), 3.21-3.62 (6H), 3.70 (m, 2H), 4.00 (m, 2H), 4.15 (m, IH), 5.32 (br s, IH, OH), 5.55 (br s, IH, NH), 6.24 (d, J = 6 Hz, IH), 6.80-7.00 (3H), 7.40 (m, IH), 7.59 (s, IH), 8.13 (s, IH), 9.10 (br s, IH), 10.96 (br s, IH, NH), 11.32 (br s, IH, NH); ESI-MS $m/z$ 615.5 (MH$^+$).

![Image 1]

2-[(R)-3-(3-Chloro-2-methyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-[1-(2-hydroxy-ethyl)-piperidin-4-ylmethyl]-1H-1,3,6-triaza-s-indacene-5,7-dione: $^1$H NMR (DMSO-$d_6$) δ 1.50 (m, 2H), 1.83 (2H), 1.98 (m, IH), 2.28 (s, 3H, CH$_3$), 2.90 (m, 2H), 3.11 (m, 2H), 3.21-3.62 (6H), 3.70 (m, 2H), 4.10 (m, 2H), 4.19 (m, IH), 5.32 (br s, IH, OH), 5.55 (br s, IH, NH), 6.24 (d, J = 6 Hz, IH), 6.99-7.07 (2H), 7.15 (m, IH), 7.40 (m, IH), 7.71 (s, IH), 8.14 (s, IH), 9.12 (br s, IH), 10.97 (br s, IH, NH), 11.31 (br s, IH, NH); ESI-MS $m/z$ 635.5 (MH$^+$).

![Image 2]

2-[(R)-3-(3-Chloro-2,6-difluoro-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-[1-(2-hydroxy-ethyl)-piperidin-4-ylmethyl]-1H-1,3,6-triaza-s-indacene-5,7-dione: $^1$H NMR (DMSO-$d_6$) δ 1.50 (m, 2H), 1.83 (2H), 1.95 (m, IH), 2.28 (s,
2-{4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-y1}-6-(3-pyrrolidin-1-yl-propyl)-1H-1,3,6-triaza-s-indacene-5,7-dione:  

$^1$H NMR (DMSCW$_6$) $\delta$ 1.78-2.09 (6H), 2.19 (s, 3H, CH$_3$), 2.22 (s, 3H, CH$_3$), 3.00 (m, 2H), 3.21 (m, 2H), 3.49-3.79 (6H), 4.00 (m, 2H), 4.18 (m, IH), 5.56 (br s, IH, NH), 6.21 (d, $J$ = 6 Hz, IH), 6.80-6.98 (3H), 7.40 (m, IH), 7.70 (s, IH), 8.14 (s, IH), 9.51 (br s, IH), 10.95 (br s, IH, NH), 11.33 (br s, IH, NH); ESI-MS mlz 585.3 (MH$^+$).

Synthesis of additional phthalimide derivatives

Scheme 57
2-(4-Chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione: To a solution of 5-amino-2-(1-methyl-piperidin-4-yl)-6-nitroisoindole-1,3-dione (1.216 g, 4.0 mmol) in MeOH (47.5 mL) was added 120 mg of Pd/C (10%) (the solution was purged with N2 before adding Pd/C) and AcOH (2.5 mL). After it was stirred under atmospheric H2 for 5 h, the reaction mixture was filtered through Celite. To the filtrate was added 4-iodo-2-methoxynicotinic aldehyde (1.052 g, 4.0 mmol) and the resulting mixture was stirred at the room temperature for 17 h, heated at 80 °C for 5 h, and then evaporated to dryness under reduced pressure. The residue was mixed with 4 M HCl/dioxane (40 mL) and H2O (3 mL), heated at 70 °C for 3 h and was evaporated under reduced pressure. The chromatography of the crude residue (150:10:1 CH2Cl2/MeOH/28% aqueous NH4OH) afforded the title compound (688 mg, 42% for 3 steps). 1H NMR (DMSO-d6) δ 1.65 (m, 2H), 2.05 (m, 2H), 2.24 (s, 3H), 2.40 (m, 2H), 2.92 (m, 2H), 4.01 (m, IH), 6.60 (d, IH, J = 6.9 Hz), 7.70 (d, J = 6.9 Hz, IH), 8.03 (s, IH), 8.05 (s, IH); ESI-MS mlz 412.4 (MH+).

![Chemical structure](image)

2-{4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-hydroxy-propoxy-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione: To a solution of 2-(4-chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione (448.3 mg, 1.35 mmol) and (R)-1-amino-3-(2,4-dimethylphenoxy)-propan-2-ol (303.0 mg, 1.55 mmol) in EtOH (10 mL) was added Et3N (410 mg, 4.05 mmol). After it was heated at 100 °C for 14 h, the reaction mixture was concentrated under reduced pressure. The chromatography of the crude residue (150:10:1 CH2Cl2/MeOH/28% aqueous NH4OH) afforded the title compound (498 mg, 45%). 1H NMR (DMSO-d6) δ 1.60 (m, 2H), 1.95 (m, 2H), 2.18 (s, 3H, CH3), 2.18 (s, 3H, CH3), 2.21 (s, 3H, CH3), 2.39 (m, 2H), 2.90 (m, 2H), 3.57 (m, IH), 3.71 (m, IH), 3.90-4.08 (3H), 4.18 (m, IH), 5.55 (d, J = 6 Hz, IH, NH), 6.22 (d, J = 6 Hz, IH), 6.83 (d, J = 6 Hz, IH), 6.92 (d, J = 6 Hz,
IH), 6.97 (s, IH), 7.39 (d, J = 6 Hz, IH), 7.64 (s, IH), 8.09 (s, IH), 10.96 (br s, IH, NH),
11.31 (br s, IH, NH); ESI-MS m/z 571.3 (MH+).

\[
\text{ESI-MS } m/z 571.3 (MH^+) .
\]

2-\{4-[(S)-3-(2,4-Dimethy 1-phenoxy)-2-hydroxy-propylamino]-2-oxo- 1,2-
dihydro-pyridin-3-yl \} -6-( 1-methyl-piperidin-4-yl)- 1H- 1,3,6-triaza-s-indacene-5,7-dione: 'H NMR (DMSO-\(d_6\)) \(\delta\) 1.60 (m, 2H), 1.95 (m, 2H), 2.18 (s, 3H, CH\(_3\)), 2.18 (s, 3H, CH\(_3\)), 2.21 (s, 3H, CH\(_3\)), 2.39 (m, 2H), 2.90 (m, 2H), 3.57 (m, IH), 3.71 (m, IH), 3.90-4.08 (3H), 4.18 (m, IH), 5.55 (d, \(J = 6\) Hz, IH, NH), 6.22 (d, \(J = 6\) Hz, IH), 6.83 (d, \(J = 6\) Hz, IH), 6.92 (d, \(J = 6\) Hz, IH), 6.97 (s, IH), 7.39 (d, \(J = 6\) Hz, IH), 7.64 (s, IH), 8.09 (s, IH), 10.96 (br s, IH, NH),
11.31 (br s, IH, NH); ESI-MS m/z 571.3 (MH+).

\[
\text{ESI-MS } m/z 573.3 (MH^+) .
\]

2-\{4-[2-Hydroxy-3 -(3-methoxy-phenoxy)-propylamino]-2-oxo- 1,2-dihydro-
pyridin-3 -yl\} -6-( 1-methyl-piperidin-4-yl)- 1H- 1,3,6-triaza-s-indacene-5,7-dione: 'H NMR (DMSCwZ\(_g\)) \(\delta\) 1.65 (m, 2H), 2.00 (m, 2H), 2.28 (s, 3H, CH\(_3\)), 2.39 (m, 2H), 2.95 (m, 2H), 3.57 (m, IH), 3.71 (m, IH), 3.73 (s, 3H, CH\(_3\)), 3.90-4.08 (3H), 4.15 (m, IH), 5.59 (d, \(J = 6\) Hz, IH, NH), 6.22 (d, \(J = 6\) Hz, IH), 6.60-6.62 (3H), 7.18 (s, IH), 7.39 (s, IH), 7.73 (s, IH),
8.11 (s, IH), 10.97 (br s, IH, NH), 11.30 (br d, \(J = 6\) Hz, IH, NH); ESI-MS m/z 573.3 (MH+).
2-\{4-\{3-(4-chloro-3-methyl-phenoxy)-2-hydroxy-propylamino\}-2-oxo-1,2-dihydro-pyridin-3-yl\}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione: \( \text{H NMR (DMSO-}^d \text{)} \delta 1.62 \text{ (m, 2H), 1.95 \text{ (m, 2H), 2.20 \text{ (s, 3H, CH}_3\text{)}, 2.28 \text{ (s, 3H, CH}_3\text{), 2.40 \text{ (m, 2H), 2.87 \text{ (m, 2H), 3.50-4.50 \text{ (4H), 5.62 \text{ (d, J = 6 Hz, IH, NH), 6.22 \text{ (d, J = 6 Hz, IH), 6.85 \text{ (d, J = 6 Hz, IH), 7.00 \text{ (s, IH), 7.28 \text{ (d, J = 6 Hz, IH), 7.39 \text{ (d, J = 6 Hz, IH), 7.76 \text{ (s, IH), 8.10 \text{ (s, IH), 10.96 \text{ (br s, IH, NH), 11.30 \text{ (br d, J = 6 Hz, IH, NH); ESI-MS mlz 591.3 (MH}^++ \text{).}}}

2-\{4-\{3-(4-tert-Butyl-phenoxy)-2-hydroxy-propylamino\}-2-oxo-1,2-dihydro-pyridin-3-yl\}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione: \( \text{H NMR (DMSO-}^d \text{)} \delta 1.22 \text{ (s, 9H), 1.62 \text{ (m, 2H), 1.98 \text{ (m, 2H), 2.20 \text{ (s, 3H, CH}_3\text{)}, 2.39 \text{ (m, 2H), 2.89 \text{ (m, 2H), 3.53 \text{ (m, IH), 3.64 \text{ (m, IH), 3.90-4.08 \text{ (3H), 4.15 \text{ (m, IH), 5.59 \text{ (d, J = 6 Hz, IH, NH), 6.22 \text{ (d, J = 6 Hz, IH), 6.90 \text{ (d, J = 6 Hz, 2H), 7.27 \text{ (d, J = 6 Hz, 2H), 7.40 \text{ (s, IH), 7.81 \text{ (s, IH), 8.11 \text{ (s, IH), 10.98 \text{ (br s, IH}_2\text{NH), 11.31 \text{ (br s, IH, NH); ESI-MS mlz 599.5 (MH}^++ \text{).}}}

- 188 -
2-{4-[2-Hydroxy-3-(2-methoxy-phenoxy)-propylamino]-2-oxo-1,2-dihydro-
pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione: 'H NMR (DMSO-\text{D}_{6}) \delta 1.95 \text{ (m, 2H)}, 2.53 \text{ (m, 2H)}, 2.69 \text{ (s, 3H, CH}_3\text{)}, 3.18 \text{ (m, 2H)}, 3.42-3.62 \text{ (3H)}, 3.74 \text{ (m, IH)}, 3.80 \text{ (s, 3H, CH}_3\text{)}, 4.01 \text{ (m, 2H)}, 4.15 \text{ (m, IH)}, 4.30 \text{ (m, IH)}, 5.59 \text{ (br s, IH, NH)}, 6.22 \text{ (d, } J = 6 \text{ Hz, IH)}, 6.82-7.04 \text{ (4H)}, 7.39 \text{ (s, IH)}, 7.80 \text{ (s, IH)}, 8.13 \text{ (s, IH)}, 9.60 \text{ (br s, IH)}, 10.97 \text{ (br s, IH, NH)}, 11.33 \text{ (br d, } J = 6 \text{ Hz, IH, NH); ESI-MS } m/z 573.3 \text{ (MH}^+\text{).}

2-{4-[2-Hydroxy-3-(4-methoxy-phenoxy)-propylamino]-2-oxo-1,2-dihydro-
pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione: 'H NMR (DMSO-40) \delta 1.95 \text{ (m, 2H)}, 2.53 \text{ (m, 2H)}, 2.80 \text{ (s, 3H, CH}_3\text{)}, 3.20 \text{ (m, 2H)}, 3.42-3.80 \text{ (4H)}, 3.70 \text{ (s, 3H, CH}_3\text{)}, 3.99 \text{ (m, 2H)}, 4.10 \text{ (m, IH)}, 4.30 \text{ (m, IH)}, 5.59 \text{ (br s, IH, NH)}, 6.22 \text{ (d, } J = 6 \text{ Hz, IH)}, 6.80-6.97 \text{ (4H)}, 7.40 \text{ (s, IH)}, 7.79 \text{ (s, IH)}, 8.13 \text{ (s, IH)}, 9.60 \text{ (br s, IH)}, 10.97 \text{ (br s, IH, NH)}, 11.32 \text{ (br d, } J = 6 \text{ Hz, IH, NH); ESI-MS } m/z 573.3 \text{ (MH}^+\text{).}
2-{4-[3-(3-Chloro-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-IH-1,3,6-triaza-s-indacene-5,7-dione:  
$^1$H NMR (DMSO-$d_6$) $\delta$

- 1.95 (m, 2H), 2.57 (m, 2H), 2.79 (s, 3H, CH$_3$), 3.19 (m, 2H), 3.35-3.60 (3H), 3.65 (m, IH), 4.0-4.19 (3H), 4.31 (m, IH), 5.65 (br s, IH, NH), 6.22 (d, $J = 6$ Hz, IH), 6.95-7.05 (3H), 7.30 (m, IH), 7.39 (m, IH), 7.79 (s, IH), 8.10 (s, IH), 9.62 (br s, IH, NH), 11.32 (br d, $J = 6$ Hz, IH, NH); ESI-MS mlz 577.3 (MH$^+$).

2-{4-[3-(4-Chloro-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-IH-1,3,6-triaza-s-indacene-5,7-dione:  
$^1$H NMR (DMSO-$d_6$) $\delta$

- 1.95 (m, 2H), 2.57 (m, 2H), 2.79 (s, 3H, CH$_3$), 3.19 (m, 2H), 3.52 (m, 2H), 3.69 (m, IH), 4.06 (m, 2H), 4.15 (m, IH), 4.35 (m, IH), 5.65 (br s, IH, NH), 6.22 (d, $J = 6$ Hz, IH), 7.02 (d, $J = 6$ Hz, 2H), 7.30 (d, $J = 6$ Hz, 2H), 7.40 (m, IH), 7.80 (s, IH), 8.13 (s, IH), 9.60 (br s, IH), 10.95 (br s, IH, NH), 11.32 (br d, $J = 6$ Hz, IH, NH); ESI-MS mlz 577.3 (MH$^+$).

2-{4-(2-Hydroxy-3-phenoxy-propylamino)-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-IH-1,3,6-triaza-s-indacene-5,7-dione:  
$^1$H NMR (DMSO-$d_6$) $\delta$

- 1.67 (m, 2H), 2.10 (m, 2H), 2.30 (s, 3H, CH$_3$), 2.42 (m, 2H), 2.95 (m, 2H), 3.51 (m, IH), 3.68 (m, 2H), 3.95-4.06 (3H), 4.15 (m, IH), 5.61 (d, $J = 6$ Hz, IH, NH), 6.22 (d, $J = 6$ Hz, IH), 6.95
(m, IH), 6.99 (d, J = 6 Hz, 2H), 7.30 (m, 2H), 7.39 (m, IH), 7.74 (s, IH), 8.11 (s, IH), 9.60 (br s, IH), 10.98 (br s, IH, NH), 11.31 (br d, J = 6 Hz, IH, NH); ESI-MS m/z 543.3 (MH⁺).

2-[(4-Hydroxy-2-pyridin-4-yl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione: ¹H NMR (DMSO-d₆) δ 1.68 (m, 2H), 2.19 (m, 2H), 2.28 (s, 3H, CH₃), 2.41 (m, 2H), 2.98 (m, 2H), 3.49 (m, IH), 3.71 (m, 2H), 4.02 (m, IH), 4.99 (m, IH), 6.09 (d, J = 6 Hz, IH, NH), 6.22 (d, J = 6 Hz, IH), 7.41 (d, J = 6 Hz, IH), 7.54 (d, J = 6 Hz, 2H), 7.80 (s, IH), 8.11 (m, IH), 8.54 (d, J = 6 Hz, 2H), 10.88 (br s, IH, NH), 11.31 (br s, IH, NH); ESI-MS m/z 514.5 (MH⁺).

2-[(4-{[(R)-3-{(4-Fluoro-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}]}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione: ¹H NMR (DMSO-d₆) δ 1.95 (m, 2H), 2.57 (m, 2H), 2.79 (s, 3H, CH₃), 3.19 (m, 2H), 3.52 (m, 2H), 3.69 (m, IH), 4.06 (m, 2H), 4.12 (m, IH), 4.33 (m, IH), 5.65 (br s, IH, NH), 6.22 (d, J = 6 Hz, IH), 6.99-7.17 (4H), 7.40 (m, IH), 7.77 (s, IH), 8.13 (s, IH), 9.69 (br s, IH), 10.97 (br s, IH, NH), 11.34 (br d, J = 6 Hz, IH, NH); ESI-MS m/z 561.3 (MH⁺).
2-{4-[(S)-3-(4-Fluoro-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-
pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione:

^1H NMR (DMSO-\textsubscript{d}6) \( \delta \) 1.95 (m, 2H), 2.57 (m, 2H), 2.79 (s, 3H, CH\textsubscript{3}), 3.19 (m, 2H), 3.52 (m, 2H), 3.69 (m, IH), 4.06 (m, 2H), 4.12 (m, IH), 4.33 (m, IH), 5.65 (br s, IH, NH), 6.22 (d, J = 6 Hz, IH), 6.99-7.17 (4H), 7.40 (m, IH), 7.77 (s, IH), 8.13 (s, IH), 9.69 (br s, IH), 10.97 (br s, IH, NH), 11.34 (br d, J = 6 Hz, IH, NH); ESI-MS \textit{ml}z 561.3 (MH\textsuperscript{+}).

2-{4-[(S)-1-Hydroxymethyl-2-(1H-imidazol-4-yl)-ethylamino]-2-oxo-
1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione:

^1H NMR (MeOH-\textsubscript{d}4) \( \delta \) 2.10 (m, 2H), 2.83 (m, 2H), 2.96 (s, 3H, CH\textsubscript{3}), 3.16-3.36 (4H), 3.67 (m, 2H), 3.85 (m, 2H), 4.33 (m, IH), 4.47 (m, IH), 6.23 (d, J = 7 Hz, IH), 7.28 (d, J = 7 Hz, IH), 7.53 (s, IH), 7.86 (s, IH), 7.86 (s, IH), 8.78 (s, IH); ESI-MS \textit{ml}z 517.5 (MH\textsuperscript{+}).

2-{4-[(R)-1-Hydroxymethyl-2-(1H-imidazol-4-yl)-ethylamino]-2-oxo-1,2-
dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione:

^1H
NMR (MeOH-\textit{d}_4)  \delta 2.10 (m, 2H), 2.83 (m, 2H), 2.96 (s, 3H, CH\textsubscript{3}), 3.16\textendash3.36 (4H), 3.67 (m, 2H), 3.85 (m, 2H), 4.33 (m, IH), 4.47 (m, IH), 6.23 (d, \textit{J} = 7 \text{ Hz}, IH), 7.28 (d, \textit{J} = 7 \text{ Hz}, IH), 7.53 (s, IH), 7.86 (s, IH), 7.86 (s, IH), 8.78 (s, IH); ESI-MS \textit{mlz} 517.5 (MH\textsuperscript{+}).

2-[4-((R)-1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-IH-1,3,6-triaza-s-indacene-5,7-dione: \textsuperscript{1}H NMR (MeOH-\textit{d}_4) \delta 2.08 (m, 2H), 2.83 (m, 2H), 2.88\textendash3.28 (4H), 2.89 (s, 3H, CH\textsubscript{3}), 3.68 (m, 2H), 3.79 (m, 2H), 4.03 (m, IH), 4.43 (m, IH), 6.08 (d, \textit{J} = 6 \text{ Hz}, IH), 7.10\textendash7.30 (6H), 7.78 (s, IH), 7.78 (s, IH); ESI-MS \textit{mlz} 527.3 (MH\textsuperscript{+}).

2-[4-[2-(1H-Imidazol-4-yl)-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-IH-1,3,6-triaza-s-indacene-5,7-dione: \textsuperscript{1}H NMR (DMSO-\textit{d}_6) \delta 1.58 (m, 2H), 2.03 (m, 2H), 2.23 (s, 3H, CH\textsubscript{3}), 2.40 (m, 2H), 2.87\textendash3.95 (4H), 3.78 (m, 2H), 3.99 (m, IH), 4.37 (t, \textit{J} = 6 \text{ Hz}, IH, NH), 6.19 (d, \textit{J} = 6 \text{ Hz}, IH), 7.04 (s, IH), 6.99\textendash7.17 (4H), 7.41 (m, IH), 7.58 (s, IH), 7.90 (s, IH), 8.10 (s, IH), 10.70 (br s, IH, NH), 11.31 (br s, IH, NH); ESI-MS \textit{mlz} 487.5 (MH\textsuperscript{+}).
2-{4-[(R)-2-Hydroxy-3-(5-methyl-indol-1-yl)-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione: *H NMR (DMSO-^d_6) δ 1.95 (m, 2H), 2.25-2.77 (2H), 2.37 (s, 3H, CH_3), 2.79 (m, 2H), 3.19 (s, 3H, CH_3), 3.30 (m, IH), 3.52 (m, 2H), 4.12-4.39 (3H), 5.70 (br s, IH, NH), 6.10 (d, J = 7 Hz, IH), 6.39 (s, IH), 6.95 (d, J = 7 Hz, IH), 7.29-7.49 (4H), 7.99 (br s, IH), 8.15 (br s, IH), 9.50 (br s, IH), 10.97 (br s, IH, NH); ESI-MS mlz 580.8 (MH^+).

\[
\begin{align*}
\text{Structure 1}
\end{align*}
\]

2-{4-[(2,3-Dihydro-benzo [1,4]dioxin-2-yl)-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione: *H NMR (DMSO-d_6) δ 1.40 (s, 3H, CH_3), 1.98 (m, 2H), 2.55 (m, 2H), 2.80 (s, 3H, CH_3), 3.18 (m, 2H), 3.53 (m, 2H), 4.11 (m, IH), 4.23-4.45 (3H), 4.51 (m, IH), 6.32 (d, J = 7 Hz, IH), 6.80-6.99 (4H), 7.45 (m, IH), 7.94 (br s, IH), 8.15 (br s, IH), 9.57 (br s, IH), 11.20 (d, J = 7 Hz, IH, NH), 11.41 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 555.3 (MH^+).

\[
\begin{align*}
\text{Structure 2}
\end{align*}
\]

2-{4-[2-Hydroxy-3-(2,3,6,7-tetrahydro-lH,5H-pyrido[3,2,1-ij]quinolin-8-yloxy)-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione: *H NMR (DMSO-^d_6) δ 1.80-1.99 (6H), 2.50-2.65 (4H), 2.80 (s, 3H, CH_3), 2.99-3.28 (6H), 3.45-3.72 (4H), 3.97 (m, 2H), 4.11 (m, IH), 4.31 (m, IH), 6.17-6.29 (2H), 6.65 (d, J = 7 Hz, IH), 7.40 (m, IH), 7.80 (br s, IH), 8.15 (br s, IH), 9.57 (br s, IH), 10.95 (br s, IH, NH), 11.33 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 638.7 (MH^+).

\[
\begin{align*}
\text{Structure 3}
\end{align*}
\]
2-[(R)-2-Hydroxy-3-(naphthalen-1-yl)-propylamino]-2-oxo-1,2-
dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione: 'H NMR (DMSO-^δ) δ 1.84 (m, 2H), 2.55 (m, 2H), 2.78 (s, 3H, CH₃), 3.18 (m, 2H), 3.55 (m, 2H), 3.70 (m, IH), 3.80 (m, IH), 4.22-4.38 (4H), 5.78 (s, IH, NH), 6.31 (d, J = 7 Hz, IH), 7.01 (d, J = 7 Hz, IH), 7.35-7.60 (6H), 7.89 (d, J = 1 Hz, IH), 8.11 (s, IH), 8.33 (d, J = 1 Hz, IH), 11.04 (br s, IH, NH), 11.34 (br d, J = 6 Hz, IH, NH); ESI-MS m/z 593.3 (MH⁺).
2-{4-[(R)-3-(Biphenyl-3-yloxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-1H,1,3,6-triaza-s-indacene-5,7-dione: \[ ^1\text{H} \text{NMR (DMSO-}d_6\text{)} \delta 1.99 (m, 2H), 2.55 (m, 2H), 2.78 (s, 3H, CH$_3$), 3.18 (m, 2H), 3.49-3.65 (4H), 3.71 (m, 1H), 4.19 (m, 2H), 4.31 (m, 1H), 5.68 (d, J = 7 Hz, 1H), 6.25 (d, J = 7 Hz, 1H), 6.99 (d, J = 7 Hz, 1H), 7.20-7.49 (7H), 7.59 (d, J = 7 Hz, 2H), 7.70 (s, 1H), 8.12 (s, 1H), 9.60 (br s, 1H), 11.01 (br s, 1H, NH), 11.33 (br d, J = 6 Hz, 1H, NH); ESI-MS mlz 619.3 (MH$^+$).

\[ \text{4-}2\text{-H} \text{ydroxy-3-}2\text{-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-1H,1,3,6-triaza-s-indacene-5,7-dione: \[ ^1\text{H} \text{NMR (DMSO-}d_6\text{)} \delta 1.99 (m, 2H), 2.55 (m, 2H), 2.79 (s, 3H, CH$_3$), 3.18 (m, 2H), 3.32-3.63 (4H), 3.70 (m, 1H), 4.09-4.20 (3H), 4.32 (m, 1H), 5.68 (d, J = 7 Hz, 1H, NH), 6.21 (d, J = 7 Hz, 1H), 6.85-7.06 (3H), 7.35-7.48 (2H), 7.77 (s, 1H), 8.13 (s, 1H), 9.60 (br s, 1H), 10.99 (br s, 1H, NH), 11.34 (br d, J = 6 Hz, 1H, NH); ESI-MS mlz 659.5 (MH$^+$).

\[ \text{4-}2\text{-H} \text{ydroxy-3-}3\text{-}2\text{-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-1H,1,3,6-triaza-s-indacene-5,7-dione: \[ ^1\text{H} \text{NMR (DMSO-}d_6\text{)} \delta 1.99 (m, 2H), 2.55 (m, 2H), 2.79 (s, 3H, CH$_3$), 3.18 (m, 2H), 3.32-3.63 (4H), 3.70 (m, 1H), 4.09-4.20 (3H), 4.32 (m, 1H), 5.68 (d, J = 7 Hz, 1H, NH), 6.21 (d, J = 7 Hz, 1H), 6.85-7.06 (3H), 7.35-7.48 (2H), 7.77 (s, 1H), 8.13 (s, 1H), 9.60 (br s, 1H), 10.99 (br s, 1H, NH), 11.34 (br d, J = 6 Hz, 1H, NH); ESI-MS mlz 659.5 (MH$^+$).
2-\{4-[(R)-2-Hydroxy-3-(2,3,4-trimethoxy-phenoxy)-propylamino]-2-oxo-1,2-
dihydro-pyridin-3-yl\}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-
dione: \({^1}\text{H}\) NMR (DMSO-\(\text{d}_6\)) \(\delta\) 1.99 (m, 2H), 2.58 (m, 2H), 2.81 (s, 3H, CH\(_3\)), 3.18 (m, 2H), 3.38-3.59 (2H), 3.68-3.85 (2H), 3.75 (s, 3H, CH\(_3\)), 3.77 (s, 3H, CH\(_3\)), 3.79 (s, 3H, CH\(_3\)), 4.02 (m, 2H), 4.15 (m, IH), 4.32 (m, IH), 5.70 (br s, IH, NH), 6.23 (d, \(J = 7\) Hz, IH), 6.68 (d, \(J = 7\) Hz, IH), 6.78 (d, \(J = 7\) Hz, IH), 7.41 (m, IH), 7.75 (s, IH), 8.13 (s, IH), 9.59 (br s, IH), 10.98 (br s, IH, NH), 11.34 (br d, \(J = 6\) Hz, IH, NH); ESI-MS \(m/z\) 633.5 (MH\(^+\)).

