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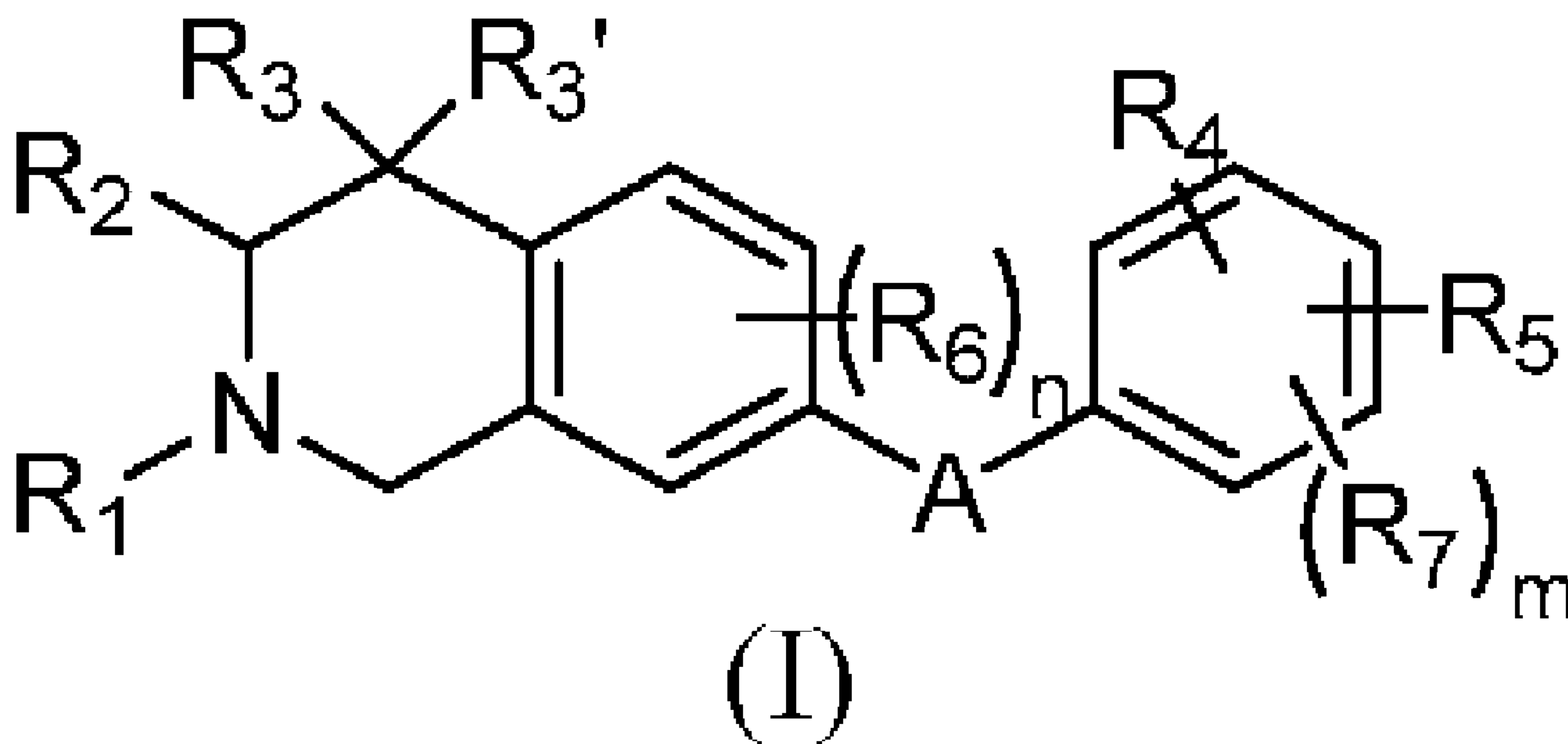
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(54) Titre : INHIBITEURS A PETITES MOLECULES CIBLANT LE RECEPTEUR DU DOMAINE DISCOIDINE 1 ET SES
UTILISATIONS

(54) Title: SMALL-MOLECULE INHIBITORS TARGETING DISCOIDIN DOMAIN RECEPTOR 1 AND USES THEREOF



(57) Abrégé/Abstract:

Compounds of formula (I), their pharmaceutically acceptable salts and stereoisomers thereof, as well as application in effectively inhibiting the enzymatic activity of discoidin domain receptor 1 and can be used as new therapeutic agents for preventing and

(57) **Abrégé(suite)/Abstract(continued):**

treating e.g. inflammation, liver fibrosis, kidney fibrosis, lung fibrosis, skin scar, atherosclerosis, and cancer. The compound of formula I is: wherein the variables are as defined herein.

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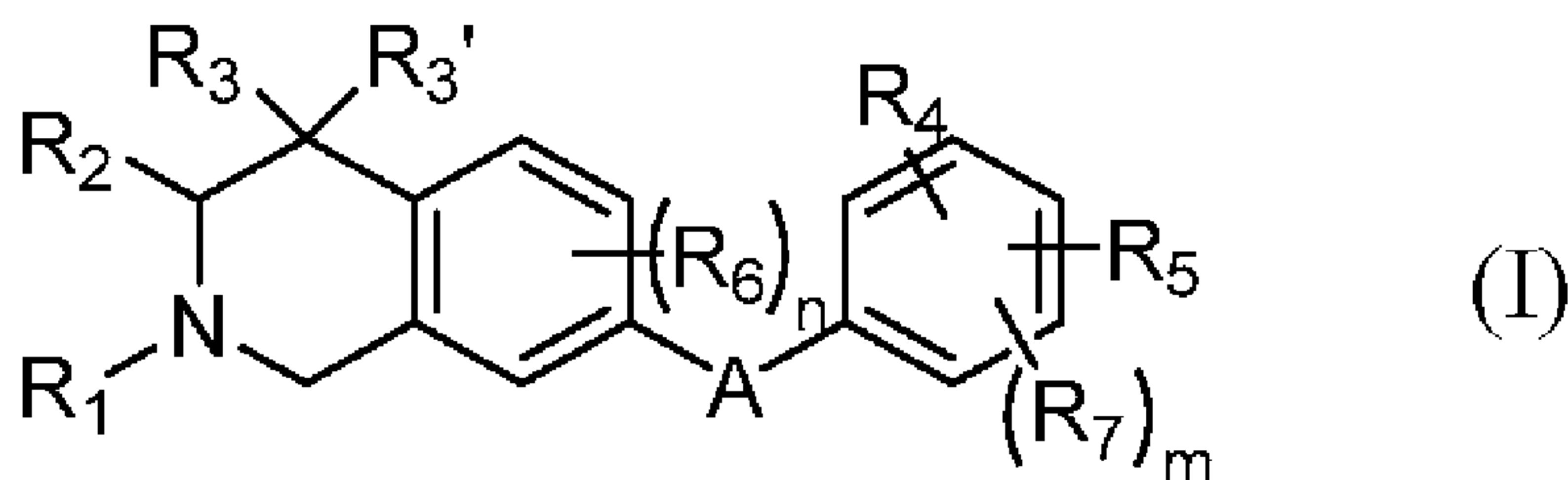
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(54) Title: SMALL-MOLECULE INHIBITORS TARGETING DISCOIDIN DOMAIN RECEPTOR 1 AND USES THEREOF



(57) Abstract: Compounds of formula (I), their pharmaceutically acceptable salts and stereoisomers thereof, as well as application in effectively inhibiting the enzymatic activity of discoidin domain receptor 1 and can be used as new therapeutic agents for preventing and treating e.g. inflammation, liver fibrosis, kidney fibrosis, lung fibrosis, skin scar, atherosclerosis, and cancer. The compound of formula I is: wherein the variables are as defined herein.

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**SMALL-MOLECULE INHIBITORS TARGETING DISCOIDIN DOMAIN
RECEPTOR 1 AND USES THEREOF**

DESCRIPTION

FEDERAL GRANT SUPPORT

5 This invention was made with government support under Grant Numbers R01CA118240 and F31 CA168350 awarded by the National Institutes of Health. The government has certain rights in the invention.

PRIORITY CLAIM

10 This application claims benefit of priority to U.S. Provisional Application Serial No. 62/067,070, filed October 22, 2014, and U.S. Provisional Application Serial No. 62/204,176, filed August 12, 2015, the entire contents of both applications being hereby incorporate by reference.

BACKGROUND

A. FIELD

15 The present disclosure belongs to the field of medicinal chemistry. In some aspects,
20 it relates to inhibitors of discoidin domain receptors and methods of use thereof.

B. RELATED ART

25 Discoidin domain receptors (DDR), including DDR1 and DDR2, are members of transmembrane receptor tyrosine kinases (RTKs) discovered in the early 1990s. Unlike other RTKs, DDRs contain two discoidin domains in the extracellular region. DDRs are activated by a number of triple-helical collagens which are most abundant components of the extracellular matrix (ECM). DDR1 is widely expressed in epithelial cells in lung, kidney, colon, brain, whereas DDR2 is primarily expressed in mesenchymal cells including fibroblasts, myofibroblasts, smooth muscle, and skeletal in kidney, skin, lung, heart, and
30 connective tissues. Studies have demonstrated that both DDR1 and DDR2 play crucial roles in fundamental cellular processes, such as proliferation, survival, differentiation, adhesion, and matrix remodeling. Deregulation of DDRs has been implicated in a number of human diseases, including fibrotic disorders, atherosclerosis, and cancer.

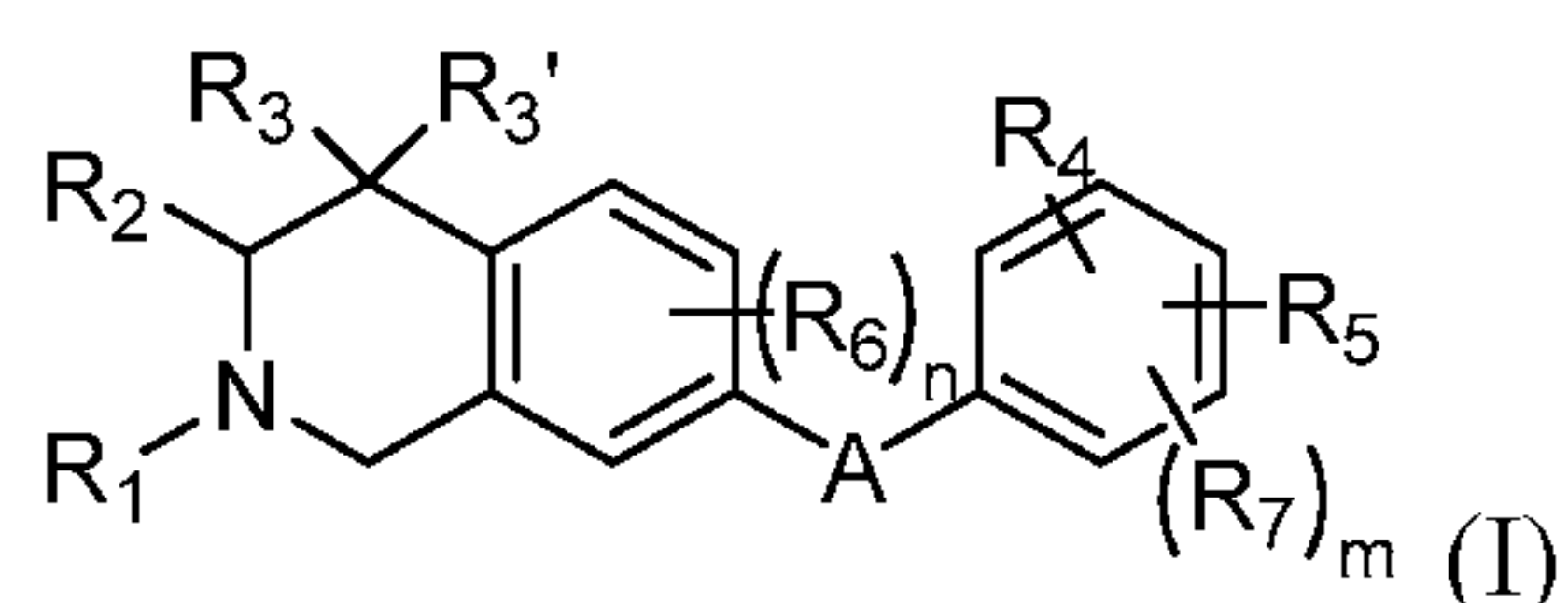
35 A number of other well-characterized kinase inhibitors, imatinib, nilotinib, dasatinib, bafetinib, ponatinib, sorafinib, pazopanib, foretinib, BIRB-796, and LCB 03-0110, are

reported to be potent inhibitors of both DDR1 and DDR2. However, all these inhibitors also
potently target many other kinases and cannot be utilized as good pharmacological probes of
DDR1. Recently, DDR1 inhibitors, 7rh and DDR1-IN-1, have been disclosed which show
increased selectivity for DDR1 and show potential promise as therapeutic agents. Given the
5 potential therapeutic utility of DDR1 inhibitors, the development of additional inhibitors,
including inhibitors with a unique pharmacore, is of therapeutic importance.

SUMMARY

In some aspects, the present disclosure provides compounds which may be used to inhibit discoidin domain receptor 1 (DDR1) and other discoidin domain receptors and/or used in the treatment of inflammatory disease and cancer.

5 In some aspects, the present disclosure provides compounds of the formula:



wherein:

A is $-NR_8C(O)-$ or $-C(O)NR_8-$; wherein:

R_8 is hydrogen, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$;

10 R_1 is $aryl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, or a substituted version of either of these groups;

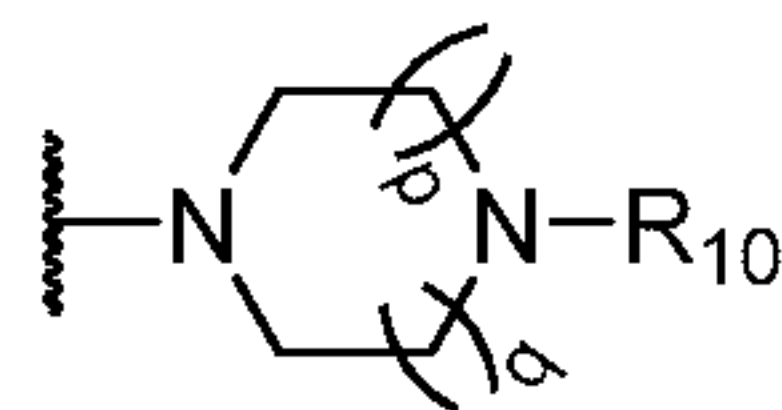
R_2 , R_3 , and R_3' are each independently hydrogen, $alkyl_{(C\leq 12)}$, $cycloalkyl_{(C\leq 12)}$, substituted $alkyl_{(C\leq 12)}$, or substituted $cycloalkyl_{(C\leq 12)}$;

R_4 is hydrogen, $alkyl_{(C\leq 12)}$, $cycloalkyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, substituted $alkyl_{(C\leq 12)}$, substituted $cycloalkyl_{(C\leq 12)}$, or substituted $aryl_{(C\leq 12)}$,

15 R_5 is hydrogen, $heteroaryl_{(C\leq 12)}$, $-X-R_9$, wherein:

X is a covalent bond, $alkanediyl_{(C\leq 8)}$, or substituted $alkanediyl_{(C\leq 8)}$;

R_9 is amino or heterocycloalkyl $_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $alkylamino_{(C\leq 12)}$, $dialkylamino_{(C\leq 12)}$, or a substituted version of any of these groups; or a group of the formula:



20

wherein:

R_{10} is hydrogen, $alkyl_{(C\leq 12)}$, $cycloalkyl_{(C\leq 12)}$, substituted $alkyl_{(C\leq 12)}$, or substituted $cycloalkyl_{(C\leq 12)}$; and

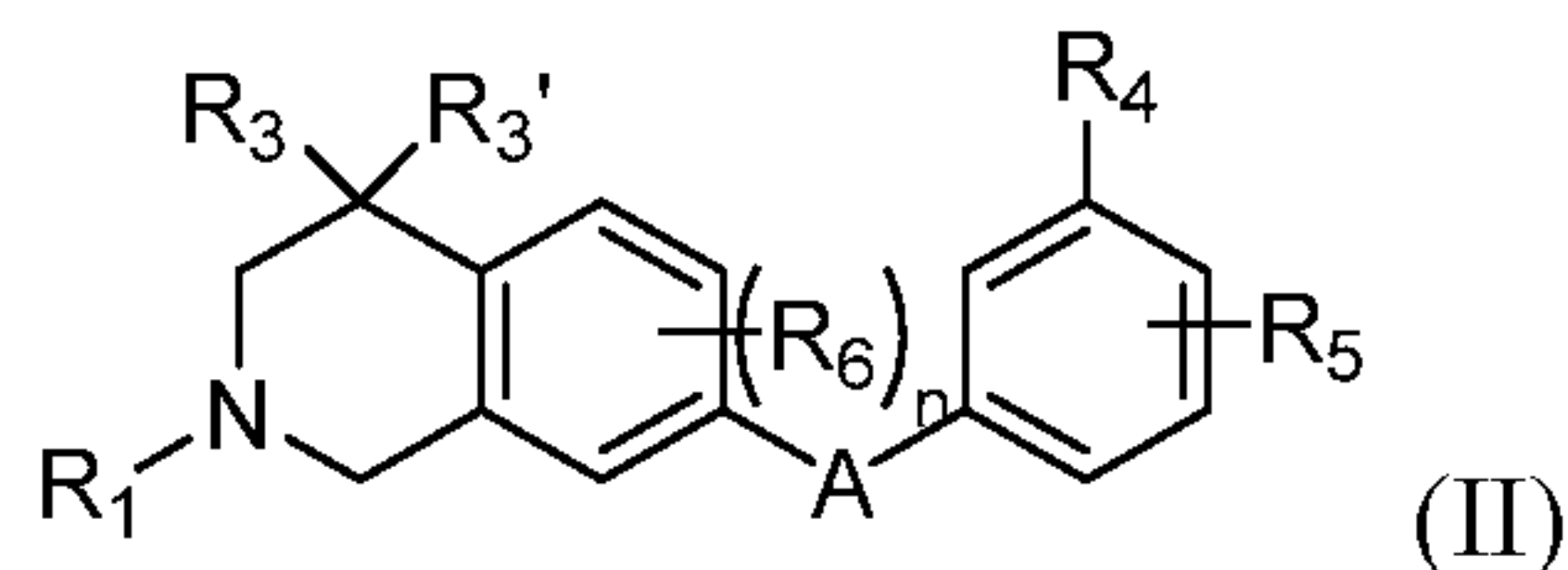
p and q are each 0, 1, or 2;

25 R_6 and R_7 are each independently amino, cyano, halo, hydroxy, hydroxysulfonyl, nitro, sulfonamide; or

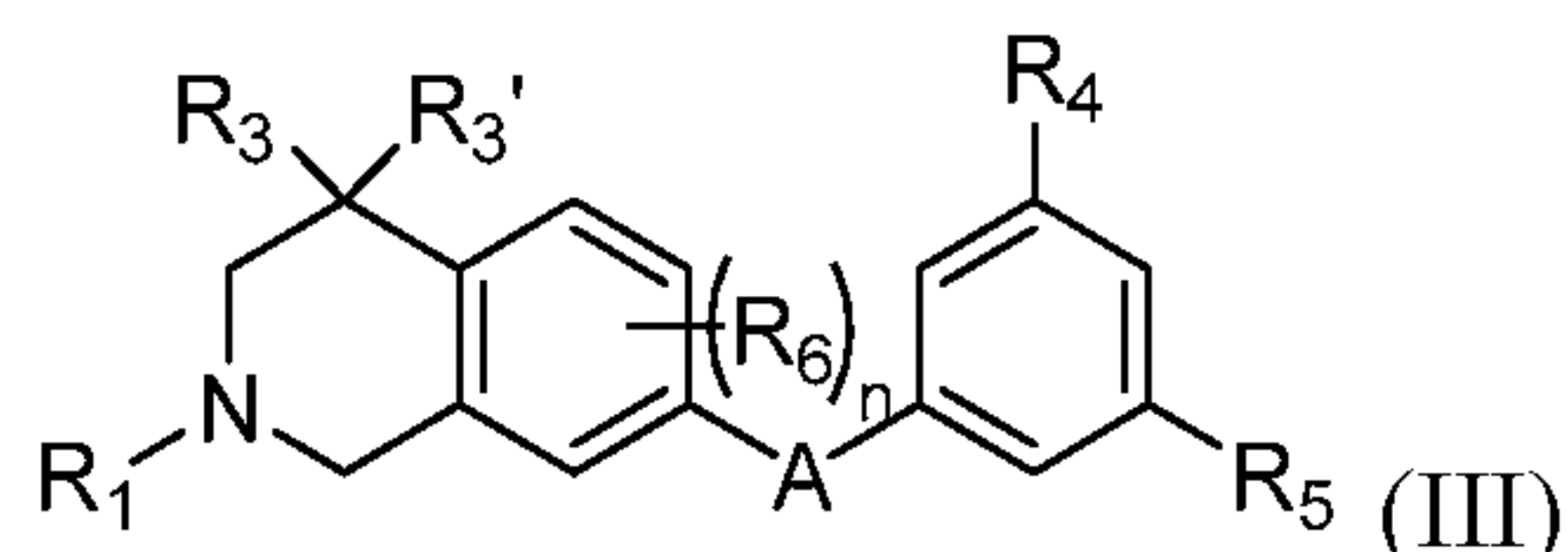
$alkyl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, or $dialkylamino_{(C\leq 8)}$; and

m and n are each independently 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof. In some embodiments, the compounds are further defined as:



5 wherein: A, R₁, R₃, R₃', R₄, R₅, R₆, and n are as defined above; or a pharmaceutically acceptable salt thereof. In some embodiments, the compounds are further defined as:



wherein: A, R₁, R₃, R₃', R₄, R₅, R₆, and n are as defined above; or a pharmaceutically acceptable salt thereof.

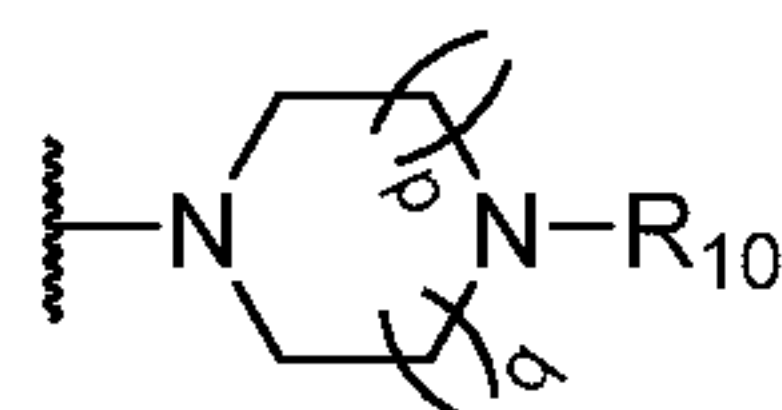
10 In some embodiments, R₁ is heteroaryl_(C≤12). In some embodiments, R₁ is 5-pyrimidinyl. In some embodiments, R₃ is alkyl_(C≤12). In some embodiments, R₃ is methyl or ethyl. In other embodiments, R₃ is hydrogen. In some embodiments, R₃' is hydrogen.

In some embodiments, R₄ is alkyl_(C≤12) or substituted alkyl_(C≤12). In some embodiments, R₄ is alkyl_(C≤12). In some embodiments, R₄ is methyl, ethyl, or isopropyl. In
15 other embodiments, R₄ is substituted alkyl_(C≤12). In some embodiments, R₄ is trifluoromethyl. In other embodiments, R₄ is cycloalkyl_(C≤12) or substituted cycloalkyl_(C≤12). In some embodiments, R₄ is cycloalkyl_(C≤12). In some embodiments, R₄ is cyclopropyl, cyclopentyl, or cyclohexyl. In other embodiments, R₄ is aryl_(C≤12). In some embodiments, R₄ is phenyl.

In some embodiments, R₅ is hydrogen. In other embodiments, R₅ is heteroaryl_(C≤12).
20 In some embodiments, R₅ is 4-methylimidazolyl. In other embodiments, R₅ is -X-R₉, wherein:

X is a covalent bond, alkanediyl_(C≤8), or substituted alkanediyl_(C≤8);

R₉ is amino or heterocycloalkyl_(C≤12), heteroaryl_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), or a substituted version of any of these groups; or a group
25 of the formula:

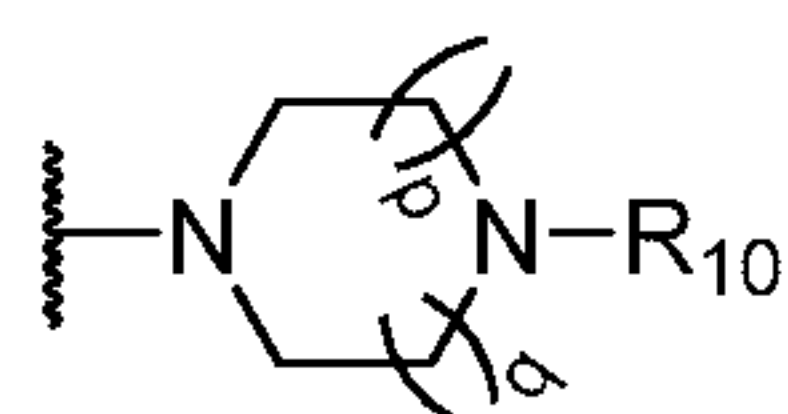


wherein:

R_{10} is hydrogen, alkyl_(C≤12), cycloalkyl_(C≤12), substituted alkyl_(C≤12), or substituted cycloalkyl_(C≤12); and

p and q are each 0, 1, or 2.

In some embodiments, X is alkanediyl_(C≤8). In some embodiments, X is $-\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2-$. In some embodiments, R_9 is heterocycloalkyl_(C≤12) or a substituted heterocycloalkyl_(C≤12). In some embodiments, R_9 is *N*-1,4-thiazinanyl, *N*-morpholinyl, *N*-piperidinyl, *N*-pyrrolidinyl, or *N*-3-dimethylaminopyrrolidinyl. In other embodiments, R_9 is dialkylamino_(C≤12) or substituted dialkylamino_(C≤12). In some embodiments, R_9 is $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$. In other embodiments, R_9 is:



wherein:

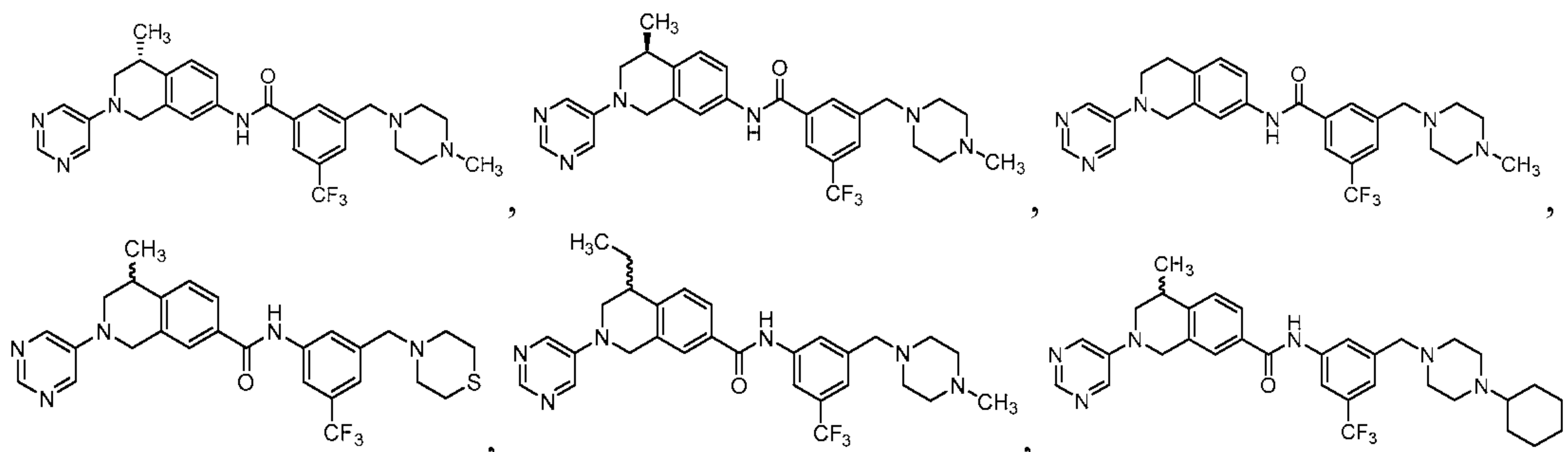
R_{10} is hydrogen, alkyl_(C≤12), cycloalkyl_(C≤12), substituted alkyl_(C≤12), or substituted cycloalkyl_(C≤12); and

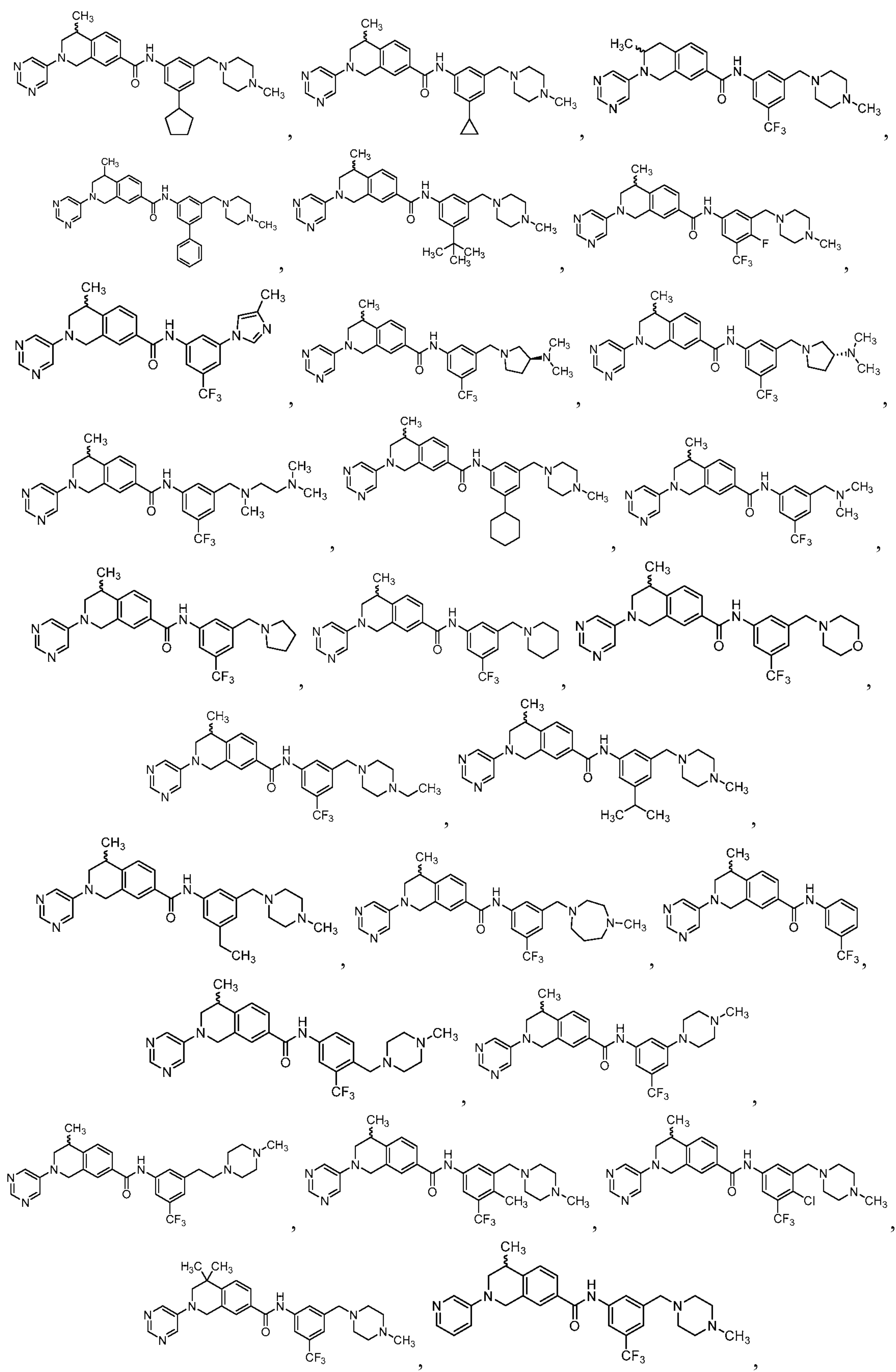
p and q are each 0, 1, or 2.

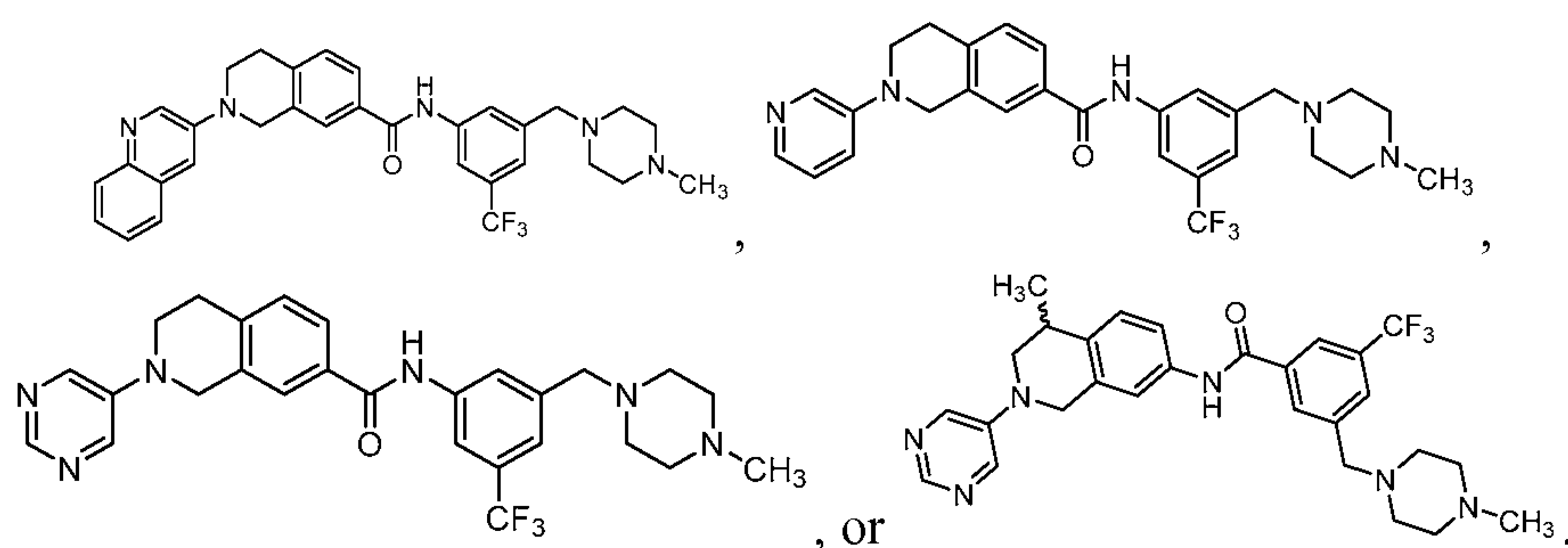
In some embodiments, R_{10} is alkyl_(C≤12) or substituted alkyl_(C≤12). In some embodiments, R_{10} is methyl or ethyl. In other embodiments, R_{10} is cycloalkyl_(C≤12) or substituted cycloalkyl_(C≤12). In some embodiments, R_{10} is cyclohexyl. In some embodiments, p is 1. In some embodiments, q is 1. In other embodiments, q is 2. In some embodiments, m is 0. In other embodiments, m is 1.

In some embodiments, R_7 is alkyl_(C≤8) or substituted alkyl_(C≤8). In some embodiments, R_7 is methyl. In other embodiments, R_7 is halo. In some embodiments, R_7 is fluoro or chloro.

In some embodiments, the compounds are further defined as:







or a pharmaceutically acceptable salt thereof.

In still another aspect, the present disclosure provides compounds of the formula:

5 4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)benzamide;

10 N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(quinolin-3-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

15 4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4,4-dimethyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

20 N-(4-chloro-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(4-methyl-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

25 4-methyl-N-(3-(2-(4-methylpiperazin-1-yl)ethyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(3-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

5 4-methyl-2-(pyrimidin-5-yl)-N-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(3-((4-methyl-1,4-diazepan-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

10 N-(3-ethyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-isopropyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-((4-ethylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

15 4-methyl-N-(3-(morpholinomethyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(3-(piperidin-1-ylmethyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

20 4-methyl-2-(pyrimidin-5-yl)-N-(3-(pyrrolidin-1-ylmethyl)-5-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-((dimethylamino)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-cyclohexyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

25 N-(3-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-(((R)-3-(dimethylamino)pyrrolidin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-(((S)-3-(dimethylamino)pyrrolidin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

5 N-(4-fluoro-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-tert-butyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

10 4-methyl-N-(5-((4-methylpiperazin-1-yl)methyl)biphenyl-3-yl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

3-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-cyclopropyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

15 N-(3-cyclopentyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-((4-cyclohexylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

20 4-ethyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-2-(pyrimidin-5-yl)-N-(3-(thiomorpholinomethyl)-5-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

3-((4-methylpiperazin-1-yl)methyl)-N-(2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-(trifluoromethyl)benzamide;

25 (S)-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

(R)-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

(S)-N-(4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)benzamide;

(R)-N-(4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)benzamide;

5 or a pharmaceutically acceptable salt thereof.

In still yet another aspect, the present disclosure provides pharmaceutical composition comprising:

- (a) a compound described herein; and
- (b) a pharmaceutically acceptable carrier.

10 In some embodiments, the pharmaceutical compositions further comprise a second chemotherapeutic compound. In some embodiments, the second chemotherapeutic compound is a nucleoside analog chemotherapeutic compound. In some embodiments, the nucleoside analog chemotherapeutic compound is gemcitabine. In other embodiments, the second chemotherapeutic compound is a taxane. In some embodiments, the second

15 chemotherapeutic compound is paclitaxel. In some embodiments, the pharmaceutical composition is formulated for administration: orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intralesionally, intramuscularly, intranasally, intraocularly, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrarectally, intrathecally, intratracheally, intratumorally, intraumbilically, intravaginally,

20 intravenously, intravesicularly, intravitreally, liposomally, locally, mucosally, parenterally, rectally, subconjunctival, subcutaneously, sublingually, topically, transbuccally, transdermally, vaginally, in crèmes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, or via localized perfusion. In some embodiments, the pharmaceutical composition is formulated for

25 oral administration. In some embodiments, the pharmaceutical composition is formulated as a unit dose.

In still yet another aspect, the present disclosure provides pharmaceutical compositions comprising:

[illegible]

In still yet another aspect, the present disclosure provides methods of treating a disease or disorder in a patient in need thereof comprising administering to the patient a therapeutically effective amount of a compound or composition described herein. In some embodiments, the disease or disorder is related to inflammation. In some embodiments, the disease or disorder is kidney fibrosis, liver fibrosis, lung fibrosis, skin scars, or atherosclerosis. In other embodiments, the disease or disorder is cancer. In some embodiments, the cancer is a carcinoma, sarcoma, lymphoma, leukemia, melanoma, mesothelioma, multiple myeloma, or seminoma. In some embodiments, the cancer is of the bladder, blood, bone, brain, breast, central nervous system, cervix, colon, endometrium, esophagus, gall bladder, gastrointestinal tract, genitalia, genitourinary tract, head, kidney, larynx, liver, lung, muscle tissue, neck, oral or nasal mucosa, ovary, pancreas, prostate, skin, spleen, small intestine, large intestine, stomach, testicle, or thyroid. In some embodiments, the cancer is a cancer of the lung, breast, brain, ovary, head and neck, liver, pancreas, or prostate. In some embodiments, the cancer is a cancer of the pancreas. In some embodiments, the cancer is pancreatic ductal adenocarcinoma. In some embodiments, the compound is administered to the patient once. In other embodiments, the compound is administered to the patient two or more times. In some embodiments, the methods further comprise a second therapy. In some embodiments, the second therapy is one or more therapeutic agents, a surgery, a radiotherapy, or an immunotherapy. In some embodiments, the second therapy is a chemotherapeutic agent. In some embodiments, the second therapy is

a nucleoside analog chemotherapeutic agent. In some embodiments, the nucleoside analog chemotherapeutic agent is gemcitabine. In other embodiments, the second therapy is a taxane. In some embodiments, the second therapy is paclitaxel.

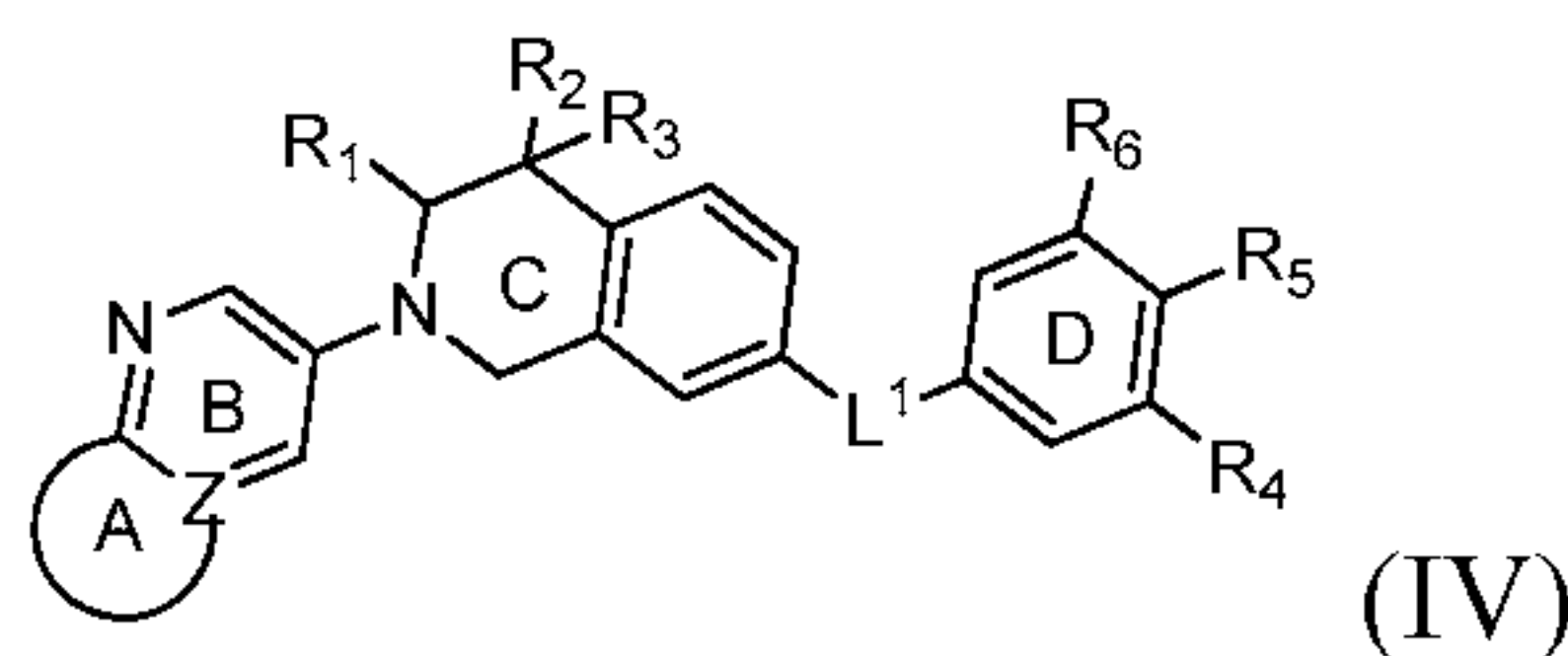
In still another aspect, the present disclosure provides methods of inhibiting discoidin domain receptor (DDR) protein comprising contacting the protein with a compound or composition described herein in an amount sufficient to inhibit the protein. In some embodiments, the protein is the discoidin domain receptor 1 protein (DDR1). In some embodiments, the methods are performed *in vivo*. In other embodiments, the methods are performed *in vitro*. In some embodiments, the methods are performed *in vivo* and comprise administering the compound to a patient in need thereof. In some embodiments, the inhibition of DDR 1 protein is sufficient to treat a disease or disorder.

In still yet another aspect, the present disclosure provides methods of treating cancer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of:

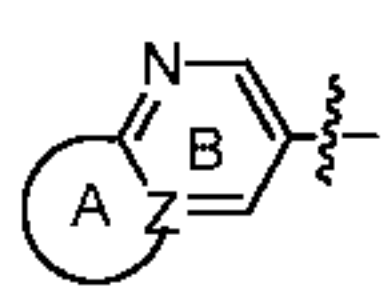
- (a) a compound or composition described herein; and
- (b) a second chemotherapeutic compound.

In some embodiments, the cancer is a cancer of the lung, breast, brain, ovary, head and neck, liver, pancreas, or prostate. In some embodiments, the cancer is a cancer of the pancreas. In some embodiments, the cancer is pancreatic ductal adenocarcinoma. In some embodiments, the methods comprise administering the compound or composition in a ratio from about 1:2 to about 5:1 relative to the second chemotherapeutic compound. In some embodiments, the ratio of the compound or composition is 2:1 relative to the second chemotherapeutic compound. In some embodiments, the second chemotherapeutic compound is a nucleoside analog. In some embodiments, the second chemotherapeutic compound is gemcitabine. In other embodiments, the second chemotherapeutic compound is a taxane. In some embodiments, the second chemotherapeutic compound is paclitaxel.

In still another aspect, the present disclosure provides compounds of formula (IV) or a pharmaceutically acceptable salt, stereoisomer or prodrug thereof:



wherein L^1 is independently selected as $-\text{CONH}-$ or $-\text{NHCO}-$;



is independently selected from:

a) single heterocycles like and ;

b) fused heterocycles like ; ; ; ; ;

R₁, R₂, R₃ are independently selected from:

5 a) H;

b) C₁~C₄ alkyl;

R₂, R₃ can further form tri, tetra, penta ring structure with the carbon atom where they are linked in the C ring;

R₄, R₅, R₆ is independently selected from:

10 a) H;

b) halogen (F, Cl, Br);

c) C₁~C₄ alkyl;

d) C₃~C₆ cycloalkyl;

e) C₁~C₄ alkyl containing F;

15 f) aryl, Het;

aryl can be phenyl, or substituted phenyl; Het is defined as the nonaromatic heterocycle, or aromatic heterocycle containing 5 ~ 6 atoms, which contains 1~4 hetero atoms such as O, N, S. Alkyl or cycloalkyl will be incorporated into any C or N position in which Het can be substituted.

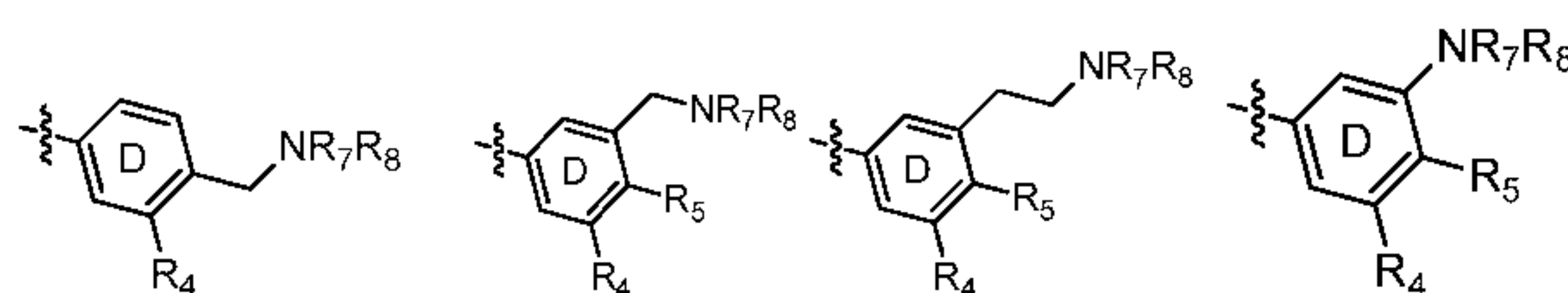
20 In some embodiments, R₁, R₂, R₃ is independently selected from:

a) H;

b) methyl, ethyl, propyl, isopropyl, cyclopropyl;

R₂, R₃ can further form tri, tetra, penta ring structure with the carbon atom where they are linked in the C ring.