2-\{4-[(R)-3-(3,5-Dimethyl-pyrazol-1-yl)-2-hydroxy-propylamino]-2-oxo-1,2-
dihydro-pyridin-3-yl\}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-
dione: \({^1}\text{H}\) NMR (DMSO-\(\text{d}_6\)) \(\delta\) 1.95 (m, 2H), 2.11 (s, 3H, CH\(_3\)), 2.23 (s, 3H, CH\(_3\)), 2.56 (m, 2H), 2.78 (s, 3H, CH\(_3\)), 3.18 (m, 2H), 3.35 (m, IH), 3.56 (m, IH), 4.01-4.18 (3H), 4.32 (m, IH), 5.80 (s, IH), 6.12 (d, \(J = 7\) Hz, IH), 6.68 (d, \(J = 6\) Hz, IH), 7.40 (m, IH), 7.99 (br s, IH), 8.13 (br s, IH), 9.56 (br s, IH), 10.99 (br s, IH, NH), 11.34 (br d, \(J = 6\) Hz, IH, NH); ESI-MS \(m/z\) 545.3 (MH\(^+\)).
Synthesis of additional phthalimide derivatives

Scheme 58

2-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-1H,3,6-triaza-s-indacene-5,7-dione: To a solution of 5-amino-2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-6-nitro-isoxindole-1,3-dione (40 mg, 0.12 mmol) in THF (6 mL) was added Raney Ni in H₂O (1 mL) and cyclohexa-1,4-diene (800 µL). After it was stirred at the room temperature for 30 min, the reaction mixture was loaded directly on the top of a column and washed with CH₂Cl₂ /MeOH/28% aqueous NH₄OH (90:10:1). The residue obtained from evaporation of the wash was mixed with 4-iodo-2-methoxynicotinaldehyde (34 mg, 0.13 mmol) and AcOH (0.5 mL)
in MeOH (10 mL). The mixture was stirred at the room temperature for 64 h, concentrated under reduced pressure, mixed with 4 M HCl/dioxane (8 mL) and H$_2$O (0.6 mL), heated at 50°C for 1.5 h, and concentrated under reduced pressure to give a crude, which was subjected to HPLC purification to furnish a fluorescent product in TFA salt form. (R)-l-Amino-3-(2,4-dimethyl-phenoxy)-propan-2-ol (45 mg, 0.24 mmol) and Et$_3$N (70 µL, 0.5 mmol) were added into the solution of this fluorescent product and the mixture was evaporated after 17.5 h of heating at 80°C. The residual crude was subjected to HPLC to afford the title compound in TFA salt form (7.86 mg, 9.2%). $^1$H NMR (DMSO-D$_6$) $\delta$ 2.13 (s, 3H, CH$_3$), 2.19 (s, 3H, CH$_3$), 3.02-4.05 (16H), 4.15 (m, IH), 5.35 (br s, IH, OH), 5.53 (br s, IH, OH), 6.23 (d, $J = 7$ Hz, IH), 6.84 (d, $J = 7$ Hz, IH), 6.92 (d, $J = 7$ Hz, IH), 6.98 (s, IH), 7.39 (d, $J = 7$ Hz, IH), 7.65 (s, IH), 8.11 (s, IH), 9.78 (br s, IH, NH), 10.94 (br s, IH, NH), 11.30 (br s, IH, NH); ESI-MS mlz 602.5 (MH$^+$).

Scheme 59

Synthesis of the compounds illustrated by Scheme 59:
2-{4-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-[(S)-1-(tetrahydro-furan-2-yl)methyl]-1H,1,3,6-triaza-s-indacene-5,7-dione: To a solution of 5-amino-6-nitro-2-[(S)-1-(tetrahydro-furan-2-yl)methyl]-isoindole-1,3-dione (29.1 mg, 0.1 mmol) in MeOH (30 mL) was added 3 mg of Pd/C (10%) (the solution was purged with N₂ before adding Pd/C). After it was stirred under atmospheric H₂ for 2 h, the reaction mixture was filtered through Celite. To the filtrate was added AcOH (1.5 mL) and 4-iodo-2-methoxynicotinic aldehyde (26.3 mg, 0.1 mmol) and the resulting mixture was stirred at the room temperature for 18 h and heated at 75 °C for 4 h, and then evaporated to dryness under reduced pressure. The residue was mixed with 4 M HCl/dioxane (8 mL) and H₂O (0.6 mL), heated at 70 °C for 4 h and evaporated to dryness under reduced pressure. The residue was subjected to HPLC purification to furnish the corresponding chloropyridone intermediate, which was then mixed with (S)-2-amino-l-(3-chloro-phenyl)-ethanol (7 mg, 0.02 mmol) and Et₃N (10 mg, 0.1 mmol) in EtOH (1.5 mL). After it was heated at 100 °C for 17 h, the reaction mixture was concentrated and subjected to HPLC purification to furnish the title compound (15.8 mg, 30% for 4 steps). ¹H NMR (DMSO-^6) δ 1.50-1.99 (4H), 3.52-3.79 (6H), 4.13 (m, IH), 4.99 (m, IH), 6.00 (br s, IH, NH), 6.20 (d, J = 6 Hz, IH), 7.35-7.39 (3H), 7.50 (d, J = 6 Hz, IH), 7.63 (s, IH), 7.88 (s, IH), 8.14 (s, IH); 10.90 (br s, IH, NH), 11.29 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 534.2 (MH⁺).

2-{4-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-1H,1,3,6-triaza-s-indacene-5,7-dione: ¹H NMR (DMSO-^6) δ 3.40-3.75 (2H), 4.98 (m, IH), 6.01 (br s, IH, NH), 6.20 (d, J = 6 Hz, IH), 7.35-7.44 (3H), 7.50 (d, J = 6 Hz, IH), 7.63 (s, IH), 7.84 (s, IH), 8.11 (s, IH), 10.91 (br s, IH, NH), 11.07 (br s, IH, NH), 11.29 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 450.4 (MH⁺).
2-{4-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-
pyridin-3 -yl } -6-( 1-methy l-piperidin-4-y l)- 1H-1,3,6-triaza-s-indacene-5 ,7-dione : 'H NMR
(DMSO-^6 ) δ 1.66 (m, 2H), 2.06 (m, 2H), 2.25 (s, 3H, CH_3 ), 2.39 (m, 2H), 2.93 (m, 2H),
3.57 (m, IH), 3.67 (m, IH), 3.96 (m, IH), 4.98 (m, IH), 6.01 (s, IH, NH), 6.20 (d, J = 6 Hz,
IH), 7.32-7.39 (3H), 7.50 (d, J = 6 Hz, IH), 7.63 (s, IH), 7.86 (s, IH), 8.11 (s, IH), 10.89 (br
s, IH, NH), 11.30 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 547.5 (MH+).

2- {4-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-
pyridin-3 -yl }-6-[1-(2-methoxy-ethyl) piperidin-4-y lmethyl]- 1H-1,3,6-triaza-s-indacene-5 ,7-
dione: 1H NMR (DMSO-40 δ 1.51 (m, 2H), 1.80-2.01 (3H), 2.92 (m, 2H), 3.25 (m, 2H), 3.29
(s, 3H), 3.42-3.78 (8H), 5.00 (m, IH), 6.01 (br s, IH, NH), 6.20 (d, J = 6 Hz, IH), 7.32-7.39
(3H), 7.50 (d, J = 6 Hz, IH), 7.64 (s, IH), 7.89 (s, IH), 8.15 (s, IH), 10.87 (br s, IH, NH),
11.30 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 605.2 (MH+).
2-\{(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino\}-2-oxo-1,2-dihydropyridin-3-yl\}\-6-(2-hydroxy-1-hydroxymethyl-1-ethyl)-1H-1,3,6-triaza-s-indacene-5,7-dione:

$^1$H NMR (DMSO-$d_6$) $\delta$ 3.51-3.85 (6H), 4.27 (m, 1H), 4.89 (br s, 2H, OH), 4.99 (m, 1H), 6.01 (br s, 1H, NH), 6.20 (d, $J = 6$ Hz, 1H), 7.32-7.41 (3H), 7.50 (d, $J = 6$ Hz, 1H), 7.64 (s, 1H), 7.85 (s, 1H), 8.11 (s, 1H), 10.89 (br s, 1H, NH), 11.29 (br d, $J = 6$ Hz, 1H, NH); ESI-MS $m/z$ 524.5 (MH$^+$).

2-\{(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino\}-2-oxo-1,2-dihydropyridin-3-yl\}\-6-(3-hydroxy-2,2-dimethyl-propyl)-1H-1,3,6-triaza-s-indacene-5,7-dione:

$^1$H NMR (DMSO-fife) $\delta$ 0.85 (6H), 3.01 (s, 2H), 3.47 (s, 2H), 3.61 (m, 1H), 3.69 (m, 1H), 4.57 (br s, 1H, OH), 4.99 (m, 1H), 6.01 (br s, 1H, NH), 6.20 (d, $J = 6$ Hz, 1H), 7.32-7.41 (3H), 7.50 (d, $J = 6$ Hz, 1H), 7.63 (s, 1H), 7.88 (s, 1H), 8.16 (s, 1H), 10.89 (br s, 1H, NH), 11.29 (br d, $J = 6$ Hz, 1H, NH); ESI-MS $m/z$ 536.3 (MH$^+$).
2-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydropyridin-3-yl]-6-(2-pyridin-3-yl-ethyl)-1H-1,3,6-triazas-indacene-5,7-dione: 'H NMR (DMSCW) δ 3.05 (m, 2H), 3.57 (m, 1H), 3.67 (m, 1H), 3.89 (m, 2H), 4.98 (m, 1H), 5.95 (br s, IH, NH), 6.19 (d, J = 6 Hz, IH), 7.30-7.41 (3H), 7.45-7.64 (3H), 7.80-8.13 (3H), 8.40-8.55 (2H), 10.89 (br s, IH, NH), 11.29 (br d, J = 6 Hz, IH, NH); ESI-MS m/z 555.7 (MH+).

2-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydropyridin-3-yl]-6-(2-pyridin-4-yl-ethyl)-1H-1,3,6-triazas-indacene-5,7-dione: 'H NMR (DMSCMO) δ 3.16 (m, 2H), 3.60 (m, IH), 3.70 (m, IH), 3.97 (m, 2H), 4.98 (m, IH), 5.99 (br s, IH, NH), 6.19 (d, J = 6 Hz, IH), 7.19-7.79 (7H), 7.80-8.19 (2H), 8.61-8.73 (2H), 10.89 (br s, IH, NH), 11.29 (br d, J = 6 Hz, IH, NH); ESI-MS m/z 555.7 (MH+).
2-{4-[{(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino}-2-oxo-1,2-dihydro-
pyridin-3-yl]}-6-((R)-2-methoxy-1-methyl-ethyl)-1H-1,3,6-triaza-s-indacene-5,7-dione: 

'H NMR (DMSO-\(\text{d}_6\)) \(\delta\) 3.23 (s, 3H), 3.50 (m, IH), 3.60 (m, IH), 3.69 (m, IH), 3.87 (t, \(J = 9\) Hz, IH), 4.48 (m, IH), 4.99 (m, IH), 6.00 (br s, IH, NH), 6.20 (d, \(J = 6\) Hz, IH), 7.32-7.42 (3H), 7.50 (d, \(J = 6\) Hz, IH), 7.63 (s, IH), 7.86 (s, IH), 8.11 (s, IH), 10.88 (br s, IH, NH), 11.29 (br d, \(J = 6\) Hz, IH, NH); ESI-MS \(m/z\) 522.3 (MH\(^+\)).

2-{4-{[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-
pyridin-3-yl]}-6-(S)-2-hydroxy-propyl)-1H-1,3,6-triaza-s-indacene-5,7-dione: 

'H NMR (DMSO-\(\text{d}_6\)) \(\delta\) 1.09 (d, \(J = 6\) Hz, 3H, CH\(_3\)), 3.43 (m, IH), 3.56 (m, 2H), 3.67 (m, IH), 3.95 (m, IH), 4.89 (m, IH, OH), 4.99 (m, IH), 6.00 (br s, IH, NH), 6.20 (d, \(J = 6\) Hz, IH), 7.30-7.39 (3H), 7.50 (d, \(J = 6\) Hz, IH), 7.63 (s, IH), 7.90 (s, IH), 8.13 (s, IH), 10.90 (br s, IH, NH), 11.29 (br d, \(J = 6\) Hz, IH, NH); ESI-MS \(m/z\) 508.3 (MH\(^+\)).
2-{4-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-
pyridin-3 -yl} -6- [2-(4-methyl-thiazol-5 -yl)-ethyl] - 1H- 1,3,6-triaza-s-indacene-5 ,7-dione : 'H
NMR (DMSO-<S>) δ 2.26 (s, 3H, CH₃), 3.18 (m, 2H), 3.50-3.82 (4H), 4.98 (m, IH), 5.97 (br s,
IH, NH), 6.20 (d, J = 6 Hz, IH), 7.30-7.39 (3H), 7.50 (d, J = 6 Hz, IH), 7.63 (s, IH), 7.87 (s,
IH), 8.1 1 (s, IH), 8.80 (s, IH), 10.88 (br s, IH, NH), 11.28 (br d, J = 6 Hz, IH, NH); ESI-MS
mlz 575.3 (MH⁺).

2-(4-((5)-2-(3-chlorophenyl)-2-hydroxyethylamino)-2-oxo-1,2-dihydropyridin-3-yl-6-
((5)-quinuclidin-3-yl)imidazo[4,5-/Jisoindole-5,7-(l//,6
H) -dione: ¹H NMR (DMSO-<S>) δ
1.72-2.18 (5H), 3.42-4.18 (8H), 4.72 (m, IH), 4.99 (m, IH), 6.01 (br s, IH, NH), 6.21 (d, J =
6 Hz, IH), 7.31-7.41 (3H), 7.50 (d, J = 6 Hz, IH), 7.64 (s, IH), 7.85 (s, IH), 8.16 (s, IH),
9.86 (br s, IH), 10.87 (br s, IH, NH), 11.31 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 559.3
(MH⁺).
2-(4-((5)-2-(3-chlorophenyl)-2-hydroxyethylamino)-2-oxo-1,2-dihydropyridin-3-yl-6-((/?)-quinuclidin-3-yl)imidazo[4,5-]Jisindoide-5,7-(1H,6//)-dione: ^1H NMR (DMSO-^6) $\delta$ 1.72-2.18 (5H), 3.42-3.79 (7H), 4.13 (m, IH), 4.72 (m, IH), 4.99 (m, IH), 6.01 (br s, IH, NH), 6.21 (d, $J = 6$ Hz, IH), 7.31-7.41 (3H), 7.50 (d, $J = 6$ Hz, IH), 7.64 (s, IH), 7.85 (s, IH), 8.16 (s, IH), 9.86 (br s, IH), 10.87 (br s, IH, NH), 11.31 (br d, $J = 6$ Hz, IH, NH); ESI-MS m/z 559.3 (MH$^+$).

2-{4-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydropyridin-3 -y]l}-6-(3-pyrrolidin-1-yl-propyl)-1H-1,3,6-triaza-s-indacene-5,7-dione: ^1H NMR (DMSO-^6) $\delta$ 1.80-2.11 (6H), 3.02 (m, 2H), 3.23 (m, 2H), 3.40-3.75 (6H), 4.99 (m, IH), 6.00 (br s, IH, NH), 6.21 (d, $J = 6$ Hz, IH), 7.31-7.41 (3H), 7.50 (d, $J = 6$ Hz, IH), 7.64 (s, IH), 7.90 (s, IH), 8.15 (s, IH), 9.56 (br s, IH), 10.88 (br s, IH$_5$NH), 11.30 (br d, $J = 6$ Hz, IH, NH); ESI-MS m/z 561.0 (MH$^+$).
2-\{(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino\}-2-oxo-1,2-dihydro-
pyridin-3-yl\}-6-(2-methoxy-ethyl)-1H,1,3,6-triaza-s-indacene-5,7-dione:

\[ ^1H \text{NMR (DMSO-} d_6\text{) } \delta 3.27 \text{ (s, 3H, CH}_3\text{), 3.52-3.79 (6H, 4.99 (m, IH), 6.00 (br s, IH, NH), 6.19 (d, J = 6 Hz, }
\text{IH), 7.31-7.41 (3H), 7.50 (d, J = 6 Hz, IH), 7.63 (s, IH), 7.88 (s, IH), 8.13 (s, IH), 10.89 (br s, IH, NH), 11.29 (br d, J = 6 Hz, IH, NH); ESI-MS } m/z 508.4 (MH}^+ \).
2-{4-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-
pyridin-3-yl}-6-(3-hydroxy-propyl)-IH-1,3,6-triaza-s-indacene-5,7-dione: 
$^1$H NMR (DMSO-$d_6$) $\delta$ 1.76 (m, 2H), 3.45-3.72 (6H), 4.52 (br s, IH, OH), 4.98 (br s, IH), 6.00 (br s, IH, NH), 6.19 (d, $J = 6$ Hz, IH), 7.32-7.42 (3H), 7.50 (d, $J = 6$ Hz, IH), 7.63 (s, IH), 7.87 (s, IH), 8.12 (s, IH), 10.90 (br s, IH, NH), 11.30 (br d, $J = 6$ Hz, IH, NH); ESI-MS $m/z$ 508.5 (MH$^+$).

2-{4-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-
pyridin-3-yl}-6-(3-imidazol-1-yl-propyl)-IH-1,3,6-triaza-s-indacene-5,7-dione: 
$^1$H NMR (DMSO-d$_6$) $\delta$ 2.21 (m, 2H), 3.55-3.79 (4H), 4.28 (m, 2H), 4.99 (br s, IH), 6.01 (br s, IH, NH), 6.20 (d, $J = 6$ Hz, IH), 7.32-7.42 (3H), 7.50 (d, $J = 6$ Hz, IH), 7.63 (s, IH), 7.68 (s, IH), 7.83 (s, IH), 7.89 (s, IH), 8.15 (s, IH), 9.09 (s, IH), 10.88 (br s, IH, NH), 11.31 (br d, $J = 6$ Hz, IH, NH); ESI-MS $m/z$ 558.3 (MH$^+$).
2-{[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(2,3-dihydroxy-propyl)-1H-1,3,6-triaza-s-indacene-5,7-dione: \(^1\)H NMR (DMSO-\(J_6\)) \(\delta\) 3.51-3.65 (3H), 3.69 (m, 1H), 3.84 (m, 1H), 4.68 (m, 1H), 4.93 (m, 1H), 4.99 (m, 1H), 6.00 (d, \(J = 6\) Hz, NH), 6.20 (d, \(J = 6\) Hz, 1H), 7.32-7.41 (3H), 7.50 (d, \(J = 6\) Hz, 1H), 7.64 (s, 1H), 7.88 (s, 1H), 8.13 (s, 1H), 10.91 (br s, 1H), 11.29 (br d, \(J = 6\) Hz, 1H); ESI-MS \(mlz\) 524.5 (MH\(^+\)).

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2-{[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-1H-1,3,6-triaza-s-indacene-5,7-dione: \(^1\)H NMR (DMSO-\(J_6\)) \(\delta\) 1.81 (m, 2H), 1.92 (m, 2H), 2.22 (m, 2H), 3.25 (m, 2H), 3.38 (ra, 2H) 3.500-3.73 (4H), 4.98 (m, 1H), 5.76 (s, 1H), 6.00 (br s, 1H), 6.19 (d, \(J = 6\) Hz, IH), 7.31-7.41 (3H), 7.50 (d, \(J = 6\) Hz, 1H), 7.63 (s, 1H), 7.87 (s, 1H), 8.13 (s, 1H), 10.89 (br s, 1H, NH), 11.29 (br d, \(J = 6\) Hz, 1H, NH); ESI-MS \(mlz\) 575.5 (MH\(^+\)).

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\]

2-{[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-[2-(1H-imidazol-4-yl)-ethyl]-1H-1,3,6-triaza-s-indacene-5,7-dione: \(^1\)H NMR (DMSO-\(J_6\)) \(\delta\) 3.02 (m, 2H), 3.58 (m, 1H), 3.69 (m, 1H), 3.88 (m, 2H), 4.98 (br s, 1H), 5.76 (s, 1H), 6.20 (d, \(J = 6\) Hz, 1H), 7.32-7.42 (3H), 7.49-7.52 (2H), 7.63 (s, 1H), 7.90 (br s, 1H), 8.05 (br S, 1H), 9.00 (s, 1H), 10.88 (br s, 1H), 11.31 (br d, \(J = 6\) Hz, 1H, NH); ESI-MS \(mlz\) 544.3 (MH\(^+\)).
2-{4-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-[1-(2-hydroxy-ethyl)-piperidin-4-ylmethyl] - 1H-1,3,6-triaza-s-indacene-5,7-dione: 1H NMR (DMSO-^6) δ 1.23 (d, J = 9 Hz, 2H), 1.58 (d, J = 9 Hz, 2H), 1.70 (m, IH), 1.95 (m, 2H), 2.39 (m, 2H), 2.87 (m, 2H), 3.35 (m, 2H), 3.42-3.52 (2H), 3.61 (m, IH), 3.69 (IH), 4.39 (br s, IH, OH), 4.99 (m, IH), 6.00 (s, IH, NH), 6.21 (d, J = 6 Hz, IH), 7.32-7.42 (3H), 7.50 (d, J = 6 Hz, IH), 7.63 (s, IH), 7.87 (s, IH), 8.13 (s, IH), 10.89 (br s, IH, NH), 11.30 (br s, IH, NH); ESI-MS mlz 591.3 (MH^+).

2-{4-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-[3-morpholin-4-yl-propyl]-1H-1,3,6-triaza-s-indacene-5,7-dione: 1H NMR (DMSO-^6) δ 1.76 (m, 2H), 2.20-2.38 (6H), 3.32-3.48 (4H), 3.52-3.77 (4H), 4.99 (m, IH), 6.00 (s, IH, NH), 6.19 (d, J = 6 Hz, IH), 7.31-7.41 (3H), 7.50 (d, J = 6 Hz, IH), 7.64 (s, IH), 7.87 (s, IH), 8.13 (s, IH), 9.56 (br s, IH), 10.89 (br s, IH, NH), 11.29 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 577.3 (MH^+).
2-{4-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydropyridin-3-yl}-6-(2-pyrrolidin-1-yl-ethyl)-1H-1,3,6-triaza-s-indacene-5,7-dione: \textsuperscript{1}H NMR (DMSO\textsuperscript{6}) \( \delta \) 1.81 (m, 2H), 2.03 (m, 2H), 3.15 (m, 2H), 3.50 (m, 2H), 3.53-3.74 (4H), 3.95 (m, 2H), 4.99 (m, IH), 6.00 (s, IH, NH), 6.21 (d, \( J = 6 \) Hz, IH), 7.29-7.41 (3H), 7.50 (d, \( J = 6 \) Hz, IH), 7.64 (s, IH), 7.92 (s, IH), 8.18 (s, IH), 9.61 (br s, IH), 10.88 (br s, IH, NH), 11.30 (br d, \( J = 6 \) Hz, IH, NH); ESI-MS \textit{mlz} 547.3 (MH\textsuperscript{+}).

2-{4-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydropyridin-3 -yl]-6-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-1H-1,3,6-triaza-s-indacene-5,7-dione: \textsuperscript{1}H NMR (DMSO\textsuperscript{6}) \( \delta \) 1.43-1.68 (4H), 1.87-2.11 (4H), 2.20 (s, 3H, CH\textsubscript{3}), 2.93 (m, IH), 3.52-3.75 (4H), 4.99 (m, IH), 6.00 (s, IH, NH), 6.21 (d, \( J = 6 \) Hz, IH), 7.29-7.41 (3H), 7.50 (d, \( J = 6 \) Hz, IH), 7.63 (s, IH), 7.87 (s, IH), 8.13 (s, IH), 10.89 (br s, IH\textsubscript{3}NH), 11.29 (br d, \( J = 6 \) Hz, IH, NH); ESI-MS \textit{mlz} 561.3 (MH\textsuperscript{+}).
2-{4-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-
pyridin-3-yl}-6-[3-(4-methyl-piperazin-1-yl)-propyl]-1H,1,3,6-triaza-s-indacene-5,7-dione:

\[ ^1\text{H NMR (OMSO-d}_6\text{)} \delta 1.90 (m, 2H), 2.50-3.80 (14H), 2.70 (s, 3H, CH\textsubscript{3}), 4.99 (m, IH), 6.01 (s, IH, NH), 6.20 (d, J = 6 Hz, IH), 7.30-7.41 (3H), 7.50 (d, J = 6 Hz, IH), 7.63 (s, IH), 7.90 (s, IH), 8.14 (s, IH), 10.87 (br s, IH, NH); ESI-MS \text{mlz} 590.5 (MH\textsuperscript{+}).

\[ 2-{4-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-
pyridin-3-yl}-6-[2-(4-methyl-piperazin-1-yl)-ethyl]-1H,1,3,6-triaza-s-indacene-5,7-dione: \]

\[ ^1\text{H NMR (DMSO-d}_6\text{)} \delta 2.35 (m, 2H), 2.68 (m, 2H), 2.75 (s, 3H, CH\textsubscript{3}), 2.90 (m, 2H), 3.10 (m, 2H), 3.30-3.77 (6H), 4.99 (m, IH), 6.01 (br s, IH, NH), 6.20 (d, J = 6 Hz, IH), 7.30-7.41 (3H), 7.49 (d, J = 6 Hz, IH), 7.63 (s, IH), 7.89 (s, IH), 8.14 (s, IH), 9.50 (br s, IH), 10.88 (br s, IH, NH), 11.30 (br d, J = 6 Hz, IH, NH); ESI-MS \text{mlz} 576.5 (MH\textsuperscript{+}).

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Synthesis of (R)-I-amino-3-(2-bromo-5-fluoro-phenoxy)-propan-2-ol

Scheme 60

A mixture of 2-[(2R)-oxiran-2-ylmethyl]-1H-isoindole-1,3(2H)-dione (1) (0.531 g, 2.6 mmol), 2-bromo-5-fluorophenol (2) (0.500 g, 2.6 mmol), and DBU (25 µL, 0.16 mmol) in p-xylene was heated at 120 °C for 12 hours. The reaction mixture was cooled and then propan-2-ol (15 mL) and hydrazine (600 µL, 18.9 mmol) were added. The resulting mixture was heated at 90 °C for 5 h and cooled to room temperature. The reaction was diluted with 1 N NaOH (30 mL) and extracted with ethyl acetate (3x20 mL). The combined extract was washed with 1 N NaOH (25 mL), dried through Na₂SO₄ and concentrated under reduced pressure to get crude (R)-l-amino-3-(2-bromo-5-fluorophenoxy)propan-2-ol (3) (0.500 g) which was used for next reaction without further purification. ESI-MS mlz 265.1 (M+1).

Synthesis of 2-[(R)-3-(2-bromo-4-fluoro-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-lH-1,3,6-triaza-s-indacen-5-one trifluoroacetic acid salt

Scheme 61

A mixture of 2-(4-chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indene-5,7-dione dihydrochloride (4) (85 mg, 18 mmol), (R)-l-amino-3-(2-bromo-5-fluorophenoxy)-propan-2-ol (50 mg, 0.18 mmol) and Et3N (375 mg, 3.71 mmol) in...
EtOH (4 mL) was heated at 100 °C for 12 h. The filtrate was concentrated and the residue was passed through small silica gel column (10% NH₄OH in MeOH/CH₂Cl₂ 1:9). Column fractions were concentrated and obtained compound was subjected to HPLC purification to afford 2-{4-[(R)-3-(2-bromo-5-fluoro-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydropyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-IH-1,3,6-triaza-s-indacen-5-one as TFA salt (5) (30 mg, 21 %). ¹H NMR (DMSO-Đ₆) □ 1.80-2.15 (m, 4H), 2.80 (s, 3H), 3.10-3.3 (m, 2H), 3.40-4.15 (m, 7H), 4.05-4.20 (m, 2H), 4.23-4.40 (m, 1H), 4.45 (s, 2H), 5.0 (br, IH), 6.24 (d, IH, J = 9.0 Hz), 6.76 -6.83(m, IH), 7.12 (dd, IH, J = 3.0, 12.0 Hz) 7.36 (t, 1 H, J = 9.0 Hz), 7.60-7.70 (m, IH), 9.45 (bs, IH), 11.10 (bs, IH), 11.24 (d, IH, J = 6.0 Hz); ESI-MS mlz 627.5 (M⁺+2).

The following compounds were synthesized as shown in scheme 61

![Chemical Structure](image)

2-{4-[(R)-3-(2-bromo-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydropyridin-3-yl]-6-(1-ethyl-piperidin-4-yl)-6,7-dihydro-IH-1,3,6-triaza-s-indacen-5-one as TFA salt (5b) was prepared from 2-(4-chloro-2-oxo-1,2-dihydropyridin-3-yl)-6-piperidin-4-yl-IH-1,3,6-triaza-s-indacene-5,7-dione dihydrochloride and (R)-l-amino-3-(2-bromo-phenoxy)-propan-2-ol. ESI-MS mlz 593.5 (M⁺).

![Chemical Structure](image)

2-{4-[(R)-3-(2-bromo-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydropyridin-3-yl]-6-(1-ethyl-piperidin-4-yl)-6,7-dihydro-IH-1,3,6-triaza-s-indacen-5-one as TFA salt (5c) was prepared from 2-(4-chloro-2-oxo-1,2-dihydropyridin-3-yl)-6-(1-ethyl-piperidin-4-yl)-
yl)-lH-1,3,6-triazas-indacene-5,7-dione dihydrochloride and (R)-l-amino-3-(2-bromo-phenoxy)-propan-2-ol. ESI-MS mlz 623.0 (M+2).

Synthesis of (R)-l-amino-3-(2-chloro-4-methoxy-phenoxy)-propan-2-ol

Scheme 62

A mixture of 2-[(2R)-oxiran-2-ylmethyl]-lH-isooindole-1,3(2H)-dione (1) (0.640 g, 3.15 mmol), 2-chloro-4-methoxyphenol (2) (0.500 g, 3.15 mmol), and DBU (25 µL, 0.16 mmol) in p-xylene was heated at 120 °C for throughnight. The reaction mixture was cooled and then propan-2-ol (15 mL) and hydrazine (600 µL, 18.9 mmol) were added. The resulting mixture was heated at 90 °C for 5 h and cooled to room temperature. The reaction was diluted with 1 N NaOH (30 mL) and extracted with ethyl acetate (3x20 mL). The combined extract was washed with 1 N NaOH (25 mL), dried through Na₂SO₄ and concentrated under reduced pressure to get crude (R)-l-amino-3-(2-chloro-4-methoxyphenoxy)propan-2-ol (3a) (0.547 g) which was used for next reaction without further purification. ESI-MS mlz 232.4 (M+1).

The following amino alcohols were synthesized using the above procedure and designated phenol unless otherwise noted

(R)-l-amino-3-(2-chloro-4-fluoro-3-methylphenoxy)propan-2-ol (3b).

Yield: 0.567 g; ESI-MS mlz 233.9 (M+1).
(R)-l-amino-3-(2-bromo-4, 6-difluorophenoxy)propan-2-ol.

Yield: 0.539 g; ESI-MS mlz 282.1 (M+) and 284.1 (M+2).
(R)-l-amino-3-(2-(trifluoromethyl)phenoxy)propan-2-ol

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \quad \text{F} \quad \text{F} \\
\end{align*}
\]

Yield: 0.594 g; ESI-MS mlz 236.1 (M+1).

(R)-l-amino-3-(2-chloro-5-fluorophenoxy)propan-2-ol.

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \quad \text{Cl} \\
\end{align*}
\]

Yield: 0.584 g; ESI-MS mlz 219.9 (M+1).

(R)-l-amino-3-(2-bromo-4-fluorophenoxy)propan-2-ol.

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \quad \text{Br} \\
\end{align*}
\]

Yield: 0.497 g; ESI-MS mlz 264.3 (M+) and 266.3 (M+2).

(R)-l-amino-3-(2-bromo-4-methylphenoxy)propan-2-ol (3g).

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \quad \text{Br} \\
\end{align*}
\]

Yield: 0.485 g; ESI-MS mlz 260.4 (M+) and 262.4 (M+2).

(R)-l-amino-3-(2-chloro-5-(trifluoromethyl)phenoxy)propan-2-ol (3h).

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \quad \text{Cl} \\
\end{align*}
\]

Yield: 0.500 g; ESI-MS mlz 270.0 (M+1).
(R)-1-amino-3-(2-bromophenoxy)propan-2-ol (3i).

![Chemical structure of (R)-1-amino-3-(2-bromophenoxy)propan-2-ol](image)

Yield: 0.533 g; ESI-MS m/z 245.8 (M+) and 247.8 (M+2).

(R)-1-amino-3-(2-bromo-4,5-difluorophenoxy)propan-2-ol (3j).

![Chemical structure of (R)-1-amino-3-(2-bromo-4,5-difluorophenoxy)propan-2-ol](image)

Yield: 0.472 g; ESI-MS m/z 282.4 (M+) and 284.4 (M+2).

(R)-1-amino-3-(2-chloro-4,5-difluorophenoxy)propan-2-ol (3k).

![Chemical structure of (R)-1-amino-3-(2-chloro-4,5-difluorophenoxy)propan-2-ol](image)

Yield: 0.527 g; ESI-MS m/z 238.1 (M+1).

(R)-1-amino-3-(2-chloro-6-fluorophenoxy)propan-2-ol (3l).

![Chemical structure of (R)-1-amino-3-(2-chloro-6-fluorophenoxy)propan-2-ol](image)

Yield: 0.532 g; ESI-MS m/z 220.1 (M+1).

(R)-1-amino-3-(2-chloro-6-fluorophenoxy)propan-2-ol (3m).

![Chemical structure of (R)-1-amino-3-(2-chloro-6-fluorophenoxy)propan-2-ol](image)

Yield: 0.473 g; ESI-MS m/z 269.9 (M+1).

(R)-1-amino-3-(2-chloro-6-fluorophenoxy)propan-2-ol (3n).
Yield: 0.519 g; ESI-MS mlz 238.4 (M+1).

(R)-l-amino-3-[(6-ethyl-1,3-benzodioxol-5-yl)oxy]propan-2-ol (3o).

Yield: 0.503 g; ESI-MS mlz 239.9 (M+1).

(R)-l-amino-3-[(6-chloro-1,3-benzodioxol-5-yl)oxy]propan-2-ol (3p).

Yield: 0.462 g; ESI-MS mlz 246.3 (M+1).

(R)-l-amino-3-(6-chloro-2-fluoro-3-methylphenoxy)propan-2-ol (3q).

Yield: 0.516 g; ESI-MS mlz 234.3 (M+1).

(R)-l-amino-3-(4-methyl-benzo[l,3]dioxol-5-yloxy)propan-2-ol (3r).

Yield: 0.550 g; ESI-MS mlz 226.3 (M+1).

(R)-l-amino-3-(4-ethyl-benzo[l,3]dioxol-5-yloxy)propan-2-ol (3s)
Yield: 0.400 g; ESI-MS mlz 240.2 (M+\(^+\)).

(R)-l-amino-3-(4-chloro-benzo[l,3]dioxol-5-yloxy)-propan-2-ol (3t)

[Diagram]

Yield: 0.450 g; ESI-MS mlz 246.5 (M+\(^+\)).

(R)-l-amino-3-(4-fluoro-2,4-dimethyl-phenoxy)-propan-2-ol (3u)

[Diagram]

Yield: 0.300 g; ESI-MS mlz 214.1 (M+\(^+\)).

(R)-l-amino-3-(3-fluoro-2,4-dimethyl-phenoxy)-propan-2-ol (3u) (300 mg) was obtained from 2-[(2R)-oxiran-2-ylmethyl]-lH-isindole-l,3(2H)-dione (1) (0.250 g, 1.78 mmol), and 3-fluoro-2,4-dimethyl-phenol (0.362 g, 1.78 mmol) by application of the above methodology.

Synthesis of 2-\{4-[(R)-3-(2-chloro-4-methoxy-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl\}-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-IH-1,3,6-triaza-s-indacen-5-one trifluoroacetic acid salt

Scheme 63

A mixture of 2-(4-chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(1-methyl-piperidin-4-yl)-IH-1,3,6-triaza-s-indacene-5,7-dione dihydrochloride (300 mg, 0.61 mmol), (R)-l-amino-3-(2-chloro-4-methoxyphenoxy)-propan-2-ol (175 mg, 0.80 mmol) and Et\(_3\)N (375 mg, 3.71 mmol) in EtOH (4 mL) was heated at 100 °C for 12 h. The reaction mixture was cooled and
concentrated under reduced pressure to dryness (700 mg). A portion of crude mixture (100 mg) was mixed with zinc dust (250 mg) in AcOH (4 mL) and heated at 90 °C for 3 h. The mixture was cooled, filtered through celite and solid was washed with 1:1 MeOHZCH₂Cl₂ (5 mL). The filtrate was concentrated and the residue was passed through small silica gel column (10% NH4OH in MeOH/CH₂CL₂ (1:9). Column fractions were concentrated and obtained compound was subjected to HPLC purification to afford 2-{4-[(R)-3-(2-chloro-4-methoxy-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1H-1,3,6-triaza-s-indacen-5-one as TFA salt (5a) (20 mg, 31.9%, 2 steps). ¹H NMR (DMSO-^d₆) δ 1.80-2.15 (m, 4H), 2.80 (s, 3H), 3.10-3.3 (m, 2H), 3.40-4.15 (m, 7H), 4.20-4.38 (m, IH), 4.45 (s, 2H), 6.22 (d, IH, J = 9.0 Hz), 6.86 (m, IH), 7.08 (s, IH), 7.12 (d, IH, J = 9.0 Hz) 7.36 (t, 1 H, J = 9.0 Hz), 7.80 (m, 2H), 9.40 (bs, IH), 11.13 (bs, IH), 11.24 (d, IH, J = 9.0 Hz); ESI-MS mlz 593.5 (M+H).

By application of the above methodology and using designated amino alcohol, the following compounds were synthesized.

2-{4-[(R)-3-(2,4-difluoro-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3 -yl}] -6-(1-methyl-piperidin-4-yl)-6,7-dihydro- IH-1,3,6-triaza-s-indacen-5-one trifluoroacetic acid salt

Yield: (22 mg, 43 % ).; ¹H NMR (DMSO-^d₆) δ 1.80-2.15 (m, 4H), 2.31 (s, 3H), 2.80 (s, 3H), 3.10-3.90 (m, 6H), 4.00-4.18 (m, 3H), 4.22-4.37 (m, IH), 4.50(s, 2H), 5.55(bs, IH), 6.21 (d, IH, J = 6.0 Hz), 7.05-7.25 (m, 2H), 7.40 (t, 1 H, J = 6.0 Hz), 7.50-8.0 (m, 2H), 9.40 (bs, IH), 11.10(bs, IH), 11.23 (d, IH, J = 9.0 Hz); ESI-MS mlz 595.5 (M+H).
Yield: (17 mg, 26%).; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.80-2.15 (m, 4H), 2.80 (s, 3H), 3.05-3.30 (m, 2H), 3.40-3.95 (m, 4H), 4.0-4.18 (m, 3H), 4.21-4.38 (m, IH), 4.46 (s, 2H), 5.58 (bs, IH), 6.21 (d, IH, $J = 6.0$ Hz), 6.90-7.0 (m, IH), 7.15-7.30 (m, 3H), 7.42-8.0 (m, 2H), 9.40 (bs, IH), 11.12 (bs, IH), 11.23 (d, IH, $J = 6.0$ Hz); ESI-MS mlz 565.5 (M$^+$+1).

$2\cdot[4\cdot[(R)-3-(2$-trifluoromethyl-phenoxy)$-2$-hydroxy-propylamino]$-2$-oxo-$1,2\cdot$dihydro-pyridin-3$\cdot$yl]$-6\cdot(1$-methyl$-piperidin-4$-yl)$-6,7$-dihydro-$1\cdot,H\cdot3,6$-triaza-s-indacen-5$\cdot$one trifluoroacetic acid salt

Yield: (19 mg, 31%).; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.80-2.15 (m, 4H), 2.82 (s, 3H), 3.1-3.35 (m, 2H), 3.40-3.95 (m, 4H), 4.0-4.40 (m, 4H), 4.46 (s, 2H), 5.57 (bs, IH), 6.18 (d, IH, $J = 6.0$ Hz), 7.0-7.33 (m, IH), 7.34-7.59 (m, 2H), 7.50-8.0 (m, 4H), 9.40 (bs, IH), 11.14 (bs, IH), 11.23 (d, IH, $J = 3.0$ Hz); ESI-MS mlz 597.2 (M$^+$+1).

$2\cdot[4\cdot[(R)-3-(2$-chloro-5-fluoro-phenox)$-2$-hydroxy-propylamino]$-2$-oxo-$1,2\cdot$dihydro-pyridin-3$\cdot$yl]$-6\cdot(1$-methyl$-piperidin-4$-yl)$-6,7$-dihydro-$1\cdot,H\cdot3,6$-triaza-s-indacen-5$\cdot$one trifluoroacetic acid salt
Yield: (18 mg, 27.9 %); $^1$H NMR (DMSO-^6) $\delta$ 1.90-2.15 (m, 4H), 2.85 (s, 3H), 3.10-3.30 (m, 2H) 3.40-3.95 (m, 4H), 4.08-4.18 (m, 3H), 4.25-4.40 (m, IH), 4.47 (s, 2H), 5.65 (bs, IH), 6.22 (d, IH, $J$ = 9.0 Hz), 6.84 (t, IH $J$ = 9.0 Hz), 7.15 (dd, IH, $J$ = 9.0, 15.0 Hz), 7.31-7.34 (m, IH), 7.40-7.55 (m, IH), 7.50-8.0 (m, 2H), 9.35 (bs, IH), 11.13 (bs, IH), 11.24 (d, IH, $J$ = 6.0 Hz); ESI-MS $mlz$ 581.5 (M$^+$+1).

2-{4-[(R)-3-(2-chloro-5-trifluoromethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1H-1,3,6-triaza-s-indacen-5-one trifluoroacetic acid salt

Yield: (15 mg, 23 %); $^1$H NMR (DMSO-$\text{d}_6$) $\delta$ 1.80-2.10 (m, 4H), 2.80 (s, 3H), 3.10-3.28 (m, 2H) 3.40-3.95 (m, 4H), 4.08-4.35 (m, 4H), 4.47 (s, 2H), 5.62 (bs, IH), 6.21 (d, IH, $J$ = 6.0 Hz), 7.28-7.40 (m, 2H), 7.50 (s, IH), 7.60-8.10 (m, 3H), 9.40 (bs, IH), 11.13 (bs, IH), 11.25 (bs, IH); ESI-MS $mlz$ 631.3 (M$^+$+1).

2-{4-{[(R)-3-(2-chloro-3,5-difluoro-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1H-1,3,6-triaza-s-indacen-5-one trifluoroacetic acid salt
Yield: (21 mg, 28 %); $^1$H NMR (DMSO-$d_6$) $\delta$ 1.80-2.10 (m, 4H), 2.80 (s, 3H), 3.10-3.80 (m, 4H), 4.08-4.20 (m, 3H), 4.21-4.40 (m, 1H), 4.49 (s, 2H), 6.22 (d, IH, $J = 6.0$ Hz), 7.00-7.15 (m, 2H), 7.30-7.40 (m, 1H), 7.50-8.10 (m, 2H), 9.35 (bs, IH), 11.13 (bs, IH), 11.24 (bs, IH); ESI-MS $m/z$ 599.5 (M$^+$+1).

2-{4-[(R)-3-(2-chloro-6-fluoro-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1H,1,3,6-triaza-s-indacen-5-one trifluoroacetic acid salt

Yield: (20 mg, 32 %); $^1$H NMR (DMSO-$d_6$) $\delta$ 1.85-2.12 (m, 4H), 2.81 (s, 3H), 3.10-3.90 (m, 4H), 4.05-4.20 (m, 3H), 4.21-4.42 (m, 1H), 4.50 (s, 2H), 5.55 (bs, IH), 6.21 (d, IH, $J = 6.0$ Hz), 7.1 1-7.19 (m, IH), 7.20-7.42 (m, 3H), 7.50-8.05 (m, 2H), 9.41 (bs, IH), 11.13 (bs, IH), 11.24 (d, IH, $J = 6.0$ Hz); ESI-MS $m/z$ 581.5 (M$^+$+1)

2-{4-[(R)-3-(2-chloro-3-trifluoromethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1H,1,3,6-triaza-s-indacen-5-one trifluoroacetic acid salt

- 223 -
Yield: (17 mg, 26 %); $^1$H NMR (DMSO-$d_6$) $\delta$ 1.80-2.10 (m, 4H), 2.81 (s, 3H), 3.10-3.85 (m, 4H) 4.10-4.65 (m, 6H), 5.60 (bs, IH), 6.24 (d, IH, $J = 6.0$ Hz), 6.90-7.29 (m, IH), 7.30-7.70 (m, 4H), 7.75-8.05 (m, IH), 9.45 (bs, IH), 11.15 (bs, IH), 11.24 (bs, IH); ESI-MS $m/z$ 631.7 (M$^+$$+$l).

2-{4-[R]-3-(2-chloro-3,5-difluoromethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl }-6-(1-methyl-piperidin-4-yl)-6,7-dihydro- IH-1,3,6-triaza-s-indacen-5-one trifluoroacetic acid salt

Yield: (20 mg, 30 %); $^1$H NMR (DMSO-$d_6$) $\delta$ 1.85-2.15 (m, 4H), 2.85 (s, 3H), 3.10-3.85 (m, 4H), 4.00-4.18 (m, IH), 4.20-4.40 (m, 4H), 4.49 (s, 2H), 5.55 (bs, IH), 6.22 (d, IH, $J = 9.0$ Hz), 7.10-7.29 (m, IH), 7.30-7.45 (m, 2H), 7.50-8.0 (m, 2H), 9.38 (bs, IH), 11.12 (bs, IH), 11.25 (d, IH $J = 6.0$ Hz); ESI-MS $m/z$ 599.7 (M$^+$$+$l).

2-{4-[(R)-3-[(6-ethyl-1,3-benzodioxol-5-yl)oxy]-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3 -yl }-6-(1-methyl-piperidin-4-yl)-6,7-dihydro- IH-1,3,6-triaza-s-indacen-5-one trifluoroacetic acid salt
Yield: (15 mg, 19%); $^1$H NMR (DMSO-$_6$) $\delta$ 1.10 (t, 3H, $J = 9.0$ Hz), 1.90-2.15 (m, 4H), 2.50 (q, 2H, $J = 9.0$, 15.0 Hz) 2.82 (s, 3H), 3.10-3.25 (m, 2H), 3.35-4.15 (m, 6H), 4.25-4.40 (m, IH), 4.47 (s, 2H), 5.50 (bs, IH), 5.91 (s, 2H), 6.20 (d, IH, $J = 6.0$ Hz), 6.75(s, IH), 6.77 (s, IH), 7.34-7.39 (m, IH), 7.50-8.0 (m, 2H), 9.38 (bs, IH), 11.13 (bs, IH), 11.23 (d, 1H , $J = 6.0$ Hz ); ESI-MS $m/z$ 601.5 (M$^+$+1).

2-{4-[(R)-3-(6-chloro-benzo[l,3]dioxol-5-yloxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-IH-1,3,6-triaza-s-indacen-5-one trifluoroacetic acid salt

Yield: (14 mg, 22%); $^1$H NMR (DMSO-$^d$) $\delta$ 1.80-2.13 (m, 4H), 2.81 (s, 3H), 3.10-3.30 (m, 2H), 3.40-4.60 (m, 3H), 3.65-4.25 (m, 4H), 4.26-4.36 (m, IH), 4.50 (s, 2H), 5.50 (bs, IH), 6.02 (s, 2H), 6.22 (d, IH, $J = 9.0$ Hz), 6.98 (s, IH), 7.10 (s, IH), 7.36 (t, IH, $J = 6.0$ Hz), 7.50-7.95 (m, 2H), 9.42 (bs, IH), 11.11 (bs, IH), 11.23 (d, 1H , $J = 6.0$ Hz ); ESI-MS $m/z$ 607.0 (M$^+$+1).
2-{(R)-3-(2-chloro-6-fluoro-5-methyl-phenoxy)-2-hydroxy-propylamino}-2-oxo-1,2-dihydro-pyridin-3-yl]-6-[(1-methyl-piperidin-4-yl)-6,7-dihydro-1H-1,3,6-triaza-s-indacen-5-one trifluoroacetic acid salt

Yield: (23 mg, 37 %); \(^1\)H NMR (DMSO-\(\text{d}_6\)) \(\delta\) 1.85-2.10 (m, 4H), 2.12 (s, 3H), 2.81 (s, 3H), 3.10-3.25 (m, 2H), 3.40-3.65 (m, 3H), 3.74-3.80 (m, 1H), 4.0-4.18 (m, 3H), 4.20-4.40 (m, 1H), 4.50 (s, 2H), 6.21 (d, \(\text{IH}\), \(J = 6.0\) Hz), 7.01-7.06 (m, \(\text{IH}\)), 7.19-7.72 (m, \(\text{IH}\)), 7.38 (m, \(\text{IH}\)), 7.60-8.0 (m, 2H), 9.44 (bs, \(\text{IH}\)), 11.12 (bs, \(\text{IH}\)), 11.24 (d, \(\text{IH}\) \(J = 9.0\) Hz); ESI-MS \(mlz\) 595.7 (M+\(\text{+H}\)).

2-{(R)-2-hydroxy-3-(4-methyl-benzo[1,3]dioxol-5-yl)-propylamino}-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1H-1,3,6-triaza-s-indacen-5-one trifluoroacetic acid salt

Yield: (32 mg, 41 %); \(^1\)H NMR (DMSO-\(\text{c}^6\)) \(\delta\) 1.82-2.10 (m, 4H), 2.20 (s, 3H), 2.79 (s, 3H), 3.15-3.30 (m, 2H), 3.45-3.85 (m, 3H), 3.90-4.03 (m, 2H), 4.10-4.20 (m, \(\text{IH}\)), 4.25-4.40 (m, \(\text{IH}\)), 4.50 (s, 2H), 6.00 (s, 2H), 6.20 (d, \(\text{IH}\) \(J = 9.0\) Hz), 6.45 (d, \(\text{IH}\) \(J = 9.0\) Hz), 6.60 (d, \(\text{IH}\) \(J = 9.0\) Hz), 7.47 (t, \(\text{IH}\) \(J = 6.0\) Hz), 7.65-8.0 (m, 2H), 9.50 (bs, \(\text{IH}\)), 11.11 (bs, \(\text{IH}\)), 11.21 (d, \(\text{IH}\) \(J = 6.0\) Hz); ESI-MS \(mlz\) 587.0 (M+\(\text{+H}\)).
2-[(R)-2-hydroxy-3-(4-ethyl-benzo[1,3]dioxol-5-yl)propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1H-1,3,6-triazas-indacen-5-one trifluoroacetic acid salt

Yield: (30 mg, 36%); 1H NMR (DMSO-^6) δ 1.13 (t, 3H, J = 9.0 Hz), 1.87-2.18 (m, 4H), 2.58 (q, 2H, J = 9.0, 15.0 Hz), 2.83 (s, 3H), 3.09-3.38 (m, 2H) 3.43-4.20 (m, 7H), 4.23-4.30 (m, IH), 4.48 (s, 2H), 5.42 (bs, IH), 5.98 (s, 2H), 6.21 (d, IH, J = 9.0 Hz), 6.39 (d, IH, J = 9.0 Hz), 6.58 (d, IH, J = 9.0 Hz), 7.39 (t, IH, J = 6.0 Hz), 7.63-8.0 (m, 2H), 9.44 (bs, IH), 11.14 (bs, IH), 11.20 (d, IH, J = 6.0 Hz); ESI-MS mlz 601.7 (M+1).

Synthesis of 2-[(R)-3-(2-bromo-4,6-difluoro-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1H-1,3,6-triazas-indacen-5-one trifluoroacetic acid salt

Scheme 64

A mixture of 2-(4-chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1H-1,3,6-triazas-indacene-5-one dihydrochloride (200 mg, 0.42 mmol), (R)-l-amino-3-(2-chloro-4-methoxyphenoxy)-propan-2-ol (150 mg, 0.53 mmol) and Et3N (420
µL, 2.9 mmol) in EtOH (3 mL) was heated at 100 °C for 12 h. The reaction mixture was cooled, concentrated and the obtained residue was subjected to HPLC purification to afford the 2-[4-{(R)-3-(2-bromo-4,6-difluoro-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl} -6-(1-methyl-piperidin-4-yl)-6,7-dihydro- 1H-1,3,6-triaza-s-indacen-5-one trifluoroacetic acid salt (5p) (35 mg, 11%). 1H NMR (DMSO-d6) δ 1.85-2.11 (m, 4H), 2.82 (s, 3H), 3.10-3.35 (m, 2H), 3.40-4.15 (m, 7H), 4.18-4.35 (m, 1H), 4.45(s, 2H), 5.55 (bs, IH), 6.22 (d, IH, J = 9.0 Hz), 7.30-7.55 (m, 3H) 7.60-8.10 (m, 2H), 9.40 (bs, IH), 11.13 (bs, IH), 11.24 (d, IH, J = 9.0 Hz); ESI-MS m/z 643.5 (M⁺)and 645.5(M⁺+2).

The following compounds were synthesized using above procedure and designated amino alcohol.

2-{4-{(R)-3-(2-bromo-4-fluoro-phenoxy)-2-hydroxy-propylamino]}-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1H-1,3,6-triaza-s-indacen-5-one trifluoroacetic acid salt

![Chemical Structure](image)

(25 mg, 8.0 %). 1H NMR (DMSO-d6) δ 1.80-2.10 (m, 4H), 2.80 (s, 3H), 3.1-3.30 (m, 2H), 3.40-4.80 (m, 4H), 4.00-4.20 (m, 3H), 4.26-4.76 (m, 1H), 4.50 (s, 2H), 5.55 (bs, IH), 6.24 (d, IH, J = 6.0 Hz), 7.10-7.20 (m, 2H), 7.21-7.39 (m, IH), 7.58-9.78 (m, IH), 7.82-8.0 (m, 2H), 9.45 (bs, IH), 11.10 (bs, IH), 11.23 (d, IH, J = 6.0 Hz); ESI-MS m/z 627.3(M⁺+2).

2-{4-{(R)-3-(2-bromo-4-methyl-phenoxy)-2-hydroxy-propylamino]}-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1H-1,3,6-triaza-s-indacen-5-one trifluoroacetic acid salt
(28 mg, 9.0 %). $^1$H NMR (DMSO-$d_6$) $\delta$ 1.90-2.10 (m, 4H), 2.25 (s, 3H), 2.80 (s, 3H), 3.10-3.30 (m, 2H), 3.40-3.75 (m, 4H), 4.05-4.18 (m, 3H), 4.20-4.40 (m, IH), 4.55 (s, 2H), 5.50 (bs, IH), 6.23 (d, IH, $J = 9.0$ Hz), 6.98-7.29 (m, 2H) 7.36-7.48 (m, 2H), 7.58-7.82 (m, IH), 7.75-7.96 (m, 2H), 9.48 (bs, IH), 11.11 (bs, IH), 11.21 (d, IH, $J = 6.0$ Hz); ESI-MS $m/z$ 621.5 (M$^+$).