25 In some embodiments, D ring is selected from:



R_4 is independently selected from:

- a) halogen (F, Cl, Br);

- b) C₁~C₄ alkyl;

- 5 c) C₃~C₆ cycloalkyl;

- d) C₁~C₄ alkyl containing F;

- e) aryl;

Aryl can be phenyl, or substituted phenyl;

R₅ is independently selected from H, F, Cl, Br, Me, OMe;

- 10 R_7 or R_8 is independently selected from:

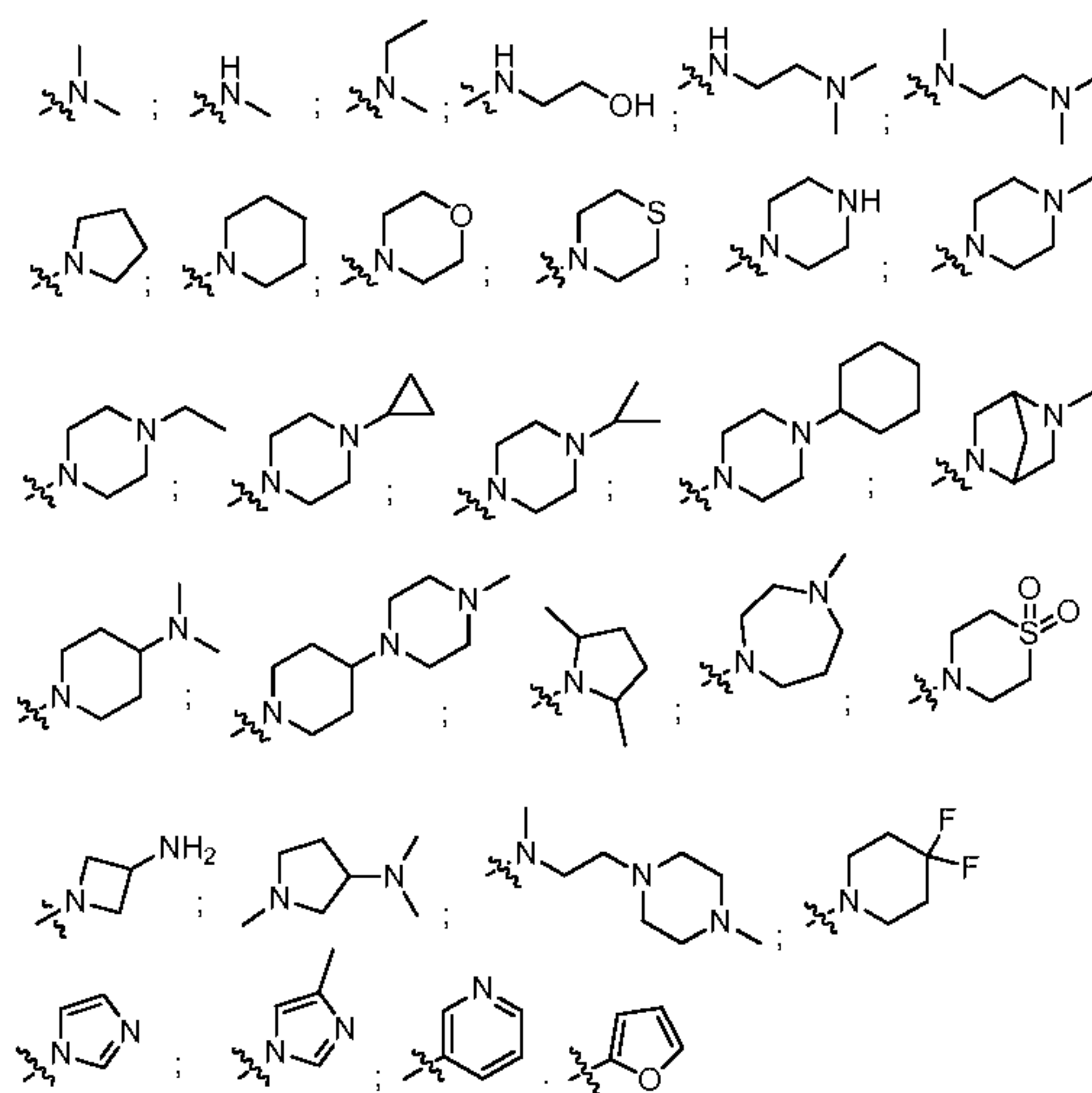
- a) H;

- b) C₁~C₃ alkyl;

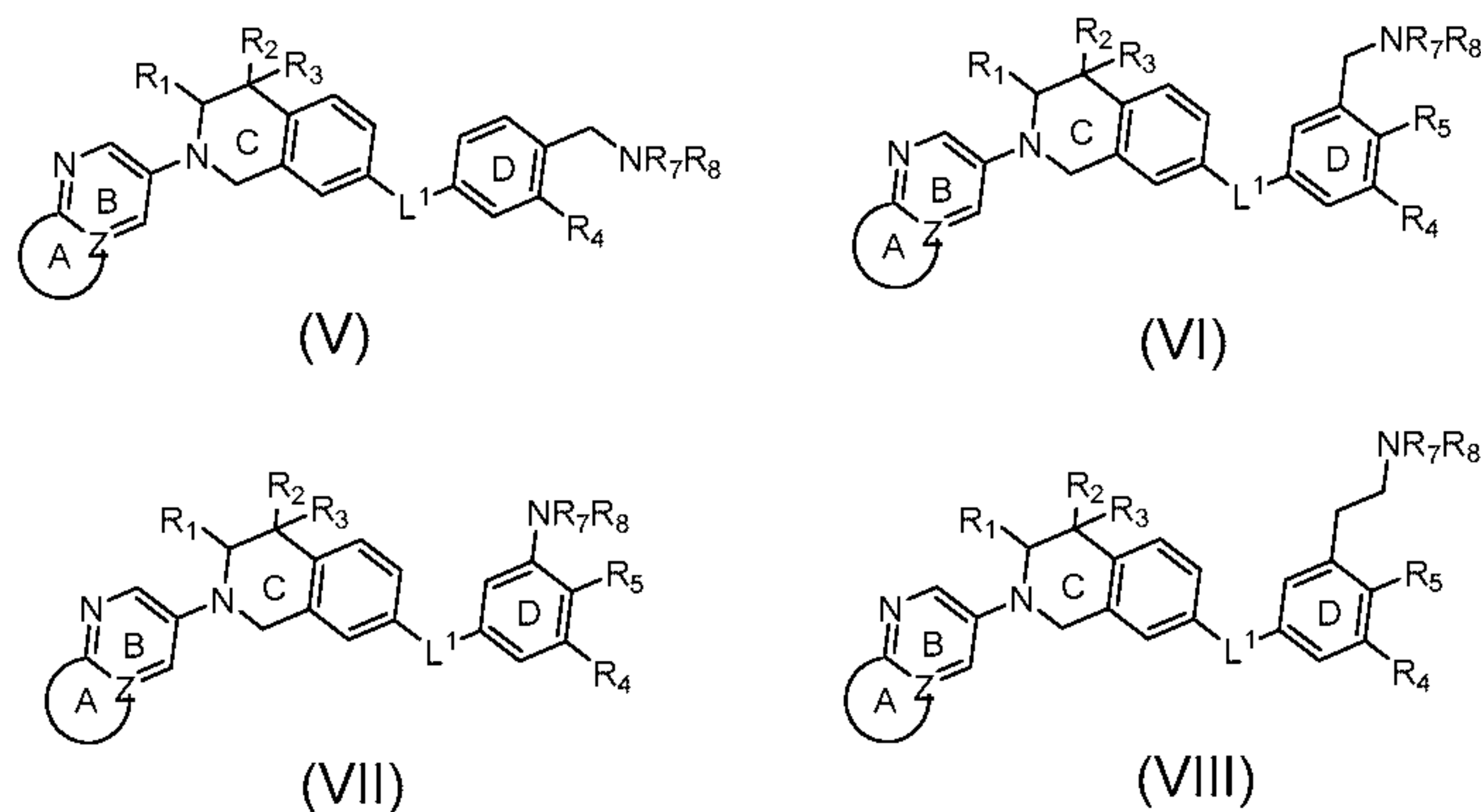
- c) C₁~C₃ alkyl containing F;

- d) C₃~C₆ cycloalkyl;

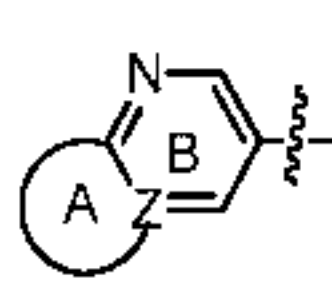
- 15 R₇ and R₈ can further form penta-, hexa-, hepta- or octatomic ring structure through C, O, N, S atoms. Alkyl or cycloalkyl will be incorporated into any C or N position in the ring which can be substituted; preferably,  is independently selected from:

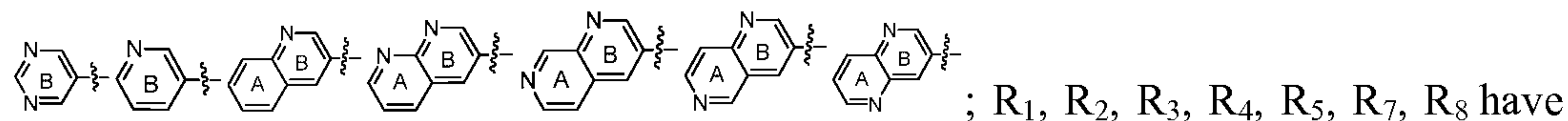


In some embodiments, the compound of formula (IV) is specially selected from:



wherein

L^1 is independently selected as $-\text{CONH}-$ or $-\text{NHCO}-$;  is independently selected from:



the same definition as above mentioned.

In some embodiments, the compounds of formula (IV) are specially selected from:

4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)benzamide;

N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(quinolin-3-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4,4-dimethyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(4-chloro-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

- 4-methyl-N-(4-methyl-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 4-methyl-N-(3-(2-(4-methylpiperazin-1-yl)ethyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 5 4-methyl-N-(3-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 4-methyl-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 4-methyl-2-(pyrimidin-5-yl)-N-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-7-
 10 carboxamide;
- 4-methyl-N-(3-((4-methyl-1,4-diazepan-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- N-(3-ethyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 15 N-(3-isopropyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- N-(3-((4-ethylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 4-methyl-N-(3-(morpholinomethyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-
 20 tetrahydroisoquinoline-7-carboxamide;
- 4-methyl-N-(3-(piperidin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 4-methyl-2-(pyrimidin-5-yl)-N-(3-(pyrrolidin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 25 N-(3-((dimethylamino)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- N-(3-cyclohexyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

- N-(3-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- N-(3-(((R)-3-(dimethylamino)pyrrolidin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 5 N-(3-(((S)-3-(dimethylamino)pyrrolidin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- N-(4-fluoro-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 10 N-(3-tert-butyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 4-methyl-N-(5-((4-methylpiperazin-1-yl)methyl)biphenyl-3-yl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 15 3-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- N-(3-cyclopropyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- N-(3-cyclopentyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 20 N-(3-((4-cyclohexylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 4-ethyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 25 4-methyl-2-(pyrimidin-5-yl)-N-(3-(thiomorpholinomethyl)-5-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 3-((4-methylpiperazin-1-yl)methyl)-N-(2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-(trifluoromethyl)benzamide;

(S)-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

(R)-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

5 (S)-N-(4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)benzamide; and

(R)-N-(4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)benzamide.

10 In still yet another aspect, the present disclosure provides pharmaceutical compositions comprising a compound described herein or a pharmaceutically acceptable salt, stereoisomer or prodrug thereof and a pharmaceutically acceptable carrier, solvent, buffer or diluent.

15 In yet another aspect, the present disclosure provides methods of treating a subject having inflammation, liver fibrosis, kidney fibrosis, lung fibrosis, skin scar and atherosclerosis, and cancer comprising administering to said subject a compound described herein or a pharmaceutically acceptable salt, stereoisomer or pro-drug thereof.

20 Other objects, features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the disclosure, are given by way of illustration only, since various changes and modifications within the spirit and scope of the disclosure will become apparent to those skilled in the art from this detailed description. Note that simply because a particular compound is ascribed to one particular generic formula doesn't mean that it cannot also belong to another generic formula.

25

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present disclosure. The disclosure may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIGS. 1A-E: DDR1 signaling in human and mouse PDA. (FIG. 1A) 168 human PDA samples were assessed for expression of *COLLAGEN I $\alpha 1$* (*COL1 $\alpha 1$*), *DDR1*, *PYK2*, and *PEAK1*. RNA-sequencing data from The Cancer Genome Atlas (TCGA) PDA cBioPortal was collected (Cerami *et al.*, 2012 and Gao *et al.*, 2013). Relative changes (G score) were assessed by comparing RNA sequencing data between normal and cancer patients to define high and low expression. (FIG. 1B) Immunohistochemical detection of phospho-DDR1 and phospho-PEAK1 in human PDA. TMAs of primary human PDA (44 samples) and matched patient-derived tumor xenograft (PATX, 150 samples) demonstrated phospho-DDR1 and phospho-PEAK1 localized to similar regions. (FIGS. 1C-1E) Histological analyses of the *KPC* (*LSL-Kras^{G12D/+}; LSL-Trp53^{R172H/+}; p48^{Cre/+}*) GEMM of PDA. (FIG. 1C) Immunohistochemical detection of phospho-Ddr1, phospho-Peak1, phospho-Pyk2, Muc1 and Sox9 in *KPC* tumors. Ddr1 activation and downstream signaling through effectors such as Peak1 and Pyk2 was present in early PanIN lesions (similar to regions positive for Muc-1 staining) and in advanced adenocarcinoma (similar to regions of Sox9 staining). Tissue from an early (3 month) and advanced (5 month) stage of the *KPC* model was evaluated. (FIG. 1D) H&E histology of normal WT pancreas and PDA in a 5 month old *KPC* mouse. (FIG. 1E) Trichrome analysis of PDA from 3 and 5 month old *KPC* animals.

FIGS. 2A-C: DDR1 expression in lung cancer and PDA. (FIG. 2A) Analyses of the expression of DDR1 and Collagen I $\alpha 1$ in lung cancer patients using the online database (Kaplan-Meier Plotter) (Gyorffy *et al.*, 2013). Lung cancer patients with high expression of *DDR1* (1,389/1,927) and those with high expression of *Collagen I $\alpha 1$* (1,309/1,927) levels displayed worse overall prognosis. (FIG. 2B) Pearson correlation of p-PEAK1 and p-DDR1 expression in human and patient-derived tumor xenograft (PATX) TMA samples. (FIG. 2C) Percent of TMA samples

positive for p-DDR1 and p-PEAK1. Scoring system is denoted as: low or no reactivity (0-1), moderate reactivity (2), strong reactivity (3), and very strong reactivity (4).

FIGS. 3A-J: Analysis of PDA GEMM for collagen deposition and Ddr1 signaling. Histological analyses of the *KPC* (*LSL-Kras*^{G12D/+}; *LSL-Trp53*^{R172H/+}; *p48*^{Cre/+}) GEMM of PDA. (FIGS. 3A-B) The KPC model recapitulated the pathological histology seen in human PDA as noted by the dense stromal reaction. (FIGS. 3C-D) Trichrome analyses depicted the enhanced desmoplasia throughout the progression of the model. (FIGS. 3E-F) Histological analyses represent metastatic lesions in the liver. Phosphorylation of Ddr1 (FIG. 3G) and Peak1 (FIG. 3H) colocalized to metastatic regions. Metastatic regions were validated by the expression of the mesenchymal marker vimentin (FIG. 3I) and the tumorigenic marker PcnA (FIG. 3J).

FIGS. 4A-H: Collagen stimulation of DDR1 signaling in human PDA cell lines. (FIG. 4A) Collagen receptor expression profile of human PDA cell lines (AsPC-1 and PANC-1). Each cell line expressed similar levels of *DDR1*, *PEAK1*, *INTEGRIN α1* (*ITG α1*), *INTEGRIN β1* (*ITG β1*), *COLLAGEN I α1* (*COL I α1*), and *COLLAGEN I α2* (*COL I α2*) as determined by PCR analysis (30 cycles). (FIG. 4B) Secretion of soluble collagen (μg) was assessed in duplicate samples of human PDA cells by Sircol analysis. AsPC-1 secreted an elevated level of collagen compared to PANC-1 cells. (FIG. 4C) Human PDA cell lines were plated on plastic (P) and stimulated with soluble collagen I (C, 10 μg/mL) for 24 hours. Lysates were probed for the indicated targets by western blot analysis. (FIG. 4D) Human PDA cell lines were plated in the presence or absence of 10 μg/ml soluble collagen I. The presence of soluble collagen enhanced the phosphorylation of Peak1 by immunofluorescence. (FIG. 4E) Immunoprecipitation (IP) analysis of DDR1. IP of DDR1 co-precipitated PYK2 and PEAK1, but did not pull down αv integrin (*ITG αV*) or phospho-β1 integrin (P-*ITG β1*) (as shown in the immunodepleted (IDE) fraction. (FIG. 4F) siRNA-mediated knockdown of DDR1 compared to mock siRNA control reduced the activation of DDR1, PYK2, SRC, PEAK1, SHC, and AKT1. Lysates were probed for the indicated targets by western blot analysis. (FIG. 4G) siRNA-mediated knockdown of DDR1 compared to mock siRNA control reduced the activation of DDR1 through immunofluorescence. (FIG. 4H) siRNA-mediated knockdown of DDR1 compared to mock siRNA control reduced the migration of human PDA cells (AsPC-1) after a 24

hour period of time via scratch migration assay. Error bars: (*, $p < 0.05$; **, $p < 0.005$; ***, $p < 0.0005$; ****, $p < 0.00005$), one-way ANOVA with Tukey's MCT.

FIGS. 5A-D: Signaling and functional consequences of DDR1 inhibition by 7rh in human PDA cell lines. (FIG. 5A) 7rh inhibited DDR1-mediated signaling in a concentration-dependent manner in human PDA cell line PANC-1. PANC-1 cells were stimulated with control (no treatment) or collagen (10 $\mu\text{g/mL}$) for 24 hr and cell lysates were probed for the indicated targets by western blot analysis. (FIG. 5B) 7rh inhibited migration of human PDA cell lines in a concentration-dependent manner over a 30 hour time period via scratch migration assay. (FIG. 5C) 7rh inhibited liquid colony formation of human PDA cell lines in a concentration-dependent manner. 250 cells/well were plated in serum containing media in the presence or absence of 7rh at the indicated concentrations. Colony formation was evaluated 1.5-2 weeks post plating. (FIG. 5D) Sensitivity of human PDA cell lines (AsPC-1 and PANC-1) to gemcitabine and 7rh assessed by MTS viability assays. Drug sensitivity was assessed in the presence of 4-fold dilutions of each drug. Combination of 7rh (250 nM or 500 nM) with a titration of gemcitabine is shown. Drug sensitivity curves and IC_{50}s were calculated with in-house software, the number replicates for each assay is shown (#) (Dineen *et al.*, 2010).

FIG. 6: Synergistic analysis of 7rh combined with gemcitabine. The combination index of 7rh (500 nM) with gemcitabine (2-2000 nM) was calculated via online CompuSyn Synergistical Analysis software (www.combosyn.com) (Chou, 2006). A combination index (CI) less than or equal to 0.9 is synergistic.

FIGS. 7A-E: 7rh reduces collagen-mediated signaling in a concentration-dependent manner *in vivo*. (FIG. 7A) Schematic representation of the animal experiment. Pan02 cells were orthotopically injected into *C57BL/6* mice. Mice were treated with a one-time oral dose of 7rh (0.1, 1, or 10 mg/kg) on day 10 post tumor cell injection (TCI). (FIGS. 7B-7D) Immunofluorescence analysis of tumor tissue from each group showing inhibition of Ddr1 activation and downstream signaling (P-Pyk2 and P-Peak1), as well a significant induction of apoptosis (cleaved caspase-3, FIG. 7E). Mean $\pm$ SEM % Area Fraction for p-Ddr1, p-Pyk2, p-Peak1 and cleaved caspase 3 are shown. *, $p < 0.05$; **, $p < 0.005$; ***, $p < 0.0005$; ****, $p < 0.00005$ v vehicle, one-way ANOVA with Tukey's MCT. Scale bar, 50 μm .

FIGS. 8A-G: 7rh inhibits Ddr1 activation in Pan02 tumors. (FIG. 8A) Schematic representation of the animal experiment. Pan02 cells were orthotopically

injected into *C57BL/6* mice. 7rh was given orally 3×/week at the indicated concentrations starting on day 10 post tumor cell injection (TCI) and ended at day 21. (FIG. 8B) Tumor H&E histology is shown. (FIGS. 8C-F) Immunofluorescence analysis of amylase (FIG. 8C), p-Ddr1 (FIG. 8D), P-Peak1 (FIG. 8E), and PCNA (FIG. 8F) expression in tumor tissue from each group is shown. Mean +/- SEM of % Area Fraction is graphed. *, $p < 0.05$; **, $p < 0.005$; ***, $p < 0.0005$; ****, $p < 0.00005$ v vehicle, one-way ANOVA with Tukey's MCT. Scale bar, 50 μ m. (FIG. 8G) The expression level of p-Peak1 in tumor lysates from each treatment group was determined by western blot analysis. Actin was used as a loading control.

FIGS. 9A-B: Inhibition of Ddr1 with 7rh does not induce observable toxicity. (FIG. 9A) Serum from *C57BL/6* mice bearing orthotopic Pan02 tumors treated with vehicle or 7rh (3.3, 10 or 30 mg/kg) 3×/week for 2 weeks was collected at the time of sacrifice. The serum level of Alb (albumin), Alt (liver transaminases), Ast (aspartate transaminase), Bun (blood urea nitrogen), Crea (creatinine), Glu (glucose), Tbil (total bilirubin), and Tp (plasma total protein) is shown. (FIG. 9B) Animal weights for each treatment group during the treatment period are displayed. *, $p < 0.05$; **, $p < 0.005$; ***, $p < 0.0005$; ****, $p < 0.00005$ v vehicle, one-way ANOVA with Tukey's MCT.

FIGS. 10A-I: 7rh reduced Ddr1-mediated tumorigenicity and signaling. (FIG. 10A) Schematic representation of the animal experiment. Mouse Pan02 cells were orthotopically injected into *C57BL/6* mice. 7rh (25 mg/kg 3×/week, n=8) was administered by oral gavage starting at day 19. (FIG. 10B) 7rh treatment reduced primary tumor burden compared to vehicle (n=10). (FIGS. 10C-10I) Tumor tissue harvested from vehicle or 7rh treated animals was evaluated by histology (FIG. 10C, H&E) and immunofluorescence (FIGS. 10D-10I). Example reactivity for amylase (FIG. 10D), p-DDR1 (FIG. 10E), p-Peak1 (FIG. 10F), p-Pyk2 (FIG. 10G), cleaved caspase (FIG. 10H), and PcnA (FIG. 10I) are shown. Mean +/- SEM % area fraction of signal intensity for each target is shown in the bar graphs. *, $p < 0.05$; **, $p < 0.005$; ***, $p < 0.0005$; ****, $p < 0.00005$. Scale bar, 50 μ m.

FIGS. 11A-G, I-L: 7rh in combination with chemotherapy improves survival of mice bearing human PDA xenografts. (FIG. 11A) Schematic representation of the animal experiment. NOD-SCID mice (n=15/grp) were orthotopically injected with AsPC-1 cells on day 0. Therapy with vehicle, 7rh (25 mg/kg, 3×/week via oral gavage), chemotherapy (gemcitabine, 12.5 mg/kg, 2×/week

given ip; + nab-paclitaxel, 5 mg/kg, 2×/week given ip), or the combination of 7rh + chemotherapy was started on day 27 post tumor cell injection (TCI). Three animals/grp were sacrificed on day 28. (FIGS. 11B & 11C) 7rh combined with chemotherapy significantly enhanced the overall median of survival compared to single agent therapy. Treatment was withdrawn from animals in the combo group that were alive at day 102 (withdrawn). (FIG. 11D) Example H&E histology. (FIGS. 11E-11K) Immunofluorescence analysis of PDA tumors from each group for pDDR1 (FIG. 11E), pPYK2 (FIG. 11F), p-PEAK1 (FIG. 11G), Vimentin (FIG. 11I), PCNA (FIG. 11J), cleaved caspase-3 (FIG. 11K) and γ H2AX (FIG. 11L) is shown. DAPI was used as a nuclear counterstain (FIGS. 11E-11K). Mean $\pm$ SEM % Area Fraction is graphed. *, $p < 0.05$; **, $p < 0.005$; ***, $p < 0.0005$; **** $p < 0.00005$ v initial group; ^, $p < 0.05$; ^^, $p < 0.005$; ^^, $p < 0.0005$; ^^^, $p < 0.00005$ v vehicle group, one-way ANOVA with Tukey's MCT. Scale bar, 50 μ m.

FIGS. 12A-C: 7rh in combination with chemotherapy reduced collagen deposition and AsPC-1 tumor weight. (FIG. 12A) Trichrome analysis of tumor tissue from mice bearing orthotopic AsPC-1 tumors treated with 7rh, chemotherapy or the combination as described in Figure 5. (FIG. 12B) Pancreas (tumor) weight v day of sacrifice is displayed. (FIG. 12C) Animal weight for each treatment group is displayed.

FIGS. 13A-J: 7rh in combination with chemotherapy reduced DDR1-mediated signaling and tumorigenicity in a GEMM of PDA. (FIG. 13A) Schematic representation of the animal experiment. *KPC* mice were enrolled in therapy cohorts (n=12/grp): vehicle, 7rh (25 mg/kg, 3×/week via oral gavage), chemotherapy (gemcitabine, 12.5 mg/kg, 2×/week given ip; + nab-paclitaxel, 5 mg/kg, 2×/week given ip), or the combination of 7rh + chemotherapy at 4 months old and survival was determined. Nine untreated animals were sacrificed at 4 months of age to determine average initial tumor burden. (FIGS. 13B-13C) 7rh combined with a chemotherapy enhanced the overall median of survival. (FIG. 13D) Example H&E histology from tissue from each treatment group is shown. (FIGS. 13E-13K) Immunofluorescence analysis of PDA tumors from each group for pDDR1 (FIG. 13E), p-PEAK1 (FIG. 13F), Vimentin (FIG. 13G), PCNA (FIG. 13H), cleaved caspase-3 (FIG. 13I) and γ H2AX (FIG. 13J) is shown. DAPI was used as a nuclear counterstain (FIG. 13E-13J). Mean $\pm$ SEM % Area Fraction is graphed. *, $p < 0.05$; **, $p < 0.005$; ***, $p < 0.0005$; **** $p < 0.00005$ v initial group; ^, $p < 0.05$; ^^, $p <$

0.005; ^{^^}, $p < 0.0005$; ^{^^^}, $p < 0.00005$ v vehicle group, one-way ANOVA with Tukey's MCT. Scale bar, 50 μm .

FIGS. 14A-C: 7rh in combination with chemotherapy reduced collagen deposition and *KPC* tumor weight. (FIG. 14A) Trichrome analysis of tumor tissue from *KPC* mice treated with 7rh, chemotherapy or the combination as described in Figure 6. (FIG. 14B) Pancreas (tumor) weight v day of sacrifice is displayed. (FIG. 14C) Animal weight for each treatment group is displayed.

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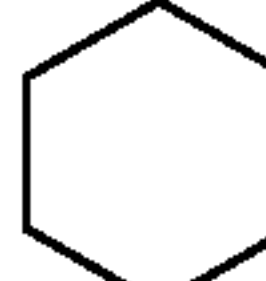
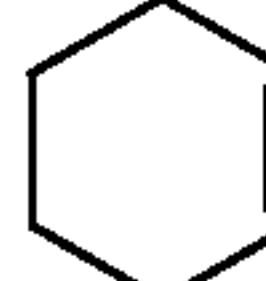
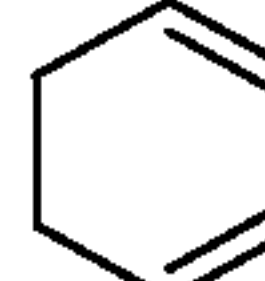
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

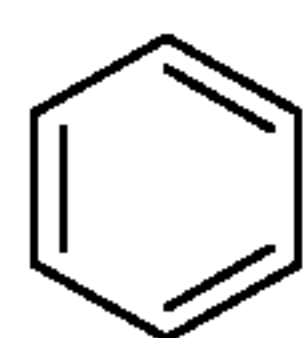
In certain aspects, the present disclosure provides compounds which may be used to inhibit the DDR1 enzyme. Inhibition of the DDR1 enzyme may be used to treat a variety of different inflammatory disease and cancer. As described herein, the compounds may be used in combination with a second chemotherapeutic agent to obtain improved activity or other pharmaceutical parameters. These and other aspects of the disclosure are described in detail below.

1. Definitions

When used in the context of a chemical group: “hydrogen” means $-H$; “hydroxy” means $-OH$; “oxo” means $=O$; “carbonyl” means $-C(=O)-$; “carboxy” means $-C(=O)OH$ (also written as $-COOH$ or $-CO_2H$); “halo” means independently $-F$, $-Cl$, $-Br$ or $-I$; “amino” means $-NH_2$; “hydroxyamino” means $-NHOH$; “nitro” means $-NO_2$; imino means $=NH$; “cyano” means $-CN$; “isocyanate” means $-N=C=O$; “azido” means $-N_3$; in a monovalent context “phosphate” means $-OP(O)(OH)_2$ or a deprotonated form thereof; in a divalent context “phosphate” means $-OP(O)(OH)O-$ or a deprotonated form thereof; “mercapto” means $-SH$; and “thio” means $=S$; “sulfonyl” means $-S(O)_2-$; “hydroxysulfonyl” means $-S(O)_2OH$; “sulfonamide” means $-S(O)_2NH_2$; and “sulfinyl” means $-S(O)-$.

In the context of chemical formulas, the symbol “ $-$ ” means a single bond, “ $=$ ” means a double bond, and “ $\equiv$ ” means triple bond. The symbol “ $----$ ” represents an optional bond, that is either no bond or a single bond. The symbol “ $====$ ” represents a single bond or a

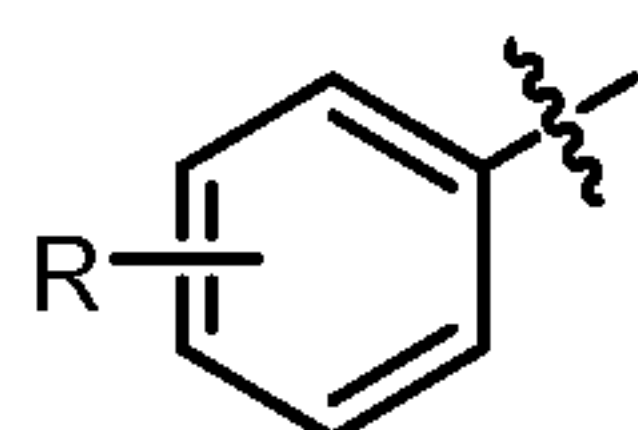
double bond. Thus, for example, the formula  includes , , , and



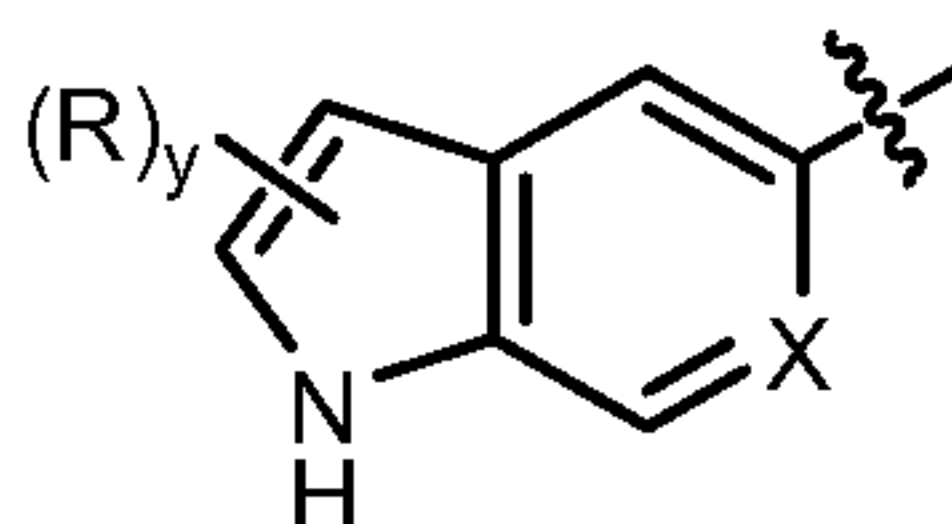
. And it is understood that no one such ring atom forms part of more than one double bond. Furthermore, it is noted that the covalent bond symbol “ $-$ ”, when connecting one or two stereogenic atoms, does not indicate any preferred stereochemistry. Instead, it covers all stereoisomers as well as mixtures thereof. The symbol “”, when drawn perpendicularly across a bond (e.g., -CH₃ for methyl) indicates a point of attachment of the group. It is noted that the point of attachment is typically only identified in this manner for larger groups in order to assist the reader in unambiguously identifying a point of attachment. The symbol “” means a single bond where the group attached to the thick end of the wedge is “out of the page.” The symbol “” means a single bond where the group attached to the thick end of the wedge is “into the page”. The symbol “” means a single bond where the

geometry around a double bond (*e.g.*, either *E* or *Z*) is undefined. Both options, as well as combinations thereof are therefore intended. Any undefined valency on an atom of a structure shown in this application implicitly represents a hydrogen atom bonded to that atom. A bold dot on a carbon atom indicates that the hydrogen attached to that carbon is oriented out of the plane of the paper.

When a group “R” is depicted as a “floating group” on a ring system, for example, in the formula:



then R may replace any hydrogen atom attached to any of the ring atoms, including a depicted, implied, or expressly defined hydrogen, so long as a stable structure is formed. When a group “R” is depicted as a “floating group” on a fused ring system, as for example in the formula:



then R may replace any hydrogen attached to any of the ring atoms of either of the fused rings unless specified otherwise. Replaceable hydrogens include depicted hydrogens (*e.g.*, the hydrogen attached to the nitrogen in the formula above), implied hydrogens (*e.g.*, a hydrogen of the formula above that is not shown but understood to be present), expressly defined hydrogens, and optional hydrogens whose presence depends on the identity of a ring atom (*e.g.*, a hydrogen attached to group X, when X equals $-\text{CH}-$), so long as a stable structure is formed. In the example depicted, R may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula above, the subscript letter “y” immediately following the group “R” enclosed in parentheses, represents a numeric variable. Unless specified otherwise, this variable can be 0, 1, 2, or any integer greater than 2, only limited by the maximum number of replaceable hydrogen atoms of the ring or ring system.

For the chemical groups and compound classes, the number of carbon atoms in the group or class is as indicated as follows: “C_n” defines the exact number (n) of carbon atoms in the group/class. “C_{≤n}” defines the maximum number (n) of carbon atoms that can be in the group/class, with the minimum number as small as possible for the group/class in question, *e.g.*, it is understood that the minimum number of carbon atoms in the group

“alkenyl_(C≤8)” or the class “alkene_(C≤8)” is two. Compare with “alkoxy_(C≤10)”, which designates alkoxy groups having from 1 to 10 carbon atoms. “C_n-n” defines both the minimum (n) and maximum number (n') of carbon atoms in the group. Thus, “alkyl_(C2-10)” designates those alkyl groups having from 2 to 10 carbon atoms. These carbon number
5 indicators may precede or follow the chemical groups or class it modifies and it may or may not be enclosed in parenthesis, without signifying any change in meaning. Thus, the terms “C5 olefin”, “C5-olefin”, “olefin_(C5)”, and “olefin_{C5}” are all synonymous.

The term “saturated” when used to modify a compound or chemical group means the compound or chemical group has no carbon-carbon double and no carbon-carbon triple
10 bonds, except as noted below. When the term is used to modify an atom, it means that the atom is not part of any double or triple bond. In the case of substituted versions of saturated groups, one or more carbon oxygen double bond or a carbon nitrogen double bond may be present. And when such a bond is present, then carbon-carbon double bonds that may occur as part of keto-enol tautomerism or imine/enamine tautomerism are not precluded. When the
15 term “saturated” is used to modify a solution of a substance, it means that no more of that substance can dissolve in that solution.

The term “aliphatic” when used without the “substituted” modifier signifies that the compound or chemical group so modified is an acyclic or cyclic, but non-aromatic hydrocarbon compound or group. In aliphatic compounds/groups, the carbon atoms can be
20 joined together in straight chains, branched chains, or non-aromatic rings (alicyclic). Aliphatic compounds/groups can be saturated, that is joined by single carbon-carbon bonds (alkanes/alkyl), or unsaturated, with one or more carbon-carbon double bonds (alkenes/alkenyl) or with one or more carbon-carbon triple bonds (alkynes/alkynyl).

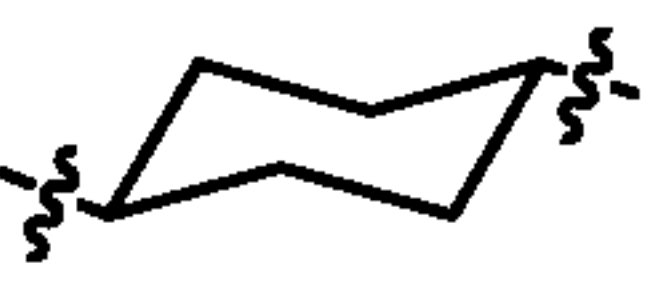
The term “aromatic” when used to modify a compound or a chemical group atom
25 means the compound or chemical group contains a planar unsaturated ring of atoms that is stabilized by an interaction of the bonds forming the ring.

The term “heterocycle” when used to described a compound or a chemical group means that the compound or chemical group is group containing a planar saturated or unsaturated, aromatic or nonaromatic ring of atoms containing one or more N, O, or S atoms.
30 The term “heterocycle” is consistent with either the term “heterocycloalkyl” or the term “heteroaryl” as those terms are described herein.

The term “alkyl” when used without the “substituted” modifier refers to a monovalent saturated aliphatic group with a carbon atom as the point of attachment, a linear or branched

acyclic structure, and no atoms other than carbon and hydrogen. The groups $-\text{CH}_3$ (Me), $-\text{CH}_2\text{CH}_3$ (Et), $-\text{CH}_2\text{CH}_2\text{CH}_3$ (*n*-Pr or propyl), $-\text{CH}(\text{CH}_3)_2$ (*i*-Pr, *i*Pr or isopropyl), $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ (*n*-Bu), $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ (*sec*-butyl), $-\text{CH}_2\text{CH}(\text{CH}_3)_2$ (isobutyl), $-\text{C}(\text{CH}_3)_3$ (*tert*-butyl, *t*-butyl, *t*-Bu or *t*Bu), and $-\text{CH}_2\text{C}(\text{CH}_3)_3$ (*neo*-pentyl) are non-limiting examples of alkyl groups. The term “alkanediyl” when used without the “substituted” modifier refers to a divalent saturated aliphatic group, with one or two saturated carbon atom(s) as the point(s) of attachment, a linear or branched acyclic structure, no carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen. The groups $-\text{CH}_2-$ (methylene), $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$, and $-\text{CH}_2\text{CH}_2\text{CH}_2-$ are non-limiting examples of alkanediyl groups. The term “alkylidene” when used without the “substituted” modifier refers to the divalent group $=\text{CRR}'$ in which R and R' are independently hydrogen or alkyl. Non-limiting examples of alkylidene groups include: $=\text{CH}_2$, $=\text{CH}(\text{CH}_2\text{CH}_3)$, and $=\text{C}(\text{CH}_3)_2$. An “alkane” refers to the class of compounds having the formula $\text{H}-\text{R}$, wherein R is alkyl as this term is defined above. When any of these terms is used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{OC}(\text{O})\text{CH}_3$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{OH}$, or $-\text{S}(\text{O})_2\text{NH}_2$. The following groups are non-limiting examples of substituted alkyl groups: $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, $-\text{CF}_3$, $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{C}(\text{O})\text{OH}$, $-\text{CH}_2\text{C}(\text{O})\text{OCH}_3$, $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{C}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{N}(\text{CH}_3)_2$, and $-\text{CH}_2\text{CH}_2\text{Cl}$. The term “haloalkyl” is a subset of substituted alkyl, in which the hydrogen atom replacement is limited to halo (*i.e.* $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$) such that no other atoms aside from carbon, hydrogen and halogen are present. The group, $-\text{CH}_2\text{Cl}$ is a non-limiting example of a haloalkyl. The term “fluoroalkyl” is a subset of substituted alkyl, in which the hydrogen atom replacement is limited to fluoro such that no other atoms aside from carbon, hydrogen and fluorine are present. The groups $-\text{CH}_2\text{F}$, $-\text{CF}_3$, and $-\text{CH}_2\text{CF}_3$ are non-limiting examples of fluoroalkyl groups.

The term “cycloalkyl” when used without the “substituted” modifier refers to a monovalent saturated aliphatic group with a carbon atom as the point of attachment, said carbon atom forming part of one or more non-aromatic ring structures, no carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen. Non-limiting examples include: $-\text{CH}(\text{CH}_2)_2$ (cyclopropyl), cyclobutyl, cyclopentyl, or cyclohexyl (Cy). The term “cycloalkanediyl” when used without the “substituted” modifier refers to a divalent saturated aliphatic group with two carbon atoms as points of attachment, no carbon-carbon double or

triple bonds, and no atoms other than carbon and hydrogen. The group  is a non-limiting example of cycloalkanediyl group. A “cycloalkane” refers to the class of compounds having the formula H-R, wherein R is cycloalkyl as this term is defined above. When any of these terms is used with the “substituted” modifier one or more hydrogen atom

5 has been independently replaced by -OH, -F, -Cl, -Br, -I, -NH₂, -NO₂, -CO₂H, -CO₂CH₃, -CN, -SH, -OCH₃, -OCH₂CH₃, -C(O)CH₃, -NHCH₃, -NHCH₂CH₃, -N(CH₃)₂, -C(O)NH₂, -C(O)NHCH₃, -C(O)N(CH₃)₂, -OC(O)CH₃, -NHC(O)CH₃, -S(O)₂OH, or -S(O)₂NH₂.

The term “alkenyl” when used without the “substituted” modifier refers to an

10 monovalent unsaturated aliphatic group with a carbon atom as the point of attachment, a linear or branched, acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no atoms other than carbon and hydrogen. Non-limiting examples include: -CH=CH₂ (vinyl), -CH=CHCH₃, -CH=CHCH₂CH₃, -CH₂CH=CH₂ (allyl), -CH₂CH=CHCH₃, and -CH=CHCH=CH₂. The term “alkenediyl” when used without

15 the “substituted” modifier refers to a divalent unsaturated aliphatic group, with two carbon atoms as points of attachment, a linear or branched, a linear or branched acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no atoms other than carbon and hydrogen. The groups -CH=CH-, -CH=C(CH₃)CH₂-, -CH=CHCH₂-, and -CH₂CH=CHCH₂- are non-limiting examples of alkenediyl groups. It

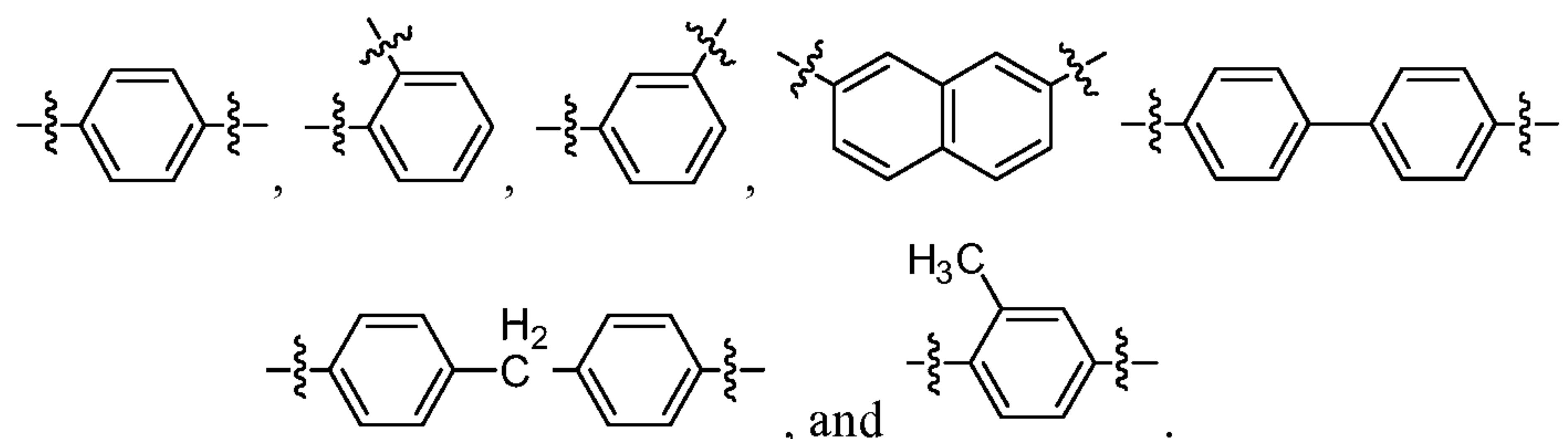
20 is noted that while the alkenediyl group is aliphatic, once connected at both ends, this group is not precluded from forming part of an aromatic structure. The terms “alkene” and “olefin” are synonymous and refer to the class of compounds having the formula H-R, wherein R is alkenyl as this term is defined above. Similarly the terms “terminal alkene” and “α-olefin” are synonymous and refer to an alkene having just one carbon-carbon double bond, wherein

25 that bond is part of a vinyl group at an end of the molecule. When any of these terms are used with the “substituted” modifier one or more hydrogen atom has been independently replaced by -OH, -F, -Cl, -Br, -I, -NH₂, -NO₂, -CO₂H, -CO₂CH₃, -CN, -SH, -OCH₃, -OCH₂CH₃, -C(O)CH₃, -NHCH₃, -NHCH₂CH₃, -N(CH₃)₂, -C(O)NH₂, -C(O)NHCH₃, -C(O)N(CH₃)₂, -OC(O)CH₃, -NHC(O)CH₃, -S(O)₂OH, or -S(O)₂NH₂. The groups

30 -CH=CHF, -CH=CHCl and -CH=CHBr are non-limiting examples of substituted alkenyl groups.

The term “aryl” when used without the “substituted” modifier refers to a monovalent unsaturated aromatic group with an aromatic carbon atom as the point of attachment, said

carbon atom forming part of a one or more six-membered aromatic ring structure, wherein the ring atoms are all carbon, and wherein the group consists of no atoms other than carbon and hydrogen. If more than one ring is present, the rings may be fused or unfused. As used herein, the term does not preclude the presence of one or more alkyl or aralkyl groups (carbon number limitation permitting) attached to the first aromatic ring or any additional aromatic ring present. Non-limiting examples of aryl groups include phenyl (Ph), methylphenyl, (dimethyl)phenyl, $-\text{C}_6\text{H}_4\text{CH}_2\text{CH}_3$ (ethylphenyl), naphthyl, and a monovalent group derived from biphenyl. The term “arenediyl” when used without the “substituted” modifier refers to a divalent aromatic group with two aromatic carbon atoms as points of attachment, said carbon atoms forming part of one or more six-membered aromatic ring structure(s) wherein the ring atoms are all carbon, and wherein the monovalent group consists of no atoms other than carbon and hydrogen. As used herein, the term does not preclude the presence of one or more alkyl, aryl or aralkyl groups (carbon number limitation permitting) attached to the first aromatic ring or any additional aromatic ring present. If more than one ring is present, the rings may be fused or unfused. Unfused rings may be connected via one or more of the following: a covalent bond, alkanediyl, or alkenediyl groups (carbon number limitation permitting). Non-limiting examples of arenediyl groups include:



An “arene” refers to the class of compounds having the formula $\text{H}-\text{R}$, wherein R is aryl as that term is defined above. Benzene and toluene are non-limiting examples of arenes. When any of these terms are used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{OC}(\text{O})\text{CH}_3$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{OH}$, or $-\text{S}(\text{O})_2\text{NH}_2$.

The term “aralkyl” when used without the “substituted” modifier refers to the monovalent group $-\text{alkanediyl-aryl}$, in which the terms alkanediyl and aryl are each used in a manner consistent with the definitions provided above. Non-limiting examples are: phenylmethyl (benzyl, Bn) and 2-phenyl-ethyl. When the term aralkyl is used with the

“substituted” modifier one or more hydrogen atom from the alkanediyl and/or the aryl group has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{OC}(\text{O})\text{CH}_3$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{OH}$, or $-\text{S}(\text{O})_2\text{NH}_2$. Non-limiting examples of substituted aralkyls are: (3-chlorophenyl)-methyl, and 2-chloro-2-phenyl-eth-1-yl.

The term “heteroaryl” when used without the “substituted” modifier refers to a monovalent aromatic group with an aromatic carbon atom or nitrogen atom as the point of attachment, said carbon atom or nitrogen atom forming part of one or more aromatic ring structures wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the heteroaryl group consists of no atoms other than carbon, hydrogen, aromatic nitrogen, aromatic oxygen and aromatic sulfur. If more than one ring is present, the rings may be fused or unfused. As used herein, the term does not preclude the presence of one or more alkyl, aryl, and/or aralkyl groups (carbon number limitation permitting) attached to the aromatic ring or aromatic ring system. Non-limiting examples of heteroaryl groups include furanyl, imidazolyl, indolyl, indazolyl (Im), isoxazolyl, methylpyridinyl, oxazolyl, phenylpyridinyl, pyridinyl (pyridyl), pyrrolyl, pyrimidinyl, pyrazinyl, quinolyl, quinazolyl, quinoxalinyl, triazinyl, tetrazolyl, thiazolyl, thienyl, and triazolyl. The term “N-heteroaryl” refers to a heteroaryl group with a nitrogen atom as the point of attachment. A “heteroarene” refers to the class of compounds having the formula $\text{H}-\text{R}$, wherein R is heteroaryl. Pyridine and quinoline are non-limiting examples of heteroarenes. When these terms are used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{OC}(\text{O})\text{CH}_3$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{OH}$, or $-\text{S}(\text{O})_2\text{NH}_2$.

The term “heterocycloalkyl” when used without the “substituted” modifier refers to a monovalent non-aromatic group with a carbon atom or nitrogen atom as the point of attachment, said carbon atom or nitrogen atom forming part of one or more non-aromatic ring structures wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the heterocycloalkyl group consists of no atoms other than carbon, hydrogen, nitrogen, oxygen and sulfur. If more than one ring is present, the rings may be fused or unfused. As used herein, the term does not preclude the presence of one or more alkyl groups (carbon number limitation permitting) attached to the ring or ring system. Also, the term does not preclude the presence of one or more double bonds in the ring or ring system, provided that

the resulting group remains non-aromatic. Non-limiting examples of heterocycloalkyl groups include aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydrofuranyl, tetrahydrothiofuranyl, tetrahydropyranyl, pyranly, oxiranyl, and oxetanyl. The term “*N*-heterocycloalkyl” refers to a heterocycloalkyl group with a nitrogen atom as the point of attachment. *N*-pyrrolidinyl is an example of such a group. When these terms are used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{OC}(\text{O})\text{CH}_3$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{OH}$, or $-\text{S}(\text{O})_2\text{NH}_2$.

The term “acyl” when used without the “substituted” modifier refers to the group $-\text{C}(\text{O})\text{R}$, in which R is a hydrogen, alkyl, cycloalkyl, alkenyl, aryl, aralkyl or heteroaryl, as those terms are defined above. The groups, $-\text{CHO}$, $-\text{C}(\text{O})\text{CH}_3$ (acetyl, Ac), $-\text{C}(\text{O})\text{CH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{CH}(\text{CH}_2)_2$, $-\text{C}(\text{O})\text{C}_6\text{H}_5$, $-\text{C}(\text{O})\text{C}_6\text{H}_4\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_2\text{C}_6\text{H}_5$, $-\text{C}(\text{O})$ (imidazolyl) are non-limiting examples of acyl groups. A “thioacyl” is defined in an analogous manner, except that the oxygen atom of the group $-\text{C}(\text{O})\text{R}$ has been replaced with a sulfur atom, $-\text{C}(\text{S})\text{R}$. The term “aldehyde” corresponds to an alkane, as defined above, wherein at least one of the hydrogen atoms has been replaced with a $-\text{CHO}$ group. When any of these terms are used with the “substituted” modifier one or more hydrogen atom (including a hydrogen atom directly attached to the carbon atom of the carbonyl or thiocarbonyl group, if any) has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{OC}(\text{O})\text{CH}_3$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{OH}$, or $-\text{S}(\text{O})_2\text{NH}_2$. The groups, $-\text{C}(\text{O})\text{CH}_2\text{CF}_3$, $-\text{CO}_2\text{H}$ (carboxyl), $-\text{CO}_2\text{CH}_3$ (methylcarboxyl), $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{NH}_2$ (carbamoyl), and $-\text{CON}(\text{CH}_3)_2$, are non-limiting examples of substituted acyl groups.

The term “alkoxy” when used without the “substituted” modifier refers to the group $-\text{OR}$, in which R is an alkyl, as that term is defined above. Non-limiting examples include: $-\text{OCH}_3$ (methoxy), $-\text{OCH}_2\text{CH}_3$ (ethoxy), $-\text{OCH}_2\text{CH}_2\text{CH}_3$, $-\text{OCH}(\text{CH}_3)_2$ (isopropoxy), $-\text{OC}(\text{CH}_3)_3$ (*tert*-butoxy), $-\text{OCH}(\text{CH}_2)_2$, $-\text{O}$ -cyclopentyl, and $-\text{O}$ -cyclohexyl. The terms “cycloalkoxy”, “alkenyloxy”, “aryloxy”, “aralkoxy”, “heteroaryloxy”, “heterocycloalkoxy”, and “acyloxy”, when used without the “substituted” modifier, refers to groups, defined as $-\text{OR}$, in which R is cycloalkyl, alkenyl, aryl, aralkyl, heteroaryl, heterocycloalkyl, and acyl, respectively. The term “alkylthio” and “acylthio” when used without the “substituted”

modifier refers to the group $-SR$, in which R is an alkyl and acyl, respectively. The term “alcohol” corresponds to an alkane, as defined above, wherein at least one of the hydrogen atoms has been replaced with a hydroxy group. The term “ether” corresponds to an alkane, as defined above, wherein at least one of the hydrogen atoms has been replaced with an alkoxy group. When any of these terms is used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, $-CN$, $-SH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2OH$, or $-S(O)_2NH_2$.

The term “alkylamino” when used without the “substituted” modifier refers to the group $-NHR$, in which R is an alkyl, as that term is defined above. Non-limiting examples include: $-NHCH_3$ and $-NHCH_2CH_3$. The term “dialkylamino” when used without the “substituted” modifier refers to the group $-NRR'$, in which R and R' can be the same or different alkyl groups, or R and R' can be taken together to represent an alkanediyl. Non-limiting examples of dialkylamino groups include: $-N(CH_3)_2$ and $-N(CH_3)(CH_2CH_3)$. The terms “cycloalkylamino”, “alkenylamino”, “arylamino”, “aralkylamino”, “heteroarylamino”, “heterocycloalkylamino”, and “alkoxyamino” when used without the “substituted” modifier, refers to groups, defined as $-NHR$, in which R is cycloalkyl, alkenyl, aryl, aralkyl, heteroaryl, heterocycloalkyl, and alkoxy, respectively. A non-limiting example of an arylamino group is $-NHC_6H_5$. The term “amido” (acylamino), when used without the “substituted” modifier, refers to the group $-NHR$, in which R is acyl, as that term is defined above. A non-limiting example of an amido group is $-NHC(O)CH_3$. The term “alkylimino” when used without the “substituted” modifier refers to the divalent group $=NR$, in which R is an alkyl, as that term is defined above. When any of these terms is used with the “substituted” modifier one or more hydrogen atom attached to a carbon atom has been independently replaced by $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, $-CN$, $-SH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2OH$, or $-S(O)_2NH_2$. The groups $-NHC(O)OCH_3$ and $-NHC(O)NHCH_3$ are non-limiting examples of substituted amido groups.

The use of the word “a” or “an,” when used in conjunction with the term “comprising” in the claims and/or the specification may mean “one,” but it is also consistent with the meaning of “one or more,” “at least one,” and “one or more than one.”

Throughout this application, the term “about” is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

The terms “comprise,” “have” and “include” are open-ended linking verbs. Any
5 forms or tenses of one or more of these verbs, such as “comprises,” “comprising,” “has,” “having,” “includes” and “including,” are also open-ended. For example, any method that “comprises,” “has” or “includes” one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

The term “effective,” as that term is used in the specification and/or claims, means
10 adequate to accomplish a desired, expected, or intended result. “Effective amount,” “Therapeutically effective amount” or “pharmaceutically effective amount” when used in the context of treating a patient or subject with a compound means that amount of the compound which, when administered to a subject or patient for treating a disease, is sufficient to effect such treatment for the disease.

As used herein, “essentially free,” in terms of a specified component, means that the
15 specified component is only present as a contaminant or in trace amounts. Thus, the total amount of the specified component resulting from any unintended contamination of a composition may be below 5%, below 1%, or below 0.1%. In some embodiments, none of the specified component can be detected in the composition using standard analytical
20 methods.

As used herein, the term “IC₅₀” refers to an inhibitory dose which is 50% of the
maximum response obtained. This quantitative measure indicates how much of a particular drug or other substance (inhibitor) is needed to inhibit a given biological, biochemical or chemical process (or component of a process, i.e. an enzyme, cell, cell receptor or
25 microorganism) by half.

An “isomer” of a first compound is a separate compound in which each molecule contains the same constituent atoms as the first compound, but where the configuration of those atoms in three dimensions differs.

As used herein, the term “patient” or “subject” refers to a living mammalian
30 organism, such as a human, monkey, cow, sheep, goat, dog, cat, mouse, rat, guinea pig, or transgenic species thereof. In certain embodiments, the patient or subject is a primate. Non-limiting examples of human subjects are adults, juveniles, infants and fetuses.

As generally used herein “pharmaceutically acceptable” refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical

judgment, suitable for use in contact with the tissues, organs, and/or bodily fluids of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio.

“Pharmaceutically acceptable salts” means salts of compounds of the present disclosure which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, 2-naphthalenesulfonic acid, 3-phenylpropionic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, acetic acid, aliphatic mono- and dicarboxylic acids, aliphatic sulfuric acids, aromatic sulfuric acids, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, carbonic acid, cinnamic acid, citric acid, cyclopentanepropionic acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, heptanoic acid, hexanoic acid, hydroxynaphthoic acid, lactic acid, laurylsulfuric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, muconic acid, *o*-(4-hydroxybenzoyl)benzoic acid, oxalic acid, *p*-chlorobenzenesulfonic acid, phenyl-substituted alkanoic acids, propionic acid, *p*-toluenesulfonic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, tartaric acid, tertiarybutylacetic acid, trimethylacetic acid, and the like. Additional examples of pharmaceutically acceptable salts are from inorganic acids that include hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, phosphoric acid, nitric acid, and from organic acids that include acetic acid, propionic acid, succinic acid, glycolic acid, stearic acid, lactic acid, malic acid, tartaric acid, lemon acid, ascorbic acid, bashing acid, maleic acid, hydroxy-maleic acid, phenylacetic acid, glutamic acid, benzoic acid, salicylic acid, sulfanilic acid, 2-acetoxy-benzoic acid, *p*-toluenesulfonic acid, methanesulfonic acid, ethane disulfonic, oxalic acid, hydroxyethyl sulfonic acid, trifluoroacetic acid *etc.* Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like. It should be recognized that the particular anion or cation forming a part of any salt of this disclosure is not critical, so long as the salt, as a whole, is pharmacologically acceptable. In some embodiments, the examples in the disclosure are the protonated salts of amines. Additional examples of pharmaceutically

acceptable salts and their methods of preparation and use are presented in *Handbook of Pharmaceutical Salts: Properties, and Use* (P. H. Stahl & C. G. Wermuth eds., Verlag Helvetica Chimica Acta, 2002) and Berg *et al.* "Pharmaceutical Salts," *J. Pharm. Sci.* 1977, 66: 1-19.

5 The term "pharmaceutically acceptable carrier," as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a chemical agent.

10 "Prevention" or "preventing" includes: (1) inhibiting the onset of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease, and/or (2) slowing the onset of the pathology or symptomatology of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease.

15 A "stereoisomer" or "optical isomer" is an isomer of a given compound in which the same atoms are bonded to the same other atoms, but where the configuration of those atoms in three dimensions differs. "Enantiomers" are stereoisomers of a given compound that are mirror images of each other, like left and right hands. "Diastereomers" are stereoisomers of a given compound that are not enantiomers. Chiral molecules contain a chiral center, also
20 referred to as a stereocenter or stereogenic center, which is any point, though not necessarily an atom, in a molecule bearing groups such that an interchanging of any two groups leads to a stereoisomer. In organic compounds, the chiral center is typically a carbon, phosphorus or sulfur atom, though it is also possible for other atoms to be stereocenters in organic and inorganic compounds. A molecule can have multiple stereocenters, giving it many
25 stereoisomers. In compounds whose stereoisomerism is due to tetrahedral stereogenic centers (e.g., tetrahedral carbon), the total number of hypothetically possible stereoisomers will not exceed 2^n , where n is the number of tetrahedral stereocenters. Molecules with symmetry frequently have fewer than the maximum possible number of stereoisomers. A 50:50 mixture of enantiomers is referred to as a racemic mixture. Alternatively, a mixture of enantiomers
30 can be enantiomerically enriched so that one enantiomer is present in an amount greater than 50%. Typically, enantiomers and/or diastereomers can be resolved or separated using techniques known in the art. It is contemplated that that for any stereocenter or axis of chirality for which stereochemistry has not been defined, that stereocenter or axis of chirality

can be present in its *R* form, *S* form, or as a mixture of the *R* and *S* forms, including racemic and non-racemic mixtures. As used herein, the phrase “substantially free from other stereoisomers” means that the composition contains $\leq 15\%$, more preferably $\leq 10\%$, even more preferably $\leq 5\%$, or most preferably $\leq 1\%$ of another stereoisomer(s).

5 “Treatment” or “treating” includes (1) inhibiting a disease in a subject or patient experiencing or displaying the pathology or symptomatology of the disease (*e.g.*, arresting further development of the pathology and/or symptomatology), (2) ameliorating a disease in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease (*e.g.*, reversing the pathology and/or symptomatology), and/or (3) effecting any
10 measurable decrease in a disease in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease.

The above definitions supersede any conflicting definition in any reference that is incorporated by reference herein. The fact that certain terms are defined, however, should not be considered as indicative that any term that is undefined is indefinite. Rather, all terms
15 used are believed to describe the disclosure in terms such that one of ordinary skill can appreciate the scope and practice the present disclosure.

2. Compounds of the Disclosure

The compounds provided by the present disclosure are shown, for example, above in
20 the Summary section and in the claims below. They may be made using the methods outlined in the Examples section and Section A below. These methods can be further modified and optimized using the principles and techniques of organic chemistry as applied by a person skilled in the art. Such principles and techniques are taught, for example, in *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (2007), which
25 is incorporated by reference herein.

Compounds of the disclosure may contain one or more asymmetrically-substituted carbon or nitrogen atoms, and may be isolated in optically active or racemic form. Thus, all chiral, diastereomeric, racemic form, epimeric form, and all geometric isomeric forms of a chemical formula are intended, unless the specific stereochemistry or isomeric form is
30 specifically indicated. Compounds may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. In some embodiments, a single diastereomer is obtained. The chiral centers of the compounds of the present disclosure can have the *S* or the *R* configuration.

Chemical formulas used to represent compounds of the disclosure will typically only show one of possibly several different tautomers. For example, many types of ketone groups are known to exist in equilibrium with corresponding enol groups. Similarly, many types of imine groups exist in equilibrium with enamine groups. Regardless of which tautomer is depicted for a given compound, and regardless of which one is most prevalent, all tautomers of a given chemical formula are intended.

Compounds of the disclosure may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (e.g., higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art, whether for use in the indications stated herein or otherwise.

In addition, atoms making up the compounds of the present disclosure are intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{13}C and ^{14}C .

Compounds of the present disclosure may also exist in prodrug form. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.), the compounds employed in some methods of the disclosure may, if desired, be delivered in prodrug form. Thus, the disclosure contemplates prodrugs of compounds of the present disclosure as well as methods of delivering prodrugs. Prodrugs of the compounds employed in the disclosure may be prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Accordingly, prodrugs include, for example, compounds described herein in which a hydroxy, amino, or carboxy group is bonded to any group that, when the prodrug is administered to a subject, cleaves to form a hydroxy, amino, or carboxylic acid, respectively.

It should be recognized that the particular anion or cation forming a part of any salt form of a compound provided herein is not critical, so long as the salt, as a whole, is pharmacologically acceptable. Additional examples of pharmaceutically acceptable salts and their methods of preparation and use are presented in *Handbook of Pharmaceutical Salts: Properties, and Use* (2002), which is incorporated herein by reference. In some aspects, the

compounds in the present disclosure may be present in their free base form or as protonated amine salts.

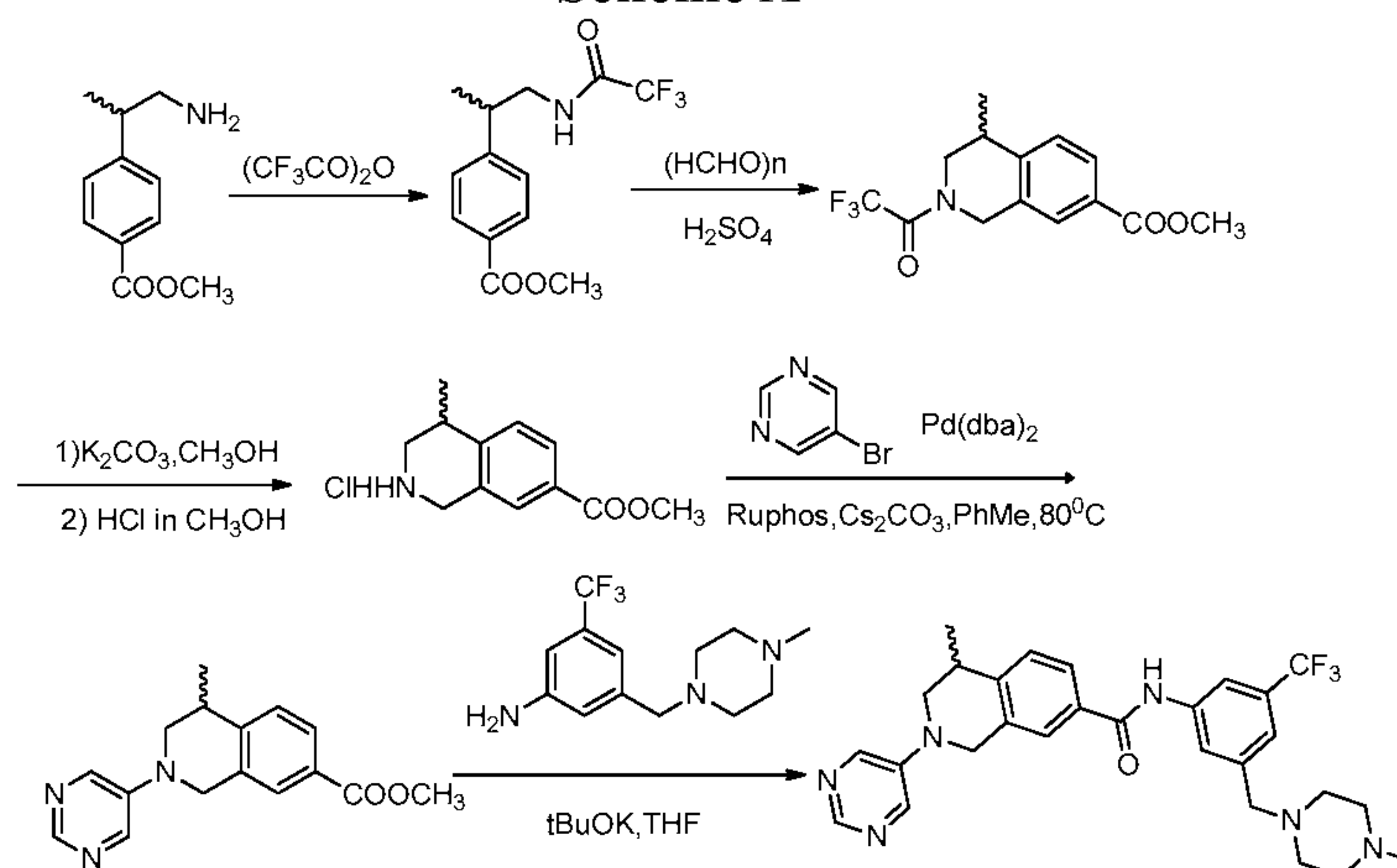
It will be appreciated that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as “solvates.” Where the solvent is water, the complex is known as a “hydrate.” It will also be appreciated that many organic compounds can exist in more than one solid form, including crystalline and amorphous forms. All solid forms of the compounds provided herein, including any solvates thereof are within the scope of the present disclosure.

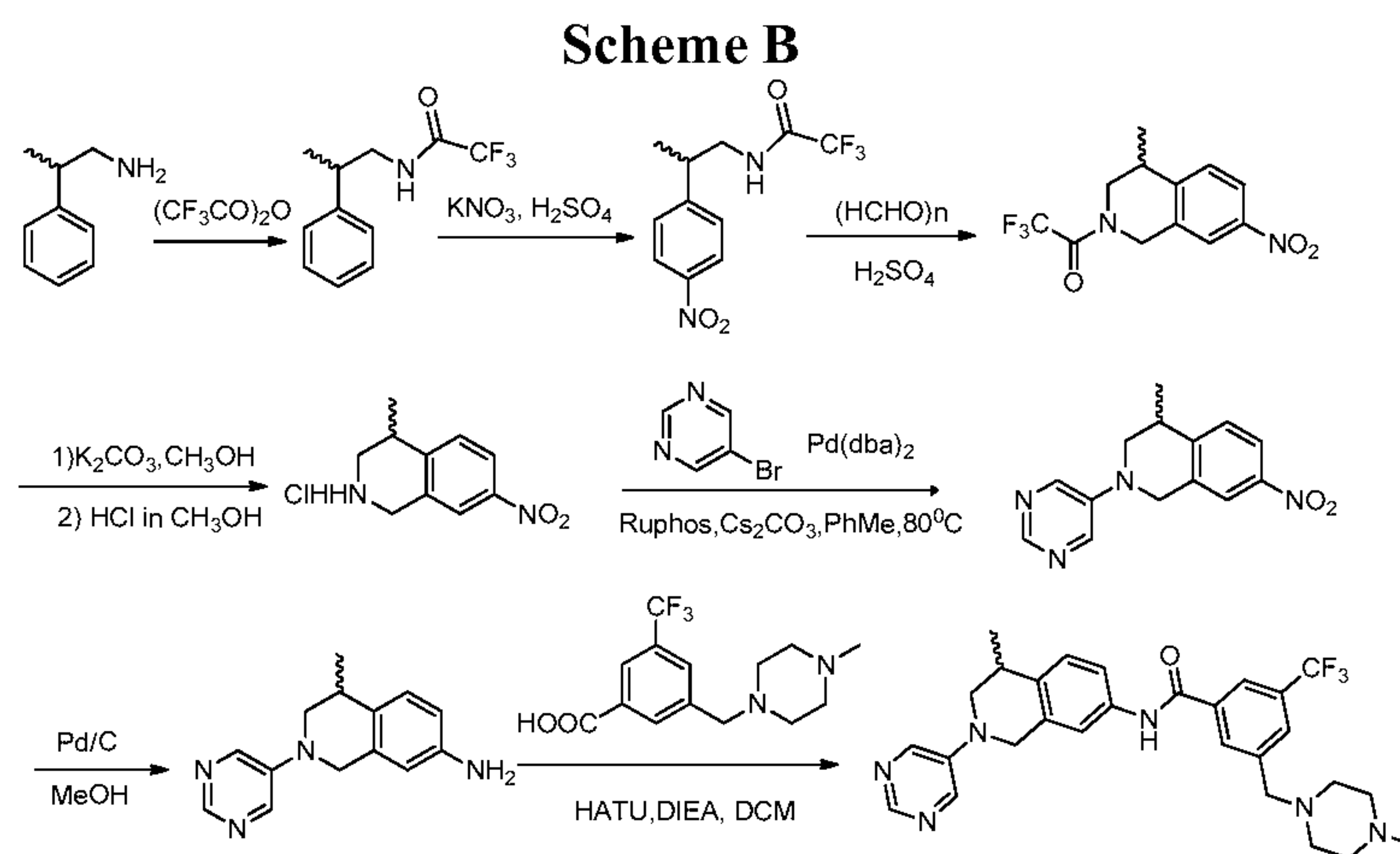
A. Synthesis

The compounds of the present disclosure can be prepared by using the following method besides the method which is widely validated in the experimental procedures or has been published in articles. Therefore the synthetic scheme below only outlines the examples and does not limit the compounds or any specific substituent.

As shown in the schemes A and B, compounds in formula I may be synthesized through five steps by using methyl 4-(1-aminopropan-2-yl)benzoate as the starting material, or through six steps by using 2-phenylpropan-1-amine as the starting material.

Scheme A





B. Metabolites-Prodrugs

- 5 The metabolites of the compounds and their pharmaceutical salts in the present disclosure, and prodrugs that are converted to the compounds and their pharmaceutical salts in the present disclosure are comprised in the claims of the present application.

C. Therapeutic Methods

- 10 In one embodiment, the present disclosure provides methods of using compounds in formula (I) and their pharmaceutical acceptable salts for preventing and treating, *e.g.*, inflammation, liver fibrosis, kidney fibrosis, lung fibrosis, skin scar, atherosclerosis and cancer. Various aspects of the therapies are provided below.

15 3. Pharmaceutical Formulations and Routes of Administration

Where clinical applications are contemplated, it will be necessary to prepare pharmaceutical compositions in a form appropriate for the intended application. Generally, this will entail preparing compositions that are essentially free of pyrogens, as well as other impurities that could be harmful to humans or animals.

- 20 One will generally desire to employ appropriate salts and buffers to render drugs stable and allow for uptake by target cells. Buffers may be employed when drugs are introduced into a patient. Aqueous compositions of the present disclosure comprise an effective amount of the drug to cells, dissolved or dispersed in a pharmaceutically acceptable carrier or aqueous medium. Such compositions also are referred to as inocula. The phrase
- 25 “pharmaceutically or pharmacologically acceptable” refers to molecular entities and compositions that do not produce adverse, allergic, or other untoward reactions when administered to an animal or a human. As used herein, “pharmaceutically acceptable carrier”

includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the drugs of the present disclosure, its use
5 in therapeutic compositions is contemplated. Supplementary active ingredients also can be incorporated into the compositions.

The active compositions of the present disclosure may include classic pharmaceutical preparations. Administration of these compositions according to the present disclosure will be via any common route so long as the target tissue is available via that route. Such routes
10 include oral, nasal, buccal, rectal, vaginal or topical route. Alternatively, administration may be by orthotopic, intradermal, subcutaneous, intramuscular, intratumoral, intraperitoneal, or intravenous injection. Such compositions would normally be administered as pharmaceutically acceptable compositions, described *supra*.

The active compounds may also be administered parenterally or intraperitoneally.
15 Solutions of the active compounds as free base or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

20 The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as
25 bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of
30 surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can

be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

5 Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a
10 powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active
15 substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

For oral administration, the compounds of the present disclosure may be incorporated
20 with excipients and used in the form of non-ingestible mouthwashes and dentifrices. A mouthwash may be prepared incorporating the active ingredient in the required amount in an appropriate solvent, such as a sodium borate solution (Dobell's Solution). Alternatively, the active ingredient may be incorporated into an antiseptic wash containing sodium borate, glycerin and potassium bicarbonate. The active ingredient may also be dispersed in
25 dentifrices, including: gels, pastes, powders and slurries. The active ingredient may be added in a therapeutically effective amount to a paste dentifrice that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants.

The compositions of the present disclosure may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts include the acid addition salts (formed with the free
30 amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms such as injectable solutions, drug release capsules and the like. For parenteral administration in an aqueous solution, for example, the
5 solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, sterile aqueous media which can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage could be dissolved in 1 ml
10 of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences," 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.
15 Moreover, for human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by FDA Office of Biologics standards.

4. Inflammatory Disease States and Conditions

Inflammation underlies many, if not all, disease states. There a variety of
20 inflammatory signaling pathways, but inflammation is always characterized by a protective response that involves immune cells, blood vessels, and molecular mediators. The purpose of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair. The classical signs of acute inflammation are pain, heat, redness, swelling, and loss of
25 function. Inflammation is a generic response, and therefore it is considered as a mechanism of innate immunity, as compared to adaptive immunity, which is specific for each pathogen.

Inflammation can be classified as either acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. A
30 series of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged inflammation, known as chronic inflammation, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process.

Inflammation is not a synonym for infection. Infection describes the interaction between the action of microbial invasion and the reaction of the body's inflammatory defensive response — the two components are considered together when discussing an infection, and the word is used to imply a microbial invasive cause for the observed inflammatory reaction. Inflammation on the other hand describes purely the body's immunovascular response, whatever the cause may be. But because of how often the two are correlated, words ending in the suffix *-itis* (which refers to inflammation) are sometimes informally described as referring to infection. Some examples of inflammatory disease states are discussed below.

A. Sepsis

Sepsis is a serious medical condition characterized by a whole-body inflammatory state caused by infection. Traditionally the term sepsis has been used interchangeably with septicaemia and septicemia (“blood poisoning”). However, these terms are no longer considered synonymous; septicemia is considered a subset of sepsis.

Symptoms of sepsis are often related to the underlying infectious process. When the infection crosses into sepsis, the resulting symptoms are that of systemic inflammatory response syndrome (SIRS): general inflammation, fever, elevated white blood cell count (leukocytosis), and raised heart rate (tachycardia) and breathing rate (tachypnea). Secondary to the above, symptoms also include flu like chills.

The immunological response that causes sepsis is a systemic inflammatory response causing widespread activation of inflammation and coagulation pathways. This may progress to dysfunction of the circulatory system and, even under optimal treatment, may result in the multiple organ dysfunction syndrome and eventually death.

The more critical subsets of sepsis are severe sepsis (sepsis with acute organ dysfunction) and septic shock (sepsis with refractory arterial hypotension). Alternatively, when two or more of the systemic inflammatory response syndrome criteria are met without evidence of infection, patients may be diagnosed simply with “SIRS.” Patients with SIRS and acute organ dysfunction may be termed “severe SIRS.”

Patients are defined as having “severe sepsis” if they have sepsis plus signs of systemic hypoperfusion; either end organ dysfunction or a serum lactate greater than 4 mmol/dL. Patient are defined as having septic shock if they have sepsis plus hypotension after an appropriate fluid bolus (typically 20 ml/kg of crystalloid). The criteria for diagnosing an adult with sepsis do not apply to infants under one month of age. In infants, only the

presence of infection plus a “constellation” of signs and symptoms consistent with the systemic response to infection are required for diagnosis.

The therapy of sepsis rests on antibiotics, surgical drainage of infected fluid collections, fluid replacement and appropriate support for organ dysfunction. This may
5 include hemodialysis in kidney failure, mechanical ventilation in pulmonary dysfunction, transfusion of blood products, and drug and fluid therapy for circulatory failure. Ensuring adequate nutrition, if necessary by parenteral nutrition, is important during prolonged illness.

A problem in the adequate management of septic patients has been the delay in administering therapy after sepsis has been recognized. Published studies have demonstrated
10 that for every hour delay in the administration of appropriate antibiotic therapy there is an associated 7% rise in mortality. A large international collaboration was established to educate people about sepsis and to improve patient outcomes with sepsis, entitled the “Surviving Sepsis Campaign.” The Campaign has published an evidence-based review of management strategies for severe sepsis, with the aim to publish a complete set of guidelines in subsequent
15 years.

Most therapies aimed at the inflammatory process itself have failed to improve outcome, but drotrecogin alfa (activated protein C, one of the coagulation factors) has been shown to decrease mortality from about 31% to about 25% in severe sepsis. To qualify for drotrecogin alfa, a patient must have severe sepsis or septic shock with an APACHE II score
20 of 25 or greater and a low risk of bleeding. Low dose hydrocortisone treatment has shown promise for septic shock patients with relative adrenal insufficiency as defined by ACTH stimulation testing.

Standard treatment of infants with suspected sepsis consists of supportive care, maintaining fluid status with intravenous fluids, and the combination of a β -lactam antibiotic
25 (such as ampicillin) with an aminoglycoside such as gentamicin.

B. Trauma

Physical trauma is a serious and body-altering physical injury, such as the removal of a limb. Blunt force trauma, a type of physical trauma caused by impact or other force applied
30 from or with a blunt object, whereas penetrating trauma is a type of physical trauma in which the skin or tissues are pierced by an object. Trauma can also be described as both unplanned, such as an accident, or planned, in the case of surgery. Both can be characterized by mild to severe tissue damage, blood loss and/or shock, and both may lead to subsequent infection,

including sepsis. The present disclosure provides to treatment of trauma, including both pre-treatment (in the case of a medical procedure) and treatment after trauma injury as occurred.

Surgery. Surgery uses operative manual and instrumental techniques on a patient to investigate and/or treat a pathological condition such as disease or injury, to help improve
5 bodily function or appearance, or sometimes for some other reason. The present disclosure can address trauma resulting from surgeries, as defined further below.

As a general rule, a procedure is considered surgical when it involves cutting of a patient's tissues or closure of a previously sustained wound. Other procedures that do not necessarily fall under this rubric, such as angioplasty or endoscopy, may be considered
10 surgery if they involve common surgical procedure or settings, such as use of a sterile environment, anesthesia, antiseptic conditions, typical surgical instruments, and suturing or stapling. All forms of surgery are considered invasive procedures; so-called noninvasive surgery usually refers to an excision that does not penetrate the structure being addressed (e.g., laser ablation of the cornea) or to a radiosurgical procedure (e.g., irradiation of a
15 tumor). Surgery can last from minutes to hours.

Surgical procedures are commonly categorized by urgency, type of procedure, body system involved, degree of invasiveness, and special instrumentation. Elective surgery is done to correct a non-life-threatening condition, and is carried out at the patient's request, subject to the surgeon's and the surgical facility's availability. Emergency surgery is surgery
20 which must be done quickly to save life, limb, or functional capacity. Exploratory surgery is performed to aid or confirm a diagnosis. Therapeutic surgery treats a previously diagnosed condition.

Amputation involves cutting off a body part, usually a limb or digit. Replantation involves reattaching a severed body part. Reconstructive surgery involves reconstruction of
25 an injured, mutilated, or deformed part of the body. Cosmetic surgery is done to improve the appearance of an otherwise normal structure. Excision is the cutting out of an organ, tissue, or other body part from the patient. Transplant surgery is the replacement of an organ or body part by insertion of another from different human (or animal) into the patient. Removing an organ or body part from a live human or animal for use in transplant is also a type of surgery.

30 When surgery is performed on one organ system or structure, it may be classed by the organ, organ system or tissue involved. Examples include cardiac surgery (performed on the heart), gastrointestinal surgery (performed within the digestive tract and its accessory organs), and orthopedic surgery (performed on bones and/or muscles).

Minimally invasive surgery involves smaller outer incision(s) to insert miniaturized instruments within a body cavity or structure, as in laparoscopic surgery or angioplasty. By contrast, an open surgical procedure requires a large incision to access the area of interest. Laser surgery involves use of a laser for cutting tissue instead of a scalpel or similar surgical instruments. Microsurgery involves the use of an operating microscope for the surgeon to see small structures. Robotic surgery makes use of a surgical robot, such as Da Vinci or Zeus surgical systems, to control the instrumentation under the direction of the surgeon.

Traumatic Hemorrhage. Traumatic hemorrhage accounts for much of the wide ranging international impact of injury, causing a large proportion of deaths and creating great morbidity in the injured. Despite differences in pre-hospital care, the acute management of traumatic hemorrhage is similar around the world and follows well accepted published guidelines. A critically injured patient's care occurs as four, often overlapping segments: the resuscitative, operative, and critical care phases. The diagnosis and control of bleeding should be a high priority during all of the phases of trauma care and is especially important in the patient who is in hemorrhagic shock. Early attempts at hemorrhage control include direct control of visible sources of severe bleeding with direct pressure, pressure dressings, or tourniquets; stabilization of long bone and pelvic fractures; and keeping the patient warm. During the resuscitative phase, warmed intravenous fluids, hypotensive resuscitation prior to surgical control of hemorrhage, and appropriate transfusion of blood and blood products are provided. In the operative phase, surgical control of the hemorrhage and any other injury, and additional transfusion is provide. Finally, the critical care phase provides for post-operative support and tissue perfusion.

C. Acute Pancreatitis

Acute pancreatitis is rapidly-onset inflammation of the pancreas. Depending on its severity, it can have severe complications and high mortality despite treatment. While mild cases are often successfully treated with conservative measures or laparoscopy, severe cases require invasive surgery (often more than one intervention) to contain the disease process.

D. Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS), also known as respiratory distress syndrome (RDS) or adult respiratory distress syndrome (in contrast with IRDS) is a serious reaction to various forms of injuries to the lung. This is the most important disorder resulting
5 in increased permeability pulmonary edema.

ARDS is a severe lung disease caused by a variety of direct and indirect insults. It is characterized by inflammation of the lung parenchyma leading to impaired gas exchange with concomitant systemic release of inflammatory mediators causing inflammation, hypoxemia and frequently resulting in multiple organ failure. This condition is life threatening and often
10 lethal, usually requiring mechanical ventilation and admission to an intensive care unit. A less severe form is called acute lung injury (ALI).

ARDS can occur within 24 to 48 hours of an injury or attack of acute illness. In such a case the patient usually presents with shortness of breath, tachypnea, and symptoms related to the underlying cause, *i.e.*, shock. Long term illnesses can also trigger it, such as malaria. The
15 ARDS may then occur sometime after the onset of a particularly acute case of the infection.

An arterial blood gas analysis and chest X-ray allow formal diagnosis by inference using the aforementioned criteria. Although severe hypoxemia is generally included, the appropriate threshold defining abnormal PaO_2 has never been systematically studied. Any cardiogenic cause of pulmonary edema should be excluded. This can be done by placing a
20 pulmonary artery catheter for measuring the pulmonary artery wedge pressure. However, this is not necessary and is now rarely done as abundant evidence has emerged demonstrating that the use of pulmonary artery catheters does not lead to improved patient outcomes in critical illness including ARDS. Plain chest X-rays are sufficient to document bilateral alveolar infiltrates in the majority of cases. While CT scanning leads to more accurate images of the
25 pulmonary parenchyma in ARDS, its has little utility in the clinical management of patients with ARDS, and remains largely a research tool.

Acute respiratory distress syndrome is usually treated with mechanical ventilation in the Intensive Care Unit. Ventilation is usually delivered through oro-tracheal intubation, or tracheostomy whenever prolonged ventilation (≥ 2 weeks) is deemed inevitable. The
30 possibilities of non-invasive ventilation are limited to the very early period of the disease or, better, to prevention in individuals at risk for the development of the disease (atypical pneumonias, pulmonary contusion, major surgery patients). Treatment of the underlying cause is imperative, as it tends to maintain the ARDS picture. Appropriate antibiotic therapy must be administered as soon as microbiological culture results are available. Empirical

therapy may be appropriate if local microbiological surveillance is efficient. More than 60% ARDS patients experience a (nosocomial) pulmonary infection either before or after the onset of lung injury. The origin of infection, when surgically treatable, must be operated on. When sepsis is diagnosed, appropriate local protocols should be enacted.

5

E. Ischemia-Reperfusion Injury

Reperfusion injury refers to damage to tissue caused when blood supply returns to the tissue after a period of ischemia. The absence of oxygen and nutrients from blood creates a condition in which the restoration of circulation results in inflammation and oxidative
10 damage through the induction of oxidative stress rather than restoration of normal function.

The damage of reperfusion injury is due in part to the inflammatory response of damaged tissues. White blood cells carried to the area by the newly returning blood release a host of inflammatory factors such as interleukins as well as free radicals in response to tissue damage. The restored blood flow reintroduces oxygen within cells that damages cellular
15 proteins, DNA, and the plasma membrane. Damage to the cell's membrane may in turn cause the release of more free radicals. Such reactive species may also act indirectly in redox signaling to turn on apoptosis. Leukocytes may also build up in small capillaries, obstructing them and leading to more ischemia.

Reperfusion injury plays a part in the brain's ischemic cascade, which is involved in
20 stroke and brain trauma. Repeated bouts of ischemia and reperfusion injury also are thought to be a factor leading to the formation and failure to heal of chronic wounds such as pressure sores and diabetic foot ulcers. Continuous pressure limits blood supply and causes ischemia, and the inflammation occurs during reperfusion. As this process is repeated, it eventually damages tissue enough to cause a wound.

25 In prolonged ischemia (60 min or more), hypoxanthine is formed as breakdown product of ATP metabolism. The enzyme xanthine dehydrogenase is converted to xanthine oxidase as a result of the higher availability of oxygen. This oxidation results in molecular oxygen being converted into highly reactive superoxide and hydroxyl radicals. Xanthine oxidase also produces uric acid, which may act as both a prooxidant and as a scavenger of
30 reactive species such as peroxynitrite. Excessive nitric oxide produced during reperfusion reacts with superoxide to produce the potent reactive species peroxynitrite. Such radicals and reactive oxygen species attack cell membrane lipids, proteins, and glycosaminoglycans, causing further damage. They may also initiate specific biological processes by redox signaling.

F. Cardiovascular Disease

Cardiovascular disease refers to the class of diseases that involve the heart or blood vessels (arteries and veins). While the term technically refers to any disease that affects the cardiovascular system, it is usually used to refer to those related to atherosclerosis (arterial disease). These conditions have similar causes, mechanisms, and treatments. Treatment of cardiovascular disease depends on the specific form of the disease in each patient, but effective treatment always includes preventive lifestyle changes discussed above. Medications, such as blood pressure reducing medications, aspirin and the statin cholesterol-lowering drugs may be helpful. In some circumstances, surgery or angioplasty may be warranted to reopen, repair, or replace damaged blood vessels

Most Western countries face high and increasing rates of cardiovascular disease. Each year, heart disease kills more Americans than cancer. Diseases of the heart alone caused 30% of all deaths, with other diseases of the cardiovascular system causing substantial further death and disability. Up until the year 2005, it was the number 1 cause of death and disability in the United States and most European countries. A large histological study (PDAY) showed vascular injury accumulates from adolescence, making primary prevention efforts necessary from childhood.

Various forms of cardiovascular disease include aneurysms, angina, arrhythmia, atherosclerosis, cardiomyopathy, cerebrovascular disease, congenital heart disease, congestive heart failure, myocarditis, valve disease, coronary artery disease, dilated cardiomyopathy, diastolic dysfunction, endocarditis, high blood pressure (hypertension), hypertrophic cardiomyopathy, mitral valve prolapse, myocardial infarction, and venous thromboembolism.

G. Autoimmune/Inflammatory Disease

The present disclosure contemplates the treatment of a variety of autoimmune and/or inflammatory disease states such as spondyloarthropathy, ankylosing spondylitis, psoriatic arthritis, reactive arthritis, enteropathic arthritis, ulcerative colitis, Crohn's disease, irritable bowel disease, inflammatory bowel disease, rheumatoid arthritis, juvenile rheumatoid arthritis, familial Mediterranean fever, amyotrophic lateral sclerosis, Sjogren's syndrome, early arthritis, viral arthritis, multiple sclerosis, or psoriasis. The diagnosis and treatment of these diseases are well documented in the literature.

H. Chemotherapy, Radiotherapy and Cytokine Therapy Toxicity

Various forms of cancer therapy, including chemotherapy, radiation, and cytokines, are associated with toxicity, sometimes severe, in the cancer patient. To the extent that the toxicity is caused at least in part by the extracellular actions of histones, the present disclosure seeks to reduce this toxicity using the pharmaceutical compositions of the present disclosure, thereby reducing or alleviating discomfort on the part of the patient, as well as permitting higher doses of the therapy.

I. Burns

In medicine, a burn may be an injury caused by heat, cold, electricity, chemicals, friction or radiation. First-degree burns are usually limited to redness (erythema), a white plaque, and minor pain at the site of injury. These burns usually extend only into the epidermis. Second-degree burns additionally fill with clear fluid, have superficial blistering of the skin, and can involve more or less pain depending on the level of nerve involvement. Second-degree burns involve the superficial (papillary) dermis and may also involve the deep (reticular) dermis layer. Third-degree burns additionally have charring of the skin, and produce hard, leather-like eschars. An eschar is a scab that has separated from the unaffected part of the body. Frequently, there is also purple fluid. These types of burns are often painless, because nerve endings have been destroyed in the burned areas. Serious burns, especially if they cover large areas of the body, can cause death; any hint of burn injury to the lungs (*e.g.*, through smoke inhalation) is a medical emergency.

Burns that injure the tissues underlying the skin, such as the muscles or bones, are sometimes categorized as fourth-degree burns. These burns are broken down into three additional degrees: fourth-degree burns result in the skin being irretrievably lost, fifth-degree burns result in muscle being irretrievably lost, and sixth-degree burns result in bone being charred.

A newer classification of “Superficial Thickness,” “Partial Thickness” (which is divided into superficial and deep categories) and “Full Thickness” relates more precisely to the epidermis, dermis and subcutaneous layers of skin and is used to guide treatment and predict outcome.

Chemical burns are usually caused by chemical compounds, such as sodium hydroxide (lye), silver nitrate, and more serious compounds (such as sulfuric acid). Most chemicals (but not all) that can cause moderate to severe chemical burns are strong acids or bases. Nitric acid, as an oxidizer, is possibly one of the worst burn-causing chemicals.

Hydrofluoric acid can eat down to the bone and its burns are often not immediately evident. Most chemicals that can cause moderate to severe chemical burns are called caustic.

Electrical burns are generally symptoms of electric shock, being struck by lightning, being defibrillated or cardioverted without conductive gel, *etc.* The internal injuries sustained
5 may be disproportionate to the size of the “burns” seen - as these are only the entry and exit wounds of the electrical current.

Burns are assessed in terms of total body surface area (TBSA), which is the percentage affected by partial thickness or full thickness burns (superficial thickness burns are not counted). The rule of nines is used as a quick and useful way to estimate the affected
10 TBSA. The first step in managing a person with a burn is to stop the burning process. With dry powder burns, the powder should be brushed off first. With other burns, the affected area should be rinsed with a large amount of clean water to remove foreign bodies and help stop the burning process. Cold water should never be applied to any person with extensive burns, as it may severely compromise the burn victim's temperature status. At this stage of
15 management, it is also critical to assess the airway status. If the patient was involved in a fire, then it must be assumed that he or she has sustained inhalation injury until proven otherwise, and treatment should be managed accordingly.

Once the burning process has been stopped, and airway status is ensured, the patient should be volume resuscitated according to the Parkland formula. This formula dictates that
20 the amount of Lactated Ringer's solution to deliver in the first twenty four hours after time of injury is:

$$\text{fluid} = 4\text{cc} \times \% \text{ TBSA} \times \text{weight in kg}$$

% TBSA excludes any first degree burn

Half of this fluid should be given in the first eight hours post injury and the rest in the
25 subsequent sixteen hours. The formula is a guide only and infusions must be tailored to urine output and central venous pressure. Inadequate fluid resuscitation causes renal failure and death. Severe edema in full thickness burns may be treated by escharotomy.

J. Cancer

30 Cancer results from the outgrowth of a clonal population of cells from tissue. The development of cancer, referred to as carcinogenesis, can be modeled and characterized in a number of ways. An association between the development of cancer and inflammation has long-been appreciated. The inflammatory response is involved in the host defense against microbial infection, and also drives tissue repair and regeneration. Considerable evidence

points to a connection between inflammation and a risk of developing cancer, *i.e.*, chronic inflammation can lead to dysplasia.

Studies have estimated that nearly 15% of worldwide cancer is associated with microbial infection. Organisms such as human papilloma virus (HPV), hepatitis B and C virus, HIV, and *Helicobacter pylori* all have been linked to cancer. In other cases, environmental conditions causing chronic irritation and subsequent inflammation can also predispose to cancer, including cigarette smoke, asbestos and silica.

In the case of some types of viral infection, virally-encoded genes can contribute to cellular transformation. An example is the HPV oncoproteins E6 and E7. However, other microbes associated with cancer do not operate in this fashion as they are not transforming. For example, certain strains of *H. pylori* contain factors that affect host cell signaling but do not contain oncogenes. Interestingly, it has been observed that *H. pylori* induces MUC1.

Other ways in which chronic inflammatory states can lead to genomic lesions and tumor initiation are chemical. For example, host cells fight microbial infection by the production of free radicals. In addition to their anti-microbial effects, these molecules lead to oxidative damage and nitration of DNA bases which increases the risk of DNA mutations even in host cells.

Yet another path to cellular dysregulation may result from the cell death that occurs in infection or other inflammatory insult. Lost cells must be repopulated by the expansion of other cells, sometimes undifferentiated precursor cells such as tissue stem cells. Not surprisingly, many inflammatory pathways function to mediate survival and proliferation. Thus, in attempting to mediating tissue repair, the inflammatory response may unwittingly provide excessive survival and proliferative signals to cells, thus leading to tumorigenesis.

Because of the link between cancer and inflammation, the ability of the compounds of the present disclosure to reduce inflammatory signalling pathways can be exploited in a pre-cancer or cancer risk situation to prevent or delay the onset of dysplastic growth.

K. Fibrosis

Fibrosis is the formation of excess fibrous connective tissue in an organ or tissue in a reparative or reactive process. This can be a reactive, benign, or pathological state. In response to injury this is called scarring and if fibrosis arises from a single cell line this is called a fibroma. Physiologically this acts to deposit connective tissue, which can obliterate the architecture and function of the underlying organ or tissue. Fibrosis can be used to

describe the pathological state of excess deposition of fibrous tissue, as well as the process of connective tissue deposition in healing.

Fibrosis is similar to the process of scarring, in that both involve stimulated cells laying down connective tissue, including collagen and glycosaminoglycans. Immune cells called macrophages, as well as any damaged tissue between surfaces called interstitium, release TGF beta. This can be because of numerous reasons, including inflammation of the nearby tissue, or a generalised inflammatory state, with increased circulating mediators. TGF beta stimulates the proliferation and activation of fibroblasts, which deposit connective tissue.

Fibrosis can occur in many tissues within the body, typically as a result of inflammation or damage, and examples include lung, including pulmonary fibrosis (idiopathic pulmonary fibrosis and cystic fibrosis), liver (cirrhosis), heart (endomyocardial fibrosis, old myocardial infarction, atrial fibrosis), and others (mediastinal fibrosis, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis, nephrogenic systemic fibrosis, Crohn's disease, keloid, scleroderma/systemic sclerosis, arthrofibrosis, Peyronie's disease, Dupuytren's contracture, adhesive capsulitis).

5. Treatment Methods

Compound of the present disclosure are generally useful as anti-inflammatories and can be used for the treatment of inflammatory conditions. They can be administered to mammalian subjects (*e.g.*, human patients) alone or in conjunction with other drugs that modulate inflammation (see below). The compounds can also be administered to subjects that are genetically and/or due to, for example, physiological and/or environmental factors, susceptible to inflammation, *e.g.*, subjects with a family history of inflammatory disease, or subjects with chronic inflammation or subject to chronic stress.

The dosage required depends on the choice of the route of administration; the nature of the formulation; the nature of the patient's illness; the subject's size, weight, surface area, age, and sex; other drugs being administered; and the judgment of the attending physician. Suitable dosages are in the range of 0.0001–100 mg/kg. Wide variations in the needed dosage are to be expected in view of the variety of compounds available and the differing efficiencies of various routes of administration. For example, oral administration would be expected to require higher dosages than administration by intravenous injection. Variations in these dosage levels can be adjusted using standard empirical routines for optimization as is well understood in the art. Administrations can be single or multiple (*e.g.*, 2-, 3-, 4-, 6-, 8-, 10-, 20-, 50-, 100-, 150-, or more times). Encapsulation of the compounds in a suitable

delivery vehicle (*e.g.*, polymeric microparticles or implantable devices) may increase the efficiency of delivery, particularly for oral delivery.

6. Combination Therapy

5 Compounds of Formula (I) may be used in combination with other drugs that are known to be useful in the treatment or amelioration of the diseases or similar diseases. In the combination administration, such other drugs may be administered, by a route administration and in an amount commonly used, and contemporaneously or sequentially with a compound of Formula. When a compound of Formula (I) is used contemporaneously with one or more
10 other drugs, a pharmaceutical composition containing one or more other known drugs and the compound of Formula (I) is preferred.

 To kill cells, inhibit cell growth, inhibit metastasis, inhibit angiogenesis or otherwise reverse or reduce the malignant phenotype of tumor cells, using the methods and compositions of the present disclosure, one would generally contact a “target” cell with an
15 agent according to the present disclosure and at least one other agent. These compositions would be provided in a combined amount effective to kill or inhibit proliferation of the cell. This process may involve contacting the cells with the agent according to the present disclosure and the other treatment at the same time. This may be achieved by contacting the cell with a single composition or pharmacological formulation that includes both agents, or
20 by contacting the cell with two distinct compositions or formulations, at the same time, wherein one composition includes the agent according to the present disclosure and the other includes the other agent.

 Alternatively, the agent according to the present disclosure may precede or follow the other agent treatment by intervals ranging from minutes to weeks. In embodiments where the
25 other agent and the agent according to the present disclosure are applied separately to the cell, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the agent according to the present disclosure and the other therapy would still be able to exert an advantageously combined effect on the cell. In such instances, it is contemplated that one would contact the cell with both modalities within about 12-24
30 hours of each other and, more preferably, within about 6-12 hours of each other, with a delay time of only about 12 hours being most preferred. In some situations, it may be desirable to extend the time period for treatment significantly, however, where several days (2, 3, 4, 5, 6 or 7) to several weeks (1, 2, 3, 4, 5, 6, 7 or 8) lapse between the respective administrations.

It also is conceivable that more than one administration of either the agent according to the present disclosure or the other therapy will be desired. Various combinations may be employed, where an agent according to the present disclosure therapy is “A” and the other therapy is “B”, as exemplified below:

5

A/B/A B/A/B B/B/A A/A/B B/A/A A/B/B B/B/B/A B/B/A/B
 A/A/B/B A/B/A/B A/B/B/A B/B/A/A B/A/B/A B/A/A/B B/B/B/A
 A/A/A/B B/A/A/A A/B/A/A A/A/B/A A/B/B/B B/A/B/B B/B/A/B

10 Other combinations are contemplated. Again, to achieve cell killing, both agents are delivered to a cell in a combined amount effective to kill the cell.