2-{$[4-[(R)-3-(2-bromo-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]6-(1-methyl-piperidin-4-yl)-6,7-dihydro-\textit{1}H-1,3,6-triaza-s-indacen-5-one$} trifluoroacetic acid salt

(18 mg, 6.0 %). $^1$H NMR (DMSO-$d_6$) $\delta$ 1.82-2.08 (m, 4H), 2.79 (s, 3H), 3.10-3.25 (m, 2H), 3.40-3.80 (m, 4H), 4.03-4.20 (m, 3H), 4.21-4.35 (m, IH), 4.55 (s, 2H), 5.50 (bs, IH), 6.23 (d, IH, $J = 6.0$ Hz), 6.88-6.93 (m, IH), 7.06-7.16 (m, IH), 7.29-7.37 (m, 2H), 7.54-7.61 (m, IH), 7.70-8.0 (m, 2H), 9.38 (bs, IH), 11.12 (bs, IH), 11.31 (d, IH, $J = 6.0$ Hz); ESI-MS $m/z$ 607.5 (M$^+$), 609.5 (M$^+$+2).

2-{$[4-[(R)-3-(2-bromo-4, 5-difluoro-phenoxy)-2-hydroxy-propylamino] -2-oxo-1,2-dihydro-pyridin-3-yl]6-(1-methyl-piperidin-4-yl)-6,7-dihydro-\textit{1}H-1,3,6-triaza-s-indacen-5-one$} trifluoroacetic acid salt
(30 mg, 9.3 %). $^1$H NMR (DMSO-d$_6$) $\delta$ 1.90-2.10 (m, 4H), 2.80 (s, 3H), 3.10-3.30 (m, 2H), 3.40-3.80 (m, 4H), 4.00-4.20 (m, 3H), 4.22-4.40 (m, IH), 4.55 (s, 2H), 5.60 (bs, IH), 6.23 (d, IH, $J = 6.0$ Hz), 7.25-7.50 (m, 3H), 7.60-8.0 (m, 2H), 9.39 (bs, IH), 11.12 (bs, IH), 11.31 (d, IH, $J = 6.0$ Hz); ESI-MS $m/z$ 643.5 (M$^+$).

2-{$4-$[(R)-2-hydroxy-3-(4-chloro-benzo[1,3]dioxol-5-yl)oxy]-propylamino] -2-oxo- 1,2-dihydro-pyridin-3 -yl}-6-( 1-methyl -piperidin-4-yl)-6,7-dihydro- 1H-1,3,6-triaza-s-indacen-5-one trifluoroacetic acid salt

(15 mg, 9.3 %). $^1$H NMR (DMSO-$d_6$) $\delta$ 1.90-2.10 (m, 4H), 2.79 (s, 3H), 3.15-3.35 (m, 2H), 3.40-3.90 (m, 4H), 3.95-4.15 (m, 3H), 4.25-4.42 (m, IH), 4.47 (s, 2H), 5.55 (bs, IH), 6.08 (s, 2H), 6.21 (d, IH, $J = 9.0$ Hz), 6.54 (d, IH, $J = 6.0$ Hz), 6.79 (d, IH, $J = 6.0$ Hz), 7.37 (t, IH, $J = 6.0$ Hz), 7.60-8.0 (m, 2H), 9.45 (bs, IH), 11.11 (bs, IH), 11.21 (d, IH, $J = 6.0$ Hz); ESI-MS $m/z$ 643.5 (M$^+$).

2-{$4-$[(R)-3-(2-fluoro-2,4-dimethyl-phenoxy)-2-hydroxy-propylamino] -2-oxo- 1,2-dihydro-pyridin-3 -yl}-6-( 1-methyl -piperidin-4-yl)-6,7-dihydro- 1H-1,3,6-triaza-s-indacen-5-one trifluoroacetic acid salt
(22 mg, 7.5%). $^1$H NMR (DMSO-d$_6$) $\delta$ 1.85-2.08 (m, 4H), 2.13 (s, 3H), 2.16 (s, 3H), 2.74 (s, 3H), 3.08-3.30 (m, 2H), 3.42-3.62 (m, 3H), 3.65-3.75 (m, IH), 3.90-4.10 (m, 3H), 4.22-4.35 (m, IH), 4.48 (s, 2H), 5.55 (bs, IH), 6.22 (d, IH, $J = 9.0$ Hz), 6.73 (d, IH, $J = 9.0$ Hz), 7.01 (t, IH, $J = 9.0$ Hz), 7.37 (t, IH, $J = 6.0$ Hz), 7.60-7.95 (m, 2H), 9.48 (bs, IH), 11.12 (bs, IH), 11.23 (d, IH, $J = 6.0$ Hz); ESI-MS m/z 575.8 (M$^+$+I).

Synthesis of 4-methyl-benzo[1,3]dioxol-5-ol

Scheme 65

To a 0°C cooled solution of benzo[1,3]dioxol-5-ol (1) (42.88 g, 310.52 mmol) and diisopropyl ethylamine (75.0 g g, 584.7 mmol) in dichloromethane (400 mL) was slowly added methoxymethyl chloride (50.0 g, 621.04 mmol) and stirred at room temperature for throughnight. The reaction mixture was washed with water (3x 200 mL), 10% sodium hydroxide (100 mL) and then with water (100 mL). The organic layer was dried and concentrated to give 5-methoxymethoxy-benzo[1,3]dioxole. (2) (43.0 g, 74.3%) as an oil. $^1$H NMR (CDCl$_3$) $\delta$ 3.39 (s, 3H), 5.07 (s, 2H), 5.89 (s, 2H), 6.48 (dd, IH, $J = 3.0$ Hz, 9.0 Hz), 6.61 (d, IH, $J = 3.0$ Hz), 6.69 (d, IH, $J = 9.0$ Hz).
Synthesis of 4-methyl-benzo[1,3]dioxol-5-ol: To a cooled (-78 °C) solution of 5-methoxymethoxy-benzo[1,3]dioxole (5.0 g, 27.35 mmol) in THF (25 mL) was slowly added 2.5 M solution of n-BuLi in hexane and stirred at nitrogen atmosphere. After 30 minutes, dimethyl sulphate (6.90 g, 54.7 mmol) was added and then resulting mixture was allowed to warm to room temperature and stirred for 7 h. The reaction was diluted with water (50 mL) and extracted with ethyl acetate (2x 50 mL). The organic layer was dried (Na$_2$SO$_4$) and concentrated under vacuum to get crude product. The obtained product was dissolved in methanol (50 mL) and 0.5 mL cone. HCl and then heated at 50 °C for 2 h. The reaction was concentrated, dissolved in ethyl acetate (50 mL) and washed with saturated sodium bicarbonate. The solvent was evaporated under vacuum to give crude product. Silica gel column chromatography (30 % CH$_2$C$_12$/Hexane) gave 4-methyl-benzo[1,3]dioxol-5-ol (3a) (3.0 g, 72 %). $^1$H NMR (CDCl$_3$) δ 2.13 (s, 3H), 4.60 (s, 3H), 5.95 (s, 2H), 6.25 (d, IH, J = 6.0 Hz), 6.52 (d, IH, J = 6.0 Hz).

Synthesis of 4-ethyl-benzo[1,3]dioxol-5-ol

Scheme 66

To a cooled (-78 °C) solution of 5-methoxymethoxy-benzo[1,3]dioxole (5.0 g, 27.35 mmol) in THF (25 mL) was slowly added 2.5 M solution of n-BuLi in hexane and stirred at nitrogen atmosphere. After 30 minutes, diethyl sulphate (8.43 g, 54.7 mmol) was added and then resulting mixture was allowed to warm to room temperature and stirred for 7 h. The reaction was diluted with water (50 mL) and extracted with ethyl acetate (2x 50 mL). The organic layer was dried (Na$_2$SO$_4$) and concentrated under vacuum to get crude product. The obtained product was dissolved in methanol (50 mL) and 0.5 mL cone. HCl and then heated at 50 °C for 2 h. The reaction was concentrated, dissolved in ethyl acetate (50 mL) and washed with saturated sodium bicarbonate. The solvent was evaporated under vacuum to give crude product. Silica gel column chromatography (30 % CH$_2$C$_12$/Hexane) gave 4-ethyl-benzo[1,3]dioxol-5-ol (3b) (2.8 g, 61 %). $^1$H NMR (CDCl$_3$) δ 1.22 (t, 3H, J = 9.0 Hz), 2.62
(q, 2H, J = 9.0, 15.0 Hz) 4.45 ( bs, IH), 5.90 (s, 2H), 6.22 (d, IH, J = 6.0 Hz), 6.52 (d, IH, J = 6.0 Hz).

Synthesis of 4-chloro-benzo[1,3]dioxol-5-ol

Scheme 67

To a cooled (-78 °C) solution of 5-methoxymethoxy-benzo[1,3]dioxole (5.0 g, 27.35 mmol) in THF (25 mL) was slowly added 2.5 M solution of n-BuLi in hexane and stirred at nitrogen atmosphere. After 30 minutes, a solution of hexachloroethane (12.95 g, 54.7 mmol) in THF (25 mL) was added and then resulting mixture was allowed to warm to room temperature and stirred for 7 h. The reaction was diluted with water (50 mL) and extracted with ethyl acetate (2x 50 mL). The organic layer was dried (Na₂SO₄) and concentrated under vacuum to get crude product. The obtained product was dissolved in methanol (50 mL) and 0.5 mL cone. HCl and then heated at 50 °C for 2 h. The reaction was concentrated, dissolved in ethyl acetate (50 mL) and washed with saturated aqueous sodium bicarbonate. The solvent was evaporated under vacuum to give crude product. Silica gel column chromatography (30 % CH₂Cl₂/Hexane) gave 4-chloro-benzo[1,3]dioxol-5-ol (3c) (2.5 g, 53 %). ¹H NMR (CDCl₃) δ 5.12 (s, 1H), 6.0 (s, 2H), 6.47 (d, IH, J = 9.0 Hz), 6.62 (d, IH, J = 9.0 Hz).

Synthesis of 3-fluoro-2,4-dimethylphenol

Scheme 68

To a cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (1.10 g, 7.84 mmol) in THF (5 mL) was slowly added 2.5 M solution of n-BuLi in hexane (3.1 mL) and stirred for 15 minutes. The reaction mixture was cooled to -78 °C and then a solution of 2-fluoro-4-
methoxy-l-methyl-benzene (1.0 g, 27.35 mmol) in THF (5 mL) was added. After stirring 20 minutes, methyl iodide (2.0 g 14.16 mmol) was added and the resulting mixture was allowed to warm to 0 °C through a period of 3 h. The reaction was diluted with 1N HCl (15 mL) and extracted with ether (3x 25 mL). The organic layer was dried (Na2SO4) and distilled out to get crude product. The obtained product was dissolved in dichloromethane (30 mL) and cooled to -78 °C. Boron tribromide (4.0 g, 15.9 mmol) was slowly added and then mixture was allowed to warm to 0 °C. After 5 h, the reaction was slowly poured in to ice water (25 mL) and extracted with dichloromethane (2x 30 mL). The organic extracts were dried and solvent was evaporated at low temperature (20 °C) and vacuum to a residue. Flash column chromatography (30 % CH2Cl2/Hexane) of the crude product gave 3-fluoro-2,4-dimethyl-phenol (3d) (0.65 g, 65 %). 1H NMR (CDCl3) δ 2.14 (s, 3H), 2.15 (s, 3H), 4.81 (s, IH), 6.45 (d, IH, J = 9.0 Hz), 6.84 (t, IH, J = 9.0 Hz).

Synthesis of IV-alkylated nitro-amino-phthalimide

Synthesis 5-Amino-6-nitro-2-(2-pyrrolidin-1-ylethyl)-1H-isoindole-1,3(2H)-dione

Scheme 69

A mixture containing phthalimide (1; 2 g, 9.7 mmol, 1.0 eq.), 2-pyrrolidin-1-ylethanamine (2a, 1.1 g, 9.7 mmol, 1.0 eq.) and imidazole 0.17 g, 2.43 mmol, 0.25 eq.) in dioxane (40 mL) was heated in a capped vial at 110 °C for 14 h. Additional 0.25 eq. of imidazole was added and reaction heated for 24 h. The mixture was cooled to room temperature and concentrated in vacuo to a solid which was used as such in the next step.

The following compounds were prepared using either of the above methods.
ESMS (m/z) 319.5 (M + H)

ESMS (m/z) 293.3 (M + H)

ESMS (m/z) 333.4 (M + H)

Yield (83%)

ESMS (m/z) 319.3 (M + H)

ESMS (m/z) 319.4 (M + H)

Yield (83%)

Synthesis of tricyclic halopyridones

2-(4-Iodo-2-methoxypyridin-3-yl)-6-(3-pyrrolidin-1-ylpropyl)imidazo[4,5-f]isoindole-5,7(IH,6H)-dione

Scheme 70

Pd/C (250 mg) was added to a solution of crude 5-amino-6-nitro-2-(3-(pyrrolidin-1-yl)propyl)isoindoline-1,3-dione in MeOH/AcOH (100 mL/5 mL) and hydrogenated for 5 h. The mixture was filtered through Celite and the filtrate was treated with 4-iodo-2-methoxynicotinaldehyde (3.2 g, 12.07 mmol) and stirred at ambient temperature open to air for 12 h and at 80 °C for 5 h. The reaction mixture was cooled to ambient temperature and
concentrated in vacuo to dryness. Purification by flash chromatography gave the title 5,6-diamino-2-(3-(pyrrolidin-1-yl)propyl)isoindoline-1,3-dione as a solid (2.02 g, 32% through 4 steps). ¹H NMR (MeOD): δ 8.15 (s, 2H), 8.01-8.08 (t, J=3 Hz, IH), 7.64 (t, J=3 Hz, IH), 3.89-3.78 (m, 2H), 3.41-3.22 (m, 2H), 2.95-2.81 (m, 6H), 2.15-1.82 (m, 7H). ESMS (m/z) 532 (M+H)⁺.

2-(4-Halo-2-oxo-1,2-dihydropyridin-3-yl)-6-(3-pyrrolidin-1-ylpropyl)imidazo[4,5-f]isoindole-5,7(lH,6H)-dione dihydrochloride

Scheme 7 1

A mixture of cone. HCl (6 mL) and iodo-methoxypyridine derivative (1.97 g, 33.7 mmol) in 45 mL of dioxane was stirred at ambient temperature protected from light for 30 h. THF (25 mL) was added to the reaction mixture and the solid was isolated by filtration, washed with Et₂O (4x15 mL), dried at 45 °C in a vacuum oven to afford the title compound as a light chocolate colored solid (1.82 g). ¹H NMR (MeOH-d₄): δ 12.74 (br s, IH), 10.60 (br s, IH), 8.14 (s, 2H), 7.73 (d, J=9 Hz, IH), 6.65 (d, J=9 Hz, IH), 3.72-3.64 (m, 1 H), 3.51-3.43 (m, IH), 3.21-3.15 (m, IH), 2.99-2.93 (m, IH), 2.07-1.82 (m, 3H). ESMS (m/z) 426.1 (M+H)⁺ for X=Cl and 518.2 (M+H)⁺ for X=I.

Synthesis of tricyclic phthalimides

Scheme 7 2
The following compounds were synthesized by this methodology:

![Chemical structures](image)

The above tricyclic phthalimides were prepared from the corresponding diamines and 4-chloro-2-methoxypyridine-3-carboxaldehyde by application of the general procedure, such as A above, or B below.

**Synthesis of 4-chloro-2-methoxypyridine-3-carboxaldehyde**

**Scheme 73**

![Chemical structures](image)

2-Methoxy-nicotinonitrile
2-Methoxy-nicotinonitrile was prepared according to the literature by reaction of the 2-chloro-nicotinonitrile with MeONa in MeOH according to Dunn, A. D.; Norrie, R.; Heterocycl. Chem.; EN; 24; 1987; 85-89.

4-Chloro-2-methoxy-nicotinonitrile (4-chloro-2-methoxy-3-cyanopyridine)

The mixture of 210 mL of THF and 18 mL of diisopropylamine (0.13 mol), degassed with nitrogen gas in an ultrasonic bath and was cooled to -78 °C. Then 1.6 M BuLi (81 mL, 0.13 mol) was added dropwise. The mixture was stirred at this temperature for 30 min, then cooled to -85 °C and a solution of 2-methoxy-nicotinonitrile (15.9 g, 0.19 mol) in 100 mL of degassed anhydrous THF was added dropwise. After 1 h of stirring at -80 °C, a solution of hexachloroethane (56.9 g, 0.240 mol) in 200 mL of THF was added causing the temperature to rise to -40 °C. The cooling bath was removed and stirred for 15 min. The reaction mixture was poured into water and extracted with ethyl acetate (2x200 mL). The extract was dried through sodium sulfate, filtered through silicagel, and evaporated under vacuum. The resulting residue was purified by column chromatography (silicagel, EtOAc/hexane, 2:1) to give 89% of product. NMR ¹H (DMSO d₆, δ ppm): 8.44 (d, 1H 6-H, J=5.5 Hz); 7.42 (d, IH, 5-H, J=5.5 Hz); 4.02 (s, 3H, CH₃O).

4-Chloro-2-methoxy-pyridine-3-carbaldehyde (4-Chloro-2-methoxynicotinonitrile)

To the solution of the nitrile (2.0 g, 0.018 mol) in 20 mL of THF was added 1.5 M DIBAL in toluene (16 mL, 2.1 eq.) at room temperature. This caused the temperature to rise to 40 °C. The mixture is stirred for 1.5 h and poured in portions into a solution of 3.5 mL of acetic acid in 50 mL of water. After the gas evolution ceased, the mixture was extracted first with hexane/THF (1:1), then with ethyl acetate. The combined extracts were dried through sodium sulfate, evaporated under vacuum; and the residue was purified by column (silicagel, hexane/EtOAc) to give 900 mg (44%) of the product. NMR ¹H (CDCl₃, δ ppm): 10.30 (s, 1H, CHO); 8.34 (d, 1H 6-H, J=5.6 Hz); 7.24 (d, IH, 5-H, J=5.6 Hz); 3.99 (s, 3H, CH₃O).
Synthesis of Tricyclic halopyridones

Scheme 74

Step 1: NaH (2.05 g, 60 wt% dispersion in oil, 5.13 mmol, 1.06 eq.) was added portionwise to a solution of the phthalimide (10.0 g, 48.3 mmol, 1.0 eq.) in degassed DMF (50 mL) and heated at 60 °C for 45 min. The mixture was cooled to room temperature and stirred throughoutnight. Then, a solution of dibromoethane (18.1 g, 96.6 mmol) in acetone (50 mL) was added dropwise. The cake was broken up and thick slurry was refluxed throughoutnight. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated in vacuo to afford 10.14 g (67%) of the desired product.

Step 2: A mixture of the bromophthalimide (1.0 g, 3.2 mmol), AcOH (10 drops) in MeOH (15 mL) was hydrogenated at atmospheric pressure and ambient temperature for 3h. The mixture was filtered through Celite, Celite was washed well with MeOH, and the filtrate was concentrated in vacuo to afford a residual solid (840 mg; 92%). ¹H NMR (CDCl₃) 7.11 (s, 2H), 4.02 (t, J=6.72 Hz, 2H), 3.86 (br s, 4H), 3.57 (t, J=6.72 Hz, 2H).

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Step 3: Aldehyde (508 mg, 2.96 mmol, 1.0 eq.) was added to a heterogeneous mixture of the
diaminophthalimide (840 mg, 2.96 mmol, 1.0 eq.) in MeOH/AcOH (3/1; 40 mL) and stirred
at ambient temperature for 48 h. The reaction mixture was concentrated in vacuo to a residual
solid and purified by flash chromatography (R_f=0.30; 20% EtOAc/DCM) to isolate fractions
corresponding to the desired product (1.25 g, 97%, 84% pure). ¹H NMR (CDCl₃) 10.90 (br s, IH),
8.18 (d, J=5.5 Hz, IH), 7.15 (d, J=5.5Hz, IH), 4.15 (t, J=6.7 Hz, 2H), 3.65 (t, J=6.7Hz,
2H). ESMS (m/z) 435.

Step 4: Bromoethylphthalimide (1 eq.) and the secondary amine (3.0 eq.) [Note: 1.2 eq. of
powdered K₂CO₃ was added if secondary amine was HCl salts) in degassed, anhydrous DMF
(0.13 M solution) and heated in capped vial at 75-80 °C for 6-48 h. The desired products were
purified by flash chromatography to afford products as shown below.

Yield 16%, MH⁺ OK
Yield 34%, MH⁺ OK
Yield 38%, MH⁺ OK

Analytical data for 2-(4-Chloro-2-methoxypyridin-3-yl)-6-{2-[(2S)-2-methylpyrrolidin-1-
¹H NMR (CDCl₃) 8.28 (br s, IH), 8.17 (d, J=5.5 Hz, IH), 8.02 (br s, IH), 7.14 (d, J=5.5 Hz,
IH), 4.01 (s, 3H), 3.41-3.09 (m, 2H), 2.47-2.19 (m, 3H), 1.91-1.78 (m, IH), 1.65-1.52 (m,
IH), 1.45-1.29 (m, IH), 1.25 (br s, IH), 1.19-1.17 (m, IH), 1.03 (d, J=3.3 Hz, 3H) 0.91-0.72
(m, IH). ESMS (m/z) 440.91.

Analytical data for 2-(4-Chloro-2-methoxypyridin-3-yl)-6-{2-[1,1-dioxidothiomorpholin-4-
yl]ethyl}imidazo[4,5-f]isoindole-5,7(1H,6H)-dione.
¹H NMR (MeOH-OD) 8.32 (d, J=5.6 Hz, IH), 8.14 (s, 2H), 7.29 (d, J=5.6 Hz, IH), 4.05-3.94
(m, 5H), 3.53-3.37 (m, 4H), 3.29-3.10 (m, 6H). ESMS (m/z) 490.3.
Step 5: The crude product from Step 4 above was dissolved in dioxane/con HCl (5/1) and stirred at ambient temperature through night. The reaction mixture was concentrated in vacuo to dryness, azeotroped with EtOH (2x) to obtain the corresponding monoHCl salts as a powder. These were used in the next steps as such.

Synthesis of lactam containing chloropyridones

Schemes 75

Step 1: Tin powder (1.96 g, 16.5 mmol, 10.0 eq.) was added to a solution of nitroaminophthalimide derivative [5-amino-2-(substituted)-6-nitroisoindoline-1,3-dione] (550 mg, 1.65 mmol) in EtOH (7 mL)/con HCl (1.7 mL) and refluxed for 24 h. Another batch of tin powder (1.96 g, 16.5 mmol) and con HCl (1.7 mL) were added and reflux continued for 15 h. The reaction mixture was decanted to remove tin, and concentrated in vacuo to a residue. The residue was dissolved in MeOH and cone. aq. NH₄OH was added until no more precipitation was observed. The reaction mixture was filtered and silica gel was added to the filtrate and concentrated in vacuo. The residue was adsorbed on silica gel and purified by flash chromatography [10% (5% aq. NH₄OH/MeOH)/DCM; R_f=0.32] to afford the desired product as a thick yellow oil (314 mg, 66%).

Step 2: A solution of the aldehyde (189 mg, 1.1 mmol, 1.0 eq.) in MeOH (10 mL) was added drop wise to a 0-5 °C solution of the lactam (0.31 g, 1.1 mmol; from step 1) in MeOH (10 mL) and stirred at room temperature for 14 h and at 50 °C for 1 d. The reaction mixture was filtered through Celite, and the filtrate was concentrated in vacuo to a residue and purified by
flash chromatography [10% (5% aq. NH₄OH/MeOH)/DCM; \( R_f = 0.40 \)] to isolate fractions corresponding to the desired product. The isolated product was used as such in the next step.

**Step 3:** Con HCl (0.8 mL) was added to a solution of the product from step 2 (225 mg, 0.51 mmol) in dioxane (3 mL) and stirred at ambient temperature throughnight and at 60 °C for 2h. The reaction mixture was concentrated in vacuo to dryness to afford 279 mg of the desired product as a grey solid. ESMS \( m/z \) 426.4. This was used as such in the next steps.

In a similar fashion was synthesized 2-((4-Chloro-2-oxo-1,2-dihydropyridin-3-yl)-6-\{[(2R)-l-ethylpyrrolidin-2-y1]methyl\}imidazo[4,5-f]isoindole-5,7(1H,6H)-dione

![Chemical structure](image)

**Synthesis of aryloxypropanolamine containing phthalimides**

2-(4-\{[(2R)-3-(2,4-dimethylphenoxy)-2-hydroxypropyl\} amino \}-2-oxo-1,2-dihydropyridin-3-yl)-6-(3-pyrrolidin-1-ylpropyl)imidazo[4,5-f]isoindole-5,7(1H,6H)-dione

**Scheme 76**

![Chemical structure](image)

(2R)-l-amino-3-(2,4-dimethylphenoxy)propan-2-ol (75 mg, 0.38 mmol, 1.2 eq.) was added to a solution of the halo-pyridone (150 mg, 0.32 mmol, 1.0 eq.) and Et₃N (150 µL, 1.05 mmol, 3.3 eq.) and heated at 100 °C for 2 h and stirred at ambient temperature throughnight. The reaction mixture was filtered and the solid was dried in a vacuum oven at 40 °C throughnight to afford the title compound as a tan colored powder (87 mg, 47%). \(^1\)H NMR (DMSOd₆): \( \delta \)

- 242 -
J = 5.7 Hz, IH), 6.97 (s, IH), 6.92 (d, J = 7.7 Hz, IH), 6.80 (d, J = 8.7 Hz, IH), 6.22 (d, J = 7.5 Hz, IH), 5.55 (d, J = 5.1 Hz, IH), 4.1 1-3.85 (m, 3H), 3.80-3.51 (m, 3H), 3.16 (d, J = 4.5 Hz, 2H), 3.21-2.56 (m, 4H), 2.21 (s, 3H), 2.19 (s, 3H), 1.91-1.78 (m, 2H), 1.65 (br s, 3H), 1.46-0.99 (m, 2H). ESMS (m/z) 585.5 (M + H)^+

2-(4-[(2R)-3-(2,4-dimethylphenoxy)-2-hydroxypropyl]amino) -2-oxo- 1,2-dihydropyridin-3 -yl)-6-(2-pyrrolidin- 1-ylethyl)imidazo [4,5-f]isoindole-5,7(IH,6H)-dione

Prepared by application of the above methodology.

Purified by HPLC; Yield 26%; ESMS (m/z) 571.5

Synthesis of aryloxypropanolamine containing lactams

2-(4-[(2R)-3-(2-Ethyl-4-methylphenoxy)-2-hydroxypropyl]amino) -2-oxo-1,2-dihydropyridin-3-yl)-6-(1-methylpiperidin-4-yl)-6,7-dihydroimidazo[4,5-f]isoindol-5(3H)-one

Zn (246 mg, 3.8 g atoms, 23.3 eq.) was added to a solution of the phthalimide derivative (95 mg, 0.163 mmol) in glacial acetic acid (~2mL) and heated at 120 °C (bath) for 2h. Reaction mixture was cooled to ambient temperature and the mixture was filtered through Celite. Celite, washed with MeOH (3 x 10 mL) and the filtrate was concentrated in vacuo and azeotroped with toluene (3x15 mL). Flash chromatography purification of the resultant residue [10% (5% aq. NH₄OH/MeOH)/DCM] afforded the desired compound as a cream solid (41 mg, 44%). R_f=0.40; more polar of the two UV and fluorescent spots of the crude material. \(^1\)H NMR (OMSO-\(d_6\): \(\delta\) 12.62 (s, 1H), 11.27 (br s, IH), 11.06 and 10.75 (br singlets, IH), 7.93 and 7.87 (s, IH), 7.1629 (br s, IH), 6.99-6.92 (m, IH), 6.76 (d, J=7.1 Hz, IH), 6.07 (br s, IH), 4.55-4.35 (m, 2H), 4.18-4.07 (m, 2H), 3.80-3.51 (m, 2H), 3.21-3.05 (br s, 2H), 2.71-2.59 (m, 2H), 2.58-2.38 (m, 5H), 2.29-2.59 (m, 4H), 2.40-1.98 (m, 5H), 1.98-1.78 (m, 3H), 1.31-1.05 (m, 3H). ESMS (m/z) 571.5 (M+H)^+.