Drugs or active ingredients used in combination with compounds of Formula (I) comprises but are not limited to: estrogen receptor modulator, androgen receptor modulator, retinoid receptor modulator, cell toxin/cell inhibitor, antiproliferative agents, protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protein kinase inhibitors, reverse transcriptase inhibitors, angiogenesis inhibitors, cell proliferation and survival signaling inhibitors, interference with the cell cycle checkpoint drugs and apoptosis inducing agent, cytotoxic drugs, protein tyrosine inhibitor, EGFR, VEGFR inhibitors, inhibitors of serine / threonine protein inhibitors, inhibitors of Bcr-Abl, c-Kit inhibitor, Met inhibitors, inhibitors of Raf, MEK inhibitor, MMP inhibitors, inhibitors of topoisomerase, histidine deacetylase inhibitors, proteasome inhibitors, inhibitors of CDK, Bcl-2 family protein inhibitor, MDM2 family protein inhibitors, inhibitors of IAP family proteins, inhibitor of STAT family proteins, PI3K, AKT inhibitors, inhibitors of integrin blockade, IFN- α , interleukin-12, COX-2 inhibitor, p53, p53 activator inhibitor, VEGF antibody, EGF antibody, *etc.*

25

In one embodiment, drugs or active ingredients used in combination with compounds of Formula (I) comprises but are not limited to: Aldesleukin, Alendronate, interferon, Alitretinoin, allopurinol, allopurinol sodium, palonosetron hydrochloride, Hemel, amino glutethimide, amifostine, amrubicin, Ann acridine, anastrozole, dolasetron, Aranesp, arglabin, arsenic trioxide, Aromasin, 5 - N cytidine, azathioprine, BCG or BCG, Bestatin hydrochloride, betamethasone acetate, betamethasone sodium phosphate, Bexarotene, bleomycin sulfate, broxuridine, bortezomib, busulfan, calcitonin, Alemtuzumab Campath, capecitabine, carboplatin, Casodex, cefesone, Seamus IL, DNR, chlorambucil, cisplatin, cladribine, cladribine, chloride phosphoric acid, Cytarabine, cyclophosphamide, Dacarbazine, Actinomycin D, DNX, dexamethasone, dexamethasone phosphate, estradiol valerate, cefdinir

30

interleukin 2, Methylprednisolone acetate, deslorelin, dexrazoxane, diethylstilbestrol, Diflucan, docetaxel, doxorubicin, doxifluridine, dronabinol, chin -166- chitosan complexes, eligard, rasburicase, epirubicin hydrochloride, aprepitant, epirubicin, alfa-epoetin, erythropoietin, Eptaplatin, levamisole, estradiol formulation, 17- β -estradiol, estramustine phosphate sodium, ethinylestradiol, Amifostine, hydroxyl phosphate, Etopophos, etoposide, Fadzole, tamoxifen, filgrastim, finasteride, floxuridine, fluconazole, fludarabine, 5- fluorine BrdU a phosphate, 5- fluorouracil, fluoxymesterone, flutamide, formestane, Cytarabine hydrochloride, Fotemustine, fulvestrant, immunoglobulin, gemcitabine, gemtuzumab ozogamicin, imatinib mesylate, carmustine capsules, goserelin, hydrocortisone, erythro-

10 hydroxy nonyl adenine, hydroxyurea, Ibritumomab Tiuxetan. Idarubicin, ifosfamide, interferon α , IFN- α 2, interferon α -2A, interferon α -2B, interferon α -n1, IFN α -n3, interferon β , interferon γ -1a, IL-2, intron A, Iressa, Irinotecan, Kytril, mushroom polysaccharide sulfate, letrozole, leucovorin, leuprolide, leuprorelin acetate, Levamisole, levorotation folinic acid calcium salt, levothyroxine sodium, levothyroxine sodium, lomustine, lonidamine,

15 dronabinol, nitrogen mustard, Mecobalamin, medroxyprogesterone acetate, megestrol acetate, melphalan, esterified estrogens, 6-Mercaptopurine, mesna, methotrexate, aminolevulinic acid methyl ester, miltefosine, minocycline, mitomycin C, mitotane, mitoxantrone anthraquinone, Trilostane, citric acid adriamycin liposome, Nedaplatin, Pegfilgrastim, oprelvekin, neupogen, nilutamide, tamoxifen, NSC-631570, recombinant human interleukin 1- β , octreotide,

20 Ondansetron hydrochloride, hydroprednisone oral solution, oxaliplatin, paclitaxel, prednisone, L-asparaginase enzyme sodium phosphate preparation, Pegasys, pentostatin, Picibanil, pilocarpine hydrochloride, adjoin THP, mithramycin, porfimer sodium, prednimustine, Prednisolone Steaglate, prednisolone, Premarin, C kappa umbilical, recombinant human erythropoietin, raltitrexed, Libby, etidronate rhenium-186, rituximab,

25 Redoxon-A, Romo peptide, pilocarpine hydrochloride tablets, octreotide, Sargramostim, semustine, Schizophyllan, sobuzoxane, Methylprednisolone, Paphos acid, stem cell therapy, streptozocin, strontium chloride -89, levothyroxine sodium, tamoxifen, tamsulosin, TNF-alfa, tastolactone, docetaxel, teceleukin, temozolomide, teniposide, propionic acid testosterone, testosterone propionate, thioguanine, thiotepa, thyroid stimulating hormone, Tiludronic acid,

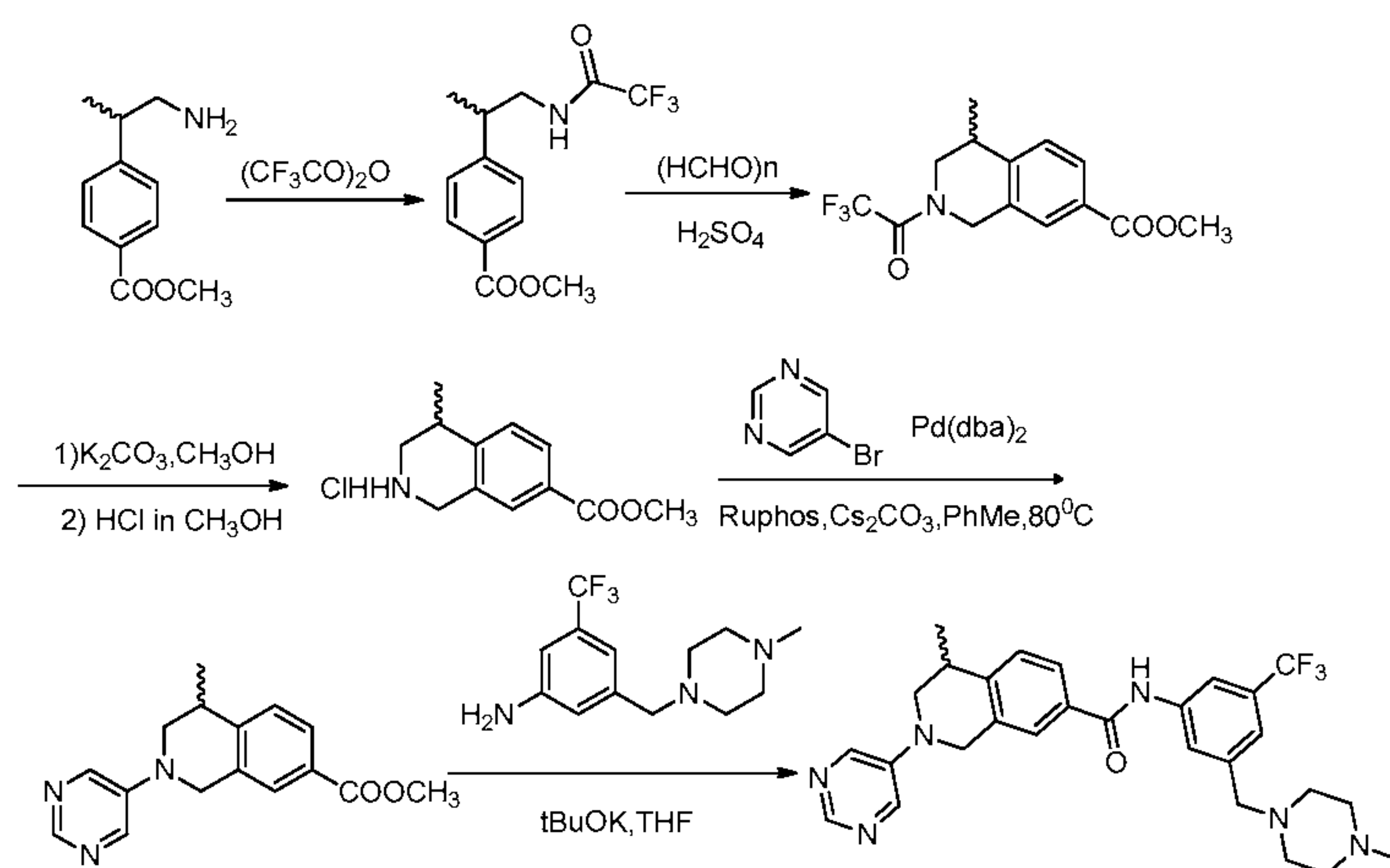
30 topotecan, toremifene, tositumomab, trastuzumab, Treosulfan, Victoria A acid, methotrexate tablets, three methyl melamine, trimetrexate, triptorelin, double hydroxy acetic acid Naphthalene of triptorelin, UFT, uridine, valrubicin, vesnarinone, alkali, vincristine, Vindesine Vinorelbine, virulizin, dextral razoxane, Zinostatin ester, ondansetron, paclitaxel, acolbifene, Interferon r-1 β , affinitak, aminopterin, Arzoxifene, Asoprisnil, atamestane,

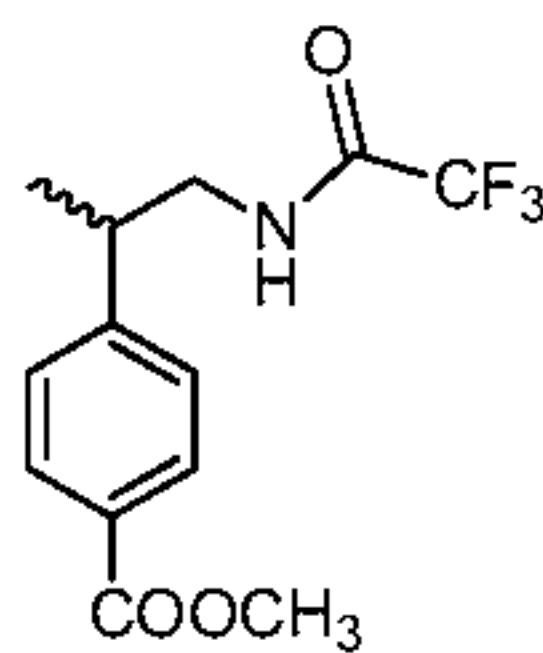
atrasentan, BAY 43-9006, Avastin, CCI-779, CDC-501, Celebrex, cetuximab, crisnatol, cypoterone acetate, decitabine, DN-101, Doxorubicin -MTC, dSLIM, dutasteride, edotecarin, eflornithine, Exatecan, Fenretinide, histamine hydrochloride, holmium -166 DOTMP, ibandronate, IFN - γ , intron -PEG, ixabepilone, intron keyhole shaped hemocyanin, L-651582, Lanreotide, lasofoxifene, Libra, lonafamib, Miproxifene, MS-209, liposome MTP-PE, MX-6, Nafarelin, Nemorubicin, Neovastat, Nolatrexed, Aolimosen, onco-TCS, osidem, paclitaxel poly glutamic acid ester, pamidronate disodium injection, PN-401, QS-21, R -1549, raloxifene, ranpirnase, 13-cis-Victoria A acid, satraplatin, seocalcitol, T-138067, Tarceva, DHA-PTX, thymosin α 1, Pirazofurin, tipifarnib, tirapazamine, TLK-286, toremifene, trans MID-lo7R, valspodar, vapreotide, vatalanib, verteporfin, Vinflunine, Z-100 and Zoledronic acid or their combination.

7. Examples

The following examples are included to demonstrate certain embodiments of the disclosure. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the disclosure, and thus can be considered to constitute exemplary modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

Example 1 - 4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2095)



Step 1. Methyl 4-(1-(2,2,2-trifluoroacetamido)propan-2-yl)benzoate

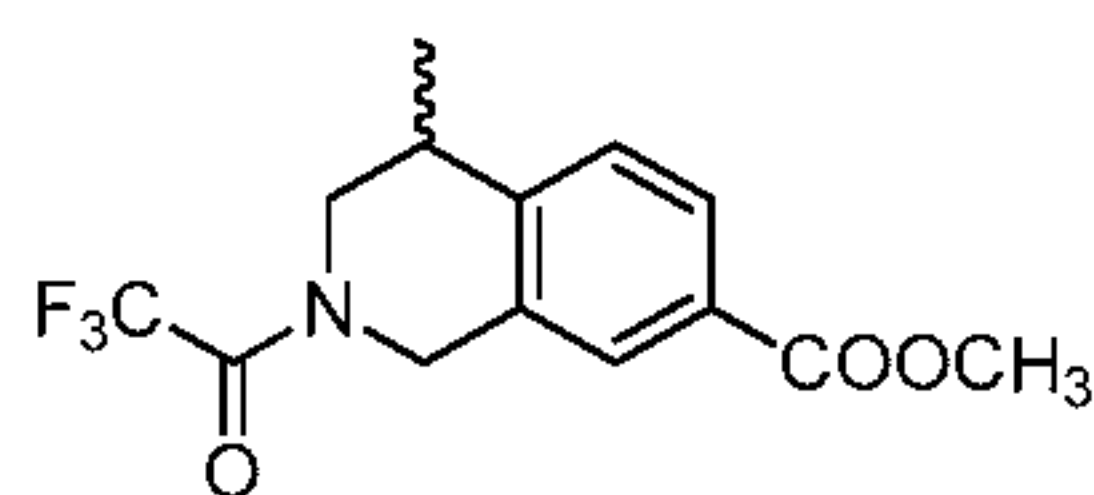
5

Methyl 4-(1-aminopropan-2-yl)benzoate (10.0 g, 51.7 mmol) was added portionwise to the well stirred trifluoroacetic anhydride (50 ml). The reaction mixture was stirred at RT for 3hrs. On completion of the reaction, the reaction mixture was poured into 100 ml of ice water, and stirred for 30 mins. The resulting solid was filtered, washed with water, and dried under vacuum to give the pure compound (9.0 g, 60% yield).

10

^1H NMR (400 MHz, CDCl_3), δ 8.01 (d, $J = 7.6$ Hz, 2 H), 7.27 (d, $J = 7.6$ Hz, 2 H), 6.14 (br s, 1 H), 3.91 (s, 1 H), 3.72-3.65 (m, 1 H), 3.43-3.36 (m, 1 H), 3.12-3.07 (m, 1 H), 1.33 (d, $J = 6$ Hz, 3 H). MS (ESI), m/z : 290 ($\text{M}^+ + \text{H}^+$).

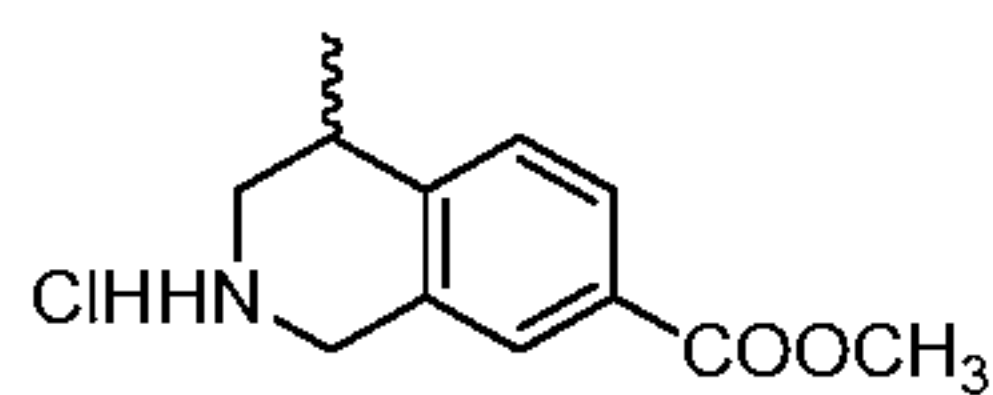
15

Step 2. Methyl 4-methyl-2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylate

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Methyl 4-(1-(2, 2, 2-trifluoroacetamido)propan-2-yl)benzoate (9.0 g, 31.1 mmol) was stirred at RT with $(\text{HCHO})_n$ (4.5 g) and $\text{con. H}_2\text{SO}_4$ for 5hrs. The clear solution was added to cold water and extracted with ethyl acetate. The organic layer was washed with saturated Na_2CO_3 , water, and dried over anhydrous Na_2SO_4 . The filtrate was concentrated under vacuum to give the title compound (8.4 g, 89% yield). MS (ESI), m/z : 302 ($\text{M}^+ + \text{H}^+$).

25

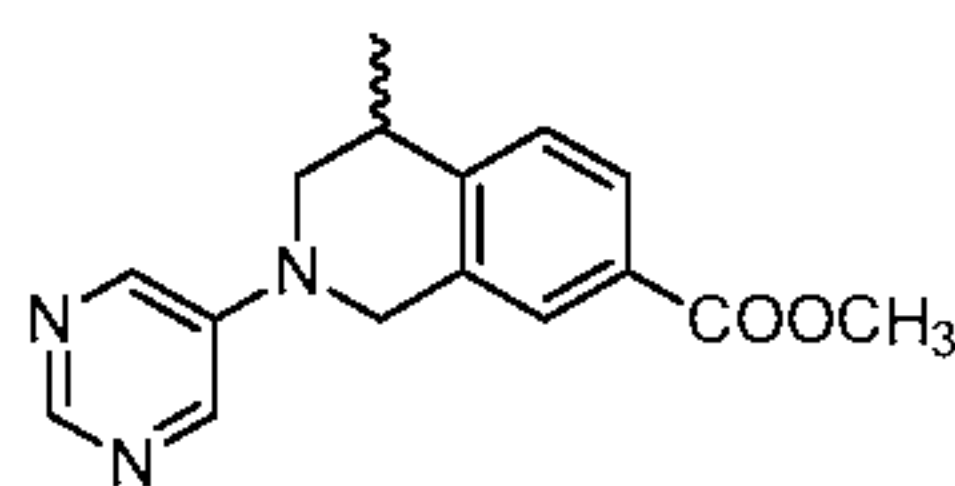
Step 3. Methyl 4-methyl-1, 2, 3, 4-tetrahydroisoquinoline-7-carboxylate hydrochloride

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Methyl 4-methyl-2-(2, 2, 2-trifluoroacetyl)-1, 2, 3, 4-tetrahydroisoquinoline-7-carboxylate (8.4 g, 27.7 mmol) was added to K_2CO_3 (5.7 g, 41.5 mmol) in methanol and water (2:1), and stirred at RT for 3 hrs. Methanol was removed from the reaction mixture and water was added, extracted with ethyl acetate, followed by washing with water. The organic

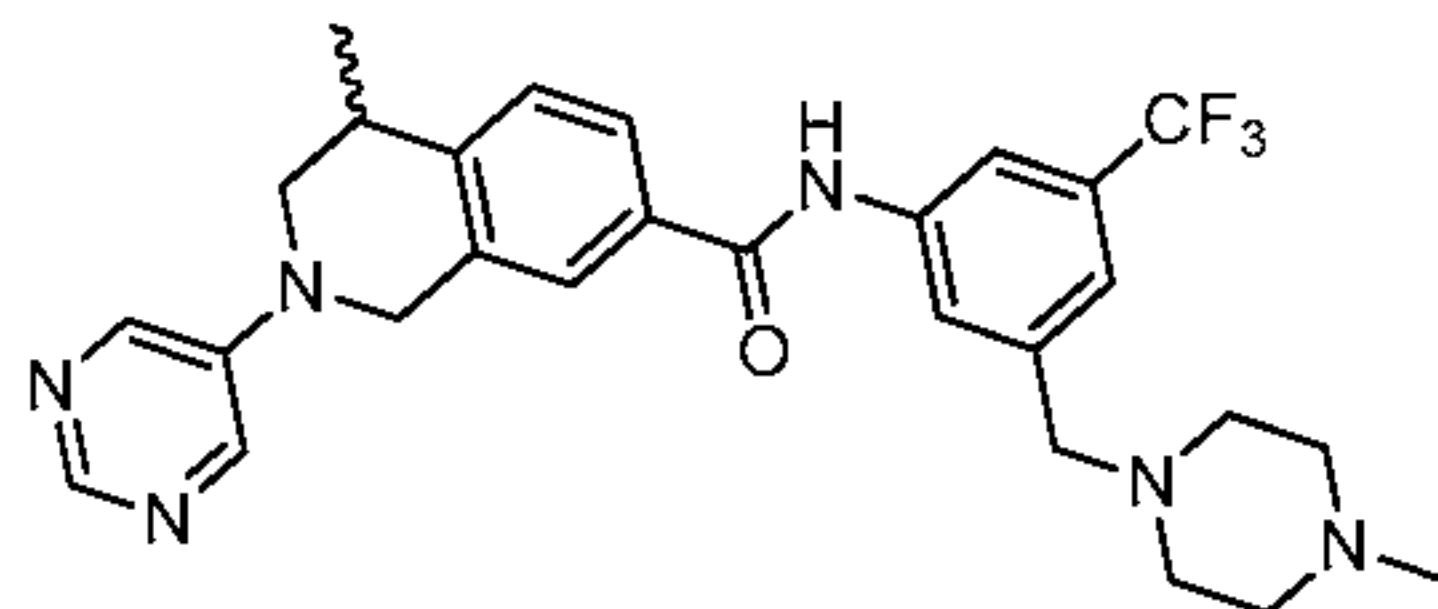
layer was dried over anhydrous Na_2SO_4 , and evaporated under reduced pressure to get the compound as colorless oil. Then the oil was diluted with methanol, and HCl solution in methanol was added dropwise. The mixture was stirred for 1hr, and the white solid was collected, and dried under reduced pressure to give the title compound (6.4 g, 95% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$), δ 9.83 (br s, 1 H), 9.67 (br s, 1 H), 7.87-7.85 (m, 2 H), 7.52 (d, $J = 8.0$ Hz, 1 H), 4.32 (s, 2 H), 3.85 (s, 3 H), 3.51-3.41 (m, 1 H), 3.31-3.26 (m, 1 H), 3.05-2.98 (m, 1 H), 1.34 (d, $J = 6.8$ Hz, 3 H). MS (ESI), m/z : 242 ($\text{M}^+ + \text{H}^+$).

Step 4. Methyl 4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylate



An oven-dried test tube, which was equipped with a magnetic stir bar and fitted with a teflon septum, was charged with the $\text{Pd}(\text{dba})_2$ (10 mmol%), Ruphos (20 mmol%), CsCO_3 (3.3 g, 10.3 mmol), methyl 4-methyl-1,2,3,4-tetrahydroisoquinoline-7-carboxylate hydrochloride (1.0 g, 4.1 mmol), and 5-bromopyrimidine (782 mg, 4.9 mmol). The vessel was evacuated and backfilled with argon and then toluene (20 mL) was added via syringe. The solution was heated to 80°C overnight, and then cooled to room temperature. The reaction mixture was filtered through a pad of Celite and concentrated under vacuum, and then purified by flash column to yield the title compound (1.0 g, 89% yield). ^1H NMR (400 MHz, CDCl_3), δ 8.70 (s, 1 H), 8.48 (s, 2 H), 7.93 (d, $J = 8.0$ Hz, 1 H), 7.89 (s, 1 H), 7.35 (d, $J = 8.0$ Hz, 1 H), 4.59 (d, $J = 15.2$ Hz, 1 H), 4.48 (d, $J = 15.2$ Hz, 1 H), 3.92 (s, 3 H), 3.63-3.60 (m, 1 H), 3.45-3.41 (m, 1 H), 3.23-3.22 (m, 1 H), 1.42 (d, $J = 7.2$ Hz, 3 H). MS (ESI), m/z : 284 ($\text{M}^+ + \text{H}^+$).

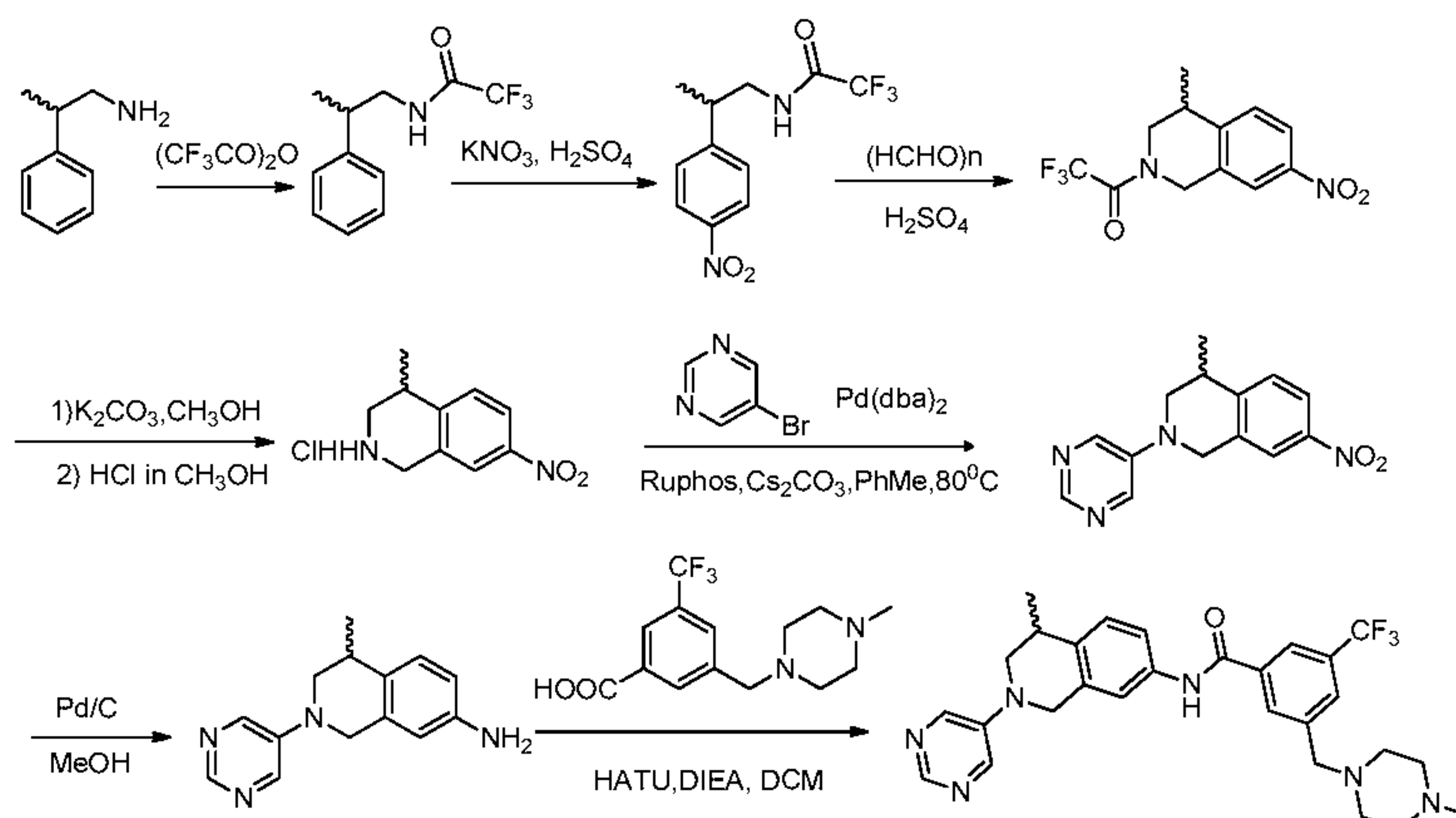
Step 5. 4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide



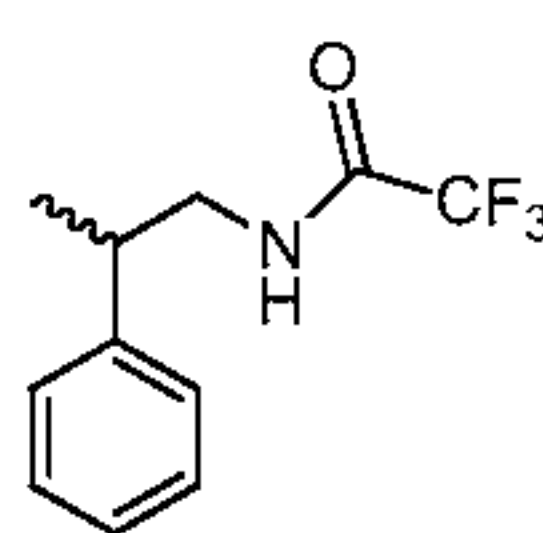
To a solution of methyl 4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylate (1 g, 3.5 mmol) and 3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)aniline (909 mg, 3.3 mmol) in anhydrous THF (20.0 mL) was added potassiumtert-butoxide (1.1 g, 9.9 mmol) portionwise at -20°C . Then the reaction mixture

was slowly warmed to room temperature and stirred for 1.0 h. After the reaction was finished by TLC, the mixture was poured into ice water with stirring and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous Na_2SO_4 . The filtrate was concentrated under vacuum. The resulting residue was purified by silica gel column to give the desired product (1.4 g, 80% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.50 (s, 1 H), 8.64-8.51 (m, 3 H), 8.19 (s, 1 H), 8.00 (s, 1 H), 7.92-7.79 (m, 2 H), 7.47 (d, $J = 7.6$ Hz, 1 H), 7.34 (s, 1 H), 4.65 (d, $J = 16.0$ Hz, 1 H), 4.53 (d, $J = 16.0$ Hz, 1 H), 3.67-3.64 (m, 1 H), 3.53 (s, 2 H), 3.49-3.47 (m, 1 H), 3.24-3.11 (m, 1 H), 2.39 (br s, 4 H), 2.34 (br s, 4 H), 2.15 (s, 3 H), 1.34 (d, $J = 5.2$ Hz, 3 H). MS (ESI), m/z : 525 ($\text{M}^+ + \text{H}^+$).

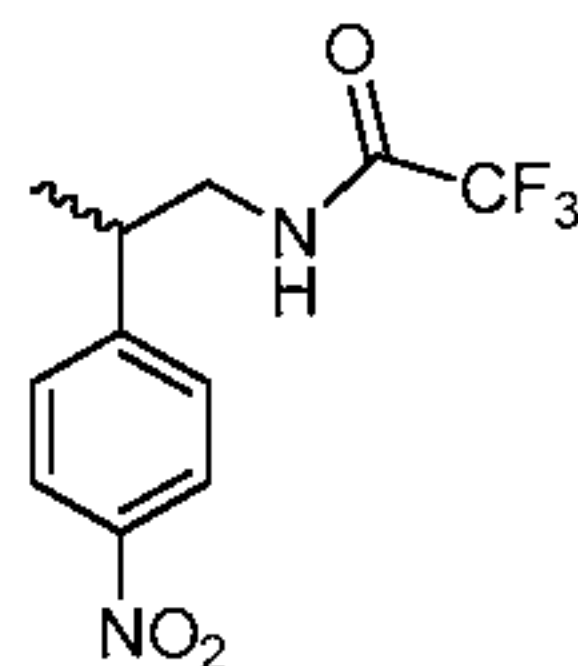
Example 2 - N-(4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)benzamide (D2217)



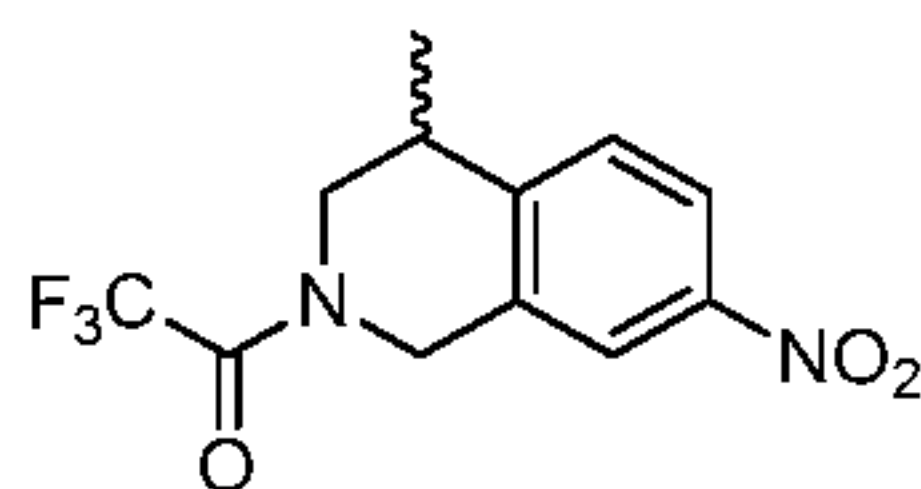
Step 1. 2, 2, 2-trifluoro-N-(2-phenylpropyl)acetamide



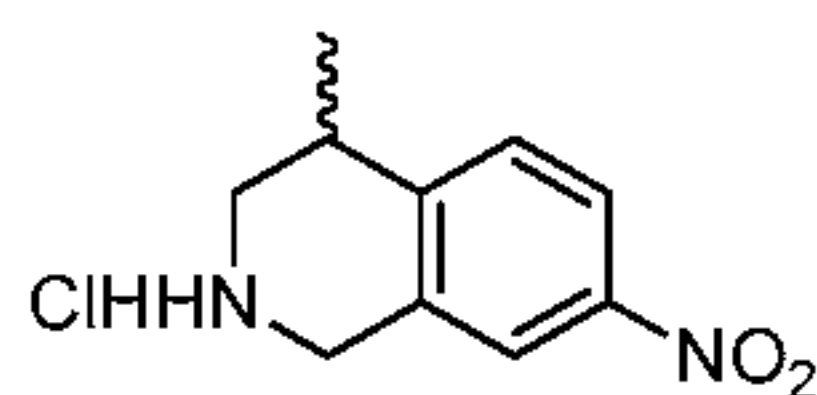
2-phenylpropan-1-amine (10.0 g, 74.0 mmol) was added portionwise to the well stirred trifluoroacetic anhydride (50 ml). The reaction mixture was stirred at RT for 3hrs. On completion of the reaction, the reaction mixture was poured into 100 ml of ice water, and stirred for 30mins. The resulting solid was filtered, washed with water, and dried under vacuum to give the pure compound (12.0 g, 70% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$), δ 9.43 (s, 1H), 7.30 (t, $J = 7.2$ Hz, 2H), 7.23-7.19 (m, 3H), 3.39-3.27 (m, 2 H), 3.04-2.96 (m, 1H), 1.19 (d, $J = 6.8$ Hz, 3H). MS (ESI), m/z : 232 ($\text{M}^+ + \text{H}^+$).

Step 2. 2, 2, 2-trifluoro-N-(2-(4-nitrophenyl)propyl)acetamide

2,2,2-trifluoro-N-(2-phenylpropyl)acetamide (12g, 51.9 mmol) was dissolved in con.H₂SO₄ at 0°C, and then potassium nitrate (5.8 g, 57.0 mmol) was added portionwise. The mixture was stirred at 0°C for 1hr. After the reaction was completed, the mixture was poured into ice water. The resulting solid was filtered, washed with water, and dried under vacuum to give the pure compound (12.6 g, 88% yield). MS (ESI), m/z: 277 (M⁺ + H⁺).

Step 3. 2, 2, 2-trifluoro-1-(4-methyl-7-nitro-3,4-dihydroisoquinolin-2(1H)-yl)ethanone

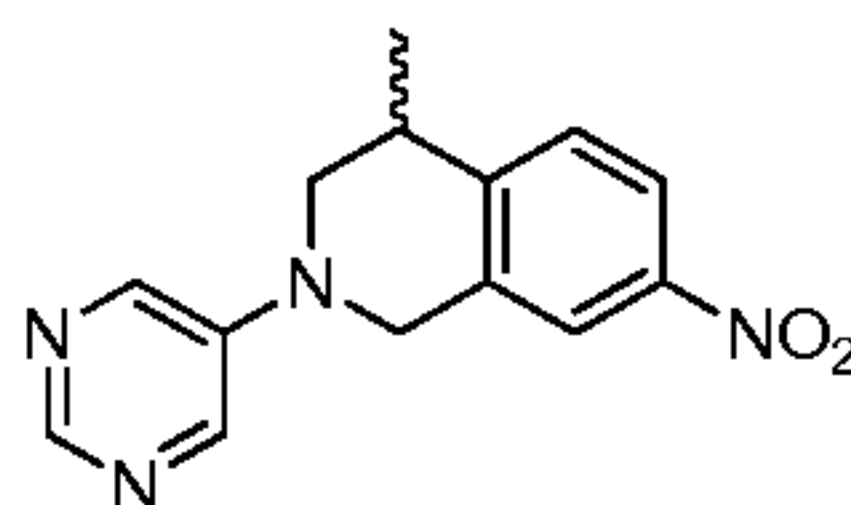
2, 2, 2-trifluoro-N-(2-(4-nitrophenyl)propyl)acetamide (12.6 g, 45.7 mmol) was stirred at RT with (HCHO)_n (6.7 g) and con.H₂SO₄ for 5hrs. The clear solution was added to cold water and extracted with ethyl acetate. The organic layer was washed with saturated Na₂CO₃, water, and dried over anhydrous Na₂SO₄. The filtrate was concentrated under vacuum to give the title compound (6.6 g, 50% yield). ¹H NMR (400 MHz, DMSO-*d*₆), δ 8.28-8.22 (m, 1 H), 8.10-8.06 (m, 1 H), 7.57 (d, J = 8.4 Hz, 1 H) 5.03-4.97 (m, 1 H), 4.88-4.72 (m, 1 H), 3.86-3.76 (m, 1 H), 3.70-3.66 (m, 1 H), 3.23-3.22 (m, 1 H), 1.24-1.20 (m, 3 H). MS (ESI), m/z: 289 (M⁺ + H⁺).

Step 4. 4-methyl-7-nitro-1,2,3,4-tetrahydroisoquinoline hydrochloride

2, 2, 2-trifluoro-1-(4-methyl-7-nitro-3,4-dihydroisoquinolin-2(1H)-yl)ethanone (6.6 g, 22.9 mmol) was added to K₂CO₃ (4.7 g, 34.4 mmol) in methanol and water(2:1), and stirred at RT for 3hrs. Methanol was removed from the reaction mixture and water was added, extracted with ethyl acetate, followed by washing with water. The organic layer was dried over anhydrous Na₂SO₄, and evaporated under reduced pressure to get the compound as colorless oil. Then the oil was diluted with methanol, and HCl solution in methanol was

added dropwise. The mixture was stirred for 1hr, and the white solid was collected, and dried under reduced pressure to give the title compound (3.7 g, 70% yield). ¹H NMR (400 MHz, DMSO-*d*₆), δ 9.91 (br s, 1 H), 9.71 (br s, 1 H), 8.21 (s, 1 H), 8.13 (d, J = 8.4 Hz, 1 H), 7.67 (d, J = 8.4 Hz, 1 H), 4.38 (s, 2 H), 3.51-3.48 (m, 1 H), 3.37-3.32 (m, 1 H), 3.10-3.02 (m, 1 H), 1.36 (d, J = 6.8 Hz, 3 H). MS (ESI), m/z: 229 (M⁺ + H⁺).

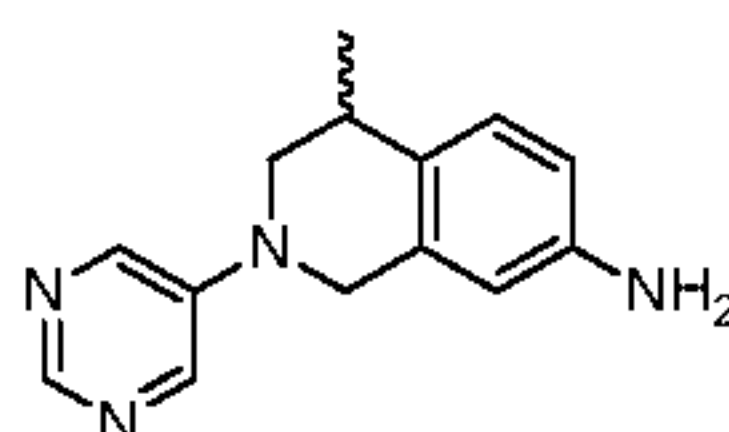
Step 5. 4-methyl-7-nitro-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline



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An oven-dried test tube, which was equipped with a magnetic stir bar and fitted with a teflon septum, was charged with the Pd(dba)₂ (10 mmol%), Ruphos (20 mmol%), CsCO₃ (3.6 g, 11.0 mmol), 4-methyl-7-nitro-1,2,3,4-tetrahydroisoquinoline hydrochloride (1.0 g, 4.4 mmol), and 5-bromopyrimidine (839 mg, 5.3 mmol). The vessel was evacuated and backfilled with argon and then toluene (20 mL) was added via syringe. The solution was heated to 80 °C overnight, and then cooled to room temperature. The reaction mixture was filtered through a pad of Celite and concentrated under vacuum, and then purified by flash column to yield the title compound (678 mg, 57% yield). MS (ESI), m/z: 271 (M⁺ + H⁺).

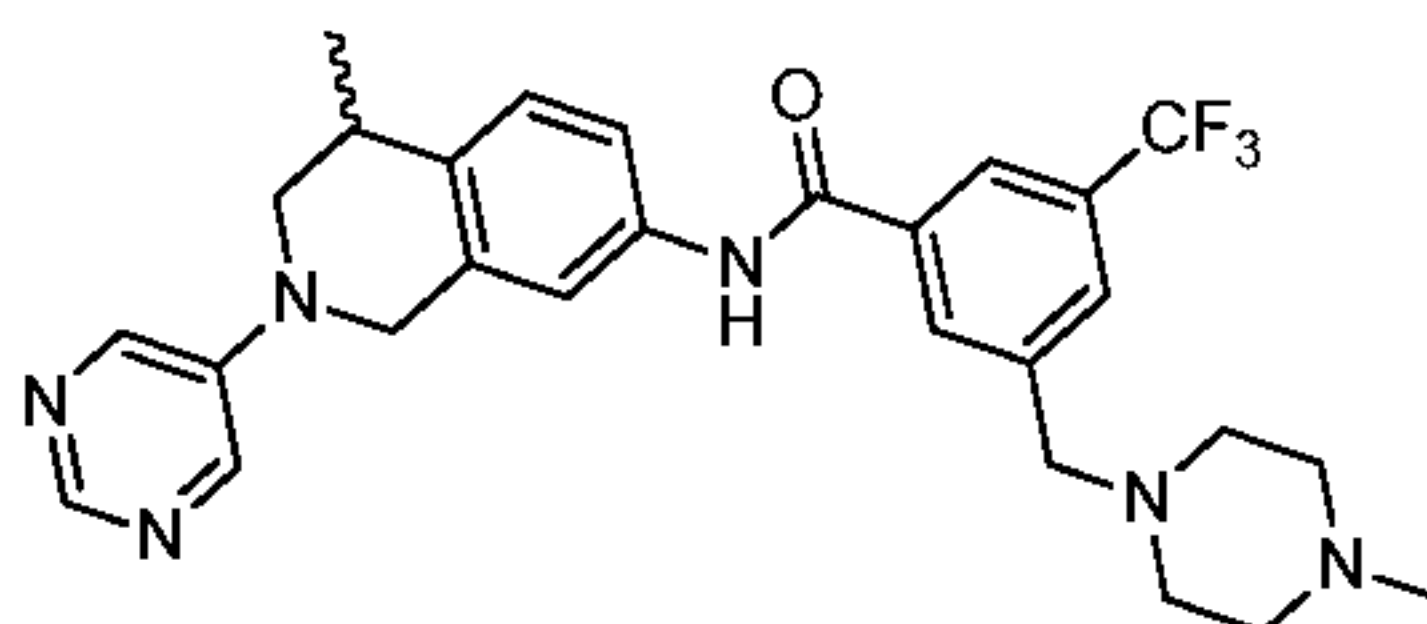
Step 6. 4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-amine



To a solution of 4-methyl-7-nitro-2-(pyrimidin-5-yl)-1, 2, 3, 4-tetrahydroisoquinoline (678 mg, 2.5 mmol) in 15 mL of methanol, Pd/C was added, and the reaction flask was evacuated and backfilled with hydrogen twice. The reaction mixture was stirred at room temperature under a hydrogen balloon for 3 hrs. The reaction mixture was filtered through a pad of Celite and concentrated under vacuum to yield the title compound (589 mg, 98% yield).

¹H NMR (400 MHz, DMSO-*d*₆), δ 8.52-8.50 (m, 3 H), 6.92 (d, J = 8.0 Hz, 1 H), 6.44 (d, J = 8.0 Hz, 1 H), 6.0 (s, 1 H), 4.92 (s, 2 H), 4.36 (d, J = 16.0 Hz, 1 H), 4.28 (d, J = 16.0 Hz, 1 H), 3.58-3.54 (m, 1 H), 3.30-3.25 (m, 1 H), 2.93-2.90 (m, 1 H), 1.20 (d, J = 6.8 Hz, 3 H). MS (ESI), m/z: 241 (M⁺ + H⁺).

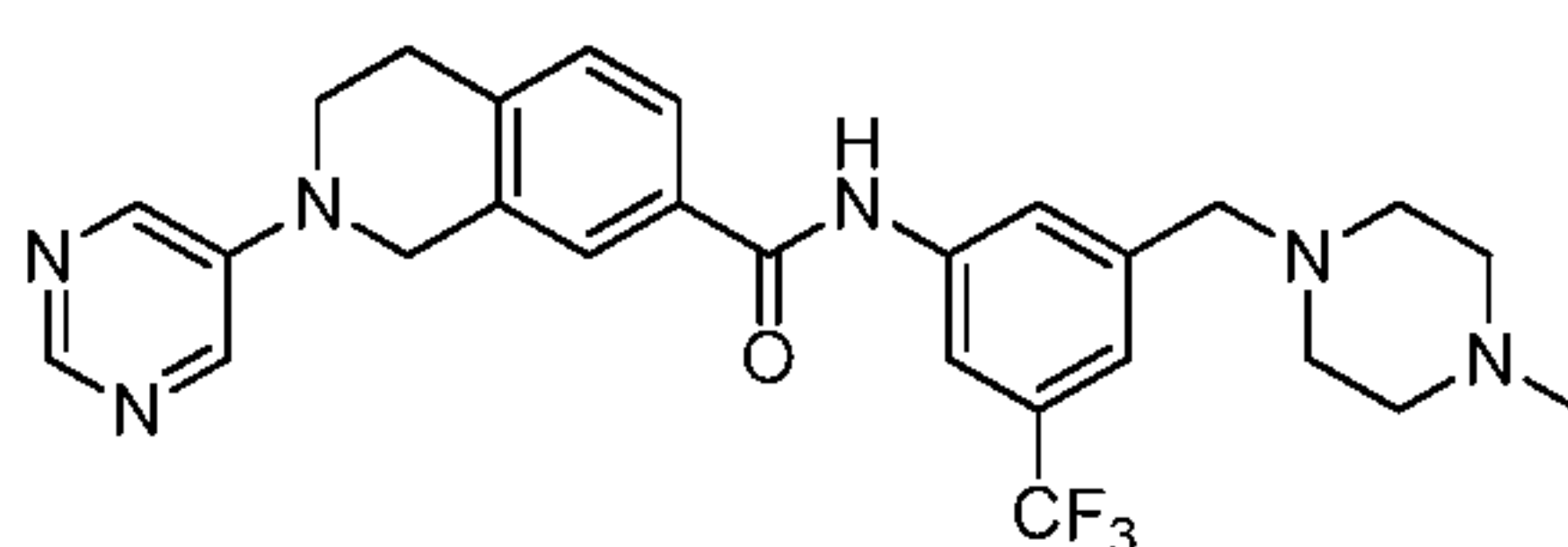
Step 7. N-(4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)benzamide



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To a solution of 3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)benzoic acid (831 mg, 2.8 mmol) in 5 mL of dichloromethane, 4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-amine (589 mg, 2.5 mmol), (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (HATU) (1.4 g, 3.8 mmol), and N,N-diisopropylethylamine (DIPEA) (0.9 mL, 5 mmol) were added. The resulting mixture was stirred at room temperature overnight. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, concentrated under vacuum, and then purified by column chromatography over silica gel to afford pure compound 4 (839 mg, 64% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.44 (s, 1 H), 8.57 (s, 2 H), 8.55 (s, 1 H), 8.19 (s, 1 H), 8.17 (s, 1 H), 7.84 (s, 1 H), 7.69 (s, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.29 (d, J = 8.0 Hz, 1 H), 4.55 (d, J = 16.0 Hz, 1 H), 4.45 (d, J = 16.0 Hz, 1 H), 3.68-3.59 (m, 3 H), 3.42-3.38 (m, 1 H), 3.08-3.07 (m, 1 H), 2.41 (br s, 4 H), 2.33 (br s, 4 H), 2.15 (s, 3 H), 1.30 (d, J = 6.8 Hz, 3 H). MS (ESI), m/z: 525 (M⁺ + H⁺).

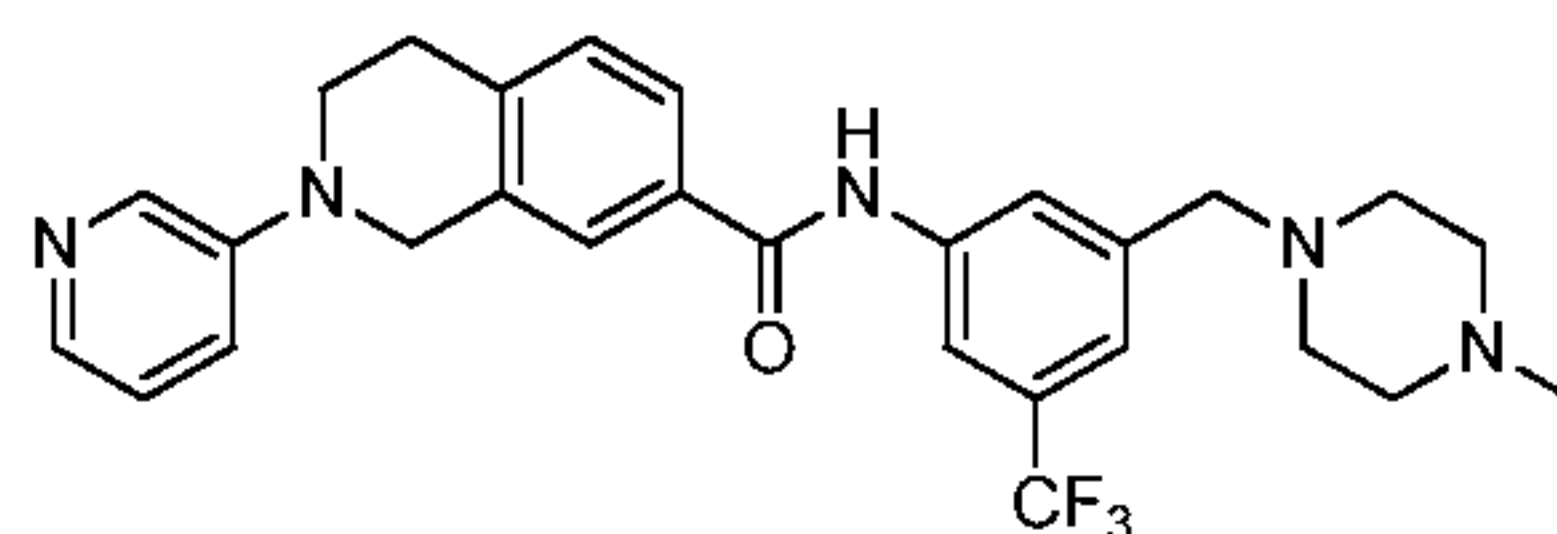
Example 3 - N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2210)



The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.49 (s, 1 H), 8.61-8.55 (s, 3 H), 8.19 (s, 1 H), 8.00 (s, 1 H), 7.88 (s, 1 H), 7.82 (d, J = 7.6 Hz, 1 H), 7.37-7.34 (m, 2 H), 4.59 (s, 2 H), 3.67 (t, J = 5.6 Hz, 2 H), 3.52 (s, 2 H), 3.01 (d, J = 5.2 Hz, 2 H), 2.39 (br s, 4 H), 2.34 (br s, 4 H), 2.14 (s, 3 H). MS (ESI), m/z: 511 (M⁺ + H⁺).