- 243 -
The following were prepared by application of the above methodology:

2-(4- [(2R)-3-(2,4-Dimethylphenoxy)-2-hydroxypropyl] amino]-2-oxo-1,2-dihydropyridin-3-yl)-6-(2-pyrrolidin-1-ylethyl)-6,7-dihydroimidazo[4,5-f]isoindol-5(3H)-one (46a) ESMS (m/z) 557.5 (M+H+); Yield (48%); purity 100%

\[
\begin{array}{c}
\text{NH} \bigcirc \text{N} \bigcirc \text{NH} \\
\text{NH} \bigcirc \text{N} \bigcirc \text{C} \bigcirc \text{N} \\
\text{O} \bigcirc \text{O} \bigcirc \text{OH} \\
\end{array}
\]

Prepared by Zn/AcOH reduction outlined above.

(R)-2-(4-(3-(2,4-dimethylphenoxy)-2-hydroxypropylamino)-2-oxo-1,2-dihydropyridin-3-yl)-6-(3-(pyrrolidin-1-yl)propyl)-6,7-dihydroimidazo[4,5-f]isoindol-5(1H)-one

\[
\begin{array}{c}
\text{NH} \bigcirc \text{N} \bigcirc \text{NH} \\
\text{NH} \bigcirc \text{N} \bigcirc \text{C} \bigcirc \text{N} \\
\text{O} \bigcirc \text{O} \bigcirc \text{OH} \\
\end{array} \xrightarrow{\text{Zn/AcOH}} \]

Scheme 77

15%; purity 99%; ESMS m/z 571.0 (MH⁺)

The O-acetate was also formed in the reaction:

\[
\begin{array}{c}
\text{NH} \bigcirc \text{N} \bigcirc \text{NH} \\
\text{NH} \bigcirc \text{N} \bigcirc \text{C} \bigcirc \text{N} \\
\text{O} \bigcirc \text{O} \bigcirc \text{O} \bigcirc \text{O} \\
\end{array}
\]

\text{10\%; purity 93\%; ESMS m/z 613.3 (MH⁺)}
The synthesis of the above presented compounds is described in Scheme 78.

\[
\begin{align*}
\text{O}_2\text{N} \quad \text{H}_2\text{N} \quad \text{N} \quad \text{H}_2\text{N} \\
\text{H}_2\text{N} \quad \text{H}_2\text{N} \\
\text{H}_2\text{N} \\
\text{H}_2\text{N}
\end{align*}
\]
5-Amino-4-chloro-2-(1-methyl-piperidin-4-yl)-6-nitro-isoindole-1,3-dione:

A suspension of 5-amino-2-(1-methyl-piperidin-4-yl)-6-nitro-isoindole-1,3-dione (3.04 g, 10 mmol) in HOAc (100 mL) was bubbled with Cl₂ gas for 5.5 h and evaporated to dryness. The residue was diluted with aqueous MeOH (25 mL, 80%) and basified with aqueous NH₄OH solution (28%) resulting a solution to which NaHSO₃ (10.4 g, 100 mmol) was added. The mixture was sonicated for 30 min and loaded on silica gel. Chromatography of the mixture with mixed solvent of CH₂Cl₂/MeOH/28% aqueous NH₄OH (20:10:1) afforded the title compound which is not pure, but was used for the next step reaction directly without further purification.

5,6-Diamino-4-chloro-2-(1-methyl-piperidin-4-yl)-isoindole-1,3-dione:

To a mixture of 5-amino-4-chloro-2-(1-methyl-piperidin-4-yl)-6-nitro-isoindole-1,3-dione (1.35 g, not pure) and 10% PaVC (500 mg) was added 2-propanol (20 mL), HCl in dioxane (4 M, 0.1 mL) and then MeOH (230 mL). After it was stirred under atmospheric hydrogen for 1.5 h, the reaction mixture was filtered over Celite. The filtrate was concentrated, diluted with 50% DCM in MeOH, basified with aqueous NH₄OH solution (28%) and evaporated. Chromatography of the mixture with mixed solvent of CH₂Cl₂/MeOH/28% aqueous NH₄OH (50:10:1) afforded the title compound (186 mg, 6% for 2 steps). ¹H NMR (DMSO-d₆) δ 1.51 (m, 2H), 1.90 (m, 2H), 2.29 (m, 2H), 2.81 (m, 2H), 3.80 (m, 1H), 5.61 (br s, 2H, NH₂), 5.93 (br s, 2H, NH₂), 6.82 (s, IH, ArH); ESI-MS m/z 309.4 (MH⁺).
4-Chloro-2-(4-chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione

4-Chloro-2-(4-chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione: A solution of 5,6-diamino-4-chloro-2-(1-methyl-piperidin-4-yl)-isoindole-1,3-dione (62.0 mg, 0.2 mmol), 4-iodo-2-methoxynicotinic aldehyde (34.3 mg, 0.2 mmol) and HOAc (1 mL) in MeOH was stirred at the room temperature for 14 h, heated at 80 °C for 4.5 h, and concentrated to result a residue which was then mixed with HCl in dioxane (4 M, 10 mL) and H2O (0.8 mL) and heated for 1.7 h at 70 °C for 1.5 h. The reaction mixture was evaporated, diluted with diluted with a mixed solvent of DCM/MeOH (1:5), basified with aqueous NH₄OH solution (28%) and evaporated. Chromatography of the residue with mixed solvent of CH₂Cl₂/MeOH/28% aqueous NH₄OH (40:10:1) afforded the title compound (70.2 mg, 78% for 2 steps). ESI-MS m/z 446.5 (MH+).

4-Chloro-2-{4-[3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione

4-Chloro-2-{4-[3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione: A solution of 4-chloro-2-(4-chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(1-methyl-piperidin-4-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione (18 mg, 0.04 mmol), (R)-l-amino-3-(2,4-dimethyl-phenoxy)-propan-2-ol (12.0 mg, 0.06 mmol) and Et₃N (0.2 mL, 1.43 mmol) in EtOH (2.0 mL) was heated at 100 °C for 19 h and then concentrated to result a residue which was subjected to HPLC purification to furnish the title compound in TFA salt form (3.98 mg,
14%). $\text{H NMR (DMSO-de)} \delta 1.95 (m, 2H), 2.15 (s, 3H), 2.19 (s, 3H), 2.51 (m, 2H), 2.80 (s, 3H), 3.18 (m, 2H), 3.50-3.80 (4H), 4.02 (m, 2H), 4.15 (m, IH), 4.30 (m, IH), 5.50 (br s, IH, NH), 6.25 (d, $J = 8$ Hz, IH), 6.80-6.94 (3H), 7.40 (m, IH), 8.08 (s, IH), 9.49 (br s, IH), 10.90 (br s, IH), 11.36 (d, $J = 6$ Hz, IH); ESI-MS $m/z$ 605.3 (MH$^+$).

8-Chloro-2-{4-[3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydropyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1,3,6-triaza-s-indacen-5-one:

$$\text{H NMR (DMSO-de)} \delta 1.95-2.12 (4H), 2.16 (s, 3H, \text{CH}_3), 2.19 (s, 3H, \text{CH}_3), 2.80 (s, 3H, \text{CH}_3), 3.19 (m, 2H), 3.50-3.75 (4H), 4.07 (m, 2H), 4.12 (m, IH), 4.30 (s, IH), 4.49 (s, 2H), 6.22 (m, IH), 6.80-6.95 (3H), 7.40 (IH), 7.95 (s, IH), 9.64 (br s, IH), 11.02 (br s, H, NH), 11.29 (br s, IH, NH); \text{ESI-MS } m/z 591.3 (\text{MH}^+)$$

8-Chloro-2-{4-[3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydropyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-1,3,6-triaza-s-indacen-5-one was mixed with zinc dust (196 mg, 1.0 mmol) in HOAc (15 mL). After it was heated at 90 $^\circ$C for 1 h, the reaction mixture was cooled to 50 $^\circ$C and diluted with a mixed solvent of MeOH:DCM (45 mL/5 mL) and filtered. The filtrate was evaporated at 95 $^\circ$C (the bath temperature) under reduced pressure to dryness. The residue was diluted with a mixed solvent of DCM/MeOH (1:5) and basified with 28% aqueous NH$_4$OH solution and concentrated. Chromatography of the residual crude with CH$_2$Cl$_2$/MeOH/2.8% aqueous NH$_4$OH (16:10:1) followed by HPLC re-purification afforded the title compound in TFA salt form (9.23 mg, 19%). $\text{H NMR (DMSO-$^d_6$)} \delta 1.95-2.12 (4H), 2.16 (s, 3H, \text{CH}_3), 2.19 (s, 3H, \text{CH}_3), 2.80 (s, 3H, \text{CH}_3), 3.19 (m, 2H), 3.50-3.75 (4H), 4.07 (m, 2H), 4.12 (m, IH), 4.30 (s, IH), 4.49 (s, 2H), 6.22 (m, IH), 6.80-6.95 (3H), 7.40 (IH), 7.95 (s, IH), 9.64 (br s, IH), 11.02 (br s, H, NH), 11.29 (br s, IH, NH); ESI-MS $m/z$ 591.3 (MH$^+$).
Synthesis of Sulfone, sulfoxide and sulfide derivatives

Scheme 79
4-(5-Amino-6-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester: A mixture of 5-amino-6-nitro-isoindole-1,3-dione (2.07 g, 10 mmol), tert-butyl 4-amino-piperidine-1-carboxylate (2.5 g, 12 mmol), imidazole (1.63 g, 24 mmol) in dioxane (100 mL) was sealed in a ChemGlass heavy wall pressure flask. After it was heated at 140 °C for 72 h, the reaction mixture was evaporated to dryness at 95 °C (the bath temperature) under reduced pressure. The chromatography of the residue with CH$_2$Cl$_2$/MeOH/28% aqueous NH$_4$OH (320:10:1) afforded the title compound (2.09 g, 54%). $^1$H NMR (CDCl$_3$) $\delta$ 1.49 (s, 9H), 1.73 (m, 2H), 2.38 (m, 2H), 2.80 (m, 2H), 4.20-4.31 (3H), 7.03 (br s, 2H, NH), 7.34 (s, IH), 8.61 (s, IH); ESI-MS mlz 391.5 (MH$^+$/). 

2-{4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-piperidin-4-yl-6,7-dihydro-3H-l,3,6-triaza-s-indacen-5-one

2-{4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-piperidin-4-yl-6,7-dihydro-3H-l,3,6-triaza-s-indacen-5-one: To a mixture of 4-(5-amino-6-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester (5.0 g, 12.8 mmol) and 10% Pd/C (500 mg) was added 2-propanol (20 mL), and then MeOH (230 mL). After it was stirred under atmospheric hydrogen for 4 h, the reaction mixture was filtered over Celite. The filtrate was mixed with 4-iodo-2-methoxynicotinic aldehyde (3.37 g, 12.8 mmol) and HOAc (13 mL), stirred at the room temperature for 16 h,
and evaporated under reduced pressure to afford an oil crude which was mixed with HCl in dioxane (4 M, 60 mL) and H$_2$O (5 mL), heated at 70 °C for 1.5 h and evaporated at 95 °C (the bath temperature) to dryness. Et$_3$N (5.35 mL, 38.4 mmol) was added to the solution of the residue in DCM (250 mL) at 0 °C under N$_2$ and followed by the addition of the solution of Boc$_2$O (3.35 g, 15.4 mmol). After it was stirred at 0 °C for 1 h and at the room temperature for 19 h, the reaction mixture was mixed slowly with MeOH (200 mL) at 0 °C and then evaporated at 70 °C (the both temperature) to dryness under reduced pressure. The residue was mixed with (R)-l-amino-3-(2,4-dimethyl-phenoxy)-propan-2-ol (2.5 g, 12.8 mmol) and Et$_3$N (5.35 mL, 38.4 mmol) in EtOH (200 mL) resulting a mixture which was heated at 100 °C for 5 h and then concentrated. Chromatography of the residual mixture with CH$_2$Cl$_2$ /MeOH/28% aqueous NH$_4$OH (250:10:1) furnished a fluorescent product which was mixed with zinc dust (5.5 g, 84 mmol) and HOAc (200 mL). After it was heated to 90 °C for 2 h, the reaction mixture was filtered and the filtrate was concentrated at 70 °C (the both temperature) under reduced pressure. The residue was mixed with HCl in dioxane (4 M, 60 mL) and H$_2$O (5 mL), heated at 70 °C for 2.5 h and evaporated at 95 °C (the bath temperature) to dryness.

The residue was basified with NH$_3$ in EtOH (2 M) and concentrated. Chromatography of the crude with CH$_2$Cl$_2$/MeOH/28% aqueous NH$_4$OH (40:10:1) afforded a fluorescent product (6.5 g). 50 mg of this product was subjected to HPLC purification to furnish the title compound in TFA salt form (37 mg). $^1$H NMR (DMSO-$d_6$) $\delta$ 1.90-2.05 (4H), 2.19 (s, 3H, CH$_3$), 2.22 (s, 3H, CH$_3$), 3.13 (m, 2H), 3.42 (m, 2H), 3.55 (m, IH), 3.69 (m, IH), 4.03 (m, 2H), 4.13 (m, IH), 4.39 (m, IH), 4.46 (s, 2H), 6.22 (d, J = 7 Hz, IH), 6.84 (d, J = 7 Hz, IH), 6.94 (d, J = 7 Hz, IH), 6.98 (s, IH), 7.39 (d, J = 7 Hz, IH), 7.55 (br s, IH), 7.85 (br s, IH), 11.14 (br s, IH, NH), 11.23 (br d, J = 6 Hz, IH, NH); ESI-MS m/z 543.5 (MH$^+$).

2-{-[4-{[(R)-3-(2,4-Dimethy l-phen oxy)-2-hydroxy-propalamino] -2-oxo- 1,2-dihydro-pyridin-3 -yl }-6-{-[1-(2-methanesulfonyl-ethyl)-piperidin-4-yl] }-6,7-dihydro-3 H-1,3,6-triaza-s-indacen-5 -one
2-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-[(2-methanesulfonyl-ethyl)-piperidin-4-yl]-6,7-dihydro-3\textsubscript{H}-1,3,6-triaza-s-indacen-5-one: A mixture of 2-[(R)-3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-piperidin-4-yl-6,7-dihydro-3\textsubscript{H}-1,3,6-triaza-s-indacen-5-one (3.04 g, 5.6 mmol) and methyl vinyl sulfone (5.94 g, 56 mmol) in a mixed solvent of EtOH (70.0 mL) and 2-propanol (70.0 mL) was heated at 100 °C for 22 h and then evaporated. Chromatography of the residue with CH\textsubscript{2}Cl\textsubscript{2}/MeOH/28% aqueous NH\textsubscript{4}OH (190:10:1) afforded title compound (2.82 g, 78%). \textsuperscript{1}H NMR (DMSO-\textsuperscript{6}) \(\delta\) 1.68-1.85 (4H), 2.15 (m, 2H), 2.18 (s, 3H, CH\textsubscript{3}), 2.21 (s, 3H, CH\textsubscript{3}), 2.75 (m, 2H), 3.05 (m, 2H), 3.08 (s, 3H, CH\textsubscript{3}), 3.54 (m, 2H), 3.70 (m, IH), 3.93-4.19 (4H), 4.43 (s, IH), 4.47 (s, IH), 5.48 (d, \(J = 6\) Hz, 0.5H, NH), 5.53 (d, \(J = 6\) Hz, 0.5H, NH), 6.20 (m, IH), 6.81 (m, IH), 6.90-6.99 (2H), 7.31-7.37 (1.5H), 7.67 (s, 0.5H), 7.80 (s, 0.5H), 7.94 (s, 0.5H), 11.14 (br d, \(J = 6\) Hz, IH, NH), 11.22 (br d, \(J = 6\) Hz, IH, NH); ESI-MS \textit{mlz} 649.5 (MH\textsuperscript{+}); Anal. Calcd for C\textsubscript{33}H\textsubscript{40}N\textsubscript{6}O\textsubscript{6}S: C, 61.09; H, 6.21; N, 12.95, S 4.94; Found: C, 60.85; H, 6.17; N, 12.87, S 4.85.

2-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-[(2-ethanesulfonyl-ethyl)-piperidin-4-yl]-6,7-dihydro-3\textsubscript{H}-1,3,6-triaza-s-indacen-5-one
2-\{(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino\}-2-oxo-1,2-dihydro-pyridin-3-yl\}-6-\{1-(2-ethanesulfonyl-ethyl)-piperidin-4-yl\}-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one: This compound was prepared by application of the above methodology. $^1$H NMR (DMSO-$^d$) $\delta$ 1.23 (t, $J = 6$ Hz, 3H, $\text{CH}_3$), 1.65-1.82 (4H), 2.15 (m, 2H), 2.19 (s, 3H, $\text{CH}_3$), 2.22 (s, 3H, $\text{CH}_3$), 2.76 (m, 2H), 3.02 (m, 2H), 3.17 (q, $J = 6$ Hz, 2H), 3.29 (m, 2H), 3.55 (m, 1H), 3.70 (m, 1H), 3.93-4.18 (4H), 4.43 (s, 1H), 4.48 (s, 1H), 5.48 (d, $J = 6$ Hz, 0.5H, NH), 5.54 (d, $J = 6$ Hz, 0.5H, NH), 6.20 (m, 1H), 6.81 (m, 1H), 6.89-6.98 (2H), 7.30-7.38 (1.5H), 7.67 (s, 0.5H), 7.80 (s, 0.5H), 7.94 (s, 0.5H), 11.15 (br d, $J = 6$ Hz, IH, NH), 11.20 (br s, IH, NH); ESI-MS $m/z$ 663.7 (MH$^+$).

Acetic acid 1-(2,4-dimethyl-phenoxy)methyl)-2-(3-\{6-\[1-(2-methanesulfonyl-ethyl)-piperidin-4-yl\]-7-oxo-1,5,6,7-tetrahydro-1,3,6-triaza-s-indacen-2-yl\}2-oxo-1,2-dihydro-pyridin-4-ylamino)-ethyl ester

Acetic acid 1-(2,4-dimethyl-phenoxy)methyl)-2-(3-\{6-\[1-(2-methanesulfonyl-ethyl)-piperidin-4-yl\]-7-oxo-1,5,6,7-tetrahydro-1,3,6-triaza-s-indacen-2-yl\}2-oxo-1,2-dihydro-pyridin-4-ylamino)-ethyl ester: A solution of 2-\{(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-
propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-[1-(2-methanesulfonyl-ethyl)-piperidin-4-yl]-6,7-dihydro-3H-l,3,6-triaza-s-indacen-5-one (65 mg, 0.1 mmol) in HOAc (20 mL) was refluxed for 32 h and was evaporated. The residue was diluted with a mixed solvent of DCM/MeOH (1:5), basified with 28% aqueous NH₄OH solution and concentrated. Chromatography of the residual crude with CH₂Cl₂/MeOH/28% aqueous NH₄OH (110:10:1) followed by HPLC re-purification afforded the title compound in TFA salt form (8.69 mg, 1.1%).

1H NMR (DMSO-^6) δ 1.99-2.12 (4H), 2.05 (s, 3H, CH₃), 2.16 (s, 3H, CH₃), 2.22 (s, 3H, CH₃), 3.15 (s, 3H, CH₃), 3.25 (m, 2H), 3.52 (m, 2H), 3.60-3.78 (5H), 3.90 (s, 1H), 4.10-4.38 (4H), 4.49 (br s, 2H), 5.43 (br s, 2H, NH), 6.28 (d, J = 8 Hz, 1H), 6.84 (d, J = 6 Hz, 1H), 6.94 (d, J = 6 Hz, 1H), 6.99 (s, 1H), 7.40 (m, 1H), 7.80 (br s, 1H), 9.80 (br s, 1H), 11.14 (br s, NH), 11.33 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 691.7 (MH+).

2-{4-[3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-[1-(2-methylsulfanyl-ethyl)-piperidin-4-yl]-6,7-dihydro-3H-l,3,6-triaza-s-indacen-5-one

A mixture of the 2-{4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-piperidin-4-yl-6,7-dihydro-3H-l,3,6-triaza-s-indacen-5-one (542 mg, 1.0 mmol), 1-chloro-2-methylsulfanyl-ethane (122 mg, 1.1 mmol), Na₂CO₃ (318 mg, 3.0 mmol) and NaI (150 mg, 1.0 mmol) in CH₃CN (20 mL) was heated at 100 °C for 22 h and then evaporated. Chromatography of the residue with CH₂Cl₂/MeOH/28% aqueous NH₄OH (200:10:1) afforded the title compound. 1H NMR (DMSO-^6) δ 1.69-1.82 (4H), 2.09 (s, 3H, CH₃), 2.09 (m, 2H), 2.19 (s, 3H, CH₃), 2.20 (s, 3H, CH₃), 2.50-2.59 (4H), 3.00 (m, 2H), 3.38 (m, 2H), 3.53 (m, IH), 3.70 (m, IH), 3.98-4.08 (3H), 4.15 (m, IH), 4.43 (s, IH), 4.47 (s, IH).
5.47 (br s, 0.5H, NH), 5.53 (br s, 0.5 H, NH), 6.20 (m, IH), 6.80-6.99 (3H), 7.30-7.36 (1.5H), 7.68 (s, 0.5H), 7.79 (s, 0.5H), 7.94 (s, 0.5H), 11.15 (br d, J = 6 Hz, IH, NH), 11.21 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 617.5 (MH+).

2-{4-[3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-[1-(2-methanesulfinyl-ethyl)-piperidin-4-yl]-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one

\[
\text{ESI-MS } \text{mlz } 633.5 (\text{MH}^+) .
\]

To a solution of 2-{4-[3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3 -yl]-6-[1-(2-methanesulfinyl-ethyl)-piperidin-4-yl]-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one (333 mg, 0.5 mmol) in HOAc (10 mL) was added H\textsubscript{2}O\textsubscript{2} (30\% in H\textsubscript{2}O, 1 mL). After it was stirred at the room temperature for 1 h, the reaction mixture was cooled down to 0 °C and diluted with aqueous MeOH (50\%, 90 mL) resulting a solution to which NaHSO\textsubscript{3} (5.2 g, 50 mmol) was added. The reaction mixture was evaporated after it was stirred at 0 °C for 1 h and the residue was diluted with a mixed solvent of DCM/MeOH (1:5), basified with 28\% aqueous NH\textsubscript{4}OH solution and concentrated. Chromatography of the residual crude with CH\textsubscript{2}Cl\textsubscript{2}/MeOH/28\% aqueous NH\textsubscript{4}OH (110:10:1) afforded the title compound (242 mg, 71\%). \textsuperscript{1}H NMR (DMSO-J \textsubscript{6}) 1.69-1.85 (4H), 2.10 (m, 2H), 2.19 (s, 3H, CH\textsubscript{3}), 2.22 (s, 3H, CH\textsubscript{3}), 2.55 (s, 3H, CH\textsubscript{3}), 2.60-2.81 (2H), 3.00 (m, 2H), 3.38 (m, 2H), 3.54 (m, IH), 3.70 (m, IH), 3.98-4.08 (3H), 4.15 (m, IH), 4.43 (s, IH), 4.48 (s, IH), 5.48 (d, J = 6 Hz, 0.5H, NH), 5.53 (d, J = 6 Hz, 0.5H, NH), 6.20 (m, IH), 6.81 (m, IH), 6.90-6.99 (2H), 7.31-7.37 (1.5H), 7.68 (s, 0.5H), 7.80 (s, 0.5H), 7.94 (s, 0.5H), 11.15 (br d, J = 6 Hz, IH, NH), 11.22 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 633.5 (MH\textsuperscript{+}).
Synthesis of additional sulfones

\[ n' = 1 \text{ or } 2 \]
[2-(5-Amino-6-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-methyl-carbamic acid tert-butyl ester: A mixture of 5-amino-6-nitro-isoindole-1,3-dione (2.07 g, 10 mmol), (2-Amino-ethyl)-methyl-carbamic acid tert-butyl ester (3.485 g, 20 mmol), imidazole (1.36 g, 20 mmol) in dioxane (30 mL) was sealed in a ChemGlass heavy wall pressure flask. After it was heated at 140 °C for 38 h, the reaction mixture was evaporated to dryness at 95 °C (the bath temperature) under reduced pressure. The chromatography of the residue with CH₂Cl₂...
/MeOH/28% aqueous NH₄OH (500:10:1) afforded the title compound (3.39 g, 93%). ¹H NMR (CDCl₃) δ 1.08 (s, 9H), 2.78 (s, 3H), 3.42 (m, 2H), 3.68 (m, 2H), 7.48 (s, IH), 8.34 (s, IH), 8.42 (br s, 2H₃NH).

2-{4-[3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-{2-[2-(methanesulfonyl-ethyl)-methyl-amino]-ethyl}-IH-1,3,6-triaza-s-indacene-5,7-dione:

A mixture of 2-(5-amino-6-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-methyl-carbamic acid tert-butyl ester (729 mg, 2.0 mmol) and TFA (7 mL) in DCM (28 mL) was stirred at the room temperature for 5 h and evaporated to dryness to result a residue which was diluted with a mixed solvent of DCM/MeOH (1:5), basified with 28% aqueous NH₄OH solution and evaporated. The residue was mixed with methyl vinyl ketone (1.27 g, 12 mmol) in a mixed solvent of ethanol (10 mL) and isopropanol (10 mL), heated at 100 °C for 38 h, cooled to the room temperature, diluted with a solution of HOAc in MeOH (5%, 100 mL). The mixture was mixed with Pd/C (100 mg) and stirred under atmospheric H₂ for 2.5 h and filtered through Celite. The filtrate was mixed with 4-chloro-2-methoxynicotinic aldehyde (377.5 mg, 2.2 mmol), stirred at the room temperature for 140 h, and evaporated under reduced pressure to afford an oil crude which was mixed with HCl in dioxane (4 M, 25 mL) and H₂O (2 mL), heated at 60 °C for 30 min and evaporated at 95 °C (the bath temperature) to a crude product. 1/20 of this crude product of was mixed with (R)-l-amino-3-(2,4-dimethyl-phenoxy)-propan-2-ol (29.3 mg, 0.15 mmol) and Et₃N (0.3 mL, 2.1 mmol) in EtOH (2 mL) resulting a mixture which was heated at 100 °C for 5 h and then concentrated. Chromatography of the residual mixture with CH₂Cl₂/MeOH/28% aqueous NH₄OH (150:10:1) furnished the title compound (42.4 mg, 27% for 6 steps). ¹H NMR (DMSO-J₆) δ 2.19 (s, 3H, CH₃), 2.21 (s, 3H, CH₃), 2.64 (s, 3H, CH₃), 2.60 (m, 2H), 2.79 (m, 2H), 2.90 (s,
3H, CH₃), 3.20 (m, 2H), 3.48 (m, IH), 3.65-3.75 (3H), 3.99 (m, 2H), 4.13 (m, IH), 5.54 (d, J = 6 Hz, IH, NH), 6.23 (d, J = 7 Hz, IH), 6.83 (d, J = 7 Hz, IH), 6.94 (d, J = 7 Hz, IH), 6.97 (s, IH), 7.41 (m, IH), 7.67 (s, IH), 8.12 (s, IH), 10.97 (br s, IH, NH), 11.29 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 637.7 (MH⁺).