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Example 4 - N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2211)



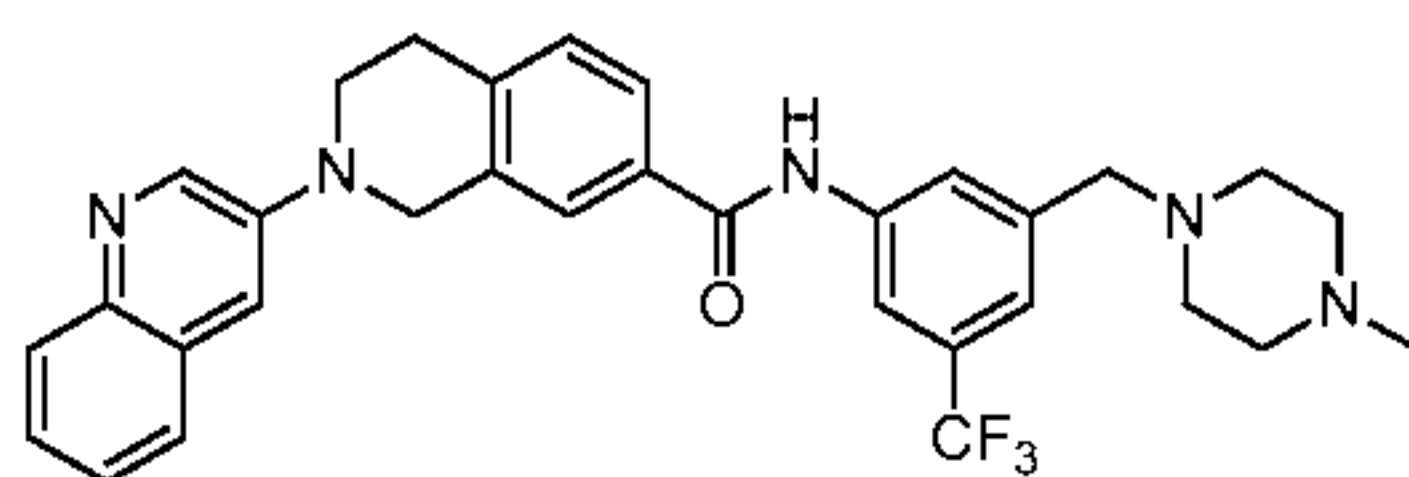
5

The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.48 (s, 1 H), 8.40 (d, *J* = 2.8 Hz, 1 H), 8.19 (s, 1 H), 8.01 (s, 1 H), 7.98 (d, *J* = 4.0 Hz, 1 H), 7.88 (s, 1 H), 7.81 (d, *J* = 8.0 Hz, 1 H), 7.41 (dd, *J* = 8.0, 2.4 Hz, 1 H), 7.36-7.34 (m, 2 H), 7.23 (dd, *J* = 8.4, 4.4 Hz, 1 H), 4.54 (s, 2 H), 3.63 (t, *J* = 5.6 Hz, 2 H), 3.54 (s, 2 H), 3.00 (t, *J* = 5.6 Hz, 2 H), 2.40 (br s, 4 H), 2.34 (br s, 4 H), 2.15 (s, 3 H). MS (ESI), *m/z*: 510(*M*⁺ + *H*⁺).

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Example 5 - N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(quinolin-3-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2568)

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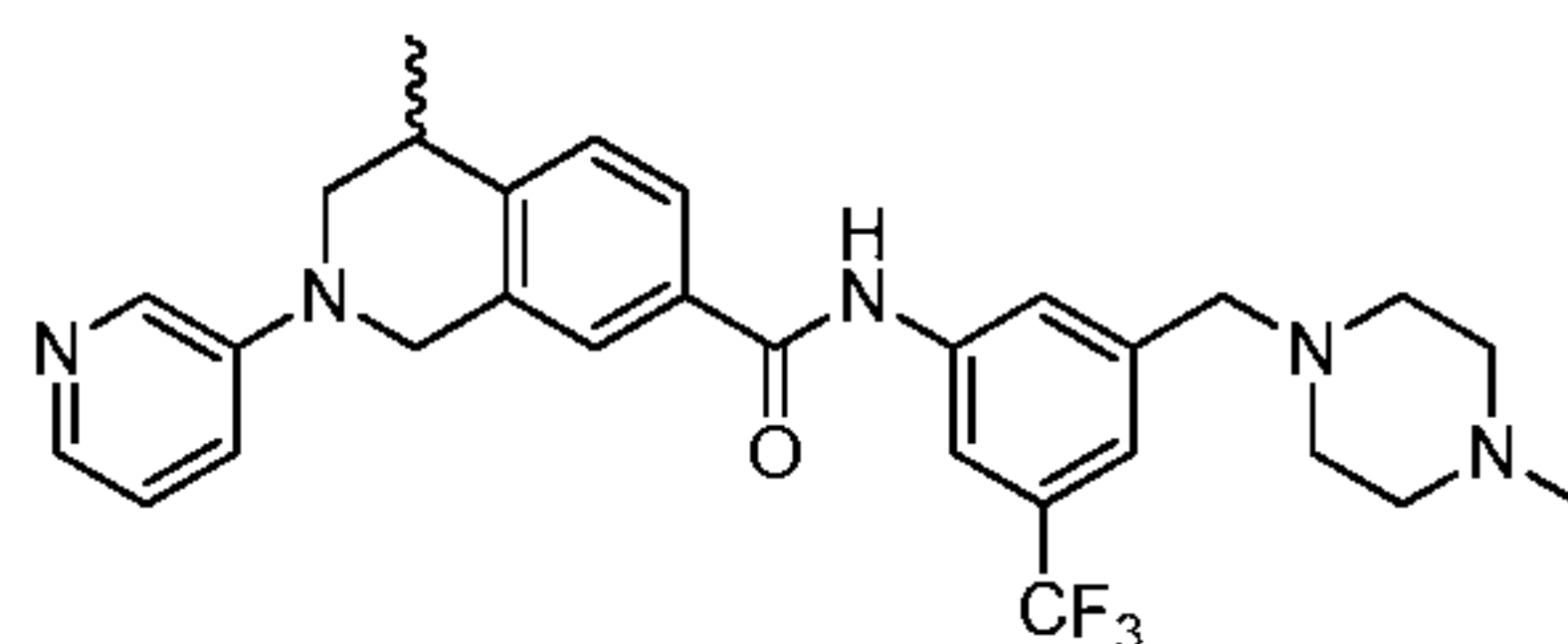


The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.49 (s, 1 H), 8.99 (d, *J* = 2.0 Hz, 1 H), 8.20 (s, 1 H), 8.02 (s, 1 H), 7.93 (s, 1 H), 7.89-7.87 (m, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.80-7.78 (m, 1 H), 7.63 (s, 1 H), 7.50-7.45 (m, 2 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.35 (s, 1 H), 4.66 (s, 2 H), 3.78 (t, *J* = 5.6 Hz, 2 H), 3.54 (s, 2 H), 3.08 (t, *J* = 5.6 Hz, 2 H), 2.40 (br s, 4 H), 2.34 (br s, 4 H), 2.16 (s, 3 H). MS (ESI), *m/z*: 560 (*M*⁺ + *H*⁺).

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Example 6 - 4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2103)

25



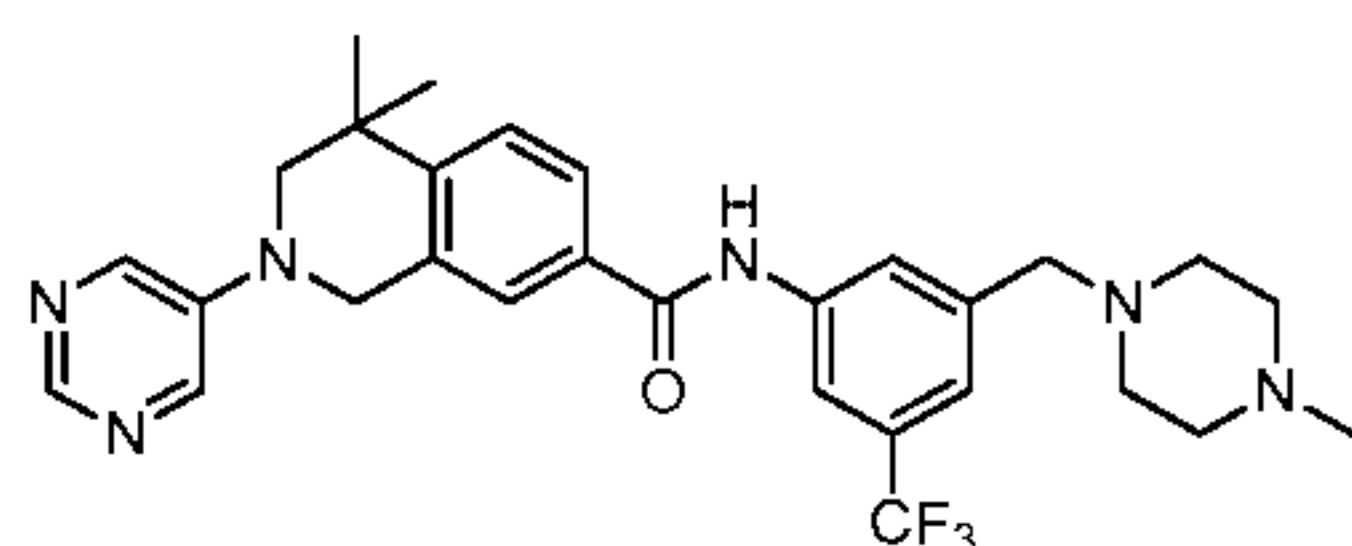
30

The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.49 (s, 1 H), 8.40 (s, 1 H), 8.19 (s, 1 H), 8.01 (s, 1 H), 7.98 (d, *J* = 3.2 Hz, 1 H), 7.87 (s, 1 H), 7.84 (d, *J* = 8.4 Hz, 1 H), 7.46 (d, *J* = 8.0 Hz, 1 H),

7.40 (d, $J = 8.0$ Hz, 1 H), 7.34 (s, 1 H), 7.26-7.25 (m, 1 H), 4.58 (d, $J = 16.0$ Hz, 1 H), 4.47 (d, $J = 16.0$ Hz, 1 H), 3.61 (d, $J = 10$ Hz, 1 H), 3.54 (s, 2 H), 3.43-3.38 (m, 1 H), 3.18 - 3.16(m, 1 H), 2.39 (br s, 4 H), 2.34 (br s, 4 H), 2.15 (s, 3 H), 1.35 (d, $J = 6.8$ Hz, 3 H). MS (ESI), m/z : 524 ($M^+ + H^+$).

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Example 7 - 4,4-dimethyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2102)

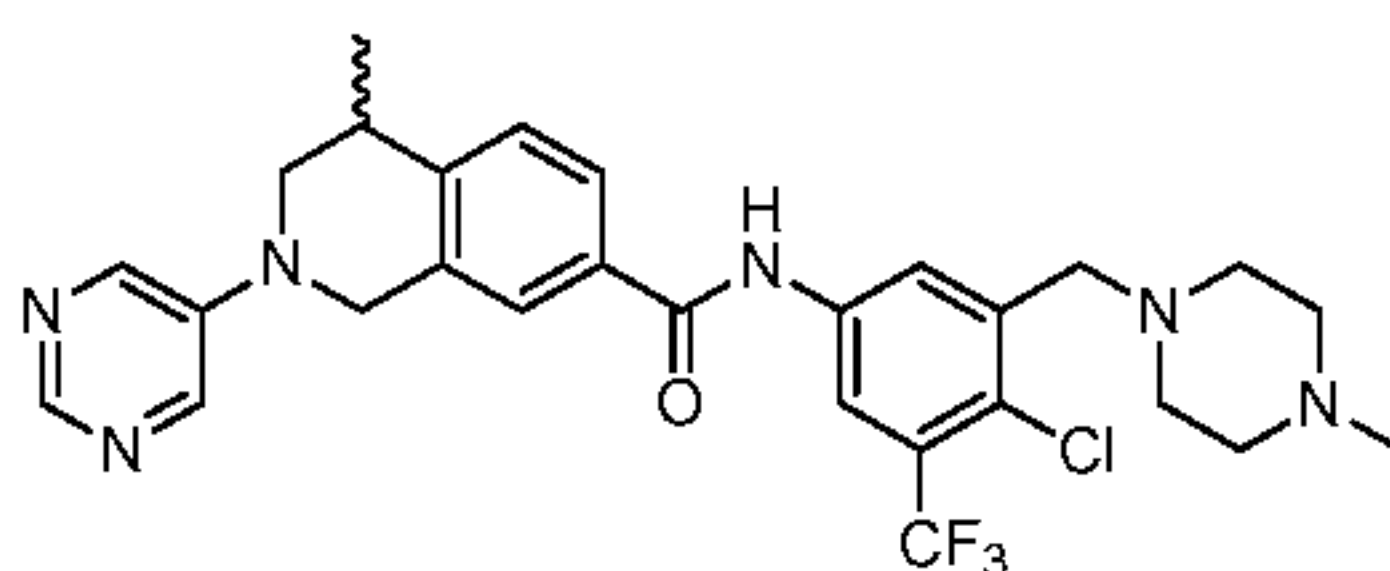


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The compound was synthesized by using the procedure similar to that of Example 1. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.37 (s, 1 H), 8.65-8.53 (s, 3 H), 8.18 (s, 1 H) 8.00 (s, 1 H), 7.90-7.77 (m, 2 H), 7.60 (d, $J = 6.8$ Hz, 1 H), 7.34 (s, 1 H), 4.58 (s, 2 H), 3.53 (s, 2 H), 3.45 (s, 2 H), 2.39 (br s, 8 H), 2.15 (s, 3 H), 1.35 (s, 6 H). MS (ESI), m/z : 539 ($M^+ + H^+$).

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Example 8 - N-(4-chloro-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2198)



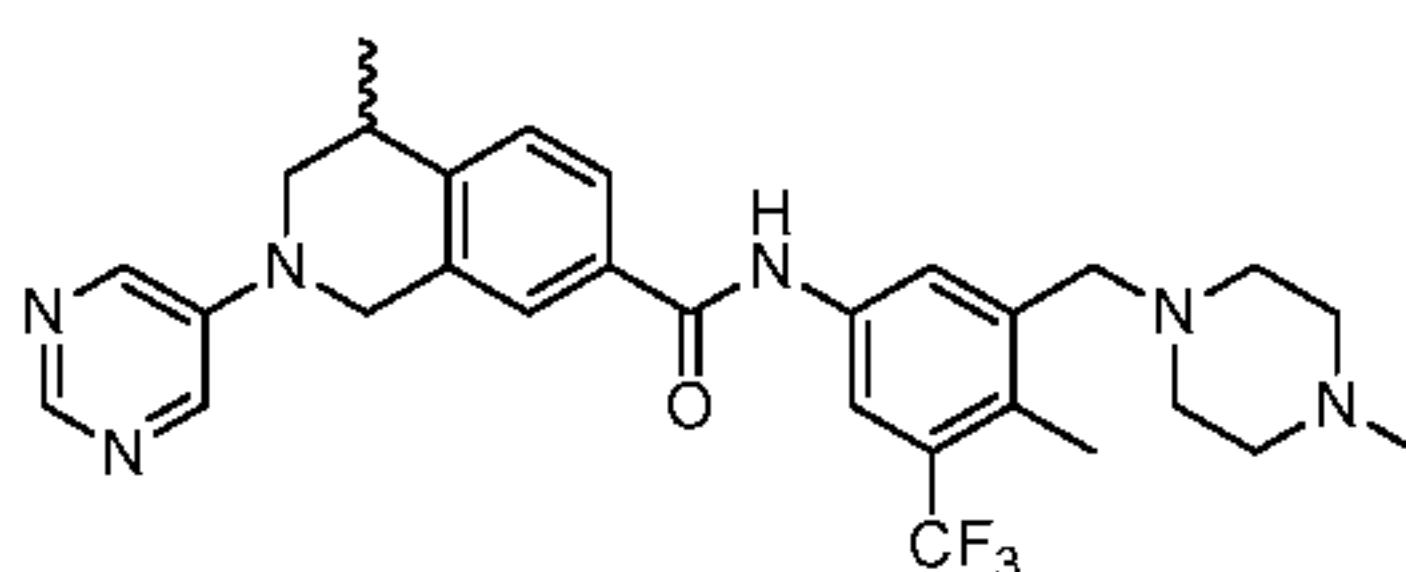
20

The compound was synthesized by using the procedure similar to that of Example 1. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.60 (s, 1 H), 8.66-8.52 (m, 3 H), 8.35 (s, 1 H), 8.23 (s, 1 H), 7.86-7.84 (m, 2 H), 7.47 (d, $J = 7.6$ Hz, 1 H), 4.65 (d, $J = 16.0$ Hz, 1 H), 4.53 (d, $J = 16.0$ Hz, 1 H), 3.68-3.62 (m, 3 H), 3.49-3.44 (m, 1 H), 3.19-3.18 (m, 1 H), 2.59-2.43 (m, 4 H), 2.37 (br s, 4 H), 2.17 (s, 3 H), 1.34 (d, $J = 6.8$ Hz, 3 H). MS (ESI), m/z : 559 ($M^+ + H^+$).

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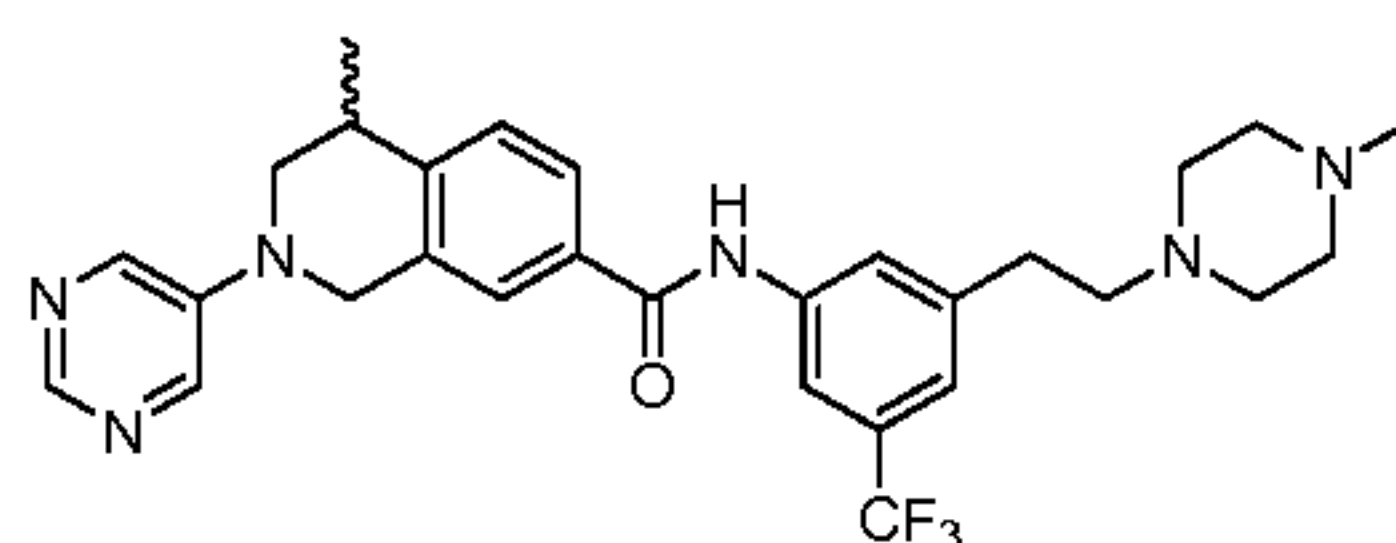
Example 9 - 4-methyl-N-(4-methyl-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2274)

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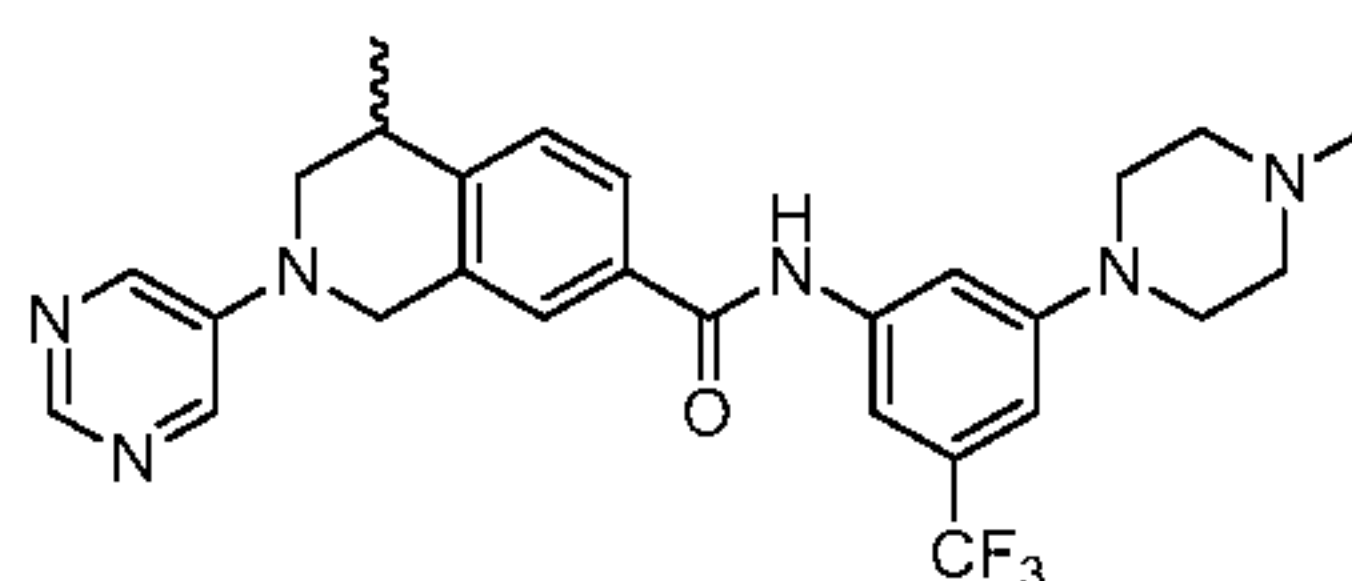
The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.40 (s, 1 H), 8.59-8.56 (m, 3 H), 8.17 (s, 1 H), 7.95 (s, 1 H), 7.85-7.83 (m, 2 H), 7.46 (d, J = 8.0 Hz, 1 H), 4.65 (d, J = 16.0 Hz, 1 H), 4.53 (d, J = 16.0 Hz, 1 H), 3.66 (dd, J = 12.0, 4.0 Hz, 1 H), 3.49-3.44 (m, 3 H), 3.18 (q, J = 5.6 Hz, 1 H), 2.42 (br s, 4 H), 2.38 (s, 3 H), 2.33 (br s, 4 H), 2.15 (s, 3 H), 1.34 (d, J = 7.2 Hz, 3 H). MS (ESI), m/z: 539 (M⁺ + H⁺).

Example 10 - 4-methyl-N-(3-(2-(4-methylpiperazin-1-yl)ethyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2276)



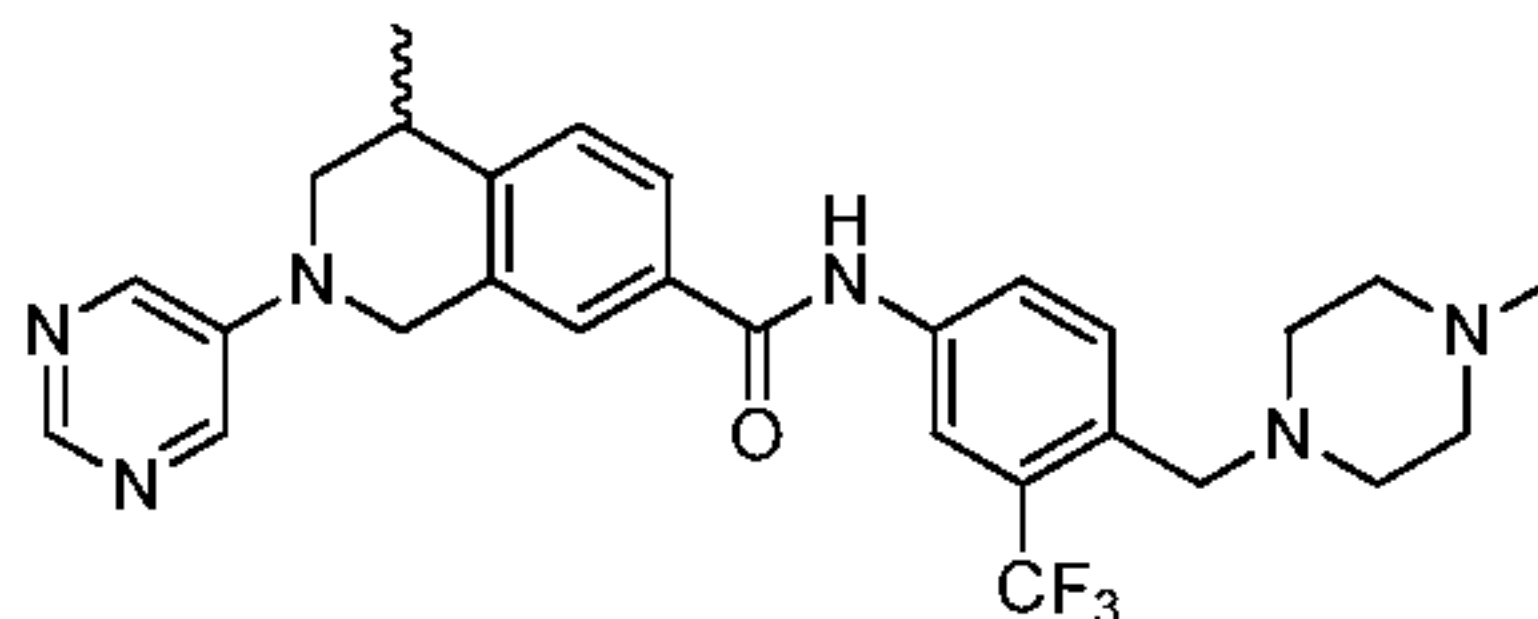
The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.42 (s, 1 H), 8.59-8.56 (s, 3 H), 8.07 (s, 1 H), 7.91 (s, 1 H), 7.85-7.83 (m, 2 H), 7.47 (d, J = 8.0 Hz, 1 H), 7.34 (s, 1 H), 4.65 (d, J = 16.0 Hz, 1 H), 4.53 (d, J = 16.0 Hz, 1 H), 3.66 (dd, J = 12.4, 4.4 Hz, 1 H), 3.47 (dd, J = 12.4, 6.4 Hz, 1 H), 3.21-3.17 (m, 1 H), 2.82 (t, J = 7.2 Hz, 2 H), 2.54 (t, J = 7.2 Hz, 2 H), 2.45 (br s, 4 H), 2.31 (br s, 4 H), 2.14 (s, 3 H), 1.34 (d, J = 6.8 Hz, 3 H). MS (ESI), m/z: 539 (M⁺ + H⁺).

Example 11 - 4-methyl-N-(3-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2188)



The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.30 (s, 1 H), 8.59-8.55 (m, 3 H), 7.84-7.82 (m, 2 H), 7.68 (s, 1 H), 7.63 (s, 1 H), 7.47 (d, J = 8.0 Hz, 1 H), 6.94 (s, 1 H), 4.65 (d, J = 16.0 Hz, 1 H), 4.53 (d, J = 16.0 Hz, 1 H), 3.66 (dd, J = 12.8, 4.4 Hz, 1 H), 3.47 (dd, J = 12.4, 6.4 Hz, 1 H), 3.23-3.16 (m, 5 H), 2.47 (t, J = 4.8 Hz, 4 H), 2.23 (s, 3 H), 1.34 (d, J = 6.8 Hz, 3 H). MS (ESI), m/z: 511 (M⁺ + H⁺).

Example 12 - 4-methyl-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2190)



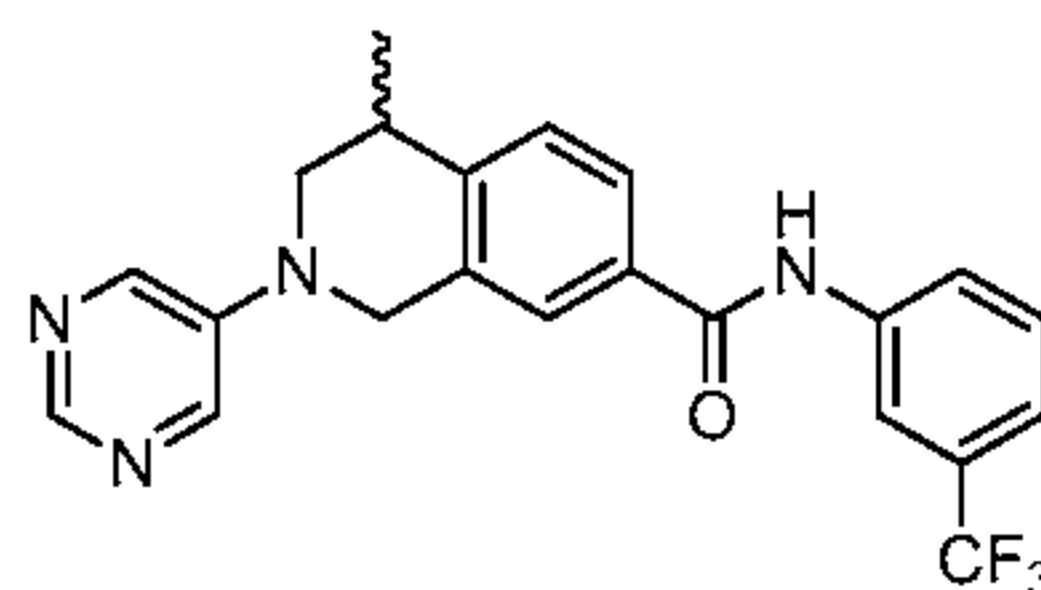
5

The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.48 (s, 1 H), 8.59-8.55 (m, 3 H), 8.20(s, 1 H), 8.05 (d, J = 8.4 Hz, 1 H), 7.85-7.83 (m, 2 H), 7.70 (d, J = 8.4 Hz, 1 H), 7.47 (d, J = 8.4 Hz, 1 H), 4.65 (d, J = 16.0 Hz, 1 H), 4.53 (d, J = 16.0 Hz, 1 H), 3.66 (dd, J = 12.8, 4.4 Hz, 1 H), 3.56 (s, 2 H), 3.47 (dd, J = 12.4, 6.0 Hz, 1 H), 3.20-3.16 (m, 1 H), 2.38 (br s, 4 H), 2.33 (br s, 4 H), 2.15 (s, 3 H), 1.34 (d, J = 6.8 Hz, 3 H). MS (ESI), m/z: 525 (M⁺ + H⁺).

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Example 13 - 4-methyl-2-(pyrimidin-5-yl)-N-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2199)

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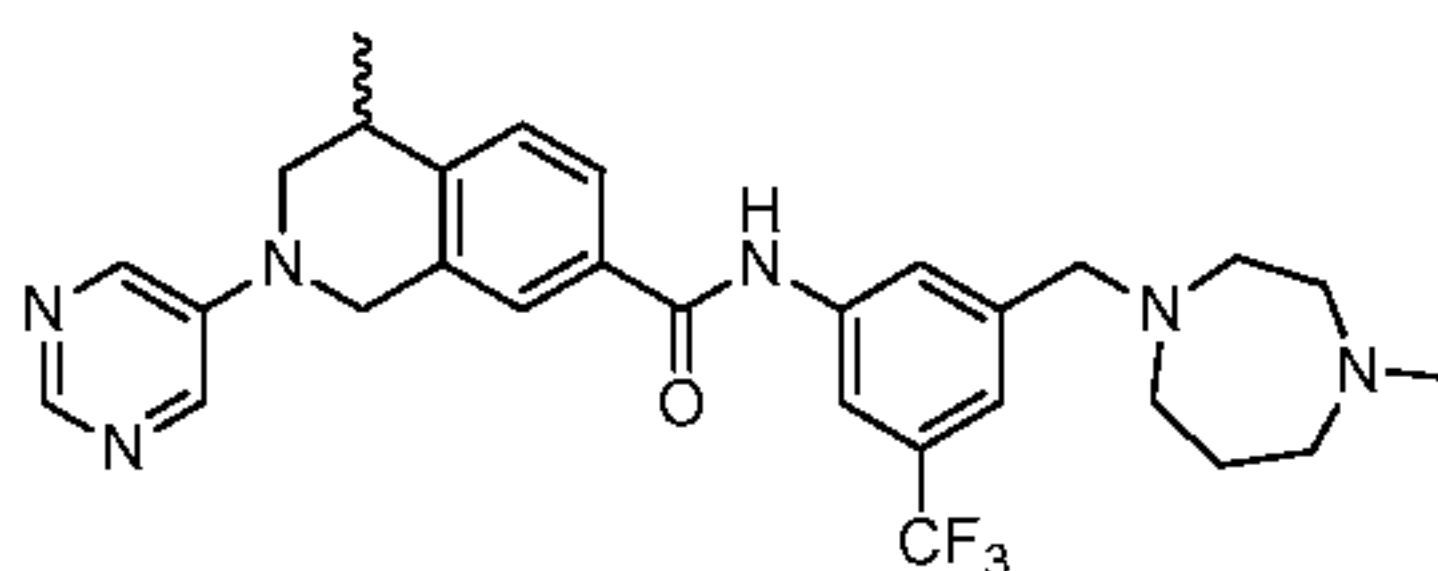


20

The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.52 (s, 1 H), 8.58 (s, 2 H), 8.57 (s, 1 H), 8.24 (s, 1 H), 8.06 (d, J = 8.0 Hz, 1 H), 7.86-7.84 (m, 2 H), 7.60 (t, J = 8.0 Hz, 1 H), 7.49-7.44 (m, 2 H), 4.65 (d, J = 16.0 Hz, 1 H), 4.53 (d, J = 16.0 Hz, 1 H), 3.66 (dd, J = 12.4, 4.4 Hz, 1 H), 3.47 (dd, J = 12.4, 6.4 Hz, 1 H), 3.21-3.17 (m, 1 H), 1.34 (d, J = 6.8 Hz, 3 H). MS (ESI), m/z: 413 (M⁺ + H⁺).

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Example 14 - 4-methyl-N-(3-((4-methyl-1,4-diazepan-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2197)



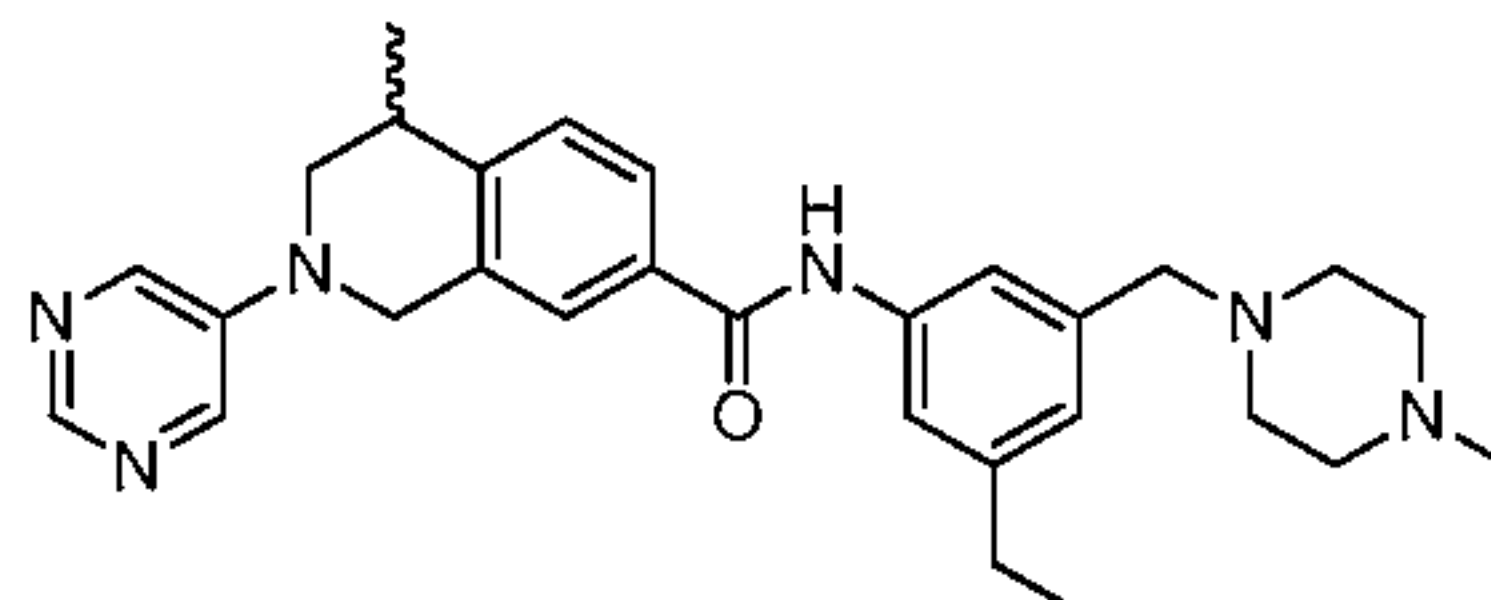
30

The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.51 (s, 1 H), 8.58 (s, 2 H), 8.57 (s, 1 H), 8.16 (s, 1 H), 8.02

(s, 1 H), 7.86-7.84 (m, 2 H), 7.47 (d, $J = 8.0$ Hz, 1 H), 7.37 (s, 1 H), 4.66 (d, $J = 16.0$ Hz, 1 H), 4.53 (d, $J = 16.0$ Hz, 1 H), 3.69-3.64 (m, 3 H), 3.49-3.45 (m, 1 H), 3.20-3.17 (m, 1 H), 2.67-2.63 (m, 4 H), 2.58-2.52 (m, 4 H), 2.25 (s, 3 H), 1.75-1.70 (m, 2 H), 1.34 (d, $J = 7.0$ Hz, 3 H). MS (ESI), m/z : 539 ($M^+ + H^+$).

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Example 15 - N-(3-ethyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2193)



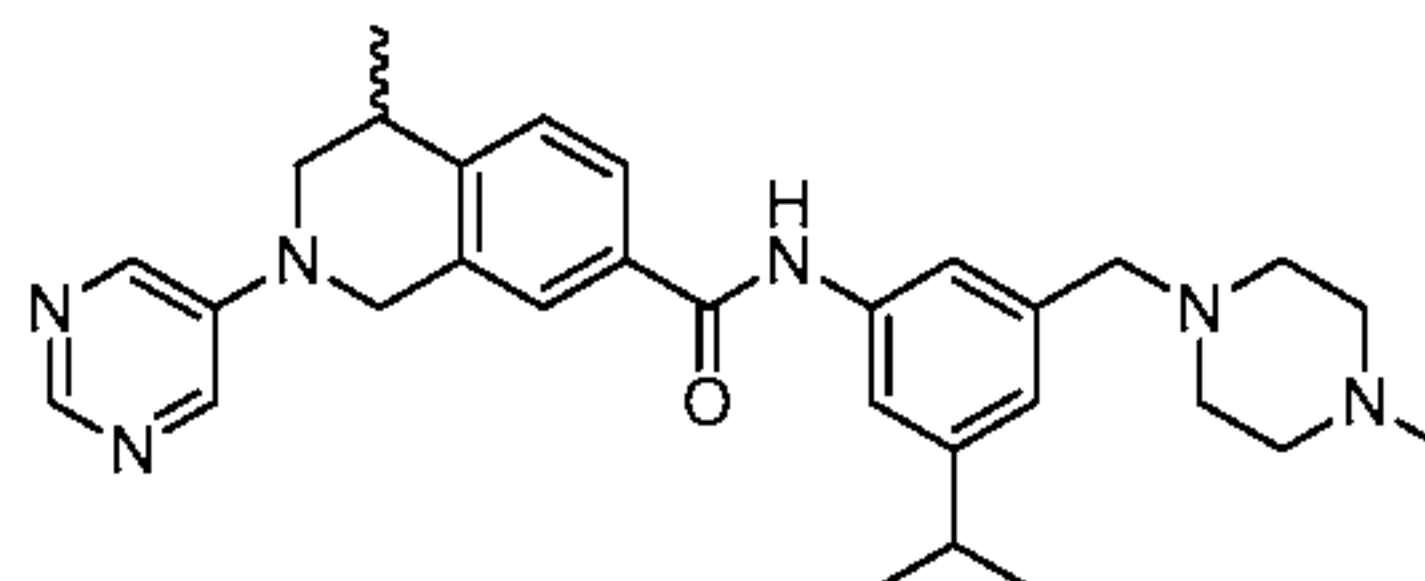
10

The compound was synthesized by using the procedure similar to that of Example 1. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.12 (s, 1 H), 8.65-8.50 (m, 3 H), 7.84-7.81 (m, 2 H), 7.57 (s, 1 H), 7.54 (s, 1 H), 7.44(d, $J = 7.2$ Hz, 1 H), 6.86 (s, 1 H), 4.64 (d, $J = 15.6$ Hz, 1 H), 4.52 (d, $J = 15.6$ Hz, 1 H), 3.67-3.64 (m, 1 H), 3.47-3.40 (m, 3 H), 3.23-3.11 (m, 1 H), 2.60-2.58 (m, 2 H), 2.46-2.22 (m, 8 H), 2.14 (s, 3 H), 1.34 (d, $J = 6.0$ Hz, 3 H), 1.19 (t, $J = 6.4$ Hz, 3 H). MS (ESI), m/z : 485 ($M^+ + H^+$).

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Example 16 - N-(3-isopropyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2187)

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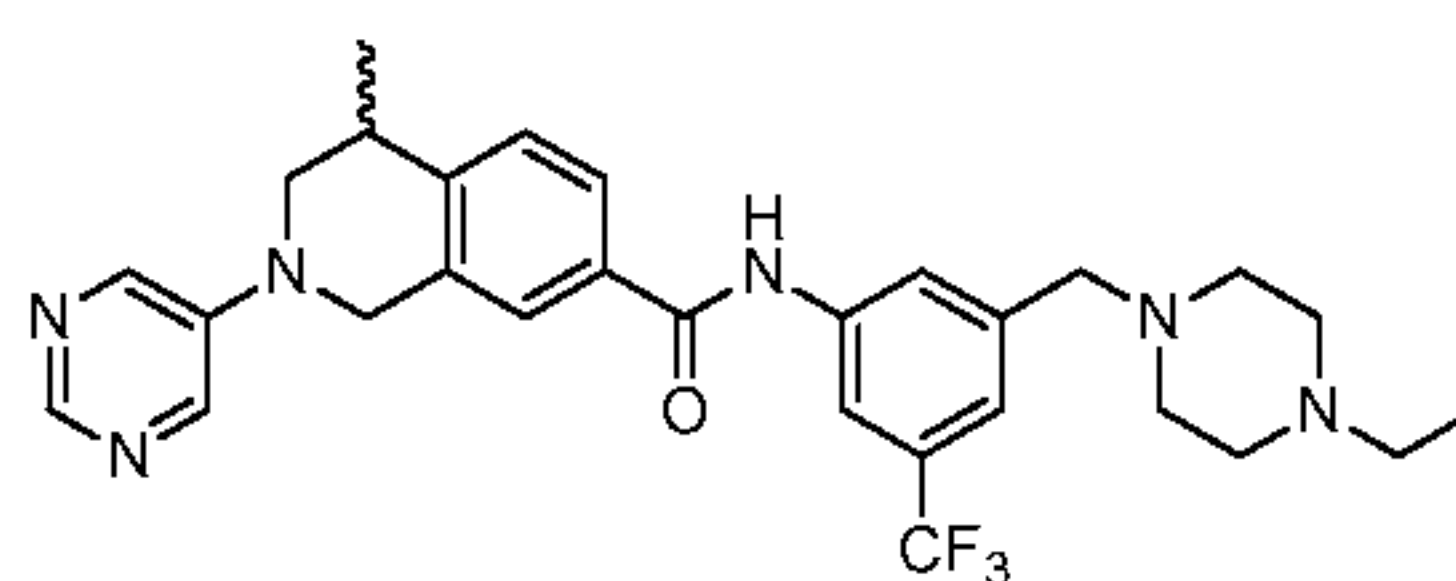


The compound was synthesized by using the procedure similar to that of Example 1. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.11 (s, 1 H), 8.61-8.53 (m, 3 H), 7.84-7.81 (m, 2 H), 7.58 (s, 1 H), 7.57 (s, 1 H), 7.44(d, $J = 7.6$ Hz, 1 H), 6.88 (s, 1 H), 4.64 (d, $J = 16.0$ Hz, 1 H), 4.52 (d, $J = 16.0$ Hz, 1 H), 3.67-3.64 (m, 1 H), 3.48-3.41 (m, 3 H), 3.18-3.17 (m, 1 H), 2.87-2.84 (m, 1 H), 2.36-2.33 (m, 8 H), 2.14 (s, 3 H), 1.34 (d, $J = 6.4$ Hz, 3 H), 1.21 (d, $J = 6.4$ Hz, 6 H). MS (ESI), m/z : 499 ($M^+ + H^+$).

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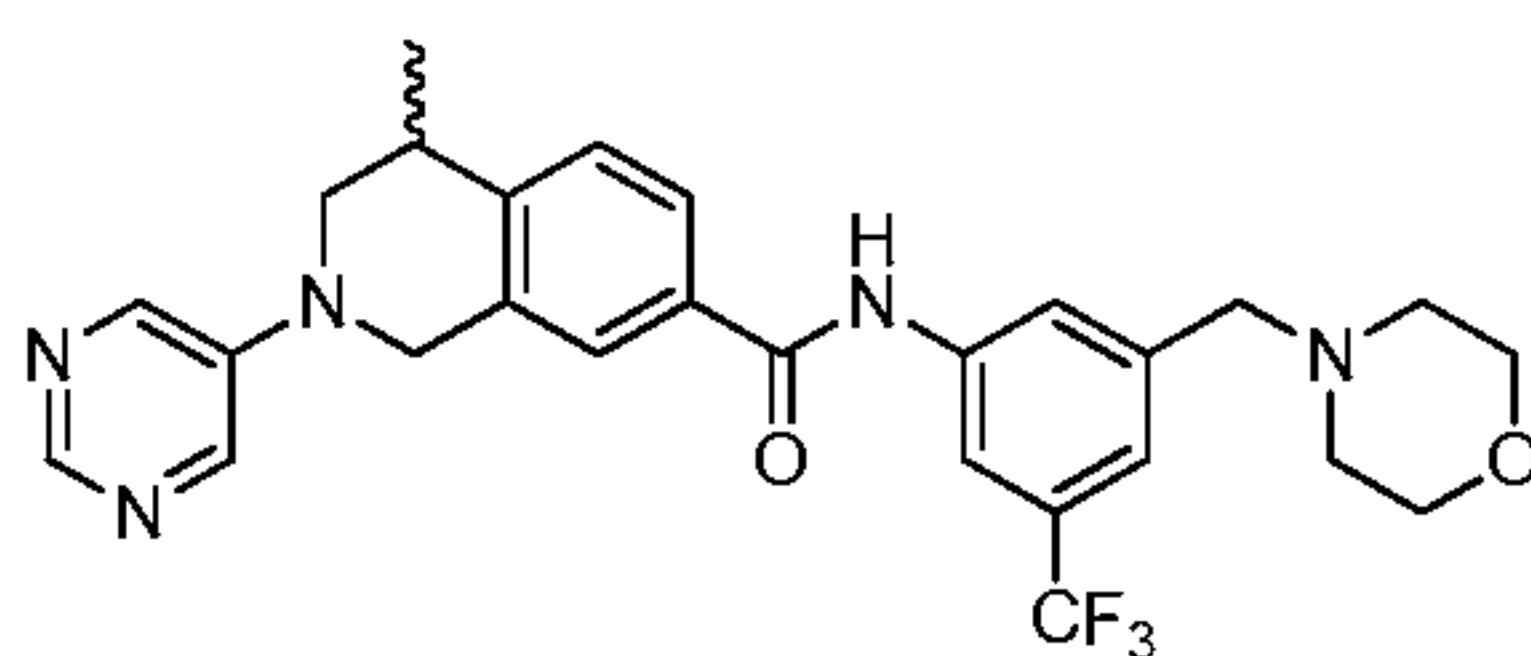
Example 17 - N-(3-((4-ethylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2275)

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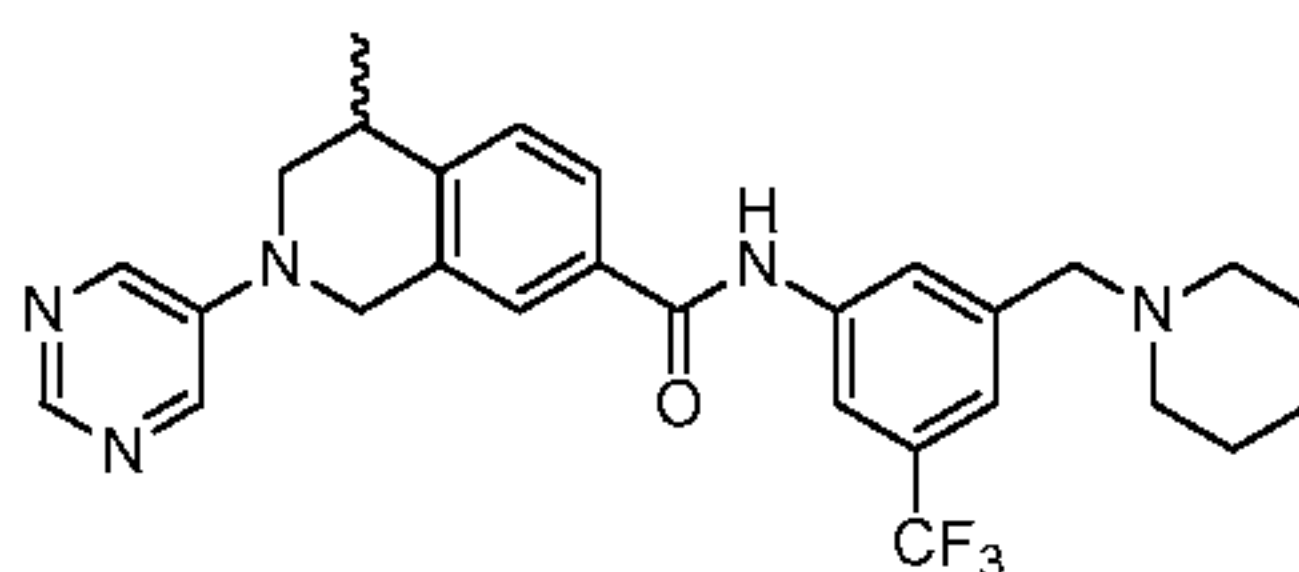
The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.50 (s, 1 H), 8.60-8.55 (m, 3 H), 8.19 (s, 1 H), 8.00 (s, 1 H), 7.86-7.84 (m, 2 H), 7.47 (d, J = 8.0 Hz, 1 H), 7.34 (s, 1 H), 4.65 (d, J = 16.0 Hz, 1 H), 4.53 (d, J = 16.0 Hz, 1 H), 3.66 (dd, J = 12.4, 4.4 Hz, 1 H), 3.54 (s, 2 H), 3.47 (dd, J = 12.8, 6.4 Hz, 1 H), 3.21-3.16 (m, 1 H), 2.48-2.33 (m, 8 H), 2.30 (q, J = 7.2 Hz, 3 H), 1.34 (d, J = 6.8 Hz, 3 H), 0.97 (t, J = 7.2 Hz, 3 H). MS (ESI), m/z: 539 (M⁺ + H⁺).