2-{(4-[3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl)-6-{2-[(2-methanesulfonyl-ethyl)-methyl-amino]-ethyl}-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one}

2-{(4-[3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl)-6-{2-[(2-methanesulfonyl-ethyl)-methyl-amino]-ethyl}-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one}: 2-4-[3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino] -2-oxo-1,2-dihydro-pyridin-3-yl}-6-[(2-methanesulfonyl-ethyl)-methyl-amino]-ethyl}-1H-1,3,6-triaza-s-indacene-5,7-dione (35 mg, 0.055 mmol) was mixed with zinc dust (196 mg, 3 mmol) and HOAc (15 mL). After it was refluxed for 30 min, the reaction mixture was filtered and the filtrate was concentrated at 70 °C (the bath temperature) under reduced pressure resulting a residue which was diluted with a mixed solvent of DCM/MeOH (10 mL:90 mL), basified with 28% aqueous NH₄OH and concentrated. Chromatography of the crude residue with CH₄Cl₂/MeOH/2 8% aqueous NH₄OH (190:10:1) afforded a fluorescent product (6.98 mg, 20%). ¹H NMR (DMSO-CD₃) δ 2.13 (s, 3H, CH₃), 2.16 (s, 3H, CH₃), 2.22 (s, 3H, CH₃), 2.65 (m, 2H), 2.80 (m, 2H), 2.85 (s, 3H, CH₃), 3.27 (m, 2H), 3.53 (m, IH), 3.60-3.71 (3H), 4.02 (m, 2H), 4.13 (m, IH), 4.48 (s, IH), 4.53 (s, IH), 5.48 (d, J = 6 Hz, 0.5H, NH), 5.53 (d, J = 6 Hz, 0.5H, NH), 6.22 (d, J = 7 Hz, IH), 6.80 (d, J = 7 Hz, IH), 6.89-6.99 (2H), 7.30-7.35 (1.5H), 7.67 (s, 0.5H), 7.79 (s, 0.5H), 7.94 (s, 0.5H), 11.15 (br m, IH, NH); ESI-MS mlz 623.5 (MH⁺).
[2-(5-Amino-6-nitro-1,3-dioxo-1,3-dihydro-isoinodol-2-yl)-propyl]-methyl-carbamic acid tert-butyl ester

\[
\text{[2-(5-Amino-6-nitro-1,3-dioxo-1,3-dihydro-isoinodol-2-yl)-propyl]-methyl-carbamic acid tert-butyl ester: } ^1H \text{NMR (CDCl}_3\text{) } \delta 1.30 (s, 9H), 1.75 (m, 2H), 2.72 (s, 3H), 3.12 (m, 2H), 3.49 (m, 2H), 7.40 (s, 1H), 8.29 (s, 1H), 8.41 (br s, 2H, NH).
\]

2 - {4-[3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino] -2-oxo- 1,2-dihydro-pyridin-3 -yl } - 6-{3-[(2-methanesulfonyl-ethyl)-methyl-amino]-propyl}-1H-1,3,6-triaza-s-indacene-5,7-dione

\[
\text{2 - {4-[3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino] -2-oxo- 1,2-dihydro-pyridin-3 -yl } - 6{-[3-[(2-methanesulfonyl-ethyl)-methyl-amino]-propyl]-1H-1,3,6-triaza-s-indacene-5,7-dione: } ^1H \text{NMR (DMSO-}^\text{d}_6\text{) } \delta 1.75 (m, 2H), 2.19 (s, 3H, CH}_3\text{), 2.21 (s, 3H, CH}_3\text{), 2.22 (s, 3H, CH}_3\text{), 2.39 (m, 2H), 2.75 (m, 2H), 3.01 (s, 3H, CH}_3\text{), 3.23 (m, 2H), 3.60 (m, 2H), 3.75 (m, 2H), 3.99 (m, 2H), 4.13 (m, IH), 5.54 (d, J = 6 Hz, IH, NH), 6.23 (d, J = 7 Hz, IH), 6.83 (d, J = 7 Hz, IH), 6.92 (d, J = 7 Hz, IH), 6.97 (s, IH), 7.41 (m, IH), 7.67 (s, IH), 8.12 (s, IH), 10.95 (br s, IH, NH), 11.29 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 651.5 (MH\text{+}).
\]

2 - {4-[3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino] -2-oxo- 1,2-dihydro-pyridin-3 -yl } - 6-{3-[(2-methanesulfonyl-ethyl)-methyl-amino]-propyl}-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one
2-\{4-\{3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino\} -2-oxo- 1,2-dihydro-pyridin-3 -yl\} -
6-\{3-[(2-methanesulfonyl-ethyl)-methyl-amino\} -propyl \} -6,7-dihydro-3 H-1,3,6-triaza-s-
indacen-5-one: 1H NMR (DMSO-\textsubscript{d6}) \( \delta \) 1.76 (m, 2H), 2.19 (s, 3H, CH\textsubscript{3}), 2.20 (s, 3H, CH\textsubscript{3}),
2.21 (s, 3H, CH\textsubscript{3}), 2.39 (m, 2H), 2.72 (m, 2H), 3.03 (s, 3H, CH\textsubscript{3}), 3.29 (m, 2H), 3.55 (m, IH),
3.67 (m, IH), 3.82 (m, IH), 4.00 (m, 2H), 4.12 (m, IH), 4.46 (s, IH), 4.50 (s, IH), 5.48 (br s,
0.5H, NH), 5.52 (br s, 0.5H, NH), 6.22 (d, \( J = 7 \) Hz, IH), 6.80 (d, \( J = 7 \) Hz, IH), 6.89-6.99
(2H), 7.32-7.37 (1.5H), 7.67 (s, 0.5H), 7.79 (s, 0.5H), 7.94 (s, 0.5H), 11.15 (br m, \( \text{IH}_3 \)NH);
ESI-MS \( m/z \) 637.7 (MH\textsuperscript{+}).

Synthesis of lactams with pyrrolidinylethyl or pyrrolidinylpropyl

\[ n'' = 1 \text{ or } 2 \]
2-\{4-\[3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino\] -2-oxo-1,2-dihydro-pyridin-3-yl\} - 6-\{3-[(2-methanesulfonyl-ethyl)-methyl-amino]-propyl\} - 6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one
Synthesis of methylated lactams.

Scheme 82

Synthesis of Nitro-aminophthalimidederivative: (S)-5-amino-2-((1-(dimethylamino)propan-2-yl)-6-nitroisoindoline-1,3-dione

Scheme 83

R¹ and R² are hydrogen or methyl

- 263 -
(l-Dimethylcarbamoyl-ethyl-^-carbamic acid tert-butyl ester

(l-Dimethylcarbamoyl-ethylty-carbamic acid tert-butyl ester: To a solution of DMAP (10 mg, 0.08 mmol) and DIEA (6.07 g, 47 mmol) in DCM (60 mL) was added a solution of dimethylamine in THF (2.0 M, 25.7 mL, 51.3 mmol) and the mixture was stirred at 0 °C for 30 min. HOBt (6.35 g, 47 mmol) was added to a solution of IV-α-tert-Boc-L-alanine (8.09 g, 42.76 mmol) in DCM (60 mL) and the mixture was stirred at 0 °C for 25 min. The two solutions were combined into one solution to which EDCI (9.03 g, 47 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h, stirred at the room temperature for 48 h and concentrated. Chromatography of the residue with CH₂Cl₂/MeOH/28% aqueous NH₄OH (240:10:1) afforded the title compound (7.95 g, 86%). ¹H NMR (CDCl₃) δ 1.30 (d, J = 6 Hz, 3H, CH₃), 1.44 (s, 9H), 2.97 (s, 3H, CH₃), 3.06 (s, 3H, CH₃), 4.62 (q, J = 6 Hz, IH), 5.51 (d, J = 6 Hz, 1H, NH).

2-Amino-N,N-dimethyl-propionamide: A solution of (l-dimethylcarbamoyl-ethyl)-carbamic acid tert-butyl ester

2-Amino-N,N-dimethyl-propionamide: A solution of (l-dimethylcarbamoyl-ethyl)-carbamic acid tert-butyl ester (7.95 g) in 20% TFA/DCM (200 mL) was stirred at the room temperature for 2 h and evaporated to result in a residue which was diluted with a mixed solvent of MeOH/DCM (100 mL/100 mL), basified with 28% aqueous NH₄OH, and concentrated. Chromatography of the residue with CH₂Cl₂/MeOH/28% aqueous NH₄OH (90:10:1) afforded the title compound (3.49 g, 81%). ¹H NMR (MeOH-^d₄) δ 1.28 (d, J = 6 Hz, 3H, CH₃), 2.95 (s, 3H, CH₃), 3.08 (s, 3H, CH₃), 4.04 (q, J = 6 Hz, IH); ESI-MS mlz 117.3 (MH⁺).

HCl salt of 2-amino-N,N-dimethyl-propylamine

HCl salt of 2-amino-N,N-dimethyl-propylamine: To a solution of 2-amino-N,N-dimethyl-propionamide (3.49 g, 30 mmol) in THF (100 mL) was added BH₃·THF complex in THF (1.0
M, 90 mL, 90 mmol) at 0°C resulting in a mixture which was stirred at the room temperature for 1 h and refluxed under N₂ for 18 h. After it was cooled to 0 °C, the reaction mixture was quenched by adding MeOH (20 mL) slowly and dropwise at 0 °C and then stirred for 16 h. Aqueous HCl (12 N, 6 mL) was added into the reaction mixture which was then heated at 80 °C for 1 h and evaporate to afford the title compound in HCl salt form (5.3 g) which was used for the next step without purification. ¹H NMR (DMSO-CD₃) δ 1.31 (d, J = 6 Hz, 3H, CH₃), 2.85 (s, 6H, 2CH₃), 3.32 (m, IH), 3.48 (m, IH), 3.80 (m, IH), 8.79 (br s, 2H, NH).

5-Amino-2-(2-dimethylamino-1-methyl-ethyl)-6-nitro-isoindole-1,3-dione:  A mixture of 5-amino-6-nitro-isoindole-1,3-dione

\[
\text{\begin{align*}
\text{O}_2\text{N} & \quad \text{N} \quad \text{N} \\
\text{O} & \\
\text{H}_2\text{N} & \\
\end{align*}}
\]

5-Amino-2-(2-dimethylamino-1-methyl-ethyl)-6-nitro-isoindole-1,3-dione:  A mixture of 5-amino-6-nitro-isoindole-1,3-dione (1.66 g, 8.0 mmol), HCl salt of 2-amino-N,N-dimethylpropylamine (5.3 g, crude, < 30 mmol), imidazole (1.36 g, 20 mmol) and Et₃N (8.4 mL, 60.07 g, 60 mmol) in dioxane (80 mL) was sealed in a ChemGlass heavy wall pressure flask. After it was heated at 130 °C for 72 h, the reaction mixture was evaporated to dryness at 95 °C (the bath temperature) under reduced pressure. The chromatography of the residue with CH₂Cl₂/MeOH/28% aqueous NH₄OH (240:10:1) afforded the title compound (1.49 g, 64 %). ¹H NMR (DMSO-CD₃) δ 1.32 (d, J = 6 Hz, 3H, CH₃), 2.09 (s, 6H, 2CH₃), 2.25 (m, IH), 2.95 (m, IH), 4.35 (m, IH), 7.43 (s, IH), 8.29 (s, IH), 8.39 (br s, 2H, NH). ESI-MS m/z 293.1 (MH⁺).

2-(4-Chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(2-dimethylamino-1-methyl-ethyl)-1H-1,3,6-triaza-s-indacene-5,7-dione

\[
\text{\begin{align*}
\text{Cl} & \quad \text{N} \\
\text{H} & \\
\text{N} & \\
\text{O} & \\
\text{N} & \\
\end{align*}}
\]

2-(4-Chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(2-dimethylamino-1-methyl-ethyl)-1H-1,3,6-triaza-s-indacene-5,7-dione:  The mixture of 5-amino-2-(2-dimethylamino-1-methyl-ethyl)-6-nitro-isoindole-1,3-dione (585 mg, 2.0 mmol) and Pd/C (60 mg) in MeOH (95 mL) was stirred under atmospheric H₂ for 2.5 h and filtered through Celite. The filtrate was mixed with 4-chloro-2-methoxynicotinic aldehyde (343.2 mg, 2.0 mmol) and HOAc (5 mL), stirred at the
room temperature for 62 h, and evaporated under reduced pressure to afford an oil crude which was mixed with HCl in dioxane (4 M, 25 mL) and H₂O (2 mL), heated at 70 °C for 1 h and evaporated. The residue was diluted with a mixed solvent of MeOH/DCM (50 mL/50 mL), basified with 28% aqueous NH₄OH, and concentrated. Chromatography of the residue with CH₂Cl₂/MeOH/28% aqueous NH₄OH (60:10:1) afforded the title compound (642 mg, 80%).

\[ \text{H} \text{NMR (DMSO-} \delta \text{) } \delta 1.39 (d, J = 6 \text{ Hz, } 3 \text{H, CH₃}), 2.14 (s, 6 \text{H, } 2 \text{CH₃}), 2.29 (m, \text{IH}), 3.04 (m, \text{IH}), 4.40 (m, \text{IH}), 6.59 (d, J = 8 \text{ Hz, IH}), 7.69 (d, J = 8 \text{ Hz, IH}), 8.04 (s, \text{IH}), 8.05 (s, \text{IH}); \text{ESI-MS } mlz 400.3 (MH⁺). \]

Synthesis of Nitroaminophthalimide

Scheme 84

2-Dimethylamino-propionamide

\[ \text{2-Dimethylamino-propionamide: A mixture of H-Ala-NH₂-HCl (7.47 g, 60 mmol), HCHO (37\%, 14.6 mL) and Pd/C (750 mg) in MeOH (200 mL) was stirred under atmospheric H₂ for 16 h and filtered through Celite. The filtrate was evaporated, diluted with a mixed solvent of MeOH/DCM (150 mL/150 mL), basified with 28\% aqueous NH₄OH, and concentrated. Chromatography of the residue with CH₂Cl₂/MeOH/2 8\% aqueous NH₄OH (60:10:1) afforded the title compound (6.43 g, 92\%). \text{H NMR (DMSO-} \delta \text{) } \delta 1.06 (d, J = 8 \text{ Hz, 3H}, \text{CH₃}); } \text{ESI-MS } mlz 479.3 (MH⁺). \]
HCl salt of 2-dimethylamino-propylamine: To a solution of 2-dimethylamino-propionamide (3.49 g, 30 mmol) in THF (100 mL) was added BH$_3$-THF complex in THF (1.0 M, 90 mL, 90 mmol) at 0 °C resulting in a mixture which was stirred at the room temperature for 1 h and refluxed under N$_2$ for 22 h. After it was cooled to 0 °C, the reaction mixture was quenched by adding MeOH (25 mL) slowly and dropwise at 0 °C and then stirred for 16 h. Aqueous HCl (12 N, 6 mL) was added into the reaction mixture which was then heated at 80 °C for 1 h and evaporate to afford the title compound in HCl salt form (5.5 g) which was used for the next step without purification.

$^1$H NMR (DMSO-$^d_6$) $\delta$ 1.06 (d, $J = 6$ Hz, 3H, CH$_3$), 2.75 (s, 6H, 2CH$_3$), 3.40 (m, IH), 3.60-3.76 (2H), 8.81 (br s, 2H).

5-Amino-2-(2-dimethylamino-propyl)-6-nitro-isoindole-1,3-dione

5-Amino-2-(2-dimethylamino-propyl)-6-nitro-isoindole-1,3-dione: A mixture of 5-amino-6-nitro-isoindole-1,3-dione (1.66 g, 8.0 mmol), HCl salt of 2-dimethylamino-propylamine (5.5 g, crude, < 30 mmol), imidazole (1.36 g, 20 mmol) and Et$_3$N (8.4 mL, 6.07 g, 60 mmol) in dioxane (80 mL) was sealed in a ChemGlass heavy wall pressure flask. After it was heated at 130 °C for 69 h, the reaction mixture was evaporated to dryness at 95 °C (the bath temperature) under reduced pressure. The chromatography of the residue with CH$_2$Cl$_2$/MeOH/28% aqueous NH$_4$OH (240:10:1) afforded the title compound (360 mg, 15 %). $^1$H NMR (DMSO-$d_6$) $\delta$ 0.88 (d, $J = 6$ Hz, 3H, CH$_3$), 2.13 (s, 6H, 2CH$_3$), 3.32 (m, 2H), 3.65 (m, IH), 7.45 (s, IH), 8.30 (s, IH), 8.40 (br s, 2H, NH). ESI-MS m/z 293.3 (MH$^+$).
2-(4-Chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(2-dimethylamino-propyl)-1H-1,3,6-triaza-s-indacene-5,7-dione

2-(4-Chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(2-dimethylamino-propyl)-1H-1,3,6-triaza-s-indacene-5,7-dione: The mixture of 5-amino-2-(2-dimethylamino-1-methyl-ethyl)-6-nitro-isoindole-1,3-dione (360 mg, 1.2 mmol) and Pd/C (40 mg) in MeOH (95 mL) was stirred under atmospheric H₂ for 24 h and filtered through Celite. The filtrate was mixed with 4-chloro-2-methoxynicotinic aldehyde (343.2 mg, 2.0 mmol) and HOAc (5 mL), stirred at the room temperature for 96 h, and evaporated under reduced pressure to afford an oil crude which was mixed with HCl in dioxane (4 M, 25 mL) and H₂O (2 mL), heated at 70 °C for 4 h and evaporated. The residue was diluted with a mixed solvent of MeOH/DCM (50 mL/50 mL), basified with 28% aqueous NH₄OH, and concentrated. Chromatography of the residue with CH₂Cl₂/MeOH/28% aqueous NH₄OH (60:10:1) afforded the title compound (281 mg, 58%).

¹H NMR (DMSO-Ç6) δ 0.95 (d, J = 6 Hz, 3H, CH₃), 2.24 (s, 6H, 2CH₃), 3.10 (m, IH), 3.45 (m, IH), 3.74 (m, IH), 6.57 (d, J = 8 Hz, IH), 7.70 (d, J = 8 Hz, IH), 8.06 (s, IH), 8.07 (s, IH); ESI-MS mlz 400.3 (MH⁺).

Synthesis of Azetidine-substituted Imidazo[4,5-f]isoindole-5,7(IH,6H)-dione compounds
3-(5-Amino-6-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-azetidine-1-carboxylic acid tert-butyl ester: A mixture of 5-amino-6-nitro-isoindole-1,3-dione (994 mg, 4.8 mmol), 3-Aminomethyl-azetidine-1-carboxylic acid tert-butyl ester (1.0 g, 5.4 mmol) and imidazole (493 mg, 7.25 mmol) in dioxane (140 mL) was sealed in a ChemGlass heavy wall pressure flask. After it was heated at 140 °C for 61 h, the reaction mixture was evaporated to dryness.
at 95 °C (the bath temperature) under reduced pressure. The chromatography of the residue with CH₂Cl₂/MeOH/28% aqueous NH₄OH (400:10:1) afforded the title compound (830 mg, 46%). ¹H NMR (MeOH-­d₄) δ 1.44 (s, 9H), 2.94 (m, 1H), 3.78 (m, 2H), 3.88 (d, J = 6 Hz, 2H), 4.00 (m, 2H), 7.44 (s, 1H), 8.52 (s, 1H); ESI-MS mlz 311.3 (MH⁺).

2-(4-Chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(1-methyl-azetidin-3-ylmethyl)-1H-1,3,6-triaza-s-indacene-5,7-dione: To a mixture of 3-(5-amino-6-nitro-1,3-dioxo-1,3-dihydroisoindol-2-ylmethyl)-azetidine-1-carboxylic acid tert-butyl ester (830 mg, 2.2 mmol) and 10% Pd/C (85 mg) was added 2-propanol (10 mL), and then MeOH (90 mL). After it was stirred under atmospheric hydrogen for 4 h, the reaction mixture was filtered over Celite. The filtrate was mixed with 4-iodo-2-methoxynicotinic aldehyde (580 g, 2.2 mmol) and HOAc (5.0 mL), stirred at the room temperature for 18 h, and evaporated under reduced pressure to afford an oil crude which was mixed with HCl in dioxane (4 M, 30 mL) and H₂O (2.5 mL), heated at 70 °C for 2.5 h and evaporated at 95 °C (the bath temperature) to dryness. The residue was diluted with a mixed solvent of DCM/MeOH (30 mL/70 mL), basified with 28% aqueous NH₄OH and concentrated. Chromatography of the crude with CH₂Cl₂/MeOH/28% aqueous NH₄OH (25:10:1) afforded a crude product which was mixed with HOAc (2.1 mL) and HCHO (37% in H₂O, 2.1mL) in a mixed solvent of MeOH/THF (24 mL/24 mL). The resulting reaction mixture was stirred at the room temperature for 10 min and followed by addition of Na(OAc)₃BH (2.54 g, 12.0 mmol). The reaction mixture was stirred at the room temperature for 63 h and then evaporated. Chromatography of the residue with CH₂Cl₂/MeOH/28% aqueous NH₄OH (90:10:1) afforded the title compound (330 mg, 38%). ESI-MS mlz 398.3 (MH⁺).
TFA salt of 2-{4-[3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-
pyridin-3-yl}-6-(1-methyl-azetidin-3-ylmethyl)-1H-1,3,6-triaza-s-indacene-5,7-dione.

To a solution of 2-(4-chloro-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(1-methyl-azetidin-3-ylmethyl)-
1H-1,3,6-triaza-s-indacene-5,7-dione (40 mg, 0.1 mmol) and (R)-l-amino-3-(2,4-dimethyl-
phenoxy)-propan-2-ol (20 mg, 0.1 mmol) in EtOH (2 mL) was added Et$_3$N (200 µL, 1.43 mmol). After it was heated at 95 °C for 22.5 h, the reaction mixture was concentrated under reduced pressure. HPLC purification of the residue afforded the title compound in TFA salt form (6.61 mg, 20%). $^1$H NMR (DMSO-$d_6$) δ 2.19 (s, 3H, CH$_3$), 2.21 (s, 3H, CH$_3$), 2.82 (s, 3H, CH$_3$), 3.09 (m, IH), 3.59 (m, IH), 3.70 (m, IH), 3.83 (m, 2H), 3.90-4.18 (7H), 5.55 (m, IH, NH), 6.23 (d, $J$ = 8 Hz, IH), 6.84 (d, $J$ = 8 Hz, IH), 6.92 (d, $J$ = 8 Hz, IH), 6.98 (s, IH), 7.41 (m, IH), 7.67 (s, IH), 8.13 (s, IH), 9.83 (br s, 1H, NH), 10.95 (br s, 1H, NH), 11.30 (d, $J$ = 6 Hz, IH); ESI-MS mlz 557.5 (MH$^+$).

TFA salt of 2-{4-[3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-
pyridin-3-yl}-6-(1-methyl-azetidin-3-yl)-1H-1,3,6-triaza-s-indacene-5,7-dione.
TFA salt of 2-{[3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-azetidin-3-yl)-IH-1,3,6-triaza-s-indacene-5,7-dione: $^1$H NMR (DMSO-$^d$) $\delta$ 2.19 (s, 3H, CH$_3$), 2.22 (s, 3H, CH$_3$), 3.00 (s, 3H, CH$_3$), 3.50-3.69 (3H), 3.95-4.29 (4H), 4.53 (m, 2H), 6.26 (d, $J$ = 8 Hz, IH), 6.84 (d, $J$ = 8 Hz, IH), 6.92 (d, $J$ = 8 Hz, IH), 6.98 (s, IH), 7.41 (m, IH), 7.72 (br s, IH), 8.17 (s, IH), 10.94 (br s, NH$_3$), 11.31 (d, $J$ = 6 Hz, IH); ESI-MS m/z 543.2 (MH$^+$).

Subthesis of lactams with variety of amine side chains

Scheme 86

Synthesis of lactams
TFA salt of (R)-2-(4-(3-(2-chloro-3,6-difluoro-4-methoxyphenoxy)-2-hydroxypropylamino)-2-oxo-1,2-dihydropyridin-3-yl)-6-(1-methylpiperidin-4-yl)-6,7-dihydroimidazo[4,5-f]isoindol-5(3H)-one: \(^1\)H NMR (DMSCW \(_{6}\)) \(\delta\) 1.95 (m, 2H), 2.20 (m, 2H), 2.75 (s, 3H, CH\(_3\)), 3.20 (m, 2H), 3.50 (m, 2H), 3.75 (m, IH), 3.85 (s, 3H, CH\(_3\)), 4.12 (m, 2H), 4.35 (m, IH), 4.50 (s, 2H), 6.22 (d, \(J = 6\) Hz, IH), 7.31 (m, IH), 7.39 (m, IH), 7.70 (s, IH), 7.88 (s, IH), 10.65 (br s, IH), 11.04 (br s, IH, NH), 11.27 (d, \(J = 6\) Hz, IH); ESI-MS \(m/z\) 629.5 (MH\(^+\)).

Synthesis of Substituted Lactams [Substituted-2-oxo-1,2-dihydropyridin-3-yl)-6,7-dihydroimidazo[4,5-f]isoindol-5(3H)-ones]
4-(5-Amino-6-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester: A mixture of 5-amino-6-nitro-isoindole-1,3-dione
4-(5-Amino-6-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester: A mixture of 5-amino-6-nitro-isoindole-1,3-dione (2.07 g, 10 mmol), tert-butyl 4-amino-piperidine-1-carboxylate (2.5 g, 12 mmol), imidazole (1.63 g, 24 mmol) in dioxane (100 mL) was sealed in a ChemGlass heavy wall pressure flask. After it was heated at 140 °C for 72 h, the reaction mixture was evaporated to dryness at 95 °C (the bath temperature) under reduced pressure. The chromatography of the residue with CH₂Cl₂/MeOH/28% aqueous NH₄OH (320:10:1) afforded the title compound (2.09 g, 54%). ¹H NMR (CDCl₃) δ 1.49 (s, 9H), 1.73 (m, 2H), 2.38 (m, 2H), 2.80 (m, 2H), 4.20-4.31 (3H), 7.03 (br s, 2H, NH), 7.34 (s, IH), 8.61 (s, IH); ESI-MS m/z 391.5 (MH⁺).

2-{4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-piperidin-4-yl-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one

2-{4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl]-6-piperidin-4-yl-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one: To a mixture of 4-(5-amino-6-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-piperidine-1-carboxylic acid tert-butyl ester (5.0 g, 12.8 mmol) and 10% Pd/C (500 mg) was added 2-propanol (20 mL), and then MeOH (230 mL). After it was stirred under atmospheric hydrogen for 4 h, the reaction mixture was filtered over Celite. The filtrate was mixed with 4-iodo-2-methoxynicotinic aldehyde (3.37 g, 12.8 mmol) and HOAc (13 mL), stirred at the room temperature for 16 h, and evaporated under reduced pressure to afford an oil crude which was mixed with HCl in dioxane (4 M, 60 mL) and H₂O (5 mL), heated at 70 °C for 1.5 h and evaporated at 95 °C (the bath temperature) to dryness. Et₃N (5.35 mL, 38.4 mmol) was added to the solution of the residue in DCM (250 mL) at 0 °C under N₂ and followed by the addition of the solution of BoC₂O (3.35 g, 15.4 mmol) in a minimum amount of DCM. After it was stirred at 0 °C for 1 h and at the room temperature for 19 h, the reaction mixture was mixed slowly with MeOH (200 mL) at 0 °C and then evaporated at 70 °C (the bath temperature) to dryness.
under reduced pressure. The residue was mixed with (R)-l-amino-3-(2,4-dimethyl-phenoxy)-
propan-2-ol (2.5 g, 12.8 mmol) and Et$_3$N (5.35 riL, 38.4 mmol) in EtOH (200 mL) resulting
in a mixture which was heated at 100 °C for 5 h and then concentrated. Chromatography of
the residual mixture with CH$_2$Cl$_2$/MeOH/28% aqueous NH$_4$OH (250:10:1) furnished a
fluorescent product which was mixed with zinc dust (5.5 g, 84 mmol) and HOAc (200 mL).
After it was heated to 90 °C for 2 h, the reaction mixture was filtered and the filtrate was
concentrated at 70 °C (the bath temperature) under reduced pressure. The residue was mixed
with HCl in dioxane (4 M, 60 mL) and H$_2$O (5 mL), heated at 70 °C for 2.5 h and evaporated
at 95 °C (the bath temperature) to dryness. The residue was basified with NH$_3$ in EtOH (2 M)
and concentrated. Chromatography of the crude with CH$_2$Cl$_2$/MeOH/2 8% aqueous NH$_4$OH
(40:10:1) afforded a fluorescent product (6.5 g). 50 mg of this product was subjected to
HPLC purification to furnish the title compound in TFA salt form (37 mg). $^1$H NMR
(DMSO-Cl$_6$) $\delta$ 1.90-2.05 (4H), 2.19 (s, 3H, CH$_3$), 2.22 (s, 3H, CH$_3$), 3.13 (m, 2H), 3.42 (m,
2H), 3.55 (m, IH), 3.69 (m, IH), 4.03 (m, 2H), 4.13 (m, IH), 4.39 (m, IH), 4.46 (s, 2H), 6.22
(d, $J = 7$ Hz, IH), 6.84 (d, $J = 7$ Hz, IH), 6.94 (d, $J = 7$ Hz, IH), 6.98 (s, IH), 7.39 (d, $J = 7$
Hz, IH), 7.55 (br s, IH), 7.85 (br s, IH), 11.14 (br s, IH$_2$,NH), 11.23 (br d, $J = 6$ Hz, IH,
NH); ESI-MS mlz 543.5 (MH$^+$).