Example 18 - 4-methyl-N-(3-(morpholinomethyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2201)



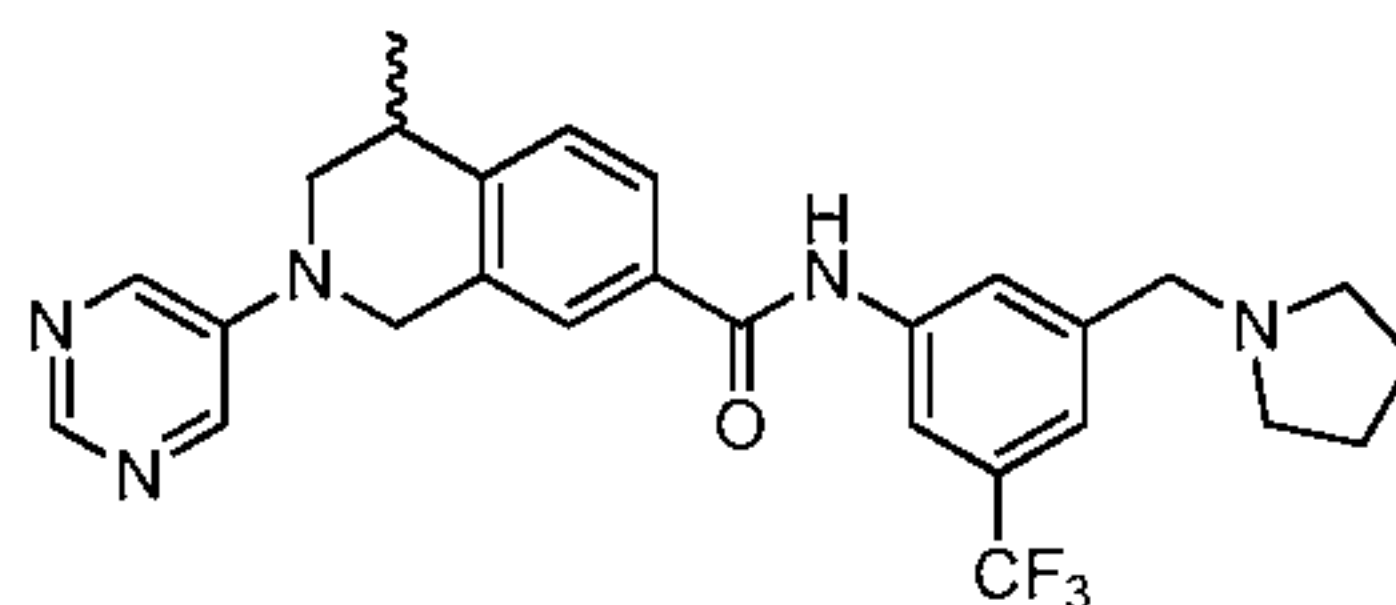
The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.49 (s, 1 H), 8.61-8.54 (m, 3 H), 8.19 (s, 1 H), 8.03 (s, 1 H), 7.87-7.85 (m, 2 H), 7.47 (d, J = 8.0 Hz, 1 H), 7.37 (s, 1 H), 4.65 (d, J = 16.0 Hz, 1 H), 4.53 (d, J = 16.0 Hz, 1 H), 3.66 (dd, J = 12.4, 4.0 Hz, 1 H), 3.60-3.59 (m, 4 H), 3.55 (s, 2 H), 3.47 (dd, J = 12.4, 6.0 Hz, 1 H), 3.21-3.17 (m, 1 H), 2.43-2.35 (m, 4 H), 1.34 (d, J = 6.8 Hz, 3 H). MS (ESI), m/z: 512 (M⁺ + H⁺).

Example 19 - 4-methyl-N-(3-(piperidin-1-ylmethyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2194)



The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.50 (s, 1 H), 8.61-8.54 (m, 3 H), 8.18 (s, 1 H), 7.99 (s, 1 H), 7.86-7.84 (m, 2 H), 7.47 (d, J = 7.6 Hz, 1 H), 7.34 (s, 1 H), 4.65 (d, J = 16.0 Hz, 1 H), 4.53 (d, J = 16.0 Hz, 1 H), 3.66 (dd, J = 12.0, 4.0 Hz, 1 H), 3.50 (s, 2 H), 3.48-3.45 (m, 1 H), 3.19-3.18 (m, 1 H), 2.40-2.30 (m, 4 H), 1.51-1.50 (m, 4 H), 1.45-1.37 (m, 2 H), 1.34 (d, J = 6.8 Hz, 3 H). MS (ESI), m/z: 510 (M⁺ + H⁺).

Example 20 - 4-methyl-2-(pyrimidin-5-yl)-N-(3-(pyrrolidin-1-ylmethyl)-5-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2573)

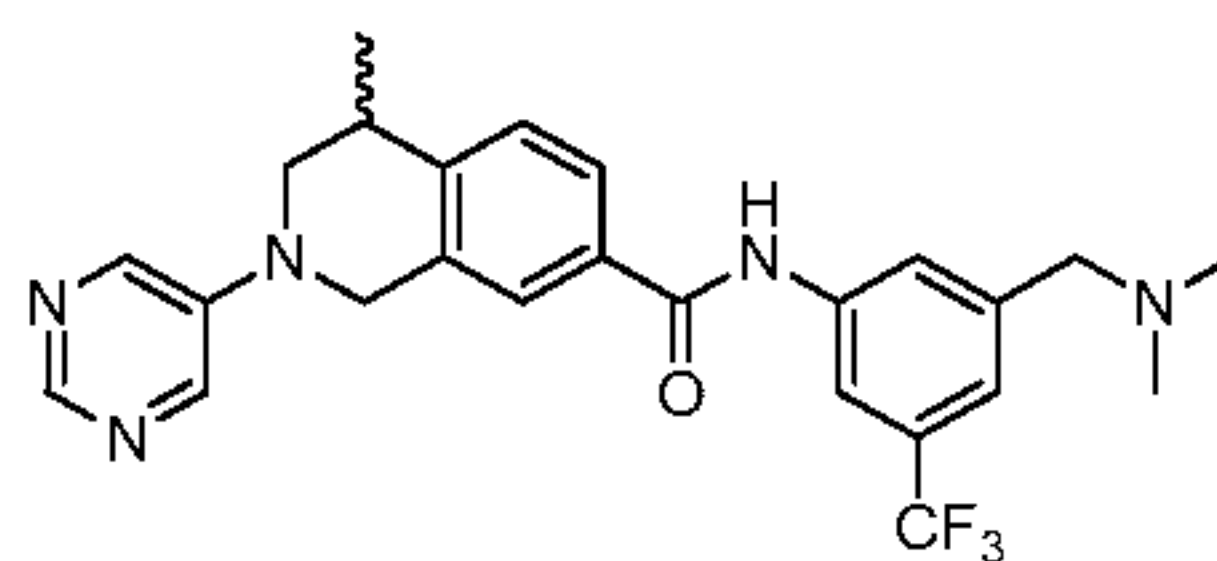


5

The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.48 (s, 1 H), 8.60-8.55 (m, 3 H), 8.18 (s, 1 H), 8.02 (s, 1 H), 7.87-7.85 (m, 2 H), 7.47 (d, J = 8.0 Hz, 1 H), 7.35 (s, 1 H), 4.65 (d, J = 16.4 Hz, 1 H), 4.53 (d, J = 16.4 Hz, 1 H), 3.68-3.64 (m, 3 H), 3.49-3.45 (m, 1 H), 3.21-3.16 (m, 1 H), 2.50-2.47 (m, 4 H), 1.76-1.70 (m, 4 H), 1.34 (d, J = 6.8 Hz, 3 H). MS (ESI), m/z: 496 (M⁺ + H⁺).

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Example 21 - N-(3-((dimethylamino)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2192)

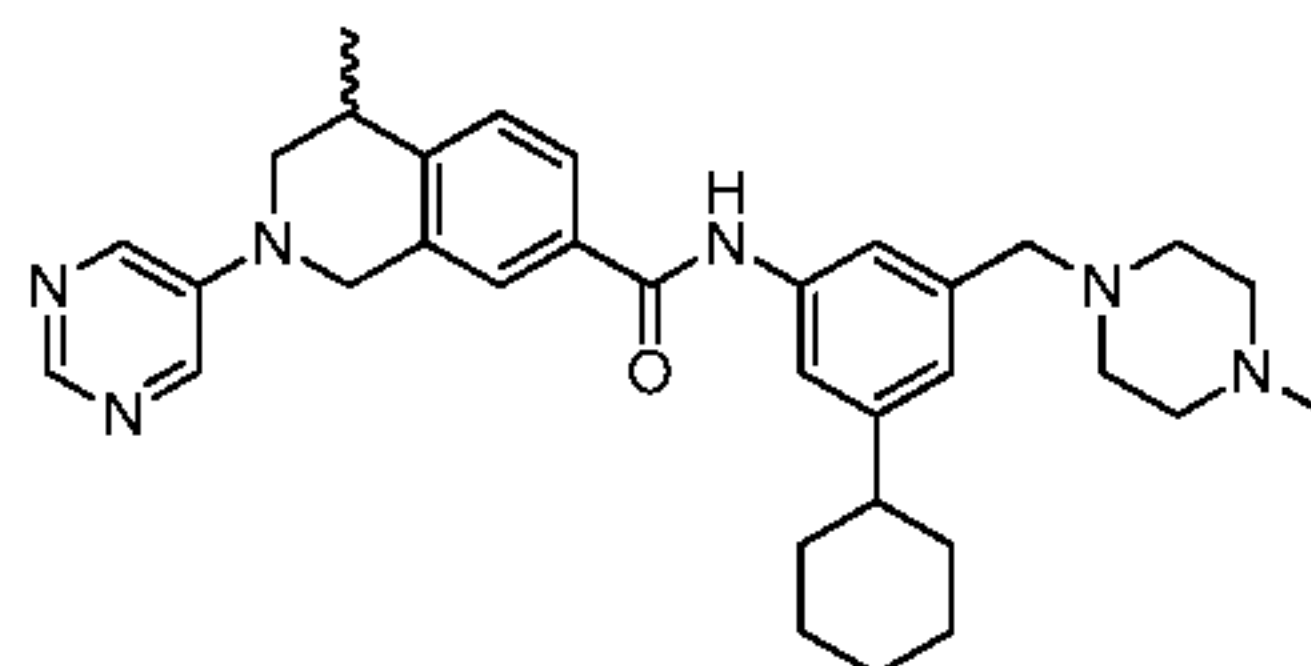


15

The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.48 (s, 1 H), 8.58-8.57 (m, 3 H), 8.18 (s, 1 H), 8.02 (s, 1 H), 7.87-7.85 (m, 2 H), 7.47 (d, J = 8.0 Hz, 1 H), 7.35 (s, 1 H), 4.65 (d, J = 16.4 Hz, 1 H), 4.53 (d, J = 16.4 Hz, 1 H), 3.66 (dd, J = 12.4, 4.4 Hz, 1 H), 3.50-3.45 (m, 3 H), 3.21-3.17 (m, 1 H), 2.19 (s, 6 H), 1.34 (d, J = 7.2 Hz, 3 H). MS (ESI), m/z: 470 (M⁺ + H⁺).

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Example 22 - N-(3-cyclohexyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2215)



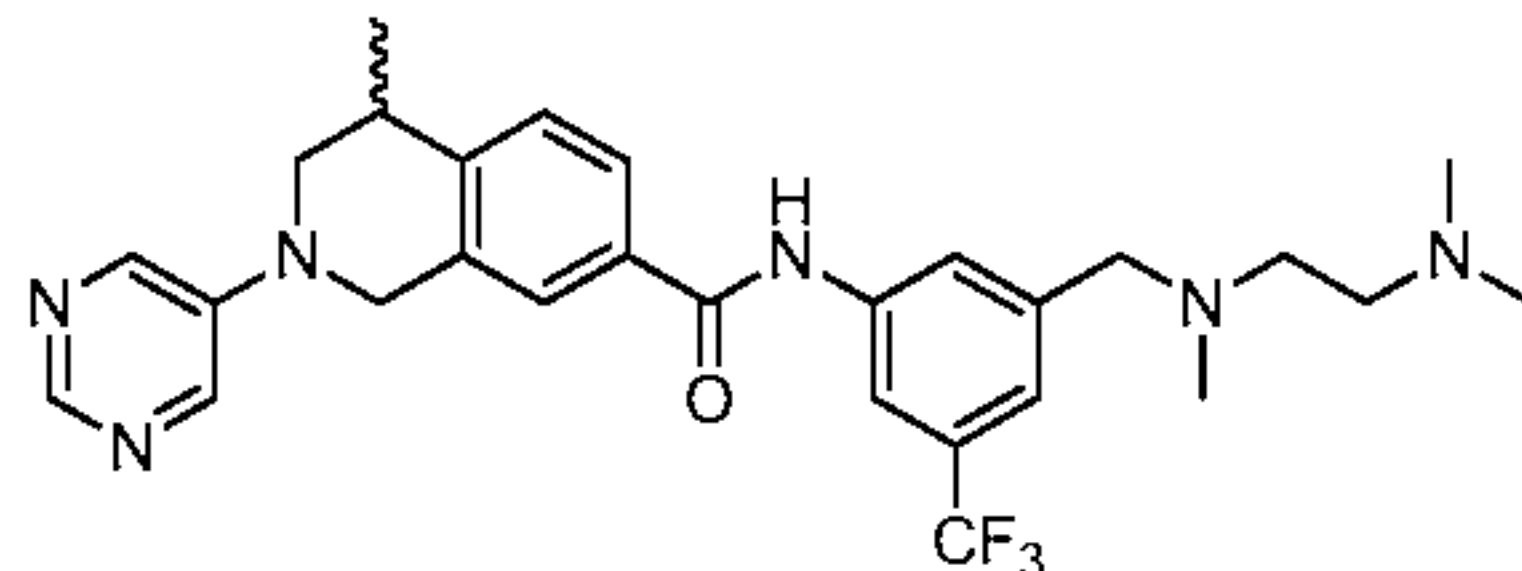
25

The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.09 (s, 1 H), 8.63-8.53 (m, 3 H), 7.84-7.81 (m, 2 H), 7.58 (s, 1 H), 7.55 (s, 1 H), 7.44 (d, J = 7.6 Hz, 1 H), 6.86 (s, 1 H), 4.64 (d, J = 16.0 Hz, 1 H), 4.52 (d, J = 16.0 Hz, 1 H), 3.67-3.65 (m, 1 H), 3.49-3.44 (m, 1 H), 3.41 (s, 2 H), 3.22-3.12 (m, 1 H), 2.34-2.21 (m, 8 H), 2.15 (s, 3 H), 1.88-1.75 (m, 4 H), 1.73-1.70 (m, 1 H), 1.40-1.33 (m, 7 H), 1.29-1.17 (m, 1 H). MS (ESI), m/z: 539 (M⁺ + H⁺).

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Example 23 - N-(3-(((2-(dimethylamino)ethyl)(methylamino)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2474)

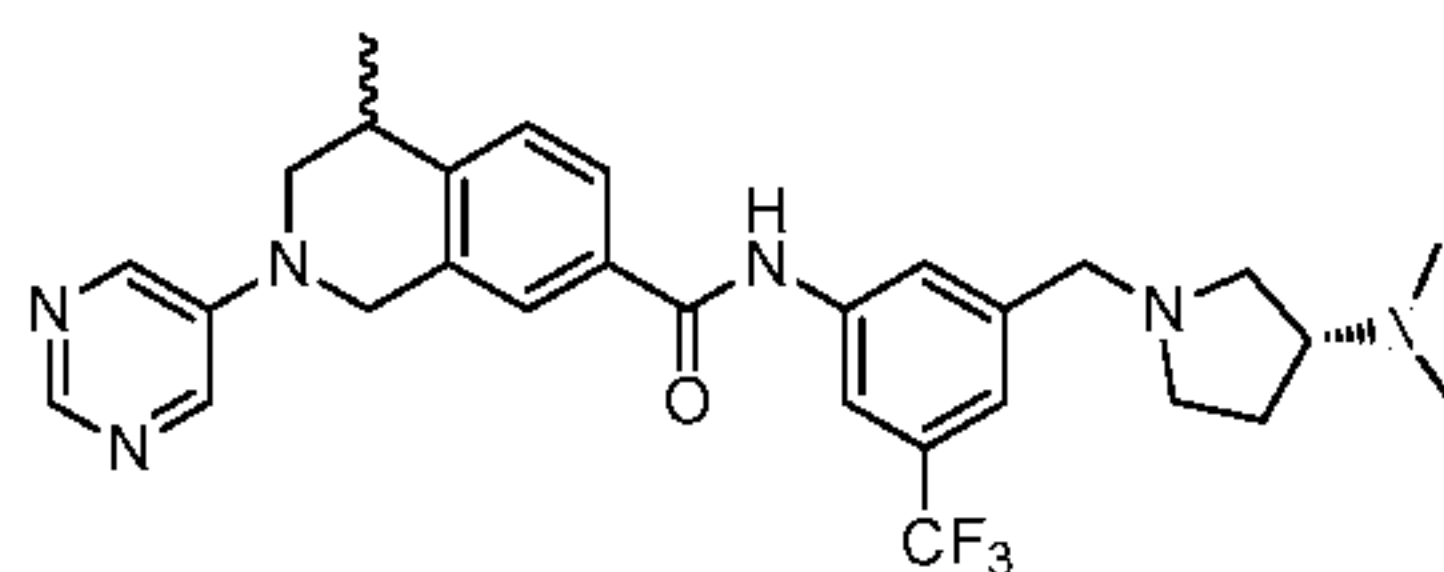
5



The compound was synthesized by using the procedure similar to that of Example 1. ^1H NMR (400 MHz, DMSO- d_6) δ 10.51 (s, 1 H), 8.67-8.51 (m, 3 H), 8.17 (s, 1 H), 8.00 (s, 1 H), 7.92-7.79 (m, 2 H), 7.47 (d, $J = 7.2$ Hz, 1 H), 7.37 (s, 1 H), 4.65 (d, $J = 16.4$ Hz, 1 H), 4.53 (d, $J = 16.4$ Hz, 1 H), 3.67-3.65 (m, 1 H), 3.57 (s, 3 H), 3.52-3.43 (m, 1 H), 3.24-3.12 (m, 1 H), 2.48-2.42 (m, 2 H), 2.42-2.32 (m, 2 H), 2.17 (s, 3 H), 2.12 (s, 6 H), 1.42-1.25 (m, 3 H). MS (ESI), m/z : 527 ($\text{M}^+ + \text{H}^+$).

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Example 24 - N-(3-(((R)-3-(dimethylamino)pyrrolidin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2473)

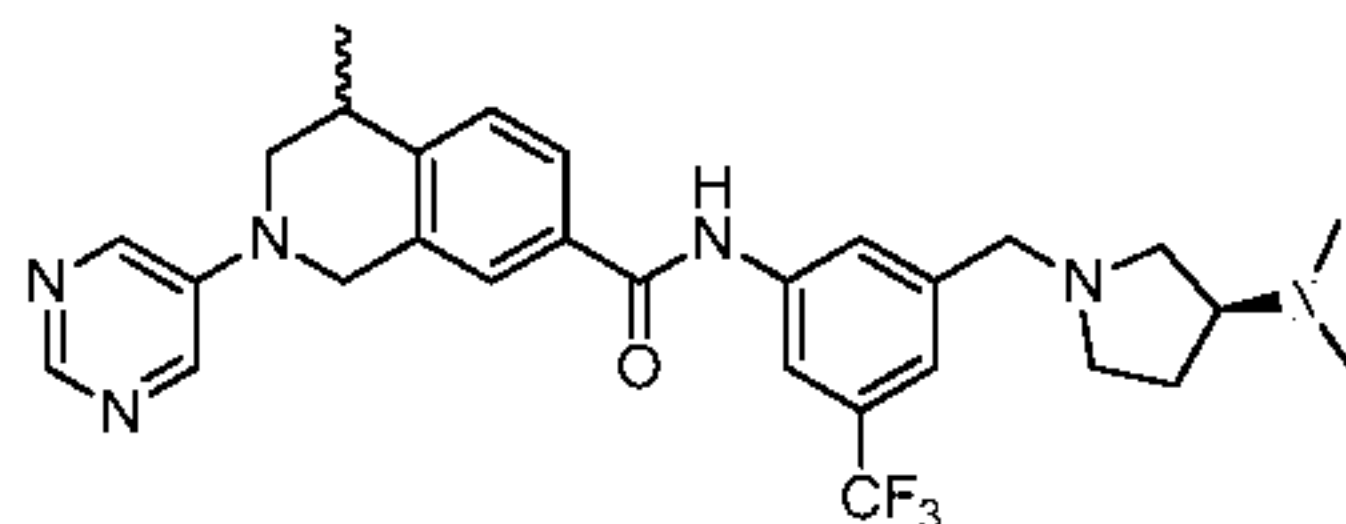


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The compound was synthesized by using the procedure similar to that of Example 1. ^1H NMR (400 MHz, DMSO- d_6) δ 10.50 (s, 1 H), 8.64-8.51 (m, 3 H), 8.17 (s, 1 H), 8.01 (s, 1 H), 7.92-7.80 (m, 2 H), 7.47 (d, $J = 6.8$ Hz, 1 H), 7.37 (s, 1 H), 4.65 (d, $J = 16.0$ Hz, 1 H), 4.53 (d, $J = 16.0$ Hz, 1 H), 3.72-3.65 (m, 2 H), 3.59-3.57 (m, 1 H), 3.53-3.42 (m, 1 H), 3.26-3.10 (m, 1 H), 2.79-2.65 (m, 2 H), 2.65-2.56 (m, 1 H), 2.50-2.40 (m, 1 H), 2.36-2.26 (m, 1 H), 2.08 (s, 6 H), 1.93-1.80 (m, 1 H), 1.69-1.56 (m, 1 H), 1.34 (d, $J = 5.2$ Hz, 3 H). MS (ESI), m/z : 539 ($\text{M}^+ + \text{H}^+$).

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Example 25 - N-(3-(((S)-3-(dimethylamino)pyrrolidin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2475)



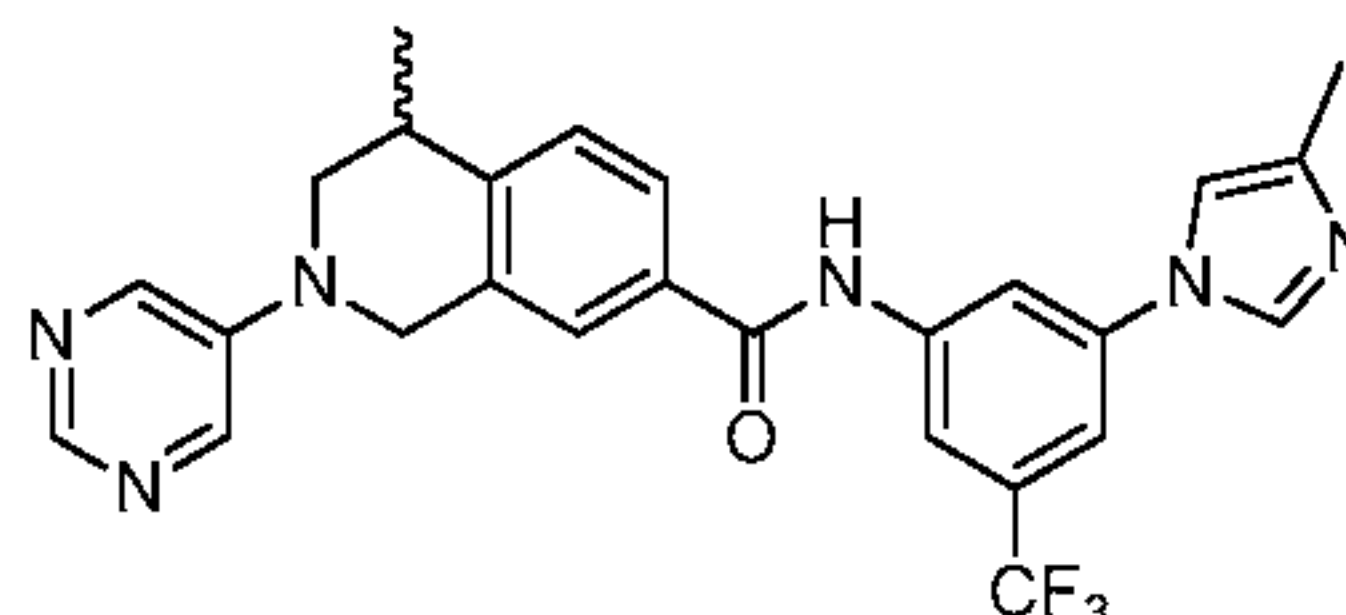
5

The compound was synthesized by using the procedure similar to that of Example 1. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.50 (s, 1 H), 8.64-8.51 (m, 3 H), 8.17 (s, 1 H), 8.01 (s, 1 H), 7.92-7.80 (m, 2 H), 7.55-7.43 (m, 1 H), 7.35 (s, 1 H), 4.65 (d, $J = 15.6$ Hz, 1 H), 4.53 (d, $J = 15.6$ Hz, 1 H), 3.76-3.62 (m, 2 H), 3.62-3.53 (m, 1 H), 3.52-3.42 (m, 1 H), 3.25-3.11 (m, 1 H), 2.79-2.65 (m, 2 H), 2.65-2.56 (m, 1 H), 2.50-2.40 (m, 1 H), 2.36-2.26 (m, 1 H), 2.08 (s, 6 H), 1.94-1.77 (m, 1 H), 1.70-1.55 (m, 1 H), 1.43-1.27 (m, 3 H). MS (ESI), m/z : 539 ($\text{M}^+ + \text{H}^+$).

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Example 26 - 4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2202)

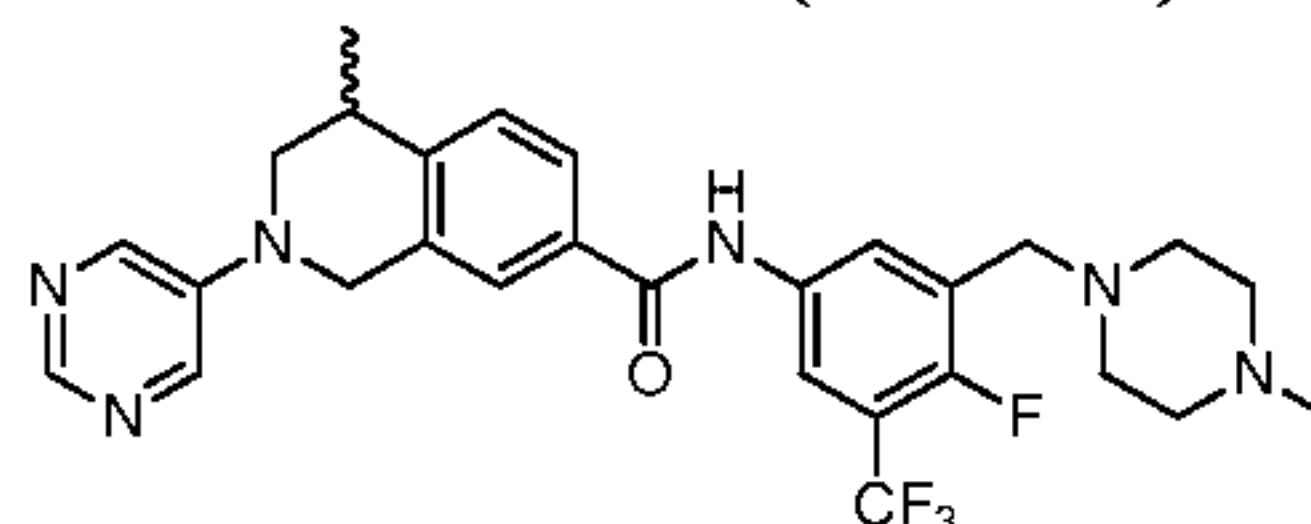


20

The compound was synthesized by using the procedure similar to that of Example 1. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.66 (s, 1 H), 8.58-8.57 (m, 3 H), 8.29 (s, 1 H), 8.20 (s, 1 H), 8.15 (s, 1 H), 7.88-7.86 (m, 2 H), 7.73 (s, 1 H), 7.51-7.48 (m, 2 H), 4.66 (d, $J = 16.0$ Hz, 1 H), 4.54 (d, $J = 16$ Hz, 1 H), 3.67 (dd, $J = 12.8, 4.8$ Hz, 1 H), 3.48 (dd, $J = 12.4, 6.4$ Hz, 1 H), 3.22-3.18 (m, 1 H), 2.18 (s, 3 H), 1.35 (d, $J = 6.8$ Hz, 3 H). MS (ESI), m/z : 493 ($\text{M}^+ + \text{H}^+$).

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Example 27 - N-(4-fluoro-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2214)

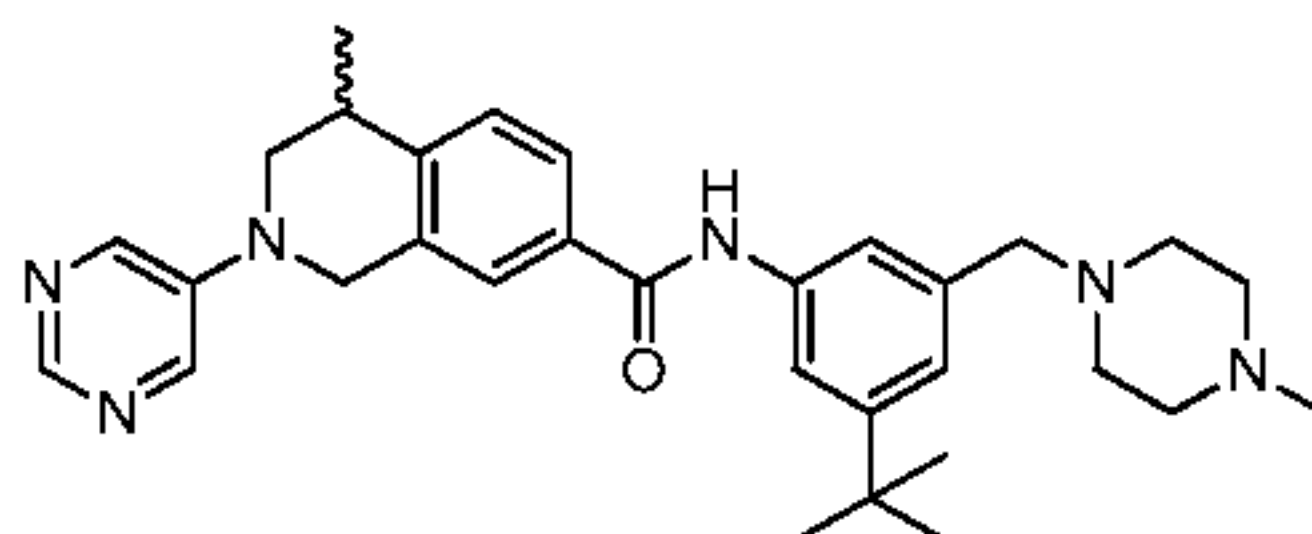


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The compound was synthesized by using the procedure similar to that of Example 1. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.53 (s, 1 H), 8.58 (s, 2 H), 8.57 (s, 1 H), 8.22 (dd, $J = 6.0, 2.5$ Hz, 1 H), 8.12 (dd, $J = 6.0, 2.5$ Hz, 1 H), 7.86-7.84 (m, 2 H), 7.47 (d, $J = 8.0$ Hz, 1 H), 4.65 (d, $J = 16.0$ Hz, 1 H), 4.53 (d, $J = 16.0$ Hz, 1 H), 3.66 (dd, $J = 12.5, 4.5$ Hz, 1 H), 3.58 (s,

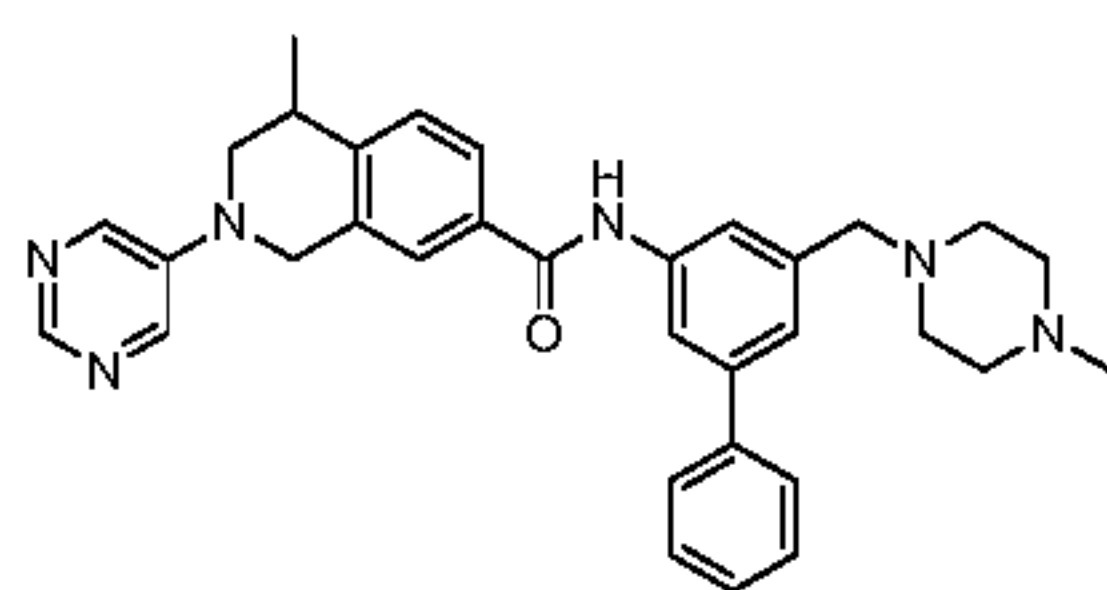
2 H), 3.47 (dd, $J = 12.5, 6.5$ Hz, 1 H), 3.22-23.16 (m, 1 H), 2.44 (br s, 4 H), 2.36-2.35 (m, 4 H), 2.15 (s, 3 H), 1.34 (d, $J = 7.0$ Hz, 3 H). MS (ESI), m/z : 543 ($M^+ + H^+$).

Example 28 - N-(3-tert-butyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2350)



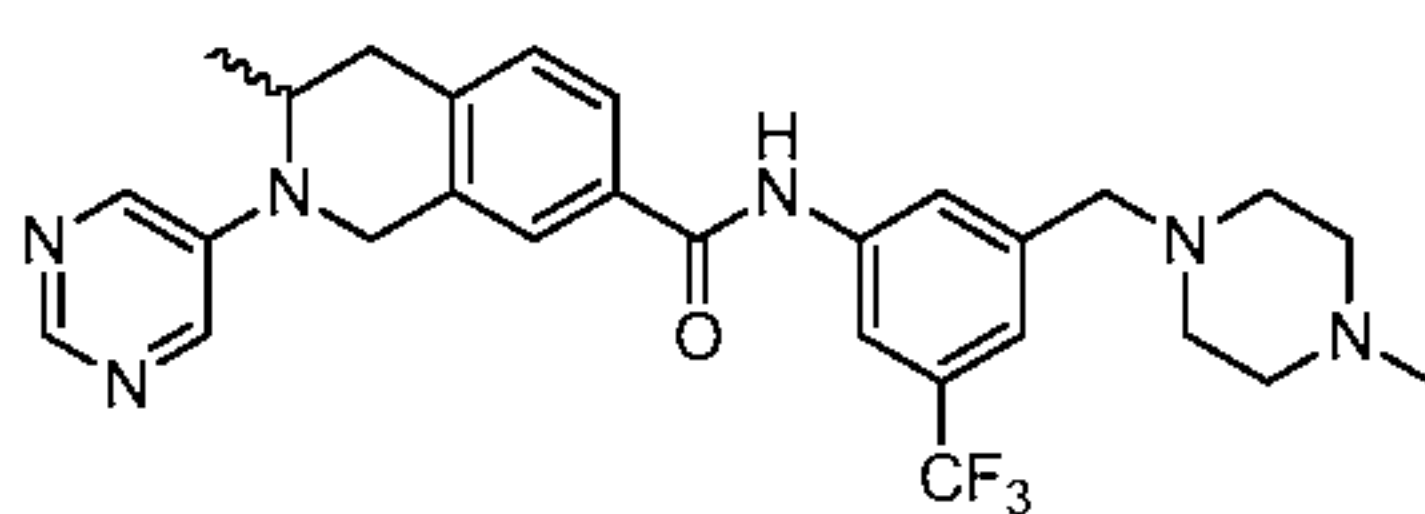
The compound was synthesized by using the procedure similar to that of Example 1. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.12 (s, 1 H), 8.58 (s, 2 H), 8.57 (s, 1 H), 7.84-7.82 (m, 2 H), 7.70 (s, 1 H), 7.63 (s, 1 H), 7.44(d, $J = 8.0$ Hz, 1 H), 7.04 (s, 1 H), 4.65 (d, $J = 16.0$ Hz, 1 H), 4.52 (d, $J = 16.0$ Hz, 1 H), 3.68-3.64 (m, 1 H), 3.49-3.45 (m, 1 H), 3.44 (s, 1 H), 3.20-3.16 (m, 1 H), 2.48-2.18 (m, 8 H), 2.15 (s, 3 H), 1.34 (d, $J = 7.0$ Hz, 3 H), 1.28 (s, 9 H). MS (ESI), m/z : 513 ($M^+ + H^+$).

Example 29 - 4-methyl-N-(5-((4-methylpiperazin-1-yl)methyl)biphenyl-3-yl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2476)



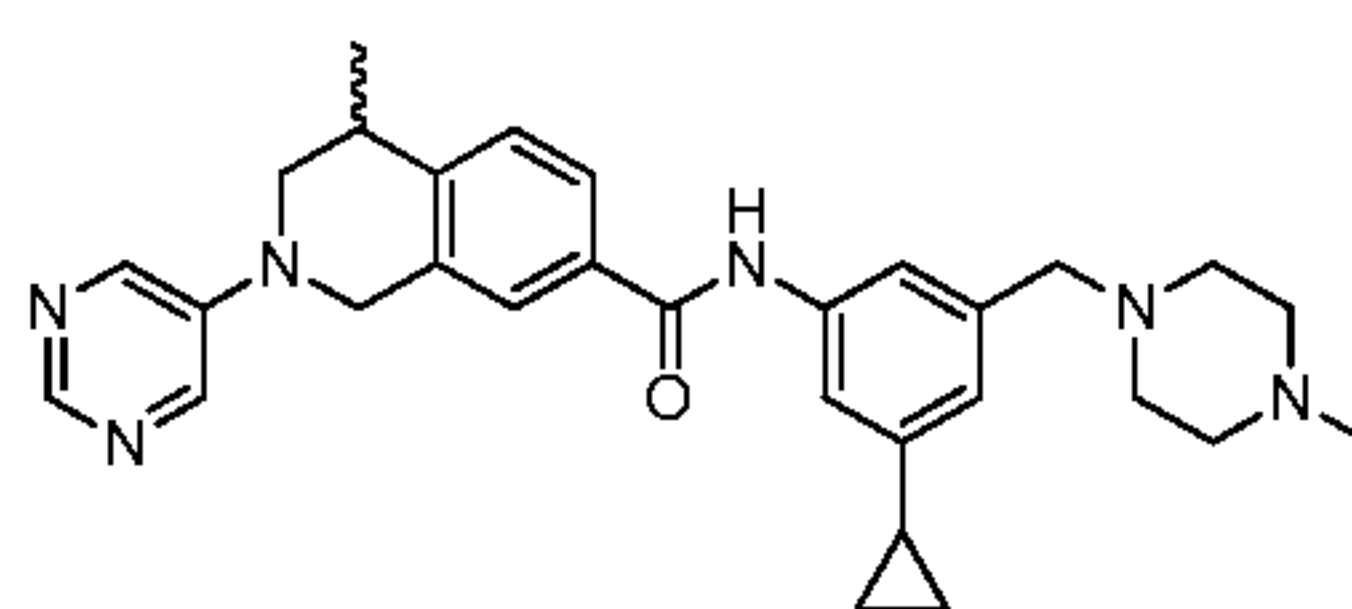
The compound was synthesized by using the procedure similar to that of Example 1. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.29 (s, 1 H), 8.58 (s, 2 H), 8.57 (s, 1 H), 8.04 (s, 1 H), 7.87-7.85 (m, 2 H), 7.76 (s, 1 H), 7.63 (d, $J = 7.5$ Hz, 2 H), 7.50-7.46 (m, 3 H), 7.38 (t, $J = 7.0$ Hz, 1 H), 7.30 (s, 1 H), 4.65 (d, $J = 16.0$ Hz, 1 H), 4.53 (d, $J = 16.0$ Hz, 1 H), 3.68-3.65 (m, 1 H), 3.52 (s, 1 H), 3.49-3.46 (m, 1 H), 3.19-3.18 (m, 1 H), 2.42 (br s, 4 H), 2.36 (br s, 4 H), 2.15 (s, 3 H), 1.34 (d, $J = 6.5$ Hz, 3 H), 1.28 (s, 9 H). MS (ESI), m/z : 533 ($M^+ + H^+$).

Example 30 - 3-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2574)



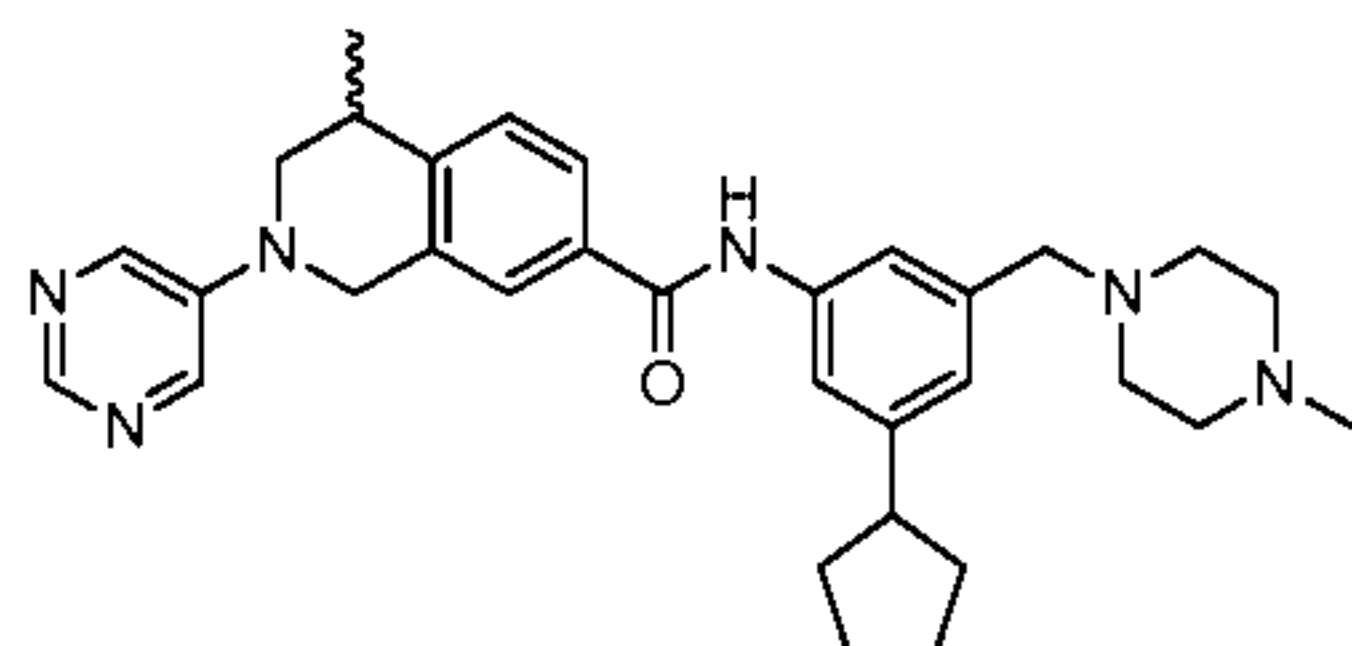
The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.52 (s, 1 H), 8.56-8.54 (m, 3 H), 8.19 (s, 1 H), 8.00 (s, 1 H), 7.90 (s, 1 H), 7.85 (d, *J* = 7.5 Hz, 1 H), 7.41 (d, *J* = 7.5 Hz, 1 H), 7.35 (s, 1 H), 4.72 (d, *J* = 16.5 Hz, 1 H), 4.60-4.50 (m, 1 H), 4.33 (d, *J* = 16.5 Hz, 1 H), 3.54 (s, 2 H), 3.25-3.22 (m, 1 H), 2.86-2.83 (m, 1 H), 2.46-2.21 (m, 8 H), 2.15 (s, 3 H), 0.99 (d, *J* = 6.0 Hz, 3 H). MS (ESI), *m/z*: 525 (*M*⁺ + *H*⁺).

Example 31 - N-(3-cyclopropyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2347)



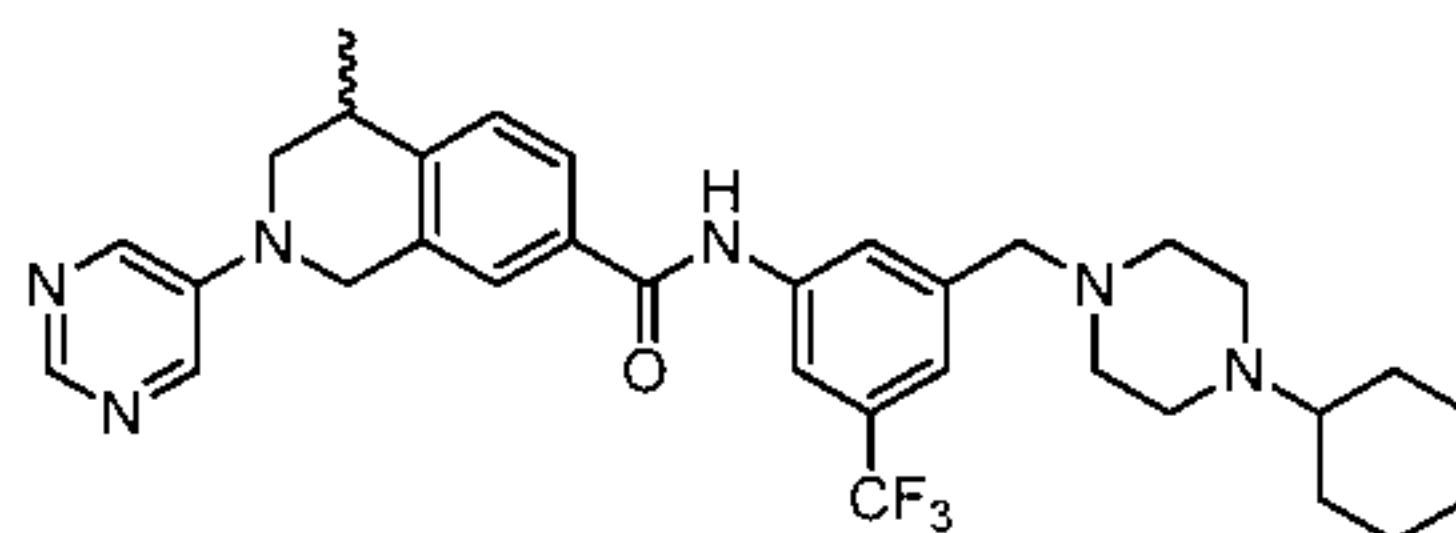
The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.09 (s, 1 H), 8.65-8.54 (m, 3 H), 7.83-7.81 (m, 2 H), 7.51 (s, 1 H), 7.44 (d, *J* = 7.5 Hz, 1 H), 7.39 (s, 1 H), 6.76 (s, 1 H), 4.64 (d, *J* = 16.0 Hz, 1 H), 4.52 (d, *J* = 16.0 Hz, 1 H), 3.67-3.64 (m, 1 H), 3.48-3.44 (m, 1 H), 3.38 (s, 2 H), 3.22-3.13 (m, 1 H), 2.47-2.21 (m, 8 H), 2.14 (s, 3 H), 1.90-1.89 (m, 1 H), 1.34 (d, *J* = 6.5 Hz, 3 H), 0.96-0.94 (m, 2 H), 0.63-0.62 (m, 2 H). MS (ESI), *m/z*: 497 (*M*⁺ + *H*⁺).

Example 32 - N-(3-cyclopentyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2196)



The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.10 (s, 1H), 8.60-8.54 (m, 3H), 7.84-7.81 (m, 2H), 7.60 (s, 1H), 7.56 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 6.89 (s, 1H), 4.64 (d, *J* = 16.0 Hz, 1H), 4.52 (d, *J* = 16.0 Hz, 1H), 3.66 (dd, *J* = 12.4, 4.4 Hz, 1H), 3.49-3.44 (m, 1H), 3.41 (s, 2H), 3.19-3.15 (m, 1H), 3.00-2.91 (m, 1H), 2.37-2.33 (m, 8H), 2.15 (s, 3H), 2.02-1.98 (m, 2H), 1.81-1.73 (m, 2H), 1.70-1.64 (m, 2H), 1.57-1.48 (m, 2H), 1.34 (d, *J* = 6.8 Hz, 3H). MS (ESI), *m/z*: 525 (*M*⁺ + *H*⁺).

Example 33 - N-(3-((4-cyclohexylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2195)



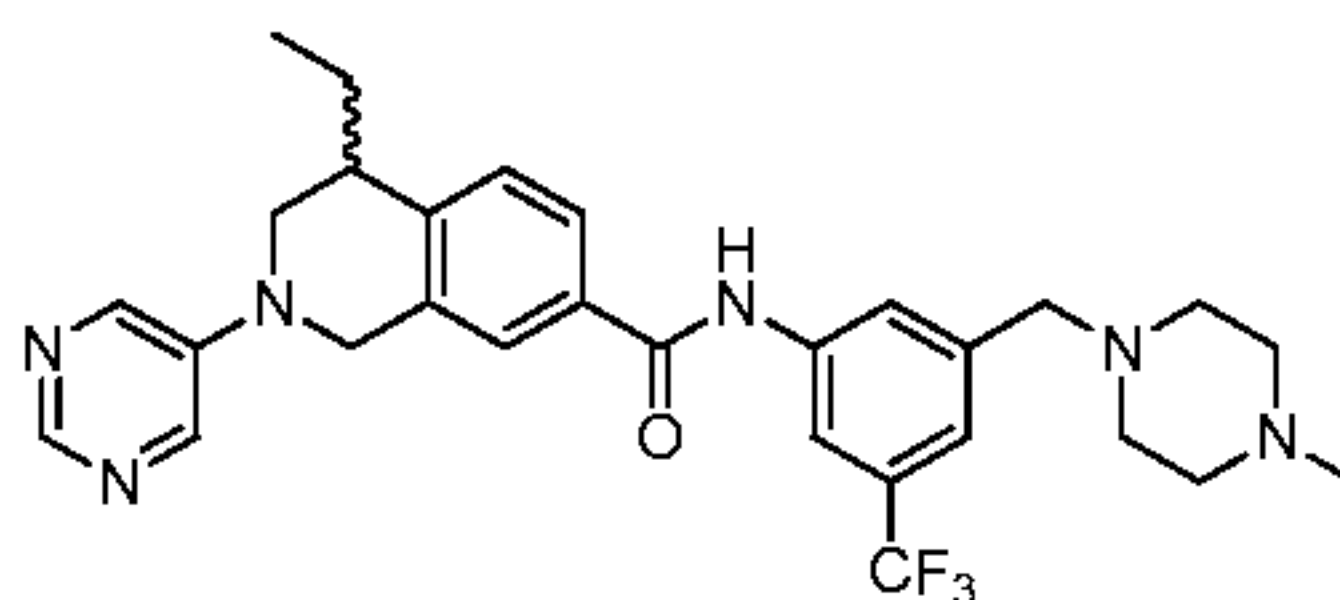
5

The compound was synthesized by using the procedure similar to that of Example 1. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.49 (s, 1 H), 8.63-8.51 (m, 3 H), 8.19 (s, 1 H), 7.99 (s, 1 H), 7.86-7.84 (m, 2 H), 7.46 (d, $J = 8.0$ Hz, 1 H), 7.33 (s, 1 H), 4.64 (d, $J = 16.4$ Hz, 1 H), 4.52 (d, $J = 16.0$ Hz, 1 H), 3.67-3.63 (m, 1 H), 3.51 (s, 2 H), 3.49-3.44 (m, 1 H), 3.19-3.17 (m, 1 H), 2.50-2.39 (m, 8 H), 2.24-2.10 (m, 1 H), 1.73-1.69 (m, 4 H), 1.55-1.53 (m, 1 H), 1.34 (d, $J = 6.8$ Hz, 3 H), 1.24-1.11 (m, 4 H), 1.10-0.97 (m, 1 H). MS (ESI), m/z : 593 ($\text{M}^+ + \text{H}^+$).

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Example 34 - 4-ethyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2213)

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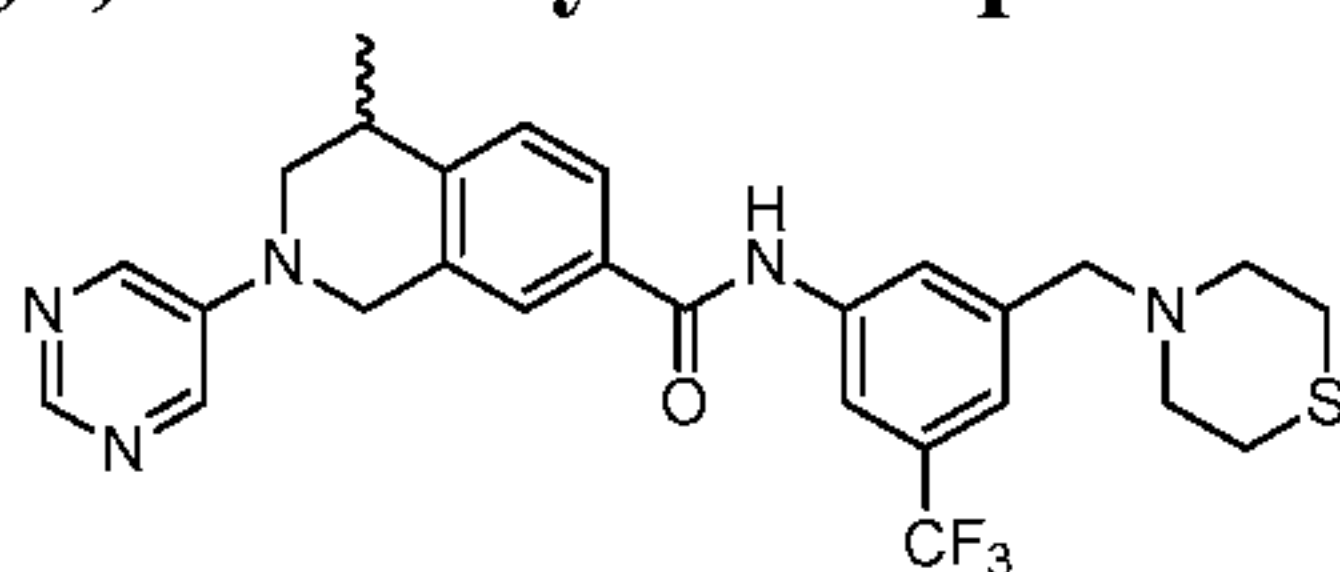


The compound was synthesized by using the procedure similar to that of Example 1. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.50 (s, 1 H), 8.61-8.52 (m, 3 H), 8.18 (s, 1 H), 8.00 (s, 1 H), 7.87-7.83 (m, 2 H), 7.43 (d, $J = 8.0$ Hz, 1 H), 7.34 (s, 1 H), 4.71 (d, $J = 16.0$ Hz, 1 H), 4.44 (d, $J = 16.0$ Hz, 1 H), 3.84-3.80 (m, 1 H), 3.54 (s, 2 H), 3.45-3.42 (m, 1 H), 3.02-2.92 (m, 1 H), 2.40 (br s, 4 H), 2.36 (br s, 4 H), 2.15 (s, 3 H), 1.71-1.67 (m, 2 H), 0.99 (t, $J = 7.2$ Hz, 3 H). MS (ESI), m/z : 539 ($\text{M}^+ + \text{H}^+$).

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Example 35 - 4-methyl-2-(pyrimidin-5-yl)-N-(3-(thiomorpholinomethyl)-5-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2191)

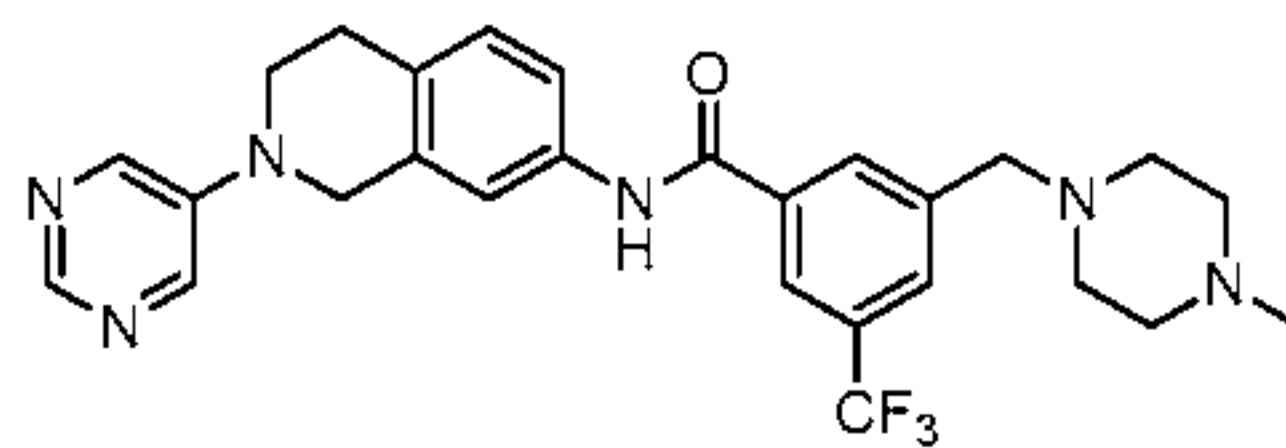
25



The compound was synthesized by using the procedure similar to that of Example 1. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.51 (s, 1 H), 8.62-8.53 (m, 3 H), 8.19 (s, 1 H), 8.01 (s, 1 H), 7.86-7.84 (m, 2 H), 7.47 (d, $J = 8.0$ Hz, 1 H), 7.35 (s, 1 H), 4.65 (d, $J = 16.4$ Hz, 1 H), 4.53 (d, $J = 16.0$ Hz, 1 H), 3.66 (dd, $J = 12.4, 4.4$ Hz, 1 H), 3.60-3.59 (m, 2 H), 3.47 (dd, $J = 12.4, 6.0$ Hz, 1 H), 3.19-3.18 (m, 1 H), 2.65-2.64 (m, 8 H), 1.34 (d, $J = 6.4$ Hz, 3 H). MS (ESI), m/z : 528 ($\text{M}^+ + \text{H}^+$).

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Example 36 - 3-((4-methylpiperazin-1-yl)methyl)-N-(2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-(trifluoromethyl)benzamide (D2212)



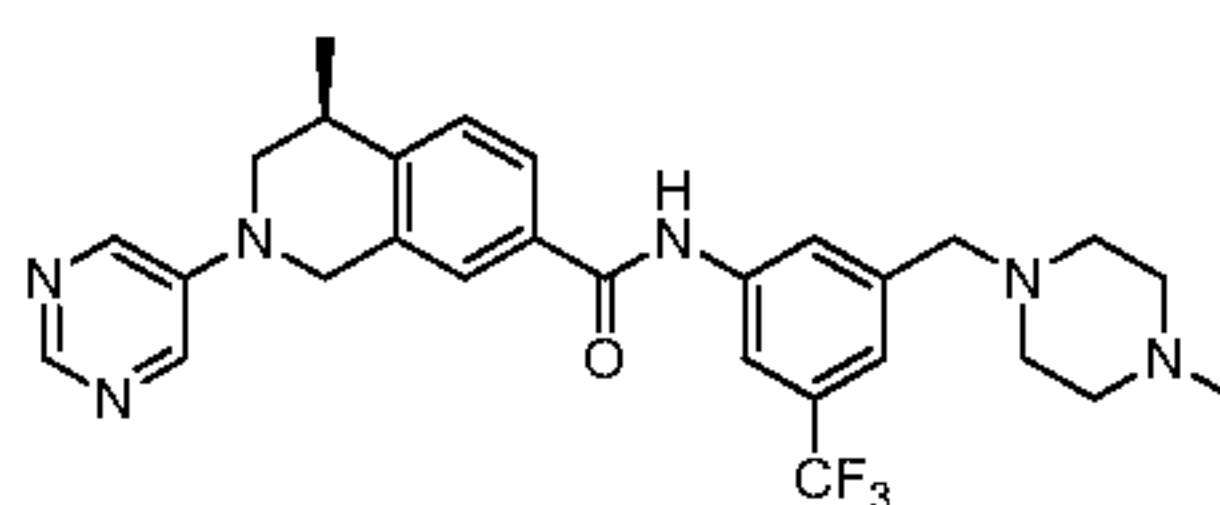
5

The compound was synthesized by using the procedure similar to that of Example 2. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.44 (s, 1 H), 8.57 (s, 2 H), 8.55 (s, 1 H) 8.20 (s, 1 H), 8.17 (s, 1 H), 7.84 (s, 1 H), 7.70 (s, 1 H), 7.55 (d, J = 8.4 Hz, 1 H), 7.19 (d, J = 8.0 Hz, 1 H), 4.51 (s, 2 H), 3.66-3.63 (m, 4 H), 2.96-2.86 (m, 2 H), 2.41 (br s, 4 H), 2.34 (br s, 4 H), 2.15 (s, 3 H). MS (ESI), m/z: 511 (M⁺ + H⁺).

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Example 37 - (S)-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2099)

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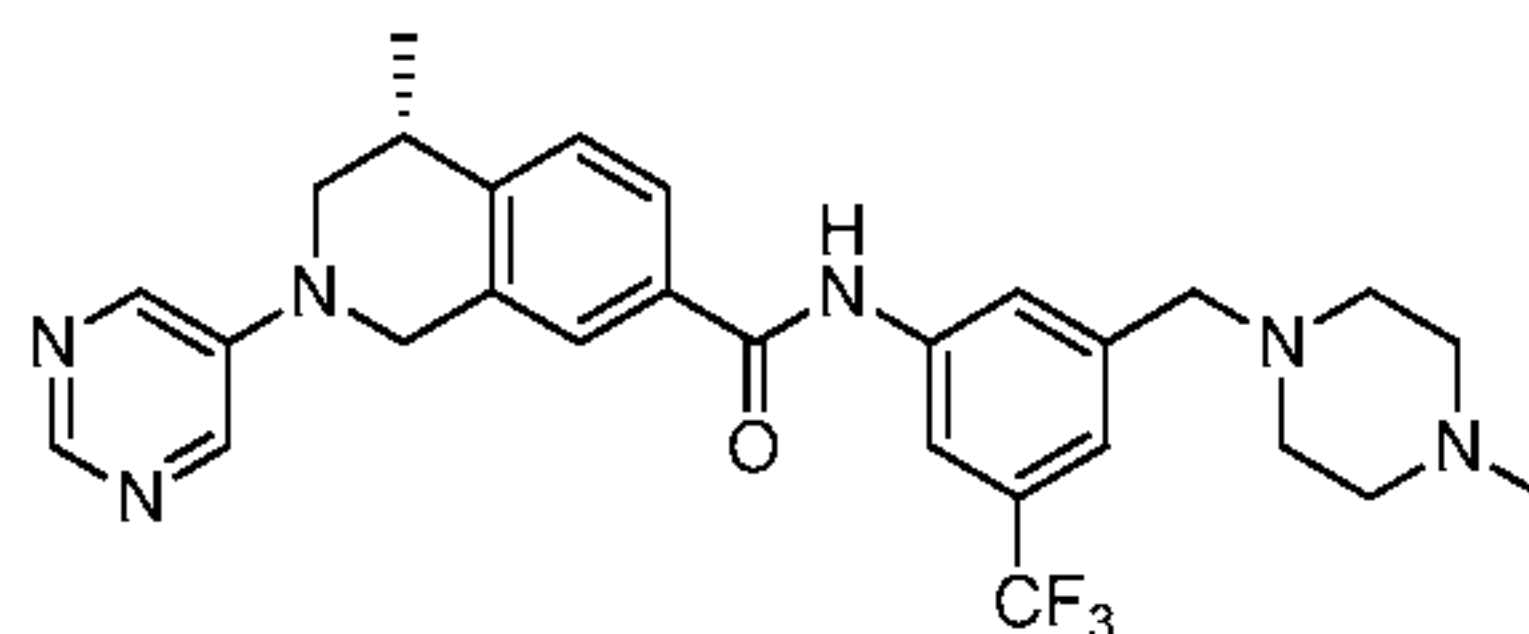


The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.50 (s, 1 H), 8.60-8.55 (m, 3 H), 8.19 (s, 1 H), 8.00 (s, 1 H), 7.86-7.84 (s, 2 H), 7.47 (d, J = 8.0 Hz, 1 H), 7.35 (s, 1 H), 4.65 (d, J = 16.0 Hz, 1 H), 4.53 (d, J = 16.0 Hz, 1 H), 3.66 (dd, J = 12.0, 3.6 Hz, 1 H), 3.54 (s, 2 H), 3.47 (dd, J = 12.4, 6.4 Hz, 1 H), 3.19-3.18 (m, 1 H), 2.40 (br s, 4 H), 2.33 (br s, 4 H), 2.15 (s, 3 H), 1.34 (d, J = 6.8 Hz, 3 H). MS (ESI), m/z: 525 (M⁺ + H⁺).

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Example 38 - (R)-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (D2200)

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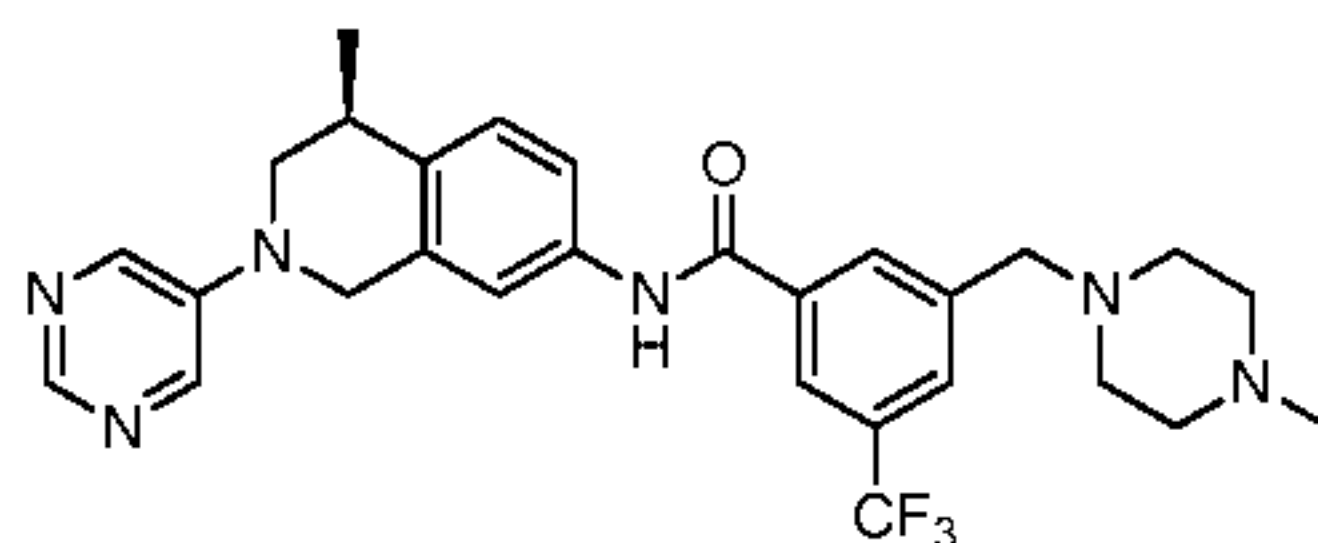
30

The compound was synthesized by using the procedure similar to that of Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.50 (s, 1 H), 8.60-8.55 (m, 3 H), 8.19 (s, 1 H), 8.00 (s, 1 H), 7.86-7.84 (m, 2 H), 7.47 (d, J = 8.0 Hz, 1 H), 7.35 (s, 1 H), 4.65 (d, J = 16.0 Hz, 1 H), 4.53 (d, J = 16.0 Hz, 1 H), 3.66 (dd, J = 12.4, 4.4 Hz, 1 H), 3.54 (s, 2 H), 3.47 (dd, J = 12.4, 6.0

35

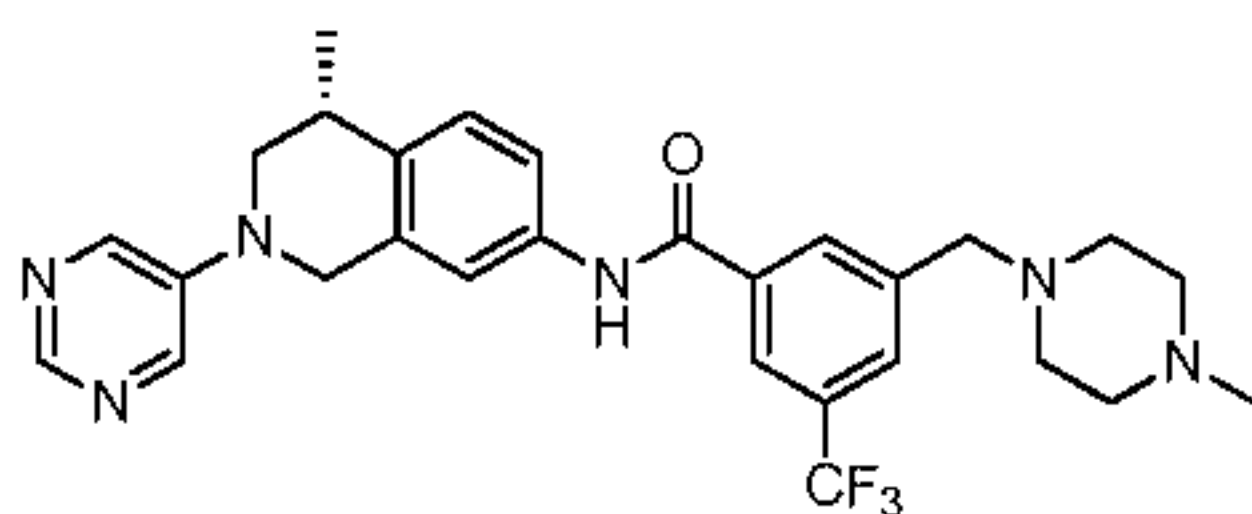
Hz, 1 H), 3.19-3.18 (m, 1 H), 2.39 (br s, 4 H), 2.34 (br s, 4 H), 2.15 (s, 3 H), 1.34 (d, J = 6.8 Hz, 3 H). MS (ESI), m/z: 525 ($M^+ + H^+$).

Example 39 - (S)-N-(4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)benzamide (D2100)



The compound was synthesized by using the procedure similar to that of Example 2. ^1H NMR (400 MHz, DMSO- d_6) δ 10.45 (s, 1 H), 8.57 (s, 2 H), 8.55 (s, 1 H), 8.19 (s, 1 H), 8.17 (s, 1 H), 7.85 (s, 1 H), 7.69 (s, 1 H), 7.58 (d, J = 8.4 Hz, 1 H), 7.30 (d, J = 8.4 Hz, 1 H), 4.55 (d, J = 16.0 Hz, 1 H), 4.45 (d, J = 16.0 Hz, 1 H), 3.68-3.60 (m, 3 H), 3.43-3.38 (m, 1 H), 3.08 (m, 1 H), 2.41 (br s, 4 H), 2.33 (br s, 4 H), 2.15 (s, 3 H), 1.30 (d, J = 6.8 Hz, 3 H). MS (ESI), m/z: 525 ($M^+ + H^+$).

Example 40 - (R)-N-(4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)benzamide (D2164)



The compound was synthesized by using the procedure similar to that of Example 2. ^1H NMR (400 MHz, DMSO- d_6) δ 10.44 (s, 1 H), 8.57 (s, 2 H), 8.55 (s, 1 H), 8.19 (s, 1 H), 8.17 (s, 1 H), 7.84 (s, 1 H), 7.69 (s, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.29 (d, J = 8.0 Hz, 1 H), 4.55 (d, J = 16.0 Hz, 1 H), 4.45 (d, J = 16.0 Hz, 1 H), 3.68-3.59 (m, 3 H), 3.42-3.38 (m, 1 H), 3.08-3.07 (m, 1 H), 2.41 (br s, 4 H), 2.33 (br s, 4 H), 2.15 (s, 3 H), 1.30 (d, J = 6.8 Hz, 3 H). MS (ESI), m/z: 525 ($M^+ + H^+$).

Example 41 - *In Vitro* Kinase Assay

The effects of compounds on the kinases DDR1 and DDR2 were assessed by using a Lantha Screen Eu kinase activity assay technology (Invitrogen, USA). Kinase reactions are performed in a 10 μL volume in low-volume 384-well plates. The kinases in reaction buffer consist of 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM MgCl_2 , and 1 mM EGTA, the concentration of Fluorescein-Poly GAT substrate (Invitrogen, USA) in the assay is 100 nM. Kinase reactions were initiated with the addition of 100 nM ATP in the presence of serials of

dilutions of compounds. The reactions were allowed to proceed for 1 h at room temperature before a 10 μ L preparation of EDTA (20 mM) and Eu-labeled antibody (4 nM) in TR-FRET dilution buffer are added. The final concentration of antibody in the assay well is 2 nM, and the final concentration of EDTA is 10 mM. The plate is allowed to incubate at room temperature for one more hour before the TR-FRET emission ratios of 665 nm/340 nm were acquired on a PerkinElmer EnVision multilabel reader (Perkin-Elmer, Inc.). Data analysis and curve fitting were performed using GraphPad Prism4 software, resulting in the half maximal inhibitory concentration (IC₅₀) shown in table 1. The functional assays of compounds on the kinase activities of c-kit and Abl were determined using the FRET-based Z'-Lyte assay system according to the manufacturer's instructions (Invitrogen, USA). Tyrosine 2 peptide was used as Abl substrate, and Ser/Thr 6 peptide was used as the substrate for c-kit. The reactions were carried out in 384-well plates in a 10 μ L of reaction volume with appropriate amount of kinases in 50 mM HEPES (pH 7.5), 10 mM MgCl₂, 1 mM EGTA, and 0.01% Brij-35. The reactions were incubated 1 h at room temperature in the presence of 2 μ M of substrate with 10 μ M of ATP (for Abl assays) or 300 μ M of ATP (kit assay) and in the presence of various concentrations of the compounds. The development reagent was then added for further 2 h room temperature incubation followed by the addition of stop solution. Fluorescence signal ratio of 445 nm (Coumarin)/520 nm (fluorescein) was examined on EnVision Multilabel Reader (Perkin-Elmer, Inc.), resulting in the half maximal inhibitory concentration (IC₅₀) shown in Table 1.

Example 42 – Materials and Methods

Cell lines. Human pancreatic cancer cell lines (AsPC-1 and Panc-1) were purchased from the American Type Culture Collection (Manassas, VA) and were fingerprinted for validation of authenticity. The murine pancreatic cancer cell line Pan02 (also known as Panc02) was obtained from the NCI (DCTD Tumor Repository). Cells were cultured in DMEM (Invitrogen) or RPMI (Invitrogen) containing 5% fetal bovine serum and maintained at 37 °C in a humidified incubator with 5% CO₂ and 95% air.

***In vitro* cytotoxicity and drug response assay.** MTS assays were conducted in 96-well plates; cells were plated on day 0 and drug was added on day 1 in 4-fold dilutions. Drugs were evaluated as single agents with a maximum concentration of 2 μ M for gemcitabine and 7rh. For combination studies 7rh was added with a fixed concentration of 250 or 500 nM with a 4-fold dilution of gemcitabine. Relative cell number was determined by adding MTS

(Promega; final concentration 333 $\mu\text{g/mL}$), incubating for 1 to 3 hours at 37 °C, and reading absorbance. Drug sensitivity curves and IC_{50}s were calculated using in-house software (Apte *et al.*, 2004).

Wound healing (scratch) assay. Cells were cultured in 6-well tissue culture plates at high density (~90% confluence) in 2 mL 5% DMEM or 5% RPMI. Uniform scratches were made down the center of each well with a p20 pipette tip. Cells were plated on respective culture conditions and allowed to sit for approximately 30 hours, or until end of possible migration. Images from the center of each well were taken at times 0, 10, 20, and 30 hours. The wound width (μm) was measured using NIS Elements AR 2.30 software. The initial wound width was used to verify consistency in scratches.

Liquid colony forming assay. Cells were cultured in 6-well tissue culture plates at low density (250 cells per well) in 2 ml 5% DMEM or 5% RPMI. Cells were plated on respective culture conditions and allowed to sit for approximately 1.5-2 weeks, or until significant colony formation. Cells were then fixed with 10% formalin and stained with crystal violet. Images were analyzed with Image J or NIS Elements.

Western blot analysis. Sub-confluent monolayers of cells were lysed, supernatants were recovered by centrifugation at 13000 rpm, protein concentrations were measured and equal amounts of total protein were separated by SDS-PAGE. Proteins were transferred to PVDF membranes (Bio-Rad, Hercules, CA) followed by blockade for 1 hour in 5% milk in TBS-T. The membranes were incubated overnight at 4°C with primary antibody. Membranes were incubated with the corresponding HRP-conjugated secondary antibody (Pierce Biotechnologies, Rockford, IL) for 1 to 2 hour. Specific bands were detected using the enhanced chemiluminescence reagent (ECL, Perkin Elmer Life Sciences, Boston, MA) on autoradiographic film.

Immunoprecipitation. Cell lines were lysed in modified radioimmunoprecipitation (RIPA) assay buffer (0.5% deoxycholate, 0.5% SDS, 1% Triton X-100, 10 mM sodium phosphate, pH 7.2, 150 mM sodium chloride, and protease inhibitor (Complete Mini)). Lysis was performed on serum-starved adherent cells after washing with chilled PBS. Lysates were allowed to rotate at 4 °C on a nutator for 1 h and then vortexed several times before centrifuging at 13,000 rpm for 10 min to pellet any insoluble material. Lysates were pre-cleared with protein A/G beads (Thermo Fisher Scientific). 200 μg cellular protein in 1 ml lysis buffer was used per immunoprecipitation reaction. 1 μg of the appropriate IgG was added with 50 μl protein A/G bead slurry to each sample; each sample was then allowed to rotate overnight at 4 °C on a nutator. Immunoprecipitated complexes were washed twice in

lysis buffer and then boiled in sample buffer and subjected to SDS-PAGE and Western blot analysis.

siRNA-mediated knockdown of DDR1. Cells were plated 18-24 hours before transfection (1×10^5 cell/well in 6 well dish) at an initial confluence of 60-80%. TransIT-siQUEST reagent and siRNA complexes were prepared and added according to manufacturer instructions (Mirus Bio LLC). siRNA complexes were added to the cells at a final siRNA complex concentration was 1 μ M. Protein was harvested 72 hours post transfection for western blot analysis. siRNA duplexes were purchased from Integrated DNA Technologies. DDR1 duplexes used were (NM_001954 duplexes 1-3):

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Duplex #1: 5'-GUCUUGUAGCUAGAACUUCUCUAAG-3' (SEQ ID NO: 1),

3'-GUCAGAACAUUCGAUCUUGAAGAGAUUC-5' (SEQ ID NO: 2);

15

Duplex #2: 5'-GCACUAGGCAGGUAAUAAUAAAGGT-3' (SEQ ID NO: 3),

3'-GACGUGAUCCGUCCAUAUAUUUUCCA-5' (SEQ ID NO: 4);

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Duplex #3: 5'-ACACUAAUAUAUGGACCUAGAUUGA-3' (SEQ ID NO: 5),

3'-AAUGUGAUUAUAUACCUGGAUCGAACU-5' (SEQ ID NO: 6).

RNA isolation/purification and RT-PCR. RNA was isolated from cell line pellets utilizing TRIzol® (Invitrogen) reagent according to the manufacturer's protocol. The samples were then eluted in RNase/DNase free water and utilized for subsequent cDNA synthesis. Purified RNA was reverse transcribed into cDNA using the iScript™ cDNA synthesis kit (Bio-Rad, Hercules, CA). The following human primer sets were used for RT-PCR:

30

DDR1-FWD: CCTCTTTGCAGGTCCTTGGTT (SEQ ID NO: 7),

DDR1-REV: AGCTCCAAGCTGCTGAAGTTG (SEQ ID NO: 8);

DDR2-FWD: AAGCTGGGAGAAGGCCAGTT (SEQ ID NO: 9),

DDR2-REV: AGGCTGGTTGGCACTGACAT (SEQ ID NO: 10);

Collα1-FWD: GACGCCATCAAGGTCTACTG (SEQ ID NO: 11);

Collα1-REV: ACGGGAATCCATCGGTCA (SEQ ID NO: 12);
Collα2-FWD: GGAGGGAACGGTCCACGAT (SEQ ID NO: 13);
Collα2-REV: GAGTCCGCGGTATCCACAA (SEQ ID NO: 14);
Itg α1-FWD: TGGGTGCTTATTGGTTCTCC (SEQ ID NO: 15);
5 Itg α1-REV: CCTCCTTTCTTGCTGTGTCTAT (SEQ ID NO: 16);
Itg β1-FWD: GAAGCTCAAGCCAGAGGATATT (SEQ ID NO: 17);
Itg β1-REV: CTGGACAAGGTGAGCAATAGAA (SEQ ID NO: 18);
PEAK1-FWD: GTTGGAGTAGCCTCCCATTATC (SEQ ID NO: 19);
PEAK1-REV: GACGCTTAGTAGGACCCAAAG (SEQ ID NO: 20);
10 RPS6-FWD: GAGCGTTCTCAACTTGGTTATTG (SEQ ID NO: 21);
RPS6-REV: GTGCTTTGGTCCTAGGTTTCT (SEQ ID NO: 22).

Animal studies. All animals were housed in pathogen-free facility with access to food and water ad libitum. C57BL/6 and NOD-SCID mice were purchased from an on-site distributor. *Kras*^{G12D/+}; *LSL-Trp53*^{R172H/+}; *p48*^{Cre/+} (*KPC*) mice were generated as previously described (Hingorani *et al.*, 2005). Mice were randomized to receive treatment as indicated in Table 1. Experiments were approved and performed in accordance with the Institutional Animal Care and Use Committee at the University of Texas Southwestern Medical Center. For endpoint studies experiments were stopped after the designated time post-tumor cell
15 implantation. For survival studies, therapy was maintained until mice were moribund. At the time of sacrifice all mice were subjected to careful necropsy where visible metastases were noted and organs harvested for tissue analysis. Liver micrometastasis was assessed by hemotoxylin and eosin staining of the anterior lobes of the liver.

25 **Table 1: Description of animal experiments**

Endpoint:	Experiment start	10 days post tumor cell injection
7rh titration	Experiment length	12 hours
	Animals	<i>C57BL/6</i> , (n=3/group)
	Treatment groups	Vehicle: 1 dose 7rh: 0.1 mg/kg, 1 dose 7rh: 1 mg/kg, 1 dose 7rh: 10 mg/kg, 1 dose
	Associated figures	FIG. 7
Endpoint:	Experiment start	10 days post tumor cell injection
7rh titration	Experiment length	21 days post tumor cell injection
	Animals	<i>C57BL/6</i> , (n=5/group)

	Treatment groups	Vehicle: 3×/week 7rh: 3.3 mg/kg, 3×/week 7rh: 10 mg/kg, 3×/week 7rh: 30 mg/kg, 3×/week
	Associated figures	FIGS 8 & 9
Endpoint:	Experiment start	19 days post tumor cell injection
7rh monotherapy	Experiment length	40 days post tumor cell injection
	Animals	<i>C57BL/6</i> , (n=16/group)
	Treatment groups	Vehicle: 3x/week 7rh: 25 mg/kg, 3x/week
	Associated figures	FIG. 10
Survival:	Experiment start	27 days post tumor cell injection
7rh +/- chemo	Experiment length	Until moribund
	Animals	Nod Scid, (n=12/group)
	Treatment groups	Vehicle: 3×/week 7rh: 25 mg/kg, 3×/week Chemotherapy: Gem (12.5 mg/kg, 2×/week), Nab-pac (5 mg/kg, 2×/week) Combination: 7rh + Chemotherapy
	Associated figures	FIGS. 11 & 12
Survival:	Experiment start	16 weeks old
7rh +/- chemo	Experiment length	Until moribund
	Animals	<i>KPC (LSL-Kras^{G12D/+}; LSL-Trp53^{R172H/+}; P48-Cre)</i> , (n=12/group)
	Treatment groups	Vehicle: 3×/week 7rh: 25 mg/kg, 3×/week Chemotherapy: Gem (12.5 mg/kg, 2×/week), Nab-pac (5 mg/kg, 2×/week) Combination: 7rh + Chemotherapy
	Associated figures	FIGS. 13 & 14

* Gem is gemcitabine; Nab-pac is nab-paclitaxel.

Histology. Immunohistochemistry was performed with antibodies against: phospho-DDR1 (Tyr792, Cell Signaling #11994), DDR1 (D1G6, Cell Signaling #5583), phospho-SRC (Tyr416, Cell Signaling #2101), phospho-PYK2 (Tyr402, Cell Signaling #3291), phospho-p130 CAS (Tyr165, Cell Signaling #4015), α -Amylase (D55H10, Cell Signaling #3796), vimentin (Millipore AB5733), phospho-FAK (Abcam #4803), activated β 1 Integrin (Millipore #2079Z), PEAK1 (Millipore 09-274) and phospho-PEAK1 (Tyr665, Millipore #ABT52). Fluorescent images were captured with Photometric Coolsnap HQ camera using NIS Elements AR 2.3 Software (Nikon). Color images were obtained with a Nikon Eclipse E600 microscope using a Nikon Digital Dx1200me camera and ACT1 software (Universal Imaging Corporation). Pictures were analyzed using NIS Elements (Nikon).

Statistical analysis. Quantification of immunohistochemistry was conducted using NIS Elements 3.2 software (Nikon Instruments). All data were analyzed using GraphPad

Prism 5.0 software (GraphPad Software Inc.). Datasets were analyzed by Student t test or ANOVA followed by Dunn post test or Tukey's MCT and results were considered as significant at $p < 0.05$. Results are shown as mean $\pm$ SEM.

5

Example 43 - Results

A. Association of DDR1 Signaling with Enhanced Malignancy

The mRNA expression of collagen I $\alpha 1$, DDR1, PYK2 and PEA1 were analyzed in human PDA patients (n=168) in TCGA (via CBioportal). Expression was divided into high and low at the median (described in materials and methods). While there was no statistically significant difference in outcome (survival) with respect to expression of these targets at a 95% confidence interval, several notable trends were identified. PDAs with high expression of collagen I $\alpha 1$ or PEA1 had a trend for worse overall survival (**FIG. 1A**). The mRNA expression of DDR1 and collagen I $\alpha 1$ in lung cancer was also evaluated using the Kaplan-Meier Plotter online database (Gyorffy *et al.*, 2013). In lung cancer, expression of DDR1 and collagen I also correlated with worse survival (**FIG. 2A**). To characterize the level of collagen-mediated DDR1 signaling in PDA, the expression of phosphorylated DDR1 and a downstream effector (PEAK1) in human pancreatic tumor samples was determined with matched patient-derived tumor xenograft (PATX) samples. Primary tumors (44) and PATX samples (150) showed robust activation of DDR1 and PEA1 (**FIG. 1B, FIG. 2B**). The overall percentages of staining positivity are shown in **FIG. 2C**. Furthermore, the expression of active Ddr1, Pyk2 and Peak1 as well as the expression of Muc1 and Sox9 in pancreatic tumors was examined from early (3 month) and later (5 month) stages of the *KPC* (*LSL-Kras^{G12D/+}; LSL-Trp53^{R172H/+}; p48^{Cre/+}*) mouse model of PDA (**FIG. 1C**). The *KPC* model recapitulated many of the pathological features seen in human PDA including a dense stromal reaction (Hingorani *et al.*, 2005) (**FIGS. 1D & 1E**). Trichrome analysis revealed robust collagen deposition throughout PDA lesions in *KPC* mice (**FIG. 1E**). Ddr1 activation and downstream signaling (Pyk2 and Peak1) was present in early pancreatic intraepithelial (PanIN) lesions as shown by correlative staining with a marker of early PDA lesions, Muc-1. Additionally, these effectors were expressed highly throughout the tumor epithelium at the later stage of the model (5-month old *KPC*) as identified by areas expressing Sox9 (**FIG. 1C**). Sox9 was expressed in the malignant epithelium and was confined to the duct-like cells; differentiated acinar and endocrine cells do not express Sox9 (Seymour *et al.*, 2008 and Furuyama *et al.*, 2011).

These data demonstrated that collagen signaling via DDR1 is active in human PDA and mouse models of the disease.

The KPC model recapitulates many of the pathological features seen in human PDA including a dense stromal reaction (Hingorani *et al.*, 2005) (FIGS. 3A-B). Trichrome analysis
5 revealed robust collagen deposition throughout PDA lesions in KPC mice (FIGS. 3C-D). Histological analyses of metastatic lesions in the liver demonstrate that collagen is deposited in liver lesions. Further these lesions show activation of Ddr1 and Peak1 as well as vimentin and PCNA positive cells. (FIGS. 3G-H). These findings indicate that collagen signaling through Ddr1 is present in primary and metastatic PDA lesions and suggest that
10 pharmacologic inhibition of Ddr1 could provide therapeutic benefit.

B. Regulation of Collagen Signaling

To determine if collagen signaling via DDR1 directly affects pancreatic cancer cell biology, the expression of genes involved in collagen signaling in human PDA cell lines (AsPC-1 and PANC-1) was determined by PCR. Each cell line expressed similar levels of
15 *DDR1*, *PEAK1*, *INTEGRIN $\alpha 1$* (*ITG $\alpha 1$*), *INTEGRIN $\beta 1$* (*ITG $\beta 1$*), *COLLAGEN I $\alpha 1$* (*COL I $\alpha 1$*), and *COLLAGEN I $\alpha 2$* (*COL I $\alpha 2$*) (FIG. 4A). The level of collagen expressed by AsPC-1 and PANC-1 cells was determined by a Sircol assay (FIG. 4B) and confirmed that AsPC-1 cells expressed high levels of collagen. These results corresponded to the high endogenous activation of DDR1 (FIG. 4C) found in AsPC-1 cells. Addition of exogenous soluble
20 collagen enhanced the phosphorylation of DDR1, SRC, and PEAK1 in PANC-1 cells but did not affect the level of DDR1 signaling in AsPC-1 cells (FIGS. 4C & 4D). Immunofluorescence was used to visualize DDR1 signaling in a cellular context. AsPC-1 and PANC-1 cells were plated on plastic or collagen and phosphorylated PEAK1 was assessed. In this context collagen stimulated PEAK1 activation in each cell line (FIG. 4D). The
25 downstream effectors of DDR1 are ill-defined (Valiathan *et al.*, 2012 and Leitinger, 2014); however, the phosphorylated PYK2 and PEAK1 was found to co-immunoprecipitated with DDR1 from AsPC-1 cells. The absence of integrin αv and $\beta 1$ in the DDR1 IP suggested that DDR1 mediated activation of these effectors is independent of integrin activation (FIG. 4E). To further define the contribution of DDR1 to collagen signaling AsPC-1 cells were
30 stimulated with collagen after siRNA-mediated knockdown of DDR1. Loss of DDR1 expression abrogated the activation of PYK, SRC, PEAK1 and AKT1 (FIG. 4F-4G), as well as cell migration (FIG. 4H). These data supported that collagen-mediated activation of DDR1 induced a signal pathway that included PYK2, SRC, PEAK1 and AKT1, which in turn

are potentially responsible for collagen-induced pathways, including chemoresistance (Mahadevan and Von Hoff, 2007 and Chauhan *et al.*, 2013), that promote tumor progression.

To demonstrate that DDR1 participates in chemoresponse in PDA the effect of the small molecule kinase inhibitor 3-(2-(Pyrazolo[1,5-a]pyrimidin-6-yl)-ethynyl) 7rh benzamide (7rh) (Gao *et al.*, 2013) on collagen-induced signaling in PANC-1 cells was evaluated. 7rh has high specificity for DDR1 versus other related kinases (IC₅₀: DDR1, 6.8 nM; DDR2, 101.4 nM; Bcr-Abl, 355 nM) based on previously published cell-free kinase assays (Gao *et al.*, 2013). 7rh inhibited DDR1-mediated signaling induced by soluble collagen (10 µg/mL) in PANC-1 cells in a concentration-dependent manner (**FIG. 5A**). At pharmacologically-relevant concentrations 7rh inhibited activation of PYK2, PEAK1, SHC, and AKT1. However, 7rh did not affect the activation of focal adhesion kinase (FAK), an effector that has not been previously associated with DDR1-induced signaling (Shintani *et al.*, 2008). Inhibition of the DDR1 signaling with 7rh also reduced cell migration (**FIG. 5B**) and colony formation (**FIG. 5C**) in a concentration-dependent manner.

Chemoresistance is a major challenge in the treatment of patients with PDA. Given the effect of 7rh on PDA colony formation and migration the effect of 7rh in combination with gemcitabine, a chemotherapy agent commonly used for the treatment of PDA, was evaluated. The efficacy of 7rh alone or in combination with gemcitabine was tested by MTS assay in AsPC-1 and PANC-1 cells plated on plastic or collagen (**Table 2**). In cells plated on plastic, 7rh reduced cell viability with an IC₅₀ of 490 nM and 380 nM in AsPC-1 and PANC-1 cells, respectively. However, 7rh at 500 nM dramatically decreased the IC₅₀ of gemcitabine in each cell line from >2000 nM to 2 nM or less (**FIG. 5D**) strongly suggesting synergy between the two agents. Analysis with CompuSyn Synergistical Analysis software (Chou, 2006) indicated that 7rh at 500 nM was synergistic with gemcitabine in AsPC-1 and PANC-1 cells (**FIG. 6**). These findings highlight the therapeutic potential of DDR1 inhibition in combination with chemotherapy for PDA.

Table 2: Collagen shifts sensitivity of human PDA cell lines to therapeutic agents.

Coating	7rh (nM)		Gemcitabine (nM) Avg IC ₅₀ s		250 nM 7rh + Gem Avg IC ₅₀ s		500 nM 7rh + Gem Avg IC ₅₀ s	
	Plastic (#)	Collagen (#)	Plastic (#)	Collagen (#)	Plastic (#)	Collagen (#)	Plastic (#)	Collagen (#)
ASPC-1	490 (6)	550 (6)	2000 (3)	2000 (3)	1725 (3)	2000 (4)	2.05 (2)	2.7 (2)
PANC-1	380 (4)	402 (4)	2000 (4)	2000 (3)	16.4 (3)	25.7 (3)	0.035 (3)	0.035 (3)

C. 7rh Benzamide Inhibits Collagen-Mediated Signaling *In vivo*

Prior pharmacokinetic studies (Gao *et al.*, 2013) established the *in vivo* half-life of 7rh to be ~12 hr in rats. To determine an appropriate dose for therapy studies, mice bearing established orthotopic Pan02 pancreatic tumors were given a single dose of 0.1, 1, or 10 mg/kg of 7rh via oral gavage **FIG. 7, Table 1**). Tumor tissue was collected 12 hours post treatment and analyzed for DDR1 activity. 7rh at 1 mg/kg and 10 mg/kg significantly reduced the phosphorylation of Ddr1 as well as downstream effectors Pyk2 and Peak1, and resulted in an increased apoptotic index (Cleaved Caspase-3) (**FIG. 7b-7e**) as shown by immunohistochemical analysis. After demonstration that 7rh can reduce DDR1 activity in the tumor microenvironment, a single agent therapy experiment was performed using a titration of 7rh for 2 weeks. Mice bearing established orthotopic Pan02 tumors were treated with 7rh (3, 10, or 30 mg/kg, 3×/week) via oral gavage (**FIG. 8, Table 1**). 7rh at 10 mg/kg and 30 mg/kg resulted in an increase in normal pancreatic tissue as determined by H&E histology and expression of amylase, a marker of normal acinar tissue (**FIG. 8B-8C**). 7rh at these concentrations also significantly reduced the level of phosphorylated Ddr1 and Peak1 (**FIG. 8D-8E**), as well as proliferation noted by the reduction of Pcnal levels (**FIG. 8F**). These findings were corroborated by western blot analysis of tumor lysates that showed a 7rh-dependent reduction of Peak1 phosphorylation (**FIG. 8G**). 7rh showed no apparent normal tissue toxicity as demonstrated by the maintenance of body weight and the lack of changes in serum metabolites specific for liver and kidney function. Metabolites analyzed included Alb (albumin), Alt (liver transaminases), Ast (aspartate transaminase), Bun (blood urea nitrogen), Crea (creatinine), Glu (glucose), Tbil (total bilirubin), and Tp (plasma total protein) (**FIG. 9A-9B**). Next, the inventors performed a single agent therapy experiment with a fixed concentration of 7rh. Mice bearing established orthotopic Pan02 tumors were treated with 7rh (25 mg/kg, 3×/week) (**FIG. 10, Table 1**). Therapy was initiated 19 days post tumor cell

injection and continued until experiment day 40, at which point animals were sacrificed (FIG. 10A). 7rh significantly reduced primary tumor weight (FIG. 10B). Histological analysis of pancreata from these animals showed that 7rh slowed progression of disease (FIG. 11C). This is consistent with increased amylase expression (FIG. 10D) and a
 5 significant decrease in Ddr1, Peak1, and Pyk2 activation (FIG. 10E-10G) in animals receiving 7rh. This was concordant with enhanced apoptosis (Cleaved Caspase-3, FIG. 10H) and reduced proliferation (Pcna, FIG. 10I) in the presence of 7rh therapy.

To assess if 7rh enhanced the efficacy of chemotherapy *in vivo*, the inventors combined 7rh with the standard of care chemotherapy of PDA (gemcitabine and nab-
 10 paclitaxel) in a xenograft model of PDA (FIG. 11A, Table 1). Immunocompromised animals bearing orthotopic AsPC-1 tumors were treated with vehicle, 7rh monotherapy (25 mg/kg, 3×/week), the standard of care regimen (chemo: gemcitabine, 15 mg/kg, 2×/week; nab-paclitaxel, 5 mg/kg, 2×/week), or the combination (combo) of 7rh and chemotherapy (FIG. 11A, Table 1). Therapy was initiated 27 days post tumor cell injection and 3 animals from
 15 each cohort were sacrificed on day 28 (one day post therapy induction) to document tumor burden at the start of therapy (initial group). Each regimen was continued until individual animals became moribund, at which point the moribund animals were sacrificed. The combination of 7rh + chemotherapy significantly enhanced the median overall survival to 98 days, compared to chemotherapy, 7rh, or vehicle at 73, 57, and 54.5 days respectively. After
 20 the median survival was achieved for the combination group, therapy was withdrawn at day 102 to assess the consequence of therapy removal (withdrawn group) (FIG. 11B-11C, FIG. 12). Tumor tissue from each group was analyzed by histology and immunohistochemistry. Combination therapy resulted in more normal pancreatic tissue (H&E), a significant reduction in collagen signaling (P-DDR1, P-PYK2, P-PEAK1), a reduction in VIMENTIN
 25 expression as well as cell proliferation (PCNA), and enhanced apoptosis (cleaved CASPASE-3) and DNA damage (γ H2AX) (FIG. 11D-G, I-L). Withdrawal of therapy from the combination group resulted in restoration of cell proliferation, VIMENTIN expression and collagen signaling to levels similar to that observed in vehicle treated animals. Additionally, the inventors noted that 7rh alone or in combination with chemotherapy reduced trichrome
 30 staining suggesting a reduction in fibrosis (FIG. 13A). Tumor weight vs survival days was plotted (FIG. 12B) and indicated that therapy with 7rh, chemotherapy, or the combination reduced primary tumor growth compared to treatment with vehicle. Animal weight was monitored throughout the experiment and no therapy-induced changes in body weight were noted (FIG. 12C).

To determine if the therapeutic efficacy of 7rh combinatorial therapy extended to more rigorous *in vivo* models, the inventors moved to a genetically engineered mouse model (GEMM) of PDA. *KPC (LSL-Kras^{G12D/+}; LSL-Trp53^{R172H/+}; p48^{Cre/+})* mice were enrolled into therapy cohorts at 4 months of age (**FIG. 13, Table 1**), a time point the inventors have found where greater than 90% of animals have established PDA. Treatment arms were the same as the AsPC-1 xenograft experiment and contained 12 animals/cohort. An additional 9 animals were sacrificed at the start of therapy to document mean tumor burden at the initiation of the experiment. Treatment with the combination regimen enhanced median of survival to 208 days compared to treatment with chemotherapy, 7rh, or vehicle at 180, 159, and 144 days respectively (**FIGS. 13B & 13C**). Immunohistochemical analyses of tumor tissue harvested at the time of sacrifice demonstrated that inhibition of Ddr1 with 7rh suppressed collagen signaling (P-Ddr1 and P-Peak1), reduced Vimentin expression and cell proliferation (Pcna) while increasing apoptosis (cleaved Caspase-3) and DNA damage (γ H2ax) (**FIGS. 13D-13J**). Chemotherapy with gemcitabine and nab-paclitaxel also reduced collagen signaling and Vimentin expression as well as decreasing the number of Pcna positive cells. Additionally, treatment with 7rh alone, chemotherapy alone or the combination induced a reduction in trichrome staining (**FIG. 14A**). Tumor weight vs survival days was plotted (**FIG. 14B**) and indicated that therapy with 7rh, conventional chemotherapy, or the combination reduced primary tumor growth compared to treatment with vehicle. Animal weight was not adversely affected by therapy (**FIG. 14C**). These data demonstrate that Ddr1 inhibition can increase the efficacy of standard of care chemotherapy in robust preclinical models of PDA.

Example 44 - Discussion

Based upon the data provided herein, the contribution of collagen-mediated DDR1 signaling to PDA progression was evaluated. The inventors demonstrated that DDR1 and downstream effectors are expressed and activated in human and mouse PDA. Additionally, a novel small molecule inhibitor, 7rh benzamide (Gao *et al.*, 2013), was evaluated effectively abrogated DDR1 signaling thereby reducing liquid colony tumor cell formation, tumor cell migration, and sensitized human PDA cell lines to gemcitabine *in vitro*. Further, 7rh was found to inhibit its target and has significant therapeutic efficacy *in vivo* at doses that are free from observable tissue toxicity. Finally, 7rh significantly improved the efficacy of standard of care chemotherapy in robust mouse models of PDA. Overall these data highlight that collagen signaling through DDR1 is a critical and pharmacologically targetable pathway in PDA.