TFA salt of 2-{4-[3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-l,2-dihydro-
pyridin-3-yl}-6-[l-(3-oxo-butyl)-piperidin-4-yl]-6,7-dihydro-3H-l,3,6-triaza-s-indacen-5-one

TFA salt of 2-{4-[3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-l,2-dihydro-
pyridin-3-yl}-6-[l-(3-oxo-butyl)-piperidin-4-yl]-6,7-dihydro-3H-l,3,6-triaza-s-indacen-5-one: A mixture of 2-{4-[(R)-3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-
dihydro-pyridin-3-yl}-6-piperidin-4-yl-6,7-dihydro-3H-l,3,6-triaza-s-indacen-5-one (54.3
mg, 1 mmol) and methyl vinyl ketone (415 µL, 5.0 mmol) in DMF (1 mL) was stirred at the
room temperature for 17 h and the reaction mixture was subjected to HPLC purification to
afford the title compound in TFA salt form (30.4 mg, 40%). \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 1.95 (2H), 2.10 (m, 2H), 2.18 (s, 3H, CH\(_3\)), 2.21 (s, 3H, CH\(_3\)), 3.05 (m, 2H), 3.19 (m, 2H), 3.26 (m, 2H), 3.50-3.61 (3H), 3.71 (m, IH), 4.00 (m, 2H), 4.12 (m, IH), 4.35 (m, IH), 4.45 (s, 2H), 6.23 (d, \(J = 7\) Hz, IH), 6.84 (d, \(J = 7\) Hz, IH), 6.93 (d, \(J = 7\) Hz, IH), 6.98 (s, IH), 7.38 (dd, \(J = 7\) Hz and 7 Hz, IH), 7.55 (br s, IH), 7.85 (br s, IH). 11.14 (br s, IH, NH), 11.25 (br d, \(J = 6\) Hz, IH, NH); ESI-MS \(m/z\) 613.5 (MH\(^+\)).

2- \{4-[3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl\}-6-(1-propyl-piperidin-4-yl)-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one

\(\text{HOAc} (500 \mu\text{L}) \text{ at } 0^\circ\text{C and the resulting reaction mixture was stirred at } 0^\circ\text{C for 20 min and followed by addition of Na(OAc)}_3 \text{BH (254 mg, 1.2 mmol). The reaction mixture was stirred at } 0^\circ\text{C for 1 h and at the room temperature for 1 h and then evaporated. Chromatography of the residue with CH\(_2\)Cl\(_2\)/MeOH/28\% aqueous NH\(_4\)OH (490:10:1) afforded the title compound (16.5 mg, 57%).} \(^1\)H NMR (DMSO-\(^{\sim}\)\(d_6\)) \(\delta\) 0.87 (t, \(J = 6\) Hz, 3H, CH\(_3\)), 1.45 (m, 2H), 1.70 (m, 2H), 1.80 (m, 2H), 2.04 (m, 2H), 2.19 (s, 3H, CH\(_3\)), 2.22 (s, 3H, CH\(_3\)), 2.97 (m, 2H), 3.55 (m, IH), 3.70 (m, IH), 3.95-4.06 (3H), 4.11 (m, IH), 4.42 (s, IH), 4.47 (s, IH), 5.47 (d, \(J = 3\) Hz, 0.5H, NH), 5.52 (d, \(J = 3\) Hz, 0.5H, NH), 6.22 (m, IH), 6.81 (m, IH), 6.89-6.99 (2H), 7.32-7.38 (1.5H), 7.68 (s, 0.5H), 7.80 (s, 0.5H), 7.94 (s, 0.5H), 11.15 (d, \(J = 6\) Hz, IH, NH), 11.21 (br d, \(J = 6\) Hz, IH, NH); ESI-MS \(m/z\) 585.5 (MH\(^+\)).

2- \{4-[3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl\}-6-(1-isopropyl-piperidin-4-yl)-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one
2-{4-[3-(2,4-Dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(l-isopropyl-piperidin-4-yl)-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one: A mixture of 2-{4-[R)-3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-piperidin-4-yl-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one (27.1 mg, 0.05 mmol), acetone (200 µL) and Ti(i-PrO)₄ (300 µL) was stirred at the room temperature for 2 h and diluted with MeOH (5 mL). NaBH₄ (190 mg, 5 mmol) was added into the reaction mixture and the mixture was stirred at the room temperature for 16 h and concentrated. Chromatography of the residue with CH₂Cl₂/MeOH/28% aqueous NH₄OH (490:10:1) afforded the title compound (2.06 mg, 7%). ¹H NMR (DMSO-cfe) δ 1.22 (s, 3H, CH₃), 1.24 (s, 3H, CH₃), 1.25-1.45 (4H), 1.80-2.30 (6H), 3.33-3.60 (2H), 3.70 (s, m, IH), 3.90-4.19 (2H), 4.35-4.50 (2H), 5.47 (m, IH, NH), 6.22 (m, IH), 6.81 (m, IH), 6.89-6.99 (2H), 7.32-7.38 (1.5H), 7.68 (s, 0.5H), 7.80 (s, 0.5H), 7.94 (s, 0.5H), 11.18 (br s, IH, NH), 11.22 (d, J = 6 Hz, IH, NH); ESI-MS mlz 585.5 (MH⁺).

6-(l-Cyclopropyl-piperidin-4-yl)-2-{4-[3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one:

6-(l-Cyclopropyl-piperidin-4-yl)-2-{4-[3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one: To a solution of 2-{4-[(R)-3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-
3-yl)-6-piperidin-4-yl-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one (54.3 mg, 0.1 mmol) and bromocyclopropane (121 mg, 1.0 mmol) in CH₃CN (8 mL) was added DIEA (129.3 mg, 1.0 mmol) and the resulting reaction mixture was stirred at the room temperature for 112 h and then evaporated. Chromatography of the residue with CH₂Cl₂/MeOH/2% aqueous NH₄OH (490:10:1) afforded the title compound (3.27 mg, 5.6%). ¹H NMR (DMSO-d₆) δ 1.70 (m, 2H), 1.80 (m, 2H), 2.04 (m, 2H), 2.19 (s, 3H, CH₃), 2.22 (s, 3H, CH₃), 2.90-3.00 (4H), 3.45 (m, IH), 3.70 (m, IH), 3.95-4.06 (3H), 4.11 (m, IH), 4.42 (s, IH), 4.47 (s, IH), 5.10-5.22 (2H), 5.47 (d, J = 3 Hz, 0.5H, NH), 5.52 (d, J = 3 Hz, 0.5H, NH), 5.81 (m, IH), 6.22 (m, IH), 6.81 (m, IH), 6.89-6.99 (2H), 7.32-7.38 (1.5H), 7.68 (s, 0.5H), 7.80 (s, 0.5H), 7.94 (s, 0.5H), 11.15 (d, J = 6 Hz, IH, NH), 11.21 (br d, J = 6 Hz, IH, NH); ESI-MS mlz 583.7 (MH⁺).

Synthesis of other Tricyclic Derivatives:
TFA salt of acetic acid l-(2,4-dimethyl-phenoxy)methyl)-2-{3-[6-(1-methyl-piperidin-4-yl)-7-oxo-1,5,6,7-tetrahydro-1,3,6-triaza-s-indacen-2-yl]-2-oxo-1,2-dihydro-pyridin-4-ylamino}-ethyl ester: A solution of 2-{4-[3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-3 H-1,3,6-triaza-s-indacen-5-one (30 mg, 0.054 mmol) in HOAc (4 mL) was heated at 100 °C for 88 h and evaporated. The residue was subjected to HPLC purification to afford the title compound in TFA salt form (17.0 mg, 44%). 1H NMR (DMSO-^6) δ 1.90-2.15 (4H), 2.05 (s, 3H, CH3), 2.16 (s, 3H, CH3), 2.22 (s, 3H, CH3), 2.81 (s, 3H, CH3), 3.20 (m, 2H), 3.52 (m, 2H), 3.78 (m, 1H), 3.90 (m, IH), 4.20 (m, 2H), 4.31 (m, IH), 4.47 (s, 2H), 5.43 (br s, IH, NH), 6.28 (d, J = 8 Hz, IH), 6.84 (d, J = 8 Hz, IH), 6.94 (d, J = 8 Hz, IH), 6.99 (s, IH), 7.41 (m, IH), 7.60 (br
s, IH), 7.85 (br s, IH), 9.60 (br s, IH, NH), 11.13 (br s, IH, NH), 11.33 (d, J = 6 Hz, IH); ESI-MS m/z 599.5 (MH+).

Synthesis of 4-[3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-3-[6-(1-methyl-piperidin-4-yl)-1,5,6,7-tetrahydro-1,3,6-triaza-s-indacen-2-yl]-1H-pyridin-2-one

TFA salt of 4-[3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-3-[6-(1-methyl-piperidin-4-yl)-1,5,6,7-tetrahydro-1,3,6-triaza-s-indacen-2-yl]-1H-pyridin-2-one: To a suspension of 2-{4-[3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one (20 mg, 0.036 mmol) in THF (3 mL) was added BH$_3$S(CH$_3$)$_2$ complex in ether (2.0 M, 2 mL, 4 mmol) at 0 °C resulting in a mixture which was stirred at the room temperature for 1 h and heated at 80 °C for 2 h. After it was cooled to 0 °C, the reaction mixture was quenched by adding MeOH (5 mL) slowly and dropwise at 0 °C and then stirred for 16 h. Aqueous HCl (12 N, 2 mL) was added into the reaction mixture which was then heated at 80 °C for 1 h and evaporated. The residue was diluted with a mixed solvent of DCM/MeOH (10 mL/10 mL), basified with 28% aqueous NH$_4$OH, and concentrated. Chromatography of the residue with CH$_2$Cl$_2$/MeOH/28% aqueous NH$_4$OH (110:10:1) furnished a crude product which was subjected to HPLC re-purification to afford the title compound in TFA salt form (1.67 mg, 7%). $^1$H NMR (DMSO-$_d_6$) δ 1.85-2.00 (4H), 2.16 (s, 3H, CH$_3$), 2.22 (s, 3H, CH$_3$), 2.81 (s, 3H, CH$_3$), 3.10 (m, 2H), 3.52 (m, 2H), 3.78-4.11 (6H), 4.62 (s, 2H), 4.85 (s, 2H), 5.43 (br s, IH, NH), 6.19 (d, J = 8 Hz, IH), 6.80 (d, J = 8 Hz, IH), 6.89-6.95 (2H), 7.32 (m, IH), 7.45 (br s, IH), 7.55 (br s, IH), 9.95 (br s, IH, NH), 11.00 (br s, IH, NH), 11.20 (br s, IH); ESI-MS m/z 543.5 (MH$^+$).
TFA salt of 2-{4-[3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-methoxy-pyridin-3-yl}-6-(1-methyl-piperidin-4-yl)-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one: To a suspension of 2-{4-[3-(2,4-dimethyl-phenoxy)-2-hydroxy-propylamino]-2-oxo-l,2-dihydro-pyridin-3-yl}-6-(1-methyl-l-piperidin-4-yl)-6,7-dihydro-3H-1,3,6-triaza-s-indacen-5-one (19 mg, 0.034 mmol) in a mixed solvent of THF/CH₃CN (1 mL/1 mL) was added a solution of TMSCH₂N₂ (2.0 M, 2 mL, 4 mmol) at 0°C. After it was stirred at 0°C for 2 h, the reaction mixture was mixed with MeOH (1 mL), stirred at the room temperature for 22 h, and purified with a preparative TLC plate to furnish a crude which was subjected to HPLC re-purification to afford the title compound in TFA salt form (4.98 mg, 21%). ¹H NMR (DMSO-d₆) δ 1.92-2.10 (4H), 2.19 (s, 3H, CH₃), 2.22 (s, 3H, CH₃), 2.81 (s, 3H, CH₃), 3.20 (m, 2H), 3.40 (s, 3H, OCH₃), 3.45-3.55 (3H), 3.68 (m, 1H), 4.00 (s, 2H), 4.12 (m, 1H), 4.30 (m, 1H), 4.43 (s, 1H), 4.48 (s, 1H), 5.47 (br s, IH, NH), 6.27 (d, J = 6 Hz, IH), 6.82 (d, J = 8 Hz, IH), 6.89-6.97 (2H), 6.98 (s, IH), 7.15 (s, 0.5H), 7.30 (s, 0.5H), 7.65-7.72 (1.5H), 7.80 (s, 0.5H), 7.95 (s, 0.5H), 9.65 (br s, IH, NH), 11.11 (br s, IH, NH); ESI-MS mlz 571.5 (MH⁺).

Synthesis of (S)-2-amino-l-(3-chlorophenyl)ethanol derivatives:
4-Iodo-2-methoxynicotinic aldehyde: To a solution of t-BuLi (1.7 M, 7.36 mL, 12.51 mmol) in 20 mL THF at -78 °C was added dropwise 2-bromomesitylene (0.91 mL, 5.95 mmol). After stirred for 1 h, 2-methoxypyridine (0.48 mL, 4.58 mmol) was added dropwise, and the mixture was warmed to 0 °C and stirred for 2 h. The solution was cooled to -78 °C and N-formyl-iV,N-trinitriethylethylenediamine (0.7 mL, 5.06 mmol) was added. The mixture was stirred at -78 °C for 30 min and then warmed to -23 °C. A hexane solution of t-BuLi (2.5 M, 2.75 mL, 6.87 mmol) was added dropwise, and the resulting yellow mixture was stirred for 3 h. The mixture was cooled to -78 °C and transferred via a double-tipped needle to a solution of iodine (2.17 g, 8.23 mmol) in 30 mL of THF at -78 °C. After stirred at -78 °C for 30 min, the cooling bath was removed and the reaction mixture was allowed to warm to the room temperature. After the reaction mixture was cooled to -5 °C, aqueous solution of NH₄Cl (20
mL) was added dropwise and stirred for 15 min. The reaction mixture was poured into brine (300 mL) and extracted with EtOAc (5 x 100 mL). The combined extracts were washed with brine (2 x 50 mL), dried over Na₂SO₄ and concentrated. The residue was purified by chromatography (25:1 hexanes/EtOAc) to afford the title compound (350 mg, 29%). ¹H NMR (CDCl₃) δ 4.05 (s, 3H, CH₃), 7.53 (d, J = 6 Hz, IH, ArH), 7.85 (d, J = 6 Hz, IH, ArH), 10.20 (s, IH, CHO).

3-[1,3]Dioxolan-2-yl-4-iodo-2-methoxy-pyridine

3-[1,3]Dioxolan-2-yl-4-iodo-2-methoxy-pyridine:  To a solution of 4-iodo-2-methoxynicotinic aldehyde (5.26 g, 20.0 mmol) and ethylene glycol (2.48 g, 40 mmol) in toluene (400 mL) was added 7-toluenesulfonic acid monohydrate (95 mg, 0.5 mmol). After it was refluxed under N₂ for 6 h, the reaction mixture was concentrated and the residue was diluted with 300 mL EtOAc and washed with 2 x 100 mL 10% Na₂CO₃ solution. The aqueous solution was extracted with EtOAc (3 x 50 mL) and the combined EtOAc extracts were washed with brine and dried over Na₂SO₄. Evaporation of solvent afforded the title product (6.07 g, 99%). ¹H NMR (CDCl₃) δ 3.95 (s, 3H), 4.07 (m, 2H), 4.33 (m, 2H), 6.25 (s, IH), 7.40 (d, J = 6Hz, IH), 7.70 (d, J = 6Hz, IH). ESI-MS m/z 308.4 (MH⁺).

(S)-I-(3-Chloro-phenyl)-2-(3-[1,3]dioxolan-2-yl-2-methoxy-pyridin-4-ylamino)-ethanol

(S)-I-(3-Chloro-phenyl)-2-(3-[1,3]dioxolan-2-yl-2-methoxy-pyridin-4-ylamino)-ethanol:  A suspension of 3-[1,3]dioxolan-2-yl-4-iodo-2-methoxy-pyridine (3.07 g, 10.0 mmol), (S)-2-amino-l-(3-chloro-phenyl)-ethanol (1.71 g, 10 mmol), CuI(190 mg, 1.0 mmol), ethylene glycol (1.86 g, 30 mmol) and K₃PO₄ (6.3 g, 30 mmol) in 2-propanol (200 mL) was sealed and heated at 75 °C for 22 h (CuI and K₃PO₄ were crushed into powders before added). After
cooled down to room temperature, the reaction mixture was loaded on silica gel. The chromatography with eluant CH₂Cl₂:MeOH = 100:1 afforded the title product (1.27 g, 38%).

¹H NMR (CDCl₃) δ 3.30 (m, IH) 3.45 (m, IH), 3.87 (s, 3H), 3.96-4.05 (4H), 4.85 n(m, IH), 6.09 (s, IH), 6.15-6.30 (2H), 7.21-7.35 (2H), 7.41 (s, IH), 7.82 (d, J = 6 Hz, IH). ESI-MS mlz 351.4 (MH⁺).

4-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridine-3-carbaldehyde

4-[(S)-2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridine-3-carbaldehyde: To a mixture of (S)-1-(3-chloro-phenyl)-2-(3-[l,3]dioxolan-2-yl-2-methoxy-pyridin-4-ylamino)-ethanol (223 mg, 0.64 mmol) and H₂O (0.75 mL) was added HCl solution in dioxane (4 M, 10 mL). After it was heated at 70 °C for 4 h, the reaction mixture was evaporated to dryness. HPLC purification of the residue afforded the title compound (20.1 mg, 11%). ¹H NMR (DMSO-d₆) δ 3.37 (m, IH) 3.58 (m, IH), 4.58 (m, IH), 5.95 (d, J = 6 Hz, IH), 7.30-7.40 (3H), 7.49 (s, IH), 9.94 (s, IH, CHO), 10.30 (m, IH, NH), 10.95 (m, IH, IH). ESI-MS mlz 293.3 (MH⁺).

6.2. Example 2: Kinase Assays

The IGFR tyrosine kinase is assayed in Kinase-Glo ATP depletion assay using the synthetic polymer poly(Glu-Tyr, 4:1) (Sigma Chemicals) as a phosphoacceptor substrate. Each reaction mixture consists of a total volume of 10 µl and contains 40 ng of the enzyme, 5 µg of poly(Glu-Tyr), 10 µM of ATP and variable concentrations of test compounds. The mixtures also contain 50 mM Tris-HCl, pH 7.5; 5 mM MgCl₂; 5 mM MnCl₂; 2 mM DTT and 0.01% Tween 20. The reaction mixtures are incubated at 37°C for 60 minutes and residual concentration of ATP in the mixture is determined by adding luciferase-containing Kinase-Glo (Promega) development reagent and counting luminescence levels using Fusion Universal Microplate Analyzer (PerkinElmer). Tested compounds are dissolved in dimethyl sulfoxide to a stock concentration of 10 mM and are typically evaluated in the assay at eight concentrations in 1 nM to 20 µM range, each in quadruplicate. The final concentration of DMSO added to the kinase assays is 0.5% or less, which has been shown to have no effect on kinase activity. IC50 values are derived by non-linear regression analysis.
using Prism 3.0 software (Graphpad Software). Other tyrosine kinases are assayed according to the same protocol after titrating amount of the enzyme to provide optimal signal-to-noise ratio and no more than 30% of total ATP consumption in the reaction conditions used.

The IGFlR tyrosine kinase is assayed in Phosphotyrosine (PT66 or PTIOO) AlphaScreen chemiluminescent assay (PerkinElmer) according to the manufacturer's recommendations. Each kinase reaction mixture consists of a total volume of 15 µl and contains 0.1 - 1 ng of the enzyme, 7 ng of biotinylated poly(Glu-Tyr) (Cis-Bio), 10 µM of ATP and variable concentrations of test compounds. The mixtures also contain 50 mM Tris-HCl, pH 7.5; 5 mM MgCl₂; 5 mM MnCl₂; 2 mM DTT and 0.01% Tween 20. The reaction mixtures are incubated at room temperature for 30 minutes. Ten (10) µl of the mixture of receptor and donor beads (as supplied by the manufacturer) is then added to the reaction and the incubation is continued for an additional 60 minutes. The reaction is stopped by addition of 10 µl of detection Buffer (62.5 mM HEPES, pH 7.4; 250 mM NaCl, 100 mM EDTA, 0.25% BSA. Data are collected as optical readings at 520-620 nm on an AlphaScreen Fusion microplate reader (PerkinElmer) and the IC50 values are calculated using the software Prism 3.0, a graphing program from GraphPad Software. Other tyrosine kinases are assayed according to the same protocol after titrating amount of the enzyme to provide optimal signal-to-noise ratio. Table III below shows exemplary data for biochemical inhibition (IC50).

6.3. Example 3. ELISA-based assay of IGFl receptor autophosphorylation inhibition in cells

MCF7 human breast cancer cells expressing IGFl receptor or an engineered human fibroblast cell line NIH 3T3 overexpressing full-length IGFlR are an exemplary cellular models in which to perform such assays. Such cells may be maintained in DMEM medium supplemented with 10% fetal bovine serum (FBS), 4% L-glutamine, 1% antibiotic solution (penicillin-Streptomycin) in a humidified atmosphere of 95% air and 5% CO₂ at 37°C. Confluent cells in T175 cell culture flasks are incubated overnight with serum-free DMEM medium. After the serum starvation step, the cells are detached and split into a standard 96-well cell culture plate (one T175 flask per plate, 30 µl of cell suspension per plate well). Tested inhibitors from their 10 mM stock solutions in DMSO are subsequently added at various concentrations in serum-free DMEM medium for 1 hour incubation at 37°C in CO₂-incubator; total DMSO concentration in both treated and control wells is adjusted to 1%. Cells are then stimulated for 10 minutes with 100 nM IGF-I added in 30 µl DMEM. After treatment, cells are lysed by addition of 30 µl of 4x lysis buffer (phosphate-buffered
saline (PBS), 2% Triton-X100, 1 mM phenylmethylsulphonyl fluoride (PMSF) and 8 mM activated orthovanadate), mixing and incubation for 15 minutes at room temperature.

To prepare assay plates, 96-well ELISA Plates (Pierce Chemical, Reacti-bind plates) were coated by goat-anti-rabbit Fc antiserum by adding 0.25 μg antiserum per well in 0.2 M sodium bicarbonate buffer per well and incubating overnight at 4 °C. After incubation, the plate is washed three times by PBS with 0.02% Tween-20, supplied with 25 ng/50 μl per well of anti-IGFIR antibody (C-20, Santa Cruz Biotechnology) and incubated for several hours to overnight. Prior to the addition of the prepared cellular lysates, the antibody solution is aspirated, wells washed with PBS and supplied with 25 μl per well of Starting Block buffer (Pierce Chemical).

To measure tyrosine phosphorylation of the beta-subunits of the IGFIR, 25-50 μl of the lysates are transferred from the stimulation plate to the wells of the prepared assay plate and incubated overnight at 4 °C. The wells are washed with PBS with 0.02% Tween-20, incubated with 50 μl of 1:3000 dilution of anti-phosphotyrosine 4G10-HRP antibody conjugate (Upstate Biotechnology) for 2 hours at room temperature and washed again. The assay plate was developed with Ultra TMB ELISA HRP substrate (Pierce Chemical) and absorbance of the wells was read at 450 nm in ELISA plate reader. Alternatively, 10-50 times larger volumes of lysates prepared as described above are incubated overnight at 4 °C with 1 μg of anti-IGFIR antibody (C-20; Santa Cruz Biotechnology) and 20 μl of 50% protein-A agarose slurry. After 3 washes with lysis buffer, pellets are resuspended in SDS-PAGE sample buffer and boiled for 3 minutes. Proteins are resolved by SDS-PAGE (7.5%) and transferred by electroblotting onto nitrocellulose membranes. Tyrosine phosphorylated IGFIR is detected by immunoblotting with anti-phosphotyrosine antibody (4G10, Upstate Biotechnology) and, in a separate identical blot, with anti-IGFIR antibody. Table III below shows exemplary data for cellular receptor phosphorylation inhibition in terms of IC50 value.

6.4. Example 4. Cell Proliferation Inhibition Assay

IGFIR and other tyrosine kinase inhibitors can inhibit the proliferation of certain cancer cell lines indicating their possible therapeutic utility for treating the corresponding cancer types. Cancer cell lines of interest and control normal lines, including CHO, HEK293, BA/F3, COLO205, PC3, DU 145, MCF7, Panel, ACHN, Hep G2, H460, K562, TT, U87-MG, CAOV-3, SK-MEL5, Karpas 299 and human multiple myeloma cell lines H929, MMIs, MMIr, UTM2C, CPM2, KMS1, My5, KMS12PE, My7, JIN3, KMS18, U266, SKMM2, RPMI-8226 are plated in white, clear-bottomed 384-well cell culture plates
at 2500-5000 cells per well and supplied with dilutions of tested compounds. After a desired period of time (typically 3 days), the number of viable cells is quantitated by using Cell Titer-Glo Luminescent Cell Viability Assay (Promega), a cell proliferation assay system based on detection of total amount of ATP present as a measure of cell metabolic activity. The plated cells are mixed with the Cell Titer-Glo developing reagent and counted in a luminescence multiwell plate reader according to the standard manufacturer’s protocol to generate IC50 curves for cell proliferation inhibition. Results are typically reported as percent of control (viability = (OD72h(compound)-ODdayθ)/(OD72h(no compound)-ODday)). Alternatively, viable cells are quantitated by using the conventional colorimetric MTT assay. The MTT assay is based on the cleavage of the yellow tetrazolium salt MTT to purple formazan crystal by metabolic active cells. The formazan is then solubilized, and the concentration determined by optical density at 570 nm. The cells plated and incubated with a compound as described above are supplemented with the solution of MTT and incubated for 2-3 hours. The growth medium is removed and dimethyl sulfoxide is added into each well to dissolve the formazan. The absorbance is measured on an ELISA plate reader with a test wavelength of 570 nm and a background subtraction wavelength of 630 nm to obtain sample signal (OD570-OD630).

Table III below shows the results of cell proliferation inhibition assay for some exemplary compounds of this invention for the following cell lines - MMIs (multiple myeloma), H929 (multiple myeloma), COLO205 (colon carcinoma), HEK293 (human normal embryonic kidney), CHO (Chinese hamster ovary). The results are reported in terms of IC50 value for a particular compound and a cell line in the standard 3-day proliferation assay using Cell Titer-Glo. Table IV below shows the results of cell proliferation assay for some exemplary compounds of this invention for the following human multiple myeloma cell lines - H929, MMIs, MMIr, UTMC2, CPM2, KMSI 1, My5, KMS 12PE, My7, JJN3, KMS18, U266, SKMM2, RPMI-8226 as well as HEK293 (human normal embryonic kidney), CHO (Chines hamster ovary). The results are reported in terms of IC50 value for a particular compound and a cell line in the standard 3-day proliferation assay using MTT assay.
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<tr>
<td>163</td>
<td><img src="image163.png" alt="Image" /></td>
<td>++</td>
<td>***</td>
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<td>+++</td>
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<td>***</td>
<td>***</td>
<td>+++</td>
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</tr>
<tr>
<td>166</td>
<td><img src="image166.png" alt="Image" /></td>
<td>++</td>
<td>***</td>
<td>***</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>
The IC50 values are represented as ranges where IC50 values in the range below 0.5 µM are indicated by "+++", between 0.5 µM and 5 µM by "++", between 5 µM and 15 µM by "+" and above 15 µM by "-". Biochemical assays are designated by the name of the tyrosine kinase and the cell proliferation assays by the name of the corresponding cell line; IC50 data for IGF1R phosphorylation inhibition in MCF7 cells as measured by ELISA assay is also included.
6.5. Example 5: Kinase Profiling

Table V shows the results of kinase inhibition profiling of one of the compounds provided herein. The results are reported in terms of degree of inhibition for a particular kinase at fixed concentration of the compound (2 μM) being tested where "-" indicates less than 10% inhibition, "+" - more than 10% but less than 30%, "++" - more than 40% but less than 75% and "+++" - more than 75% inhibition of the target protein kinase compared to the activity of the kinase in a control to which no test compound has been added. Kinase profiling technique which has been used to evaluate compounds is described above and

<table>
<thead>
<tr>
<th>Structure</th>
<th>HEK IC50</th>
<th>CHO IC50</th>
<th>H929 IC50</th>
<th>MM1S IC50</th>
<th>MM1R IC50</th>
<th>U251 IC50</th>
<th>CPM2 IC50</th>
<th>KMS11 IC50</th>
<th>KMS12PE IC50</th>
<th>JUN IC50</th>
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<th>SKM1M2 IC50</th>
<th>RPMI-8226 IC50</th>
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<tbody>
<tr>
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<td>B</td>
<td>B</td>
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<td>D</td>
<td>D</td>
<td>D</td>
<td>C</td>
<td>D</td>
</tr>
</tbody>
</table>

The IC50 values of multiple myeloma cell line proliferation inhibition are represented as ranges where IC50 values in the range below 0.5 μM are indicated by "A", between 0.5 μM and 1 μM by "B", between 1 µM and 5 μM by "C", between 5 μM and 20 μM by "D", and at or above 20 μM by "E".
further technical details can be found at Upstate Biotechnologies Web site (http://www.upstatebiotech.com).

Table V

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Percent Inhibition</th>
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</thead>
<tbody>
<tr>
<td>KIT</td>
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</tr>
<tr>
<td>FGFR1</td>
<td>+++</td>
</tr>
<tr>
<td>FLT1</td>
<td>+++</td>
</tr>
<tr>
<td>IGFIR</td>
<td>+++</td>
</tr>
<tr>
<td>IR</td>
<td>+++</td>
</tr>
<tr>
<td>MET</td>
<td>-</td>
</tr>
<tr>
<td>PDGFRb</td>
<td>+</td>
</tr>
<tr>
<td>TRKA</td>
<td>+++</td>
</tr>
<tr>
<td>AbI</td>
<td>++</td>
</tr>
<tr>
<td>Src</td>
<td>+++</td>
</tr>
<tr>
<td>ErbB4</td>
<td>+</td>
</tr>
<tr>
<td>Flt3</td>
<td>+++</td>
</tr>
<tr>
<td>Flt4</td>
<td>+++</td>
</tr>
<tr>
<td>KDR</td>
<td>++</td>
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</tr>
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<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>PKA</td>
<td>-</td>
</tr>
<tr>
<td>CDK1/Cyclin B</td>
<td>-</td>
</tr>
<tr>
<td>cRaf</td>
<td>-</td>
</tr>
</tbody>
</table>

All publications, patents and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.
What is claimed is:

1. A compound according to formula 1, or a stereoisomer, tautomer, salt, hydrate or prodrug thereof:

```
X^1
W^1---W^2---W^3
    X^2
        W^4---W^5---W^6
            X^3
```

wherein:

- each W^1 through W^6 is independently a carbon atom or a nitrogen atom with the proviso that when any W^1 through W^6 is N, then the corresponding substituent(s) X^1 through X^6 is (are) absent;
- each X^1 through X^3 and X^5 and X^6 is independently selected from hydrogen, hydroxy, halogen, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted acylamino, optionally substituted sulfonamido, optionally substituted ureido, trifluoromethyl, trifluoromethoxy, nitro, cyano, optionally substituted aryl or heteroaryl, aryloxy or heteroaryloxy, arylamino or heteroarylamino (substituted by one or more groups selected from lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, carboxamide, sulfonamide, sulfamide, ureido, methylenedioxy, ethylenedioxy, primary, secondary or tertiary amino, mono or dialkyl amido, heterocyclylamido, optionally substituted heterocyclyl or cycloalkyl, optionally substituted heterocyclylalkyl, heteroalkyl), nitrogen-heterocyclyl, connected either by its nitrogen, or a carbon atom (such as piperazino, homopiperazino, morpholino, thiomorpholino, thiomorpholino-S-oxide, thiomorpholino-S,S-dioxide, pyrroldidino, piperidino, azetidino), nitrogen-heterocyclyl-alkyl, connected either by its nitrogen or a carbon atom (such as piperazinomethyl, piperazinoethyl, homopiperazinomethyl, morpholinomethyl, thiomorpholinomethyl, thiomorpholino-S-oxide-methyl, thiomorpholino-S,S-dioxide-methyl, pyrroldinomethyl, piperdinomethyl, azetidinomethyl, all optionally substituted by groups selected from hydroxyalkyl, lower alkoxyalkyl, primary, secondary, or tertiary amino-alkyl, lower alkyl cycloalkyl or heterocycloalkyl); wherein aryl and heteroaryl groups can be bicyclic; and wherein any adjacent pair of X^1 through X^3 can be joined to form a cycloalkyl, cycloheteroalkyl, aryl or heteroaryl ring fused to the ring comprising W^1 through W^3,
wherein a fused ring is naphthyl, benzodioxolyl, benzofuranyl, benzodioxinyl, dihydrobenzodioxinyl or quinolinyl;

\[ \text{X}^4 \text{ is selected from hydrogen, hydroxy, halogen, trifluoromethyl, } \]
trifluoromethoxy, optionally substituted (alkyl, alkenyl, alkynyl, alkoxy, cycloalkoxy, cycloalkyl, heterocycloalkyl), optionally substituted (aryl, heteroaryl, arylalkyl, heteroarylalkyl, aryloxy, heteroaryloxy, arylalkoxy, heteroaryalkoxy, arythio, heteroarythio, arylsulfoxyl, heteroarylsulfoxyl, arylsulfonyl, heteroarylsulfonyl, arylsulfonylamido, heteroarylsulfonylamido, arylaminosulfonyl, heteroarylaminosulfonyl), by substituents selected from halogen, hydroxy, amino, cyano, nitro, carboxamido, sulfonamido, alkoxy, amino, lower-alkylamino, di-lower-alkylamino, cycloalkyl, cycloalkylalkyl, cycloalkoxy, cycloalkylalkoxy, trifluoromethyl, trifluoromethoxy, methylenedioxy, ethylenedioxy, methanesulfonyl, trifluoromethanesulfonyl, dialkylaminoalkyl, dialkylaminoalkoxy, heterocyclyl, heteroalkyl and heterocyclylalkyl; or is selected from the following groups:

\[
\begin{align*}
&\text{wherein: m is an integer from 1 to 4, and n is an integer from 0 to 4; R^2 is selected from} \\
&\text{optionally substituted aryl, or heteroaryl, -(CH}_2{)}_0\text{-aryl, -(CH}_2{)}_o\text{-heteroaryl, -(CH}_2{)}_p\text{-M'-aryl,} \\
&\text{-(CH}_2{)}_p\text{-M'-heteroaryl substituted by a substituent independently selected from a group} \\
&\text{consisting of hydrogen, hydroxy, halogen, trifluoromethyl, trifluoromethoxy,} \\
&\text{trifluoromethyloxy, trifluoromethanesulfonyl, 2,2,2-trifluoroethoxy, lower alkyl, lower} \\
&\text{alkenyl, lower alkynyl, cycloalkyl, methylenedioxy, ethylenedioxy, trimethylene,} \\
&\text{dimethylenedioxy, cyano, nitro, primary, secondary or tertiary amino, such as dimethylamino,} \\
&\text{carboxamido, sulfonamide, lower alkylsulfonyl, lower alkylsulfinyl, lower alkylthio, lower} \\
&\text{alkylthioalkyl, lower alkylsulfonylalkyl, optionally substituted aryl or heteroaryl, wherein} \\
&M^1 \text{is a -(CH}_2{)}_2\text{- or a heteroatom O, S, or N-R*; R^3 is selected from optionally substituted} \\
&\text{aryl, heteroaryl, -(CH}_2{)}_o\text{-aryl, -(CH}_2{)}_o\text{-heteroaryl, -(CH}_2{)}_p\text{-M'-aryl,} \\
&\text{-(CH}_2{)}_p\text{-M'-heteroaryl, substituted by a substituent independently selected from a group} \\
&\text{consisting of hydrogen, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, trifluoromethyloxy,} \\
&\text{trifluoromethanesulfonyl, 2,2,2-trifluoroethoxy, lower alkyl, lower alkenyl, lower} \\
&\text{alkynyl, cycloalkyl, methylenedioxy, ethylenedioxy, trimethylene, dimethylenedioxy, cyano, nitro,} \\
&\text{primary, secondary or tertiary amino, such as dimethylamino, carboxamido, sulfonamide,} \\
&\text{lower alkylsulfonyl, lower alkylsulfinyl, lower alkylthio, lower alkylthioalkyl, lower} \\
&\text{alkylthioalkyl, lower}
\end{align*}
\]
alkylsulfonylalkyl, optionally substituted aryl or heteroaryl, wherein \( M^2 \) is a heteroatom O, S, or N-R**; \( R** \) is selected from hydrogen, hydroxy, lower alkyl, lower alkoxy, acyl, optionally substituted aryl, heteroaryl, alkylsulfonyl or arylsulfonyl; and each \((CH_2)_m\) or \((CH_2)_n\) can be optionally substituted with one or more groups selected from hydrogen, halogen, hydroxy, carboxamido, lower alkylcarbonyl, hydroxy-lower alkyl, hydroxycycloalkyl, optionally substituted (primary, secondary or tertiary amino, lower alkoxy, lower alkyl, lower heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aryloxy or heteroaryloxy), by groups selected from halogen, hydroxy, amino, lower alkyl, lower alkoxy, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethanesulfonyl, cyano, nitro, carboxamido, lower alkylthio, lower alkylsulfonyl, lower alkylsulfonyl, arylthio, arylsulfonyl, arylsulfonyl, lower alkylcarbonyl, arylcarbonyl) all groups optionally substituted by groups selected from hydrogen, halogen, lower alkyl, trifluoromethyl, trifluoromethoxy, lower alkoxy, lower alkylthio, hydroxy, sulfonamido, and lower acylamino; or \((CH_2)_m\) and \((CH_2)_n\) can form a cyclic structure and one or more methylene of \((CH_2)_m\) or \((CH_2)_n\) can be replaced by a heteroatom selected from O, N and S;

\( Y^1 \) is independently selected from:

\[
\begin{align*}
\text{O} & & \text{S} & & \text{N} & & \text{O-S} & & \text{F-F}
\end{align*}
\]

wherein: \( q \) is an integer from 0 to 4; \( R#_10 \) is selected from hydrogen, lower alkyl, hydroxy and lower alkoxy; each \((CH_2)_q\) can be optionally substituted with one or more groups selected from hydrogen, lower alkyl, heteroalkyl, heterocyclo, hydroxy-lower alkyl, cycloalkyl and hydroxycycloalkyl, wherein such substituents can be joined to form a cyclic structure and wherein one or more of the methylene groups of \((CH_2)_q\) can be replaced by a carbonyl group (C=O);

\( Y^2 \) is independently selected from:

\[
\begin{align*}
\text{O} & & \text{S} & & \text{N} & & \text{O-S} & & \text{F-F}
\end{align*}
\]

wherein: \( r \) is an integer from 0 to 4; \( R#_11 \) is selected from hydrogen, lower alkyl, hydroxy and lower alkoxy; each \((CH_2)_r\) can be optionally substituted with one or more groups selected from hydrogen, lower alkyl, heteroalkyl, heterocyclo, hydroxy-lower alkyl, cycloalkyl, hydroxycycloalkyl, wherein such substituents can be joined to form a cyclic structure, and
wherein one or more of the methylene groups of \((\text{CH}_2)_r\) can be replaced by a carbonyl group \((\text{C}=\text{O})\); and

\[ R^1 \text{ is independently selected from optionally substituted heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heterocyclyloxyalkyl, heteroalkyl, heterocyclylaminoalkyl, aminoalkyl, lower alkylaminoalkyl, di-(lower alkyl)-aminoalkyl, aminocycloalkyl, alkylaminocycloalkyl, di-(lower alkyl)-aminocycloalkyl, di-(lower alkyl)-aminocycloalkylalkyl, by groups selected from hydrogen, lower alkyl, hydroxy, lower alkoxy, amino, amidino, carboxamido, sulfonamido, hydroxy, cyano, primary, secondary or tertiary amino, halo, azido, lower alkoxyalkyl, cyanoalkyl, azidoalkyl, haloalkyl, hydroxyalkyl, methanesulfonylalkyl, primary, secondary or tertiary amino-alkyl, optionally substituted aryl, heteroaryl, heteroalkyl, heterocyclyl, cycloalkyl, alkenyl and alkynyl. \]
2. The compound according to claim 1, wherein $X^4$ is selected from:

<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Chemical Structure</th>
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<tbody>
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</tbody>
</table>

wherein:

- $L$ is selected from $O$, $S$, $N-R^9$;
- $R^9$ is selected from hydrogen, lower alkyl, cycloalkyl, alkenyl, alkynyl, heteroalkyl, heterocyclyl, optionally substituted aryl, heteroaryl, arylalkyl, heteroarylalkyl by groups selected from hydrogen, halogen, lower alkyl, lower alkoxy, trifluoromethyl,
trifluoromethoxy, lower Ikylthio, nitro, azido, cyano, amido and ureido; and
each $X_i$ is independently selected from hydrogen, lower alkyl, halogen, lower
alkoxy, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, azido, cyano, nitro,
methylenedioxy, trimethylene and dimethylenedioxy.

3. The compound according to claim 1, wherein $X^4$ is selected from

![Chemical Structure Diagram]

wherein:

$X^A$ is hydrogen, halogen, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl,
alkoxy, cycloalkoxy, alkythio, cycloalkylthio, alkylsulfonyl, cycloalkylsulfonyl, aryl,
heteroaryl, arylalkyl, heteroaryalkyl, arythio, arylsulfonyl, heteroaryltio,
heteroarylsulfonyl; trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl,
dialkyamino, monoalkylamino, amino, nitro, cyano;

$X^B$ is hydrogen, halogen, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl,
alkoxy, cycloalkoxy, alkythio, cycloalkylthio, alkylsulfonyl, cycloalkylsulfonyl, aryl,
heteroaryl, arylalkyl, heteroaryalkyl, arythio, arylsulfonyl, heteroaryltio,
heteroarylsulfonyl; trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl,
dialkyamino, monoalkylamino, amino, nitro, cyano;

$X^C$ is hydrogen, halogen, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl,
alkoxy, cycloalkoxy, alkythio, cycloalkylthio, alkylsulfonyl, cycloalkylsulfonyl, aryl,
heteroaryl, arylalkyl, heteroaryalkyl, arythio, arylsulfonyl, heteroaryltio,
heteroarylsulfonyl; trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl,
dialkyamino, monoalkylamino, amino, nitro, cyano;

$X^D$ is hydrogen, halogen, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl,
alkoxy, cycloalkoxy, alkythio, cycloalkylthio, alkylsulfonyl, cycloalkylsulfonyl, aryl,
heteroaryl, arylalkyl, heteroaryalkyl, arythio, arylsulfonyl, heteroaryltio,
heteroarylsulfonyl; trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl,
dialkyamino, monoalkylamino, amino, nitro, cyano;
X*E is hydrogen, halogen, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylsulfonyl, cycloalkylsulfonyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylthio, arylsulfonyl, heteroarylt thio, heteroarylsulfonyl; trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl, dialkylamino, monoalkylamino, amino, nitro, cyano;

X*B and X*C or independently X*C and X*D or independently X*D and X*E are taken together to form a 5-7 membered heterocyclic ring, optionally substituted with a lower alkyl or halogen; and

X*B and X*C or independently X*C and X*D or independently X*D and X*E are taken together to form a condensed aromatic or heteroaromatic ring optionally substituted with lower alkyl, lower alkoxy, halogen, trifluoromethyl, cyano, or nitro.

4. The compound according to claim 1, wherein R^1 is selected from the group consisting of:

wherein:
R\textsuperscript{13} is selected from hydrogen, lower alkyl, heteroalkyl, heterocyclyl, cycloalkyl and heterocycloalkyl;

R\textsuperscript{14} is selected from hydrogen, hydroxy, lower alkoxy, di-(lower alkyl)amino, lower alkyl, heteroalkyl, heterocyclyl, cycloalkyl, heterocycloalkyl, lower alkoxyalkyl, cyanoalkyl, azidoalkyl, nitroalkyl, ketoalkyl, methanesulfonylalkyl, aminoalkyl, lower alkylaminoalkyl, di-(lower alkyl)aminoalkyl, optionally substituted aryl, heteroaryl, arylalkyl, heteroarylalkyl;

R\textsuperscript{15} is selected from hydrogen, amino, lower alkylamino, di-(lower alkyl)amino, hydroxy, lower alkoxy, heteroalkyl, lower alkoxyalkyl, aminoalkyl, lower alkylaminoalkyl and di-(lower alkyl)aminoalkyl;

a is an integer from 0 to 4; and

t, u , v are independent integers from 0 to 5.

5. The compound according to claim 1, wherein R\textsuperscript{1} is selected from:
6. The compound according to claim 1, wherein the methylene chain between the connection and the heteroatom in $R^1$ may be optionally substituted by one or more hydrogen, lower alkyl, hydroxy, hydroxy-lower alkyl, lower alkoxy, carboxamido or sulfonamido; and one of the methylene groups can be substituted by a heteroatom, such as $0, NR^{***}$ or $S, S=O,$ or $S(=O)_2,$ wherein $R^{***}$ is selected from hydrogen, hydroxy, lower alkyl, lower alkoxy.
heteroalkyl, hydroxyalkyl, aminoalkyl, lower alkylaminoalkyl and di-(lower alkyl)aminoalkyl.

7. The compound according to claim 1 having the following formula (Ia):

   ![Chemical Structure](image1)

   wherein $W^1$ is nitrogen or carbon.

8. The compound according to claim 1 having the following formula (Ib):

   ![Chemical Structure](image2)

9. The compound according to claim 1 having the following formula (Ic):

   ![Chemical Structure](image3)

10. The compound according to claim 1 having the following formula (Id):

    ![Chemical Structure](image4)

11. The compound according to claim 1 having the following formula (Ie):

    ![Chemical Structure](image5)
12. The compound according to claim 1 having the following formula (Ia):

13. The compound according to claim 1 having the following formula (Ib):

14. The compound according to claim 1 having the following formula (Ic):

15. The compound according to claim 1 having the following formula (Id):
16. The compound according to claim 1 having the following formula (Ij):

[Chemical structure image]

17. The compound according to claim 1 having the following formula (Ik):

[Chemical structure image]

18. The compound according to claim 1 having the following formula (Ii):

[Chemical structure image]

wherein $X^{20}$ to $X^{24}$ are each independently selected from hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl, cycloalkyl, heterocycloalkyl, cyano, nitro, ureido, primary, secondary or tertiary
amino, methylenedioxy, ethylenedioxy and difluoromethylenedioxy.

19. The compound according to claim 1 having the following formula (Im):

\[
\text{[Chemical structure image]}
\]

wherein \(X^{20}\) to \(X^{24}\) are each independently selected from hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl, cycloalkyl, heterocycloalkyl, cyano, nitro, ureido, primary, secondary or tertiary amino, methylenedioxy, ethylenedioxy and difluoromethylenedioxy.

20. The compound according to claim 1 having the following formula (In):

\[
\text{[Chemical structure image]}
\]

wherein \(X^{20}\) to \(X^{24}\) are each independently selected from hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl, cycloalkyl, heterocycloalkyl, cyano, nitro, ureido, primary, secondary or tertiary amino, methylenedioxy, ethylenedioxy and difluoromethylenedioxy.
amino, methylenedioxy, ethylenedioxy and difluoromethylenedioxy.

21. The compound according to claim 1 having the following formula (Io):

![Chemical structure](image)

wherein $X^{20}$ to $X^{24}$ are each independently selected from hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl, cycloalkyl, heterocycloalkyl, cyano, nitro, ureido, primary, secondary or tertiary amino, methylenedioxy, ethylenedioxy and difluoromethylenedioxy.

22. The compound according to claim 1 having the following formula (Ip):

![Chemical structure](image)

wherein $X^{30}$ to $X^{34}$ are independently selected from hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl, cycloalkyl, heterocycloalkyl, cyano, nitro, ureido, primary, secondary or tertiary amino, methylenedioxy, ethylenedioxy and difluoromethylenedioxy.

23. The compound according to claim 1 having the following formula (Iq):
wherein $X^{30}$ to $X^{34}$ are independently selected from hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl, cycloalkyl, heterocycloalkyl, cyano, nitro, ureido, primary, secondary or tertiary amino, methylenedioxy, ethylenedioxy and difluoromethylenedioxy.

24. The compound according to claim 1 having the following formula (Ir):

wherein $X^{30}$ to $X^{34}$ are independently selected from hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl, cycloalkyl, heterocycloalkyl, cyano, nitro, ureido, primary, secondary or tertiary amino, methylenedioxy, ethylenedioxy and difluoromethylenedioxy.

25. The compound according to claim 1 having the following formula (Is):
wherein $X^{30}$ to $X^{34}$ are independently selected from hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl, cycloalkyl, heterocycloalkyl, cyano, nitro, ureido, primary, secondary or tertiary amino, methylenedioxy, ethylenedioxy and difluoromethylenedioxy.

26. The compound according to claim 1 having the following formula (I):

wherein $X^{40}$ to $X^{44}$ are independently selected from hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, heteroalkyl, cycloalkyl, heterocycloalkyl, cyano, nitro, ureido, primary, secondary or tertiary amino, methylenedioxy, ethylenedioxy and difluoromethylenedioxy.

27. The compound according to claim 1 having the following formula (Iu):
wherein $X^{40}$ to $X^{44}$ are independently selected from hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoromethoxy, heteroalkyl, cycloalkyl, heterocycloalkyl, cyano, nitro, ureido, primary, secondary or tertiary amino, methylenedioxy, ethylenedioxy and difluoromethylenedioxy.

28. The compound according to claim 1 having the following formula (Iv):

![Chemical Structure](image)

wherein $X^{40}$ to $X^{44}$ are independently selected from hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoromethoxy, heteroalkyl, cycloalkyl, heterocycloalkyl, cyano, nitro, ureido, primary, secondary or tertiary amino, methylenedioxy, ethylenedioxy and difluoromethylenedioxy.

29. The compound according to claim 1 having the following formula (Iw):
wherein X\textsuperscript{40} to X\textsuperscript{44} are independently selected from hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoromethoxy, heteroalkyl, cycloalkyl, heterocycloalkyl, cyano, nitro, ureido, primary, secondary or tertiary amino, methylenedioxy, ethylenedioxy and difluoromethylenedioxy.

30. The compound according to any one of claims 1 to 29, wherein the compound is:

(R)-2-(4-(3-(2,4-dimethylphenoxy)-2-hydroxypropylamino)-2-oxo-1,2-dihydropyridin-3-yl)-6-(1-methylpiperidin-4-yl)-6,7-dihydroimidazo[4,5-f]isoindol-5(1H)-one;

(R)-2-(4-(3-(2,4-dimethylphenoxy)-2-hydroxypropylamino)-2-oxo-1,2-dihydropyridin-3-yl)-6-((1-(2-(methylsulfonyl)ethyl)piperidin-4-yl)-6,7-dihydroimidazo[4,5-f]isoindol-5(1H)-one;

(R)-2-(4-(3-(2,4-dimethylphenoxy)-2-hydroxypropylamino)-2-oxo-1,2-dihydropyridin-3-yl)-6-(3-(pyrrolidin-1-yl)propyl)-6,7-dihydroimidazo[4,5-f]isoindol-5(1H)-one;

(R)-2-(4-(3-(2-bromophenoxy)-2-hydroxypropylamino)-2-oxo-1,2-dihydropyridin-3-yl)-6-(1-methylpiperidin-4-yl)-6,7-dihydroimidazo[4,5-f]isoindol-5(1H)-one;

(R)-2-(4-(3-(6-ethylbenzo[d][1,3]dioxol-5-yl oxy)-2-hydroxypropylamino)-2-oxo-1,2-dihydropyridin-3-yl)-6-(1-methylpiperidin-4-yl)-6,7-dihydroimidazo[4,5-f]isoindol-5(1H)-one;

(R)-2-(4-(3-(2-chloro-4-methoxyphenoxy)-2-hydroxypropylamino)-2-oxo-1,2-dihydropyridin-3-yl)-6-(1-methylpiperidin-4-yl)-6,7-dihydroimidazo[4,5-f]isoindol-5(1H)-one or

(R)-2-(4-(3-(2,4-dimethylphenoxy)-2-hydroxypropylamino)-2-oxo-1,2-dihydropyridin-3-yl)-6-(1-(3-oxobutyl)piperidin-4-yl)-6,7-dihydroimidazo[4,5-f]isoindol-5(1H)-one.

31. A pharmaceutical composition comprising a compound according to any of claims 1 to 30 and one or more pharmaceutically acceptable diluents, excipients or carriers.
32. A method of modulating a tyrosine kinase activity comprising contacting the tyrosine kinase with a compound according to any one of claims 1 to 30.

33. The method of claim 32, wherein said tyrosine kinase is selected from the group consisting of Alk, AxI, CSFR, DDR1, DDR2, EphB4, EphA2, EGFR, Flt-I, Flt3, Flt4, FGFR1, FGFR2, FGFR3, FGFR4, HER2, HER3, HER4, IR, IGFlR, IRR, Kit, KDR/Flk-l, Mer, PDGFR.alpha., PDGFR.beta., Ret, Ros, Ron, Tie1, Tie2, TrkA, TrkB and TrkC.

34. The method of claim 32, wherein said tyrosine kinase is selected from the group consisting of AbI, Arg, Ack, Blk, Bmx, Brk, Btk, Csk, Fak, Fes, Fgr, Fps, Frk, Fyn, Hck, Itk, JakI, Jak2, Jak3, Lck, Lyn, Src, Syk, Tec, Yes and Zap70.

35. A method of treating or preventing a condition or disorder related to tyrosine kinase activity comprising administering a compound according to any one of Claims 1 to 30.

36. The method of claim 35, wherein said condition or disorder is selected from the group consisting of cancer, diabetes, restenosis, arteriosclerosis, psoriasis, angiogenic diseases and immunologic disorder.

37. A method of inhibiting a tyrosine kinase activity comprising contacting the tyrosine kinase with a compound according to any one of claims 1 to 30.