Physiological chemoresistance can result from the accumulation of ECM proteins in the tumor microenvironment, a common characteristic of PDA. Dysregulation of ECM-driven signaling can contribute to the hostile programs of cancer cells (Valiathan *et al.*, 2012). This fibrotic network contributes to the development of a complex tumor microenvironment that promotes PDA development, invasion, metastasis and resistance to chemotherapy (Li *et al.*, 2012). However, the ECM-mediated signaling pathways that drive these programs are unclear.

The matricellular protein Sparc (secreted protein acidic and rich in cysteine) was found previously to reduce collagen I signaling through Ddr1 and that loss of *Sparc* accelerated PDA progression with a concordant increase in Ddr1 signaling (Aguilera *et al.*, 2014). Furthermore, prior reports on the expression of SPARC in pancreatic tumor cells demonstrated that there is a reduction in SPARC expression by promoter hypermethylation in a high frequency of pancreatic tumor cells and other epithelial cancer cells (Sato *et al.*, 2003 and Cheetham *et al.*, 2008). Additionally, it was reported that restoration of SPARC expression enhanced radiosensitivity and chemosensitivity in pre-clinical models of colon cancer (Tai *et al.*, 2005) and that SPARC expression enhanced chemoresponse in cancer patients (Von Hoff *et al.*, 2011 and Lindner *et al.*, 2015). Thus there was compelling evidence that loss of tumor cell expression of SPARC correlated with tumor progression and poor chemoresponse. Without wishing to be bound by any theory, it is believed that these observations can be explained by the fact that SPARC inhibits collagen-induced DDR1 activation. This is consistent with reports that collagen signaling is associated with chemoresistance in PDA cell lines (Mahadevan and Von Hoff, 2007 and Erkan *et al.*, 2008) and that DDR1 confers resistance to chemotherapy and mediates pro-survival signals (Cader *et al.*, 2013; Ongusaha *et al.*, 2003 and Das *et al.*, 2006).

These studies relied on syngeneic, xenograft and genetic models of PDA. Pan02 (also known as Panc02) cells were utilized because this cell line grows in C57Bl/6 immunocompetent animals, a useful system to evaluate initial toxicity and efficacy of DDR1 inhibition with 7rh. AsPC-1 cells, a commonly used human PDA cell line, were employed because these cells express high levels of endogenous DDR1 activation *in vitro* and grow robustly *in vivo*. The KPC model of PDA was also used, which incorporates two common genetic lesions present in human PDA (e.g., KRAS activation and p53 loss). Without wishing to be bound by any theory, it is believed that this model is well-suited for endpoint and survival studies as mice develop advanced PDA with 100% penetrance at approximately 3-4

months of age and tumor progression recapitulates many of the characteristics of human PDA (Hingorani *et al.*, 2005).

DDR1 is up-regulated in fibrotic diseases and contributes to the initiation and progression of fibrosis (Kerhoch *et al.*, 2012). Reduced collagen deposition in tumors from mice treated with 7rh were observed, thus inhibition of DDR1 might improve response to chemotherapy in a cell autonomous manner and also improve drug delivery without disrupting the function of cancer associated fibroblasts. DDR1 inhibition has also been shown to reduce tumorigenicity in multiple tumor models (Shintani *et al.*, 2008; Kim *et al.*, 2011; Valencia *et al.*, 2012 and Li *et al.*, 2015). Silencing DDR1 by siRNA has been shown to reduce metastatic activity in lung cancer models (Miao *et al.*, 2013 and Valencia *et al.*, 2012) and enhance chemosensitivity to genotoxic drugs in breast cancer cells (Das *et al.*, 2006). Additionally, DDR1 expression and activity is reported to correlate with worse outcome in a cohort of gastric cancer patients. This study shows 7rh-mediated inhibition of DDR1 in gastric cancer cells reduced tumorigenic characteristics *in vitro* and tumor growth *in vivo*.

Several small molecule inhibitors (imatinib, nilotinib and dasatinib) that target Breakpoint Cluster Region-Abelson kinase (BCR-ABL) also potently inhibit DDR1/DDR2 activity (Day *et al.*, 2008 and Rix *et al.*, 2007). Thus, the potential activity of imatinib and vinorelbine in a phase I/II trial in metastatic breast cancer patients (Maass *et al.*, 2014), as well as dasatinib in numerous clinical trials in solid tumors (Roskoski, 2015), could be due in part to the inhibition of DDRs. Dasatinib in particular has demonstrated promising therapeutic efficacy in lung cancer cells (Ding *et al.*, 2008) and squamous cell carcinoma (SCC) patients (Pitini *et al.*, 2013) harboring gain-of-function DDR2 mutations.

The data suggest that inhibition of collagen-mediated DDR1 activity can improve the efficacy of standard chemotherapy of pancreatic cancer.

Example 45 – Kinase Inhibition of Other Compounds

Table 3 - IC₅₀ (nM) values of part of compounds on various kinases inhibition

Example number	Compound number	IC ₅₀ (nM unless otherwise noted)			
		DDR1	DDR2	Bcr-Abl	c-Kit
1	D2095	38.3	1.8 μ M	2.1 μ M	>10 μ M
2	D2217	444.5	5.8 μ M	1.4 μ M	>10 μ M
3	D2210	441.5	8.0 μ M	664.1	>10 μ M
4	D2211	328.0	4.3 μ M	>10 μ M	>10 μ M
5	D2568	571.5	3.6 μ M	4.5 μ M	8.7 μ M
6	D2103	70.9	1.2 μ M	6.1 μ M	>10 μ M
7	D2102	223	4.5 μ M	>10 μ M	>10 μ M
8	D2198	65.9	914.7	>10 μ M	>10 μ M
9	D2274	159	1.1 μ M	>10 μ M	>10 μ M

Example number	Compound number	IC ₅₀ (nM unless otherwise noted)			
		DDR1	DDR2	Bcr-Abl	c-Kit
10	D2276	36.7	449	>10 μ M	>10 μ M
11	D2188	132.4	2.2 μ M	>10 μ M	>10 μ M
12	D2190	19.9	334	546.5	>10 μ M
13	D2199	191	10 μ M	>10 μ M	>10 μ M
14	D2197	25.6	604	>10 μ M	>10 μ M
15	D2193	50.5	1.4 μ M	>10 μ M	>10 μ M
16	D2187	35.7	647.0	7.2 μ M	>10 μ M
17	D2275	39.1	527	>10 μ M	>10 μ M
18	D2201	193.4	4.5 μ M	>10 μ M	>10 μ M
19	D2194	166.5	2.2 μ M	>10 μ M	>10 μ M
20	D2573	222.0	2.3 μ M	>10 μ M	>10 μ M
21	D2192	254	6.7 μ M	>10 μ M	>10 μ M
22	D2215	71.6	457.0	>10 μ M	>10 μ M
23	D2474	31.4	1.2 μ M	10 μ M	>10 μ M
24	D2473	18	671.8	6.7 μ M	>10 μ M
25	D2475	29.6	861.6	10 μ M	>10 μ M
26	D2202	19.4	432	7.2 μ M	>10 μ M
27	D2214	48.8	1.4 μ M	>10 μ M	>10 μ M
28	D2350	66.6	939.5	4.3 μ M	>10 μ M
29	D2476	44.6	1.4 μ M	10 μ M	>10 μ M
30	D2574	544.5	7.6 μ M	>10 μ M	>10 μ M
31	D2347	89.0	1.1 μ M	10 μ M	>10 μ M
32	D2196	20.6	306.5	4.8 μ M	>10 μ M
33	D2195	79.9	945	>10 μ M	>10 μ M
34	D2213	85.3	2.0 μ M	>10 μ M	>10 μ M
35	D2191	209.4	3.7 μ M	>10 μ M	>10 μ M
36	D2212	353.8	7.8 μ M	>10 μ M	>10 μ M
37	D2099	294.3	4.2 μ M	>10 μ M	>10 μ M
38	D2200	42.6	514.5	>10 μ M	>10 μ M
39	D2100	630.5	>10 μ M	>10 μ M	>10 μ M
40	D2164	66.2	1.4 μ M	>10 μ M	>10 μ M

* * * * *

All of the compounds, compositions, and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure.

- 5 While the disclosure may have focused on several embodiments or may have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations and modifications may be applied to the compounds, compositions, and methods without departing from the spirit, scope, and concept of the disclosure. All variations and modifications apparent to those skilled in the art are deemed to be within the spirit, scope,
- 10 and concept of the disclosure as defined by the appended claims.

REFERENCES

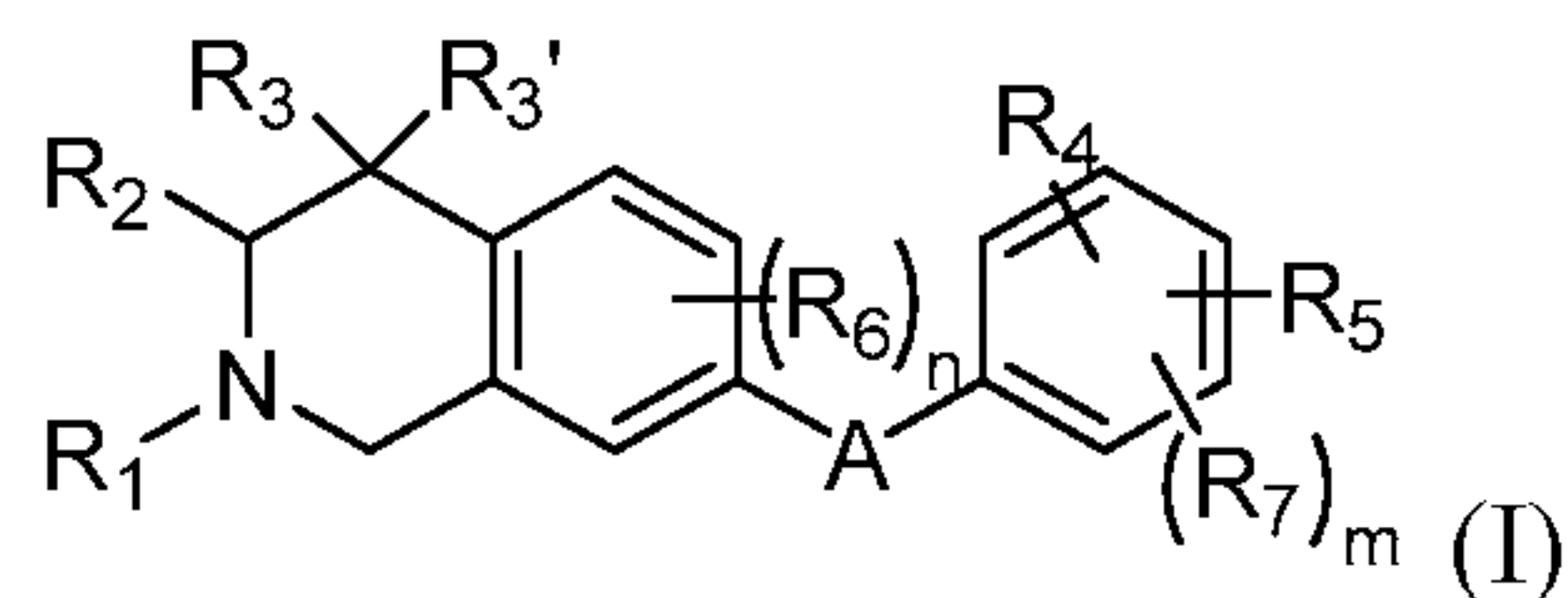
The following references to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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What is claimed is:

1. A compound of the formula:



wherein:

A is $\text{--NR}_8\text{C(O)--}$ or $\text{--C(O)NR}_8\text{--}$; wherein:

R_8 is hydrogen, $\text{alkyl}_{(\text{C}\leq 6)}$, or substituted $\text{alkyl}_{(\text{C}\leq 6)}$;

R_1 is $\text{aryl}_{(\text{C}\leq 12)}$, $\text{heteroaryl}_{(\text{C}\leq 12)}$, or a substituted version of either of these groups;

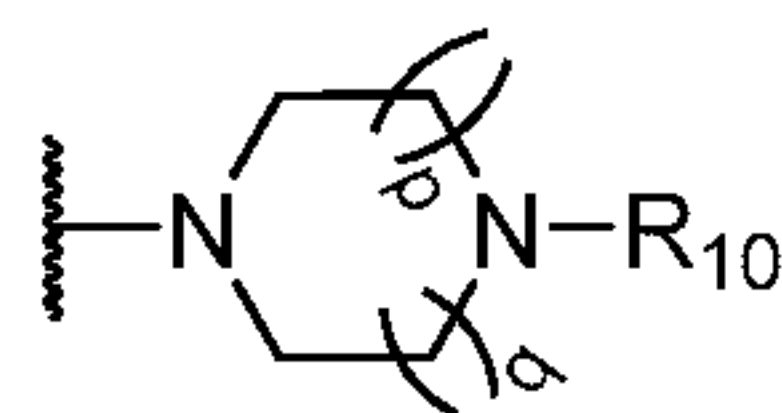
R_2 , R_3 , and R_3' are each independently hydrogen, $\text{alkyl}_{(\text{C}\leq 12)}$, $\text{cycloalkyl}_{(\text{C}\leq 12)}$, substituted $\text{alkyl}_{(\text{C}\leq 12)}$, or substituted $\text{cycloalkyl}_{(\text{C}\leq 12)}$;

R_4 is hydrogen, $\text{alkyl}_{(\text{C}\leq 12)}$, $\text{cycloalkyl}_{(\text{C}\leq 12)}$, $\text{aryl}_{(\text{C}\leq 12)}$, substituted $\text{alkyl}_{(\text{C}\leq 12)}$, substituted $\text{cycloalkyl}_{(\text{C}\leq 12)}$, or substituted $\text{aryl}_{(\text{C}\leq 12)}$,

R_5 is hydrogen, $\text{heteroaryl}_{(\text{C}\leq 12)}$, --X--R_9 , wherein:

X is a covalent bond, $\text{alkanediyl}_{(\text{C}\leq 8)}$, or substituted $\text{alkanediyl}_{(\text{C}\leq 8)}$;

R_9 is amino or $\text{heterocycloalkyl}_{(\text{C}\leq 12)}$, $\text{heteroaryl}_{(\text{C}\leq 12)}$, $\text{alkylamino}_{(\text{C}\leq 12)}$, $\text{dialkylamino}_{(\text{C}\leq 12)}$, or a substituted version of any of these groups; or a group of the formula:



wherein:

R_{10} is hydrogen, $\text{alkyl}_{(\text{C}\leq 12)}$, $\text{cycloalkyl}_{(\text{C}\leq 12)}$, substituted $\text{alkyl}_{(\text{C}\leq 12)}$, or substituted $\text{cycloalkyl}_{(\text{C}\leq 12)}$; and

p and q are each 0, 1, or 2;

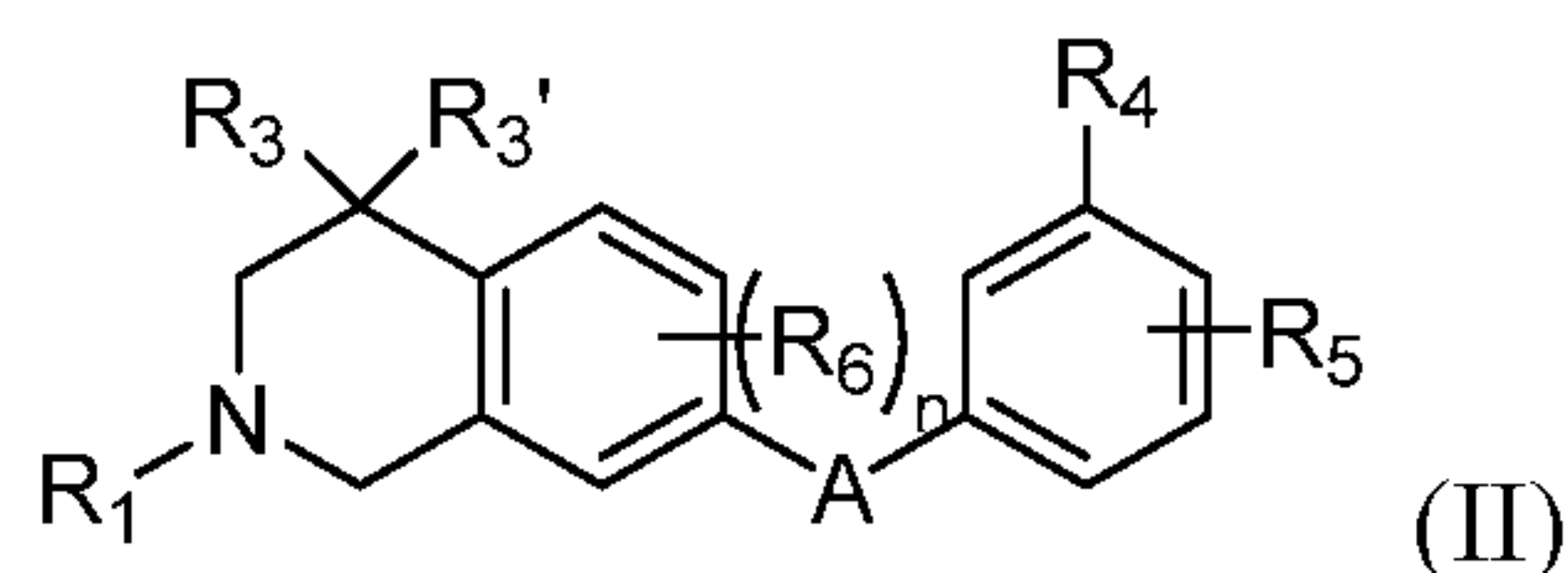
R_6 and R_7 are each independently amino, cyano, halo, hydroxy, hydroxysulfonyl, nitro, sulfonamide; or

alkyl_(C≤8), acyl_(C≤8), alkoxy_(C≤8), amido_(C≤8), acyloxy_(C≤8), alkylamino_(C≤8),
or dialkylamino_(C≤8); and

m and n are each independently 0, 1, 2, or 3;

or a pharmaceutically acceptable salt thereof.

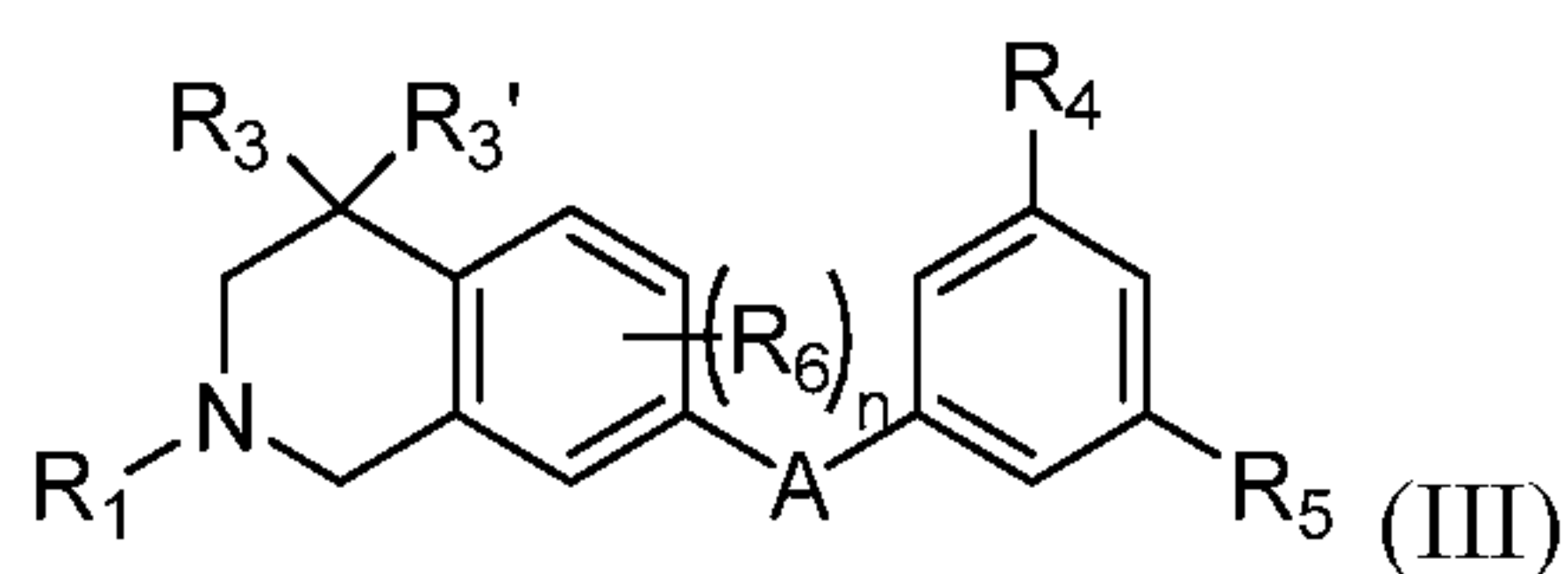
2. The compound of claim 1, wherein the compound is further defined as:



wherein: A, R₁, R₃, R₃', R₄, R₅, R₆, and n are as defined above;

or a pharmaceutically acceptable salt thereof.

3. The compound of either claim 1 or claim 2, wherein the compound is further defined as:



wherein: A, R₁, R₃, R₃', R₄, R₅, R₆, and n are as defined above;

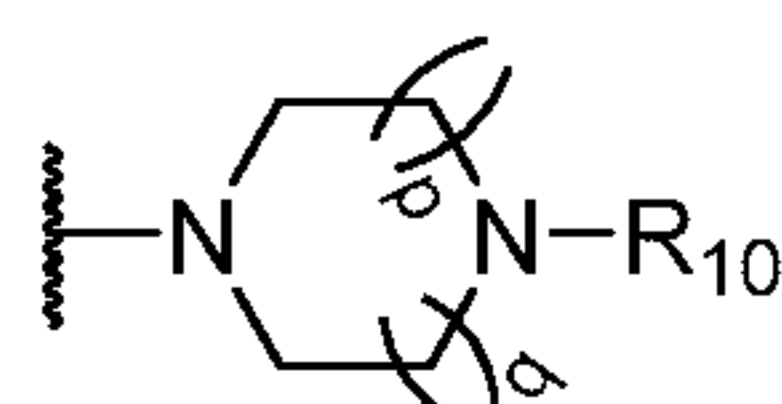
or a pharmaceutically acceptable salt thereof.

4. The compound according to any one of claims 1-3, wherein R₁ is heteroaryl_(C≤12).
5. The compound of claim 4, wherein R₁ is 5-pyrimidinyl.
6. The compound according to any one of claims 1-5, wherein R₃ is alkyl_(C≤12).
7. The compound of claim 6, wherein R₃ is methyl or ethyl.
8. The compound according to any one of claims 1-5, wherein R₃ is hydrogen.
9. The compound according to any one of claims 1-8, wherein R₃' is hydrogen.
10. The compound according to any one of claims 1-9, wherein R₄ is alkyl_(C≤12) or substituted alkyl_(C≤12).
11. The compound of claim 10, wherein R₄ is alkyl_(C≤12).
12. The compound of claim 11, wherein R₄ is methyl, ethyl, or isopropyl.

13. The compound of claim 10, wherein R_4 is substituted alkyl_(C≤12).
14. The compound of claim 13, wherein R_4 is trifluoromethyl.
15. The compound according to any one of claims 1-9, wherein R_4 is cycloalkyl_(C≤12) or substituted cycloalkyl_(C≤12).
16. The compound of claim 15, wherein R_4 is cycloalkyl_(C≤12).
17. The compound of claim 16, wherein R_4 is cyclopropyl, cyclopentyl, or cyclohexyl.
18. The compound according to any one of claims 1-9, wherein R_4 is aryl_(C≤12).
19. The compound of claim 18, wherein R_4 is phenyl.
20. The compound according to any one of claims 1-19, wherein R_5 is hydrogen.
21. The compound according to any one of claims 1-19, wherein R_5 is heteroaryl_(C≤12).
22. The compound of claim 21, wherein R_5 is 4-methylimidazolyl.
23. The compound according to any one of claims 1-19, wherein R_5 is $-X-R_9$, wherein:

X is a covalent bond, alkanediyl_(C≤8), or substituted alkanediyl_(C≤8);

R_9 is amino or heterocycloalkyl_(C≤12), heteroaryl_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), or a substituted version of any of these groups; or a group of the formula:



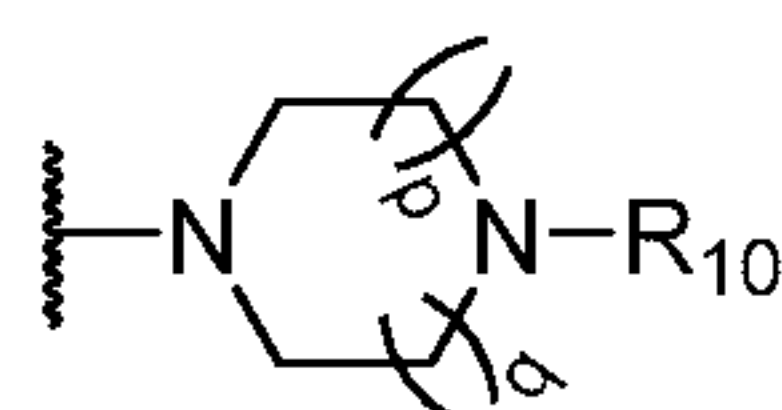
wherein:

R_{10} is hydrogen, alkyl_(C≤12), cycloalkyl_(C≤12), substituted alkyl_(C≤12), or substituted cycloalkyl_(C≤12); and

p and q are each 0, 1, or 2.

24. The compound of claim 23, wherein X is alkanediyl_(C≤8).
25. The compound of claim 24, wherein X is $-\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2-$.
26. The compound according to any one of claims 23-25, wherein R_9 is heterocycloalkyl_(C≤12) or a substituted heterocycloalkyl_(C≤12).

27. The compound of claim 26, wherein R_9 is *N*-1,4-thiazinanyl, *N*-morpholinyl, *N*-piperidinyl, *N*-pyrrolidinyl, or *N*-3-dimethylaminopyrrolidinyl.
28. The compound according to any one of claims 23-25, wherein R_9 is dialkylamino_(C≤12) or substituted dialkylamino_(C≤12).
29. The compound of claim 28, wherein R_9 is $-N(CH_3)CH_2CH_2N(CH_3)_2$.
30. The compound according to any one of claims 23-25, wherein R_9 is:



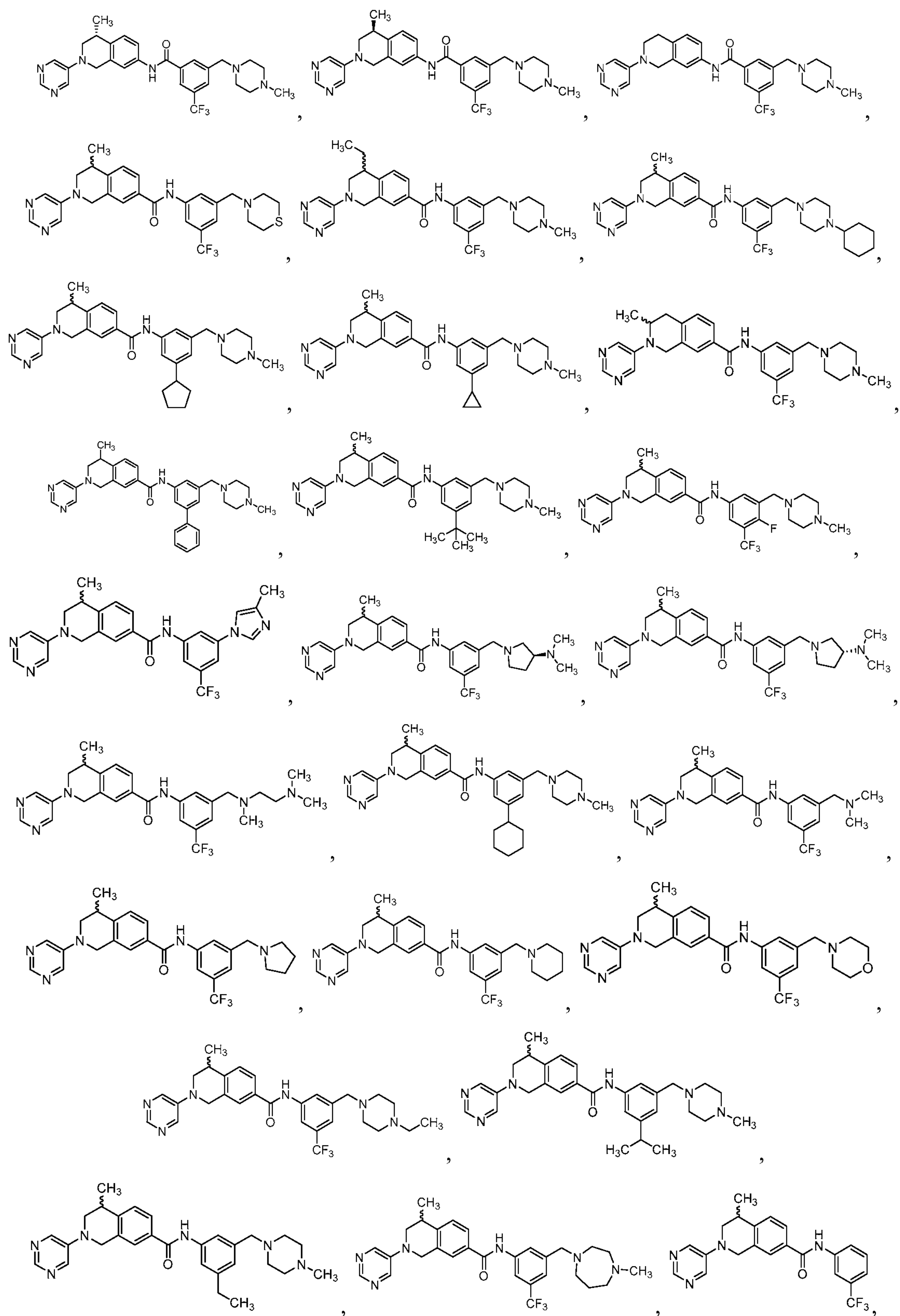
wherein:

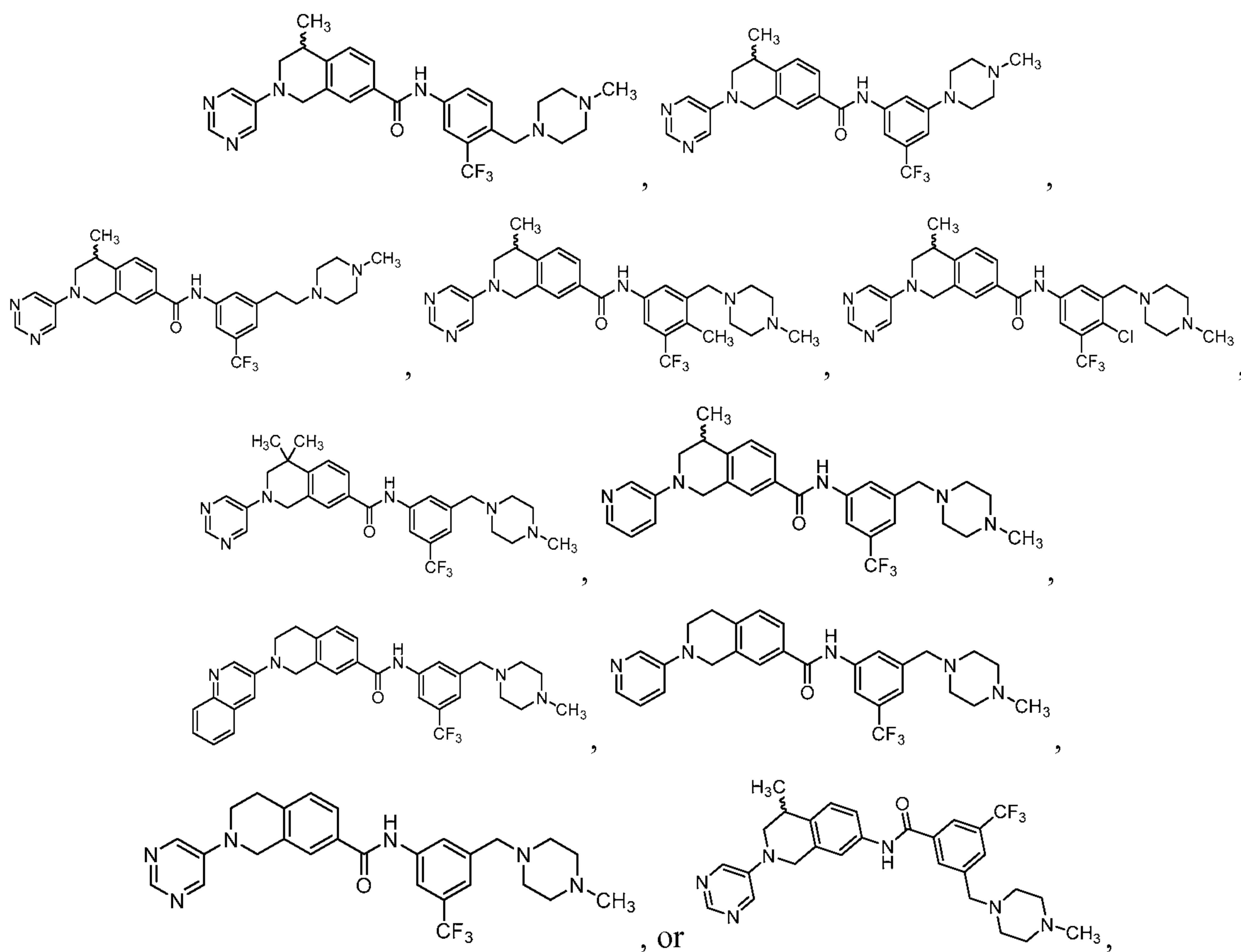
R_{10} is hydrogen, alkyl_(C≤12), cycloalkyl_(C≤12), substituted alkyl_(C≤12), or substituted cycloalkyl_(C≤12); and

p and q are each 0, 1, or 2.

31. The compound of claim 30, wherein R_{10} is alkyl_(C≤12) or substituted alkyl_(C≤12).
32. The compound of claim 31, wherein R_{10} is methyl or ethyl.
33. The compound of claim 30, wherein R_{10} is cycloalkyl_(C≤12) or substituted cycloalkyl_(C≤12).
34. The compound of claim 33, wherein R_{10} is cyclohexyl.
35. The compound according to any one of claims 30-34, wherein p is 1.
36. The compound according to any one of claims 30-35, wherein q is 1.
37. The compound according to any one of claims 30-35, wherein q is 2.
38. The compound according to any one of claims 1-37, wherein m is 0.
39. The compound according to any one of claims 1-37, wherein m is 1.
40. The compound according to any one of claims 1-39, wherein R_7 is alkyl_(C≤8) or substituted alkyl_(C≤8).
41. The compound of claim 40, wherein R_7 is methyl.
42. The compound according to any one of claims 1-39, wherein R_7 is halo.
43. The compound of claim 42, wherein R_7 is fluoro or chloro.

44. The compound according to any one of claims 1-43, wherein the compound is further defined as:





or a pharmaceutically acceptable salt thereof.

45. A compound of the formula:

4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)benzamide;

N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(quinolin-3-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4,4-dimethyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(4-chloro-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(4-methyl-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(3-(2-(4-methylpiperazin-1-yl)ethyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(3-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-2-(pyrimidin-5-yl)-N-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(3-((4-methyl-1,4-diazepan-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-ethyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-isopropyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-((4-ethylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(3-(morpholinomethyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(3-(piperidin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-2-(pyrimidin-5-yl)-N-(3-(pyrrolidin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-((dimethylamino)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-cyclohexyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-(((R)-3-(dimethylamino)pyrrolidin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-(((S)-3-(dimethylamino)pyrrolidin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(4-fluoro-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-tert-butyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(5-((4-methylpiperazin-1-yl)methyl)biphenyl-3-yl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

3-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-cyclopropyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-cyclopentyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-((4-cyclohexylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-ethyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-2-(pyrimidin-5-yl)-N-(3-(thiomorpholinomethyl)-5-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

3-((4-methylpiperazin-1-yl)methyl)-N-(2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-(trifluoromethyl)benzamide;

(S)-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

(R)-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

(S)-N-(4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)benzamide;

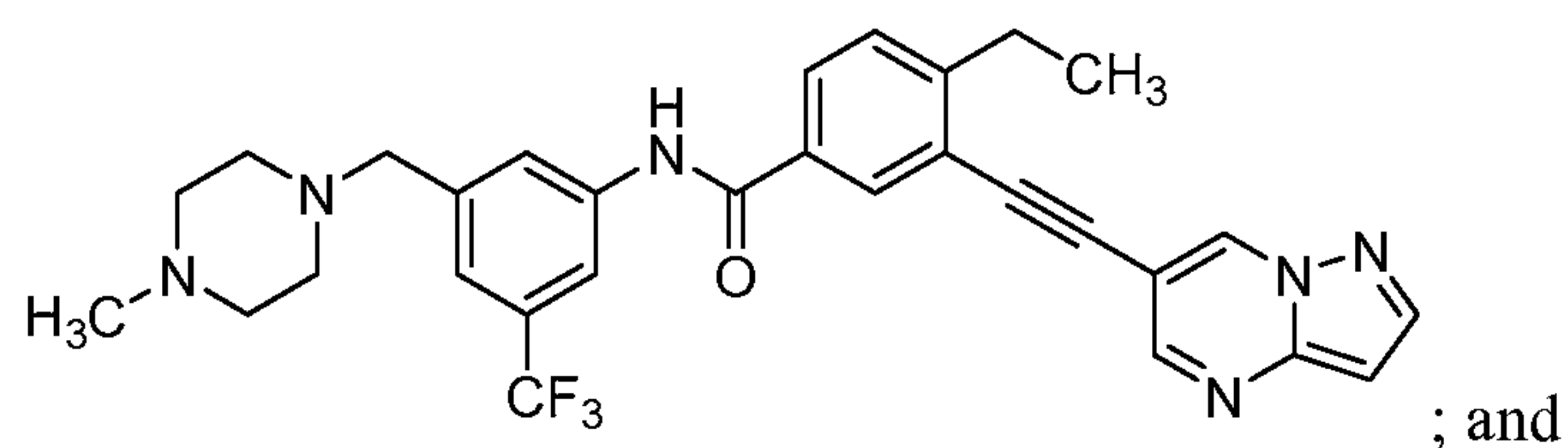
(R)-N-(4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)benzamide;

or a pharmaceutically acceptable salt thereof.

46. A pharmaceutical composition comprising:
 - (a) a compound according to any one of claims 1-45; and
 - (b) a pharmaceutically acceptable carrier.
47. The pharmaceutical composition of claim 46, wherein the pharmaceutical composition further comprises a second chemotherapeutic compound.
48. The pharmaceutical composition of claim 47, wherein the second chemotherapeutic compound is a nucleoside analog chemotherapeutic compound.
49. The pharmaceutical composition of claim 48, wherein the nucleoside analog chemotherapeutic compound is gemcitabine.
50. The pharmaceutical composition of claim 47, wherein the second chemotherapeutic compound is a taxane.
51. The pharmaceutical composition of claim 50, wherein the second chemotherapeutic compound is paclitaxel.
52. The pharmaceutical composition according to any one of claims 46-51, wherein the pharmaceutical composition is formulated for administration: orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intralesionally,

intramuscularly, intranasally, intraocularly, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrarectally, intrathecally, intratracheally, intratumorally, intraumbilically, intravaginally, intravenously, intravesicularly, intravitreally, liposomally, locally, mucosally, parenterally, rectally, subconjunctival, subcutaneously, sublingually, topically, transbuccally, transdermally, vaginally, in crèmes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, or via localized perfusion.

53. The pharmaceutical composition of claim 52, wherein the pharmaceutical composition is formulated for oral administration.
54. The pharmaceutical composition according to any one of claims 46-53, wherein the pharmaceutical composition is formulated as a unit dose.
55. A pharmaceutical composition comprising:
 - (a) a compound of the formula:

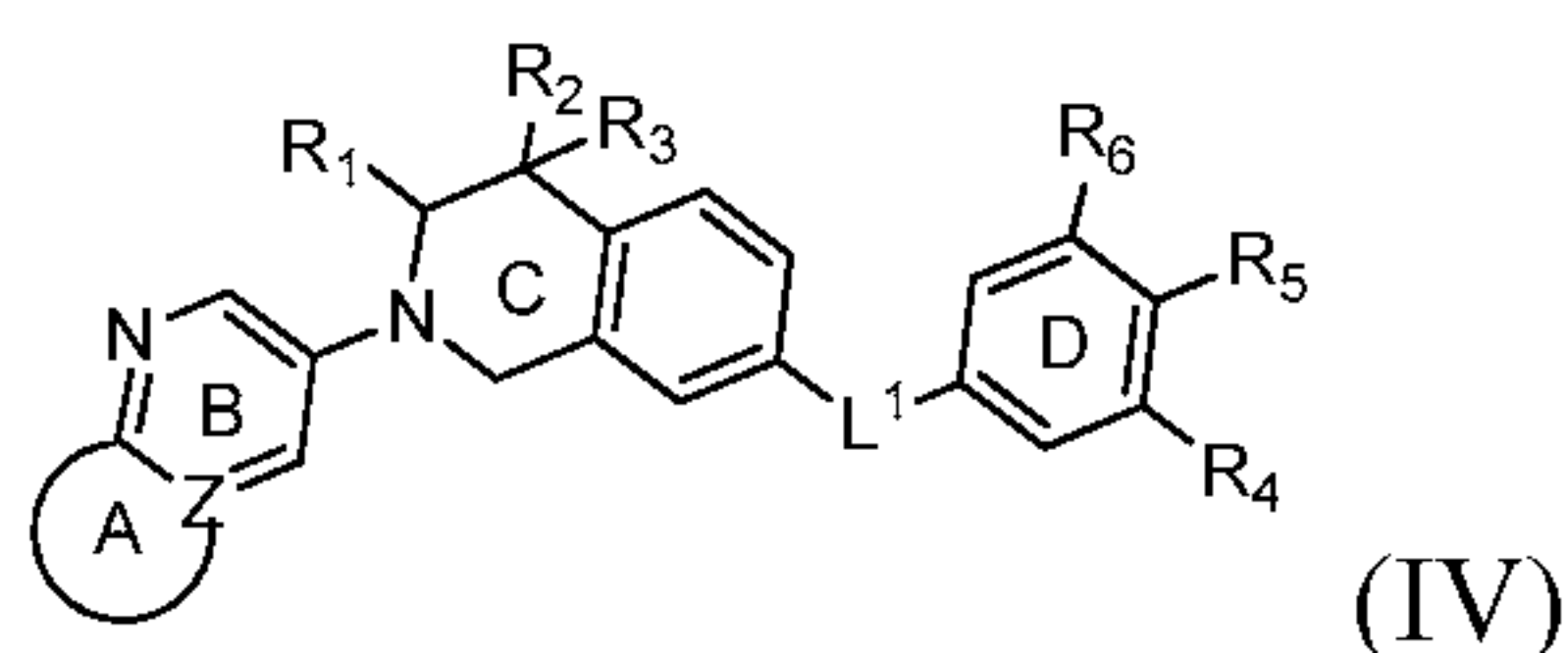


- (b) a second chemotherapeutic compound.
56. The pharmaceutical composition of claim 55, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.
57. The pharmaceutical composition of either claim 55 or claim 56, wherein the pharmaceutical composition is formulated for oral administration.
58. The pharmaceutical composition according to any one of claims 55-57, wherein the second chemotherapeutic compound is a nucleoside analog.
59. The pharmaceutical composition of claim 58, wherein the second chemotherapeutic compound is gemcitabine.
60. The pharmaceutical composition according to any one of claims 55-57, wherein the second chemotherapeutic compound is a taxane.
61. The pharmaceutical composition of claim 60, wherein the second chemotherapeutic compound is paclitaxel.

62. The pharmaceutical composition according to any one of claims 55-57, wherein the composition is formulated as a unit dose.
63. A method of treating a disease or disorder in a patient in need thereof comprising administering to the patient a therapeutically effective amount of a compound or composition according to any one of claims 1-62.
64. The method of claim 63, wherein the disease or disorder is related to inflammation.
65. The method of claim 64, wherein the disease or disorder is kidney fibrosis, liver fibrosis, lung fibrosis, skin scars, or atherosclerosis.
66. The method of claim 63, wherein the disease or disorder is cancer.
67. The method of claim 66, wherein the cancer is a carcinoma, sarcoma, lymphoma, leukemia, melanoma, mesothelioma, multiple myeloma, or seminoma.
68. The method of claim 66, wherein the cancer is of the bladder, blood, bone, brain, breast, central nervous system, cervix, colon, endometrium, esophagus, gall bladder, gastrointestinal tract, genitalia, genitourinary tract, head, kidney, larynx, liver, lung, muscle tissue, neck, oral or nasal mucosa, ovary, pancreas, prostate, skin, spleen, small intestine, large intestine, stomach, testicle, or thyroid.
69. The method according to any one of claims 66-68, wherein the cancer is a cancer of the lung, breast, brain, ovary, head and neck, liver, pancreas, or prostate.
70. The method of claim 69, wherein the cancer is a cancer of the pancreas.
71. The method of claim 70, wherein the cancer is pancreatic ductal adenocarcinoma.
72. The method according to any one of claims 63-69, wherein the compound is administered to the patient once.
73. The method according to any one of claims 63-69, wherein the compound is administered to the patient two or more times.
74. The method according to any one of claims 63-73, wherein the method further comprises a second therapy.
75. The method of claim 74, wherein the second therapy is one or more therapeutic agents, a surgery, a radiotherapy, or an immunotherapy.

76. The method of either claim 74 or claim 75, wherein the second therapy is a chemotherapeutic agent.
77. The method of claim 76, wherein the second therapy is a nucleoside analog chemotherapeutic agent.
78. The method of claim 77, wherein the nucleoside analog chemotherapeutic agent is gemcitabine.
79. The method of claim 76, wherein the second therapy is a taxane.
80. The method of claim 79, wherein the second therapy is paclitaxel.
81. A method of inhibiting discoidin domain receptor (DDR) protein comprising contacting the protein with a compound or composition according to any one of claims 1-62 in an amount sufficient to inhibit the protein.
82. The method of claim 81, wherein the protein is the discoidin domain receptor 1 protein (DDR1).
83. The method of either claim 81 or claim 82, wherein the method is performed *in vivo*.
84. The method of either claim 81 or claim 82, wherein the method is performed *in vitro*.
85. The method of claim 83, wherein the method is performed *in vivo* and comprises administering the compound to a patient in need thereof.
86. The method of claim 85, wherein the inhibition of DDR 1 protein is sufficient to treat a disease or disorder.
87. A method of treating cancer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of:
 - (a) a compound or composition according to any one of claims 1-62; and
 - (b) a second chemotherapeutic compound.
88. The method of claim 87, wherein the cancer is a cancer of the lung, breast, brain, ovary, head and neck, liver, pancreas, or prostate.
89. The method of claim 88, wherein the cancer is a cancer of the pancreas.
90. The method of claim 89, wherein the cancer is pancreatic ductal adenocarcinoma.

91. The method according to any one of claims 87-90, wherein the method comprises administering the compound or composition in a ratio from about 1:2 to about 5:1 relative to the second chemotherapeutic compound.
92. The method of claim 91, wherein the ratio of the compound or composition is 2:1 relative to the second chemotherapeutic compound.
93. The method according to any one of claims 87-92, wherein the second chemotherapeutic compound is a nucleoside analog.
94. The method of claim 93, wherein the second chemotherapeutic compound is gemcitabine.
95. The method according to any one of claims 87-92, wherein the second chemotherapeutic compound is a taxane.
96. The method of claim 95, wherein the second chemotherapeutic compound is paclitaxel.
97. A compound of formula (IV) or a pharmaceutically acceptable salt, stereoisomer or prodrug thereof:



wherein L^1 is independently selected as $-\text{CONH}-$ or $-\text{NHCO}-$;

is independently selected from:

a) single heterocycles like and ;

b) fused heterocycles like ;

R_1, R_2, R_3 are independently selected from:

- a) H;
- b) $\text{C}_1\sim\text{C}_4$ alkyl;

R_2, R_3 can further form tri, tetra, penta ring structure with the carbon atom where they are linked in the C ring;

R_4, R_5, R_6 is independently selected from:

- a) H;
- b) halogen (F, Cl, Br);
- c) $C_1\sim C_4$ alkyl;
- d) $C_3\sim C_6$ cycloalkyl;
- e) $C_1\sim C_4$ alkyl containing F;
- f) aryl, Het;

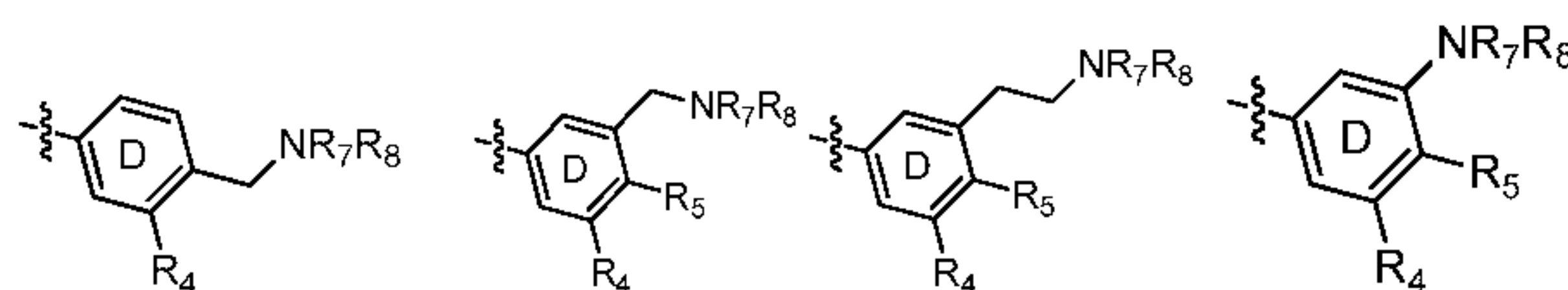
aryl can be phenyl, or substituted phenyl; Het is defined as the nonaromatic heterocycle, or aromatic heterocycle containing 5 ~ 6 atoms, which contains 1~4 hetero atoms such as O, N, S. Alkyl or cycloalkyl will be incorporated into any C or N position in which Het can be substituted.

98. The compound of claim 97, wherein R_1, R_2, R_3 is independently selected from:

- a) H;
- b) methyl, ethyl, propyl, isopropyl, cyclopropyl;

R_2, R_3 can further form tri, tetra, penta ring structure with the carbon atom where they are linked in the C ring.

99. The compound of claim 97, wherein D ring is selected from:



R_4 is independently selected from:

- a) halogen (F, Cl, Br);
- b) $C_1\sim C_4$ alkyl;
- c) $C_3\sim C_6$ cycloalkyl;
- d) $C_1\sim C_4$ alkyl containing F;
- e) aryl;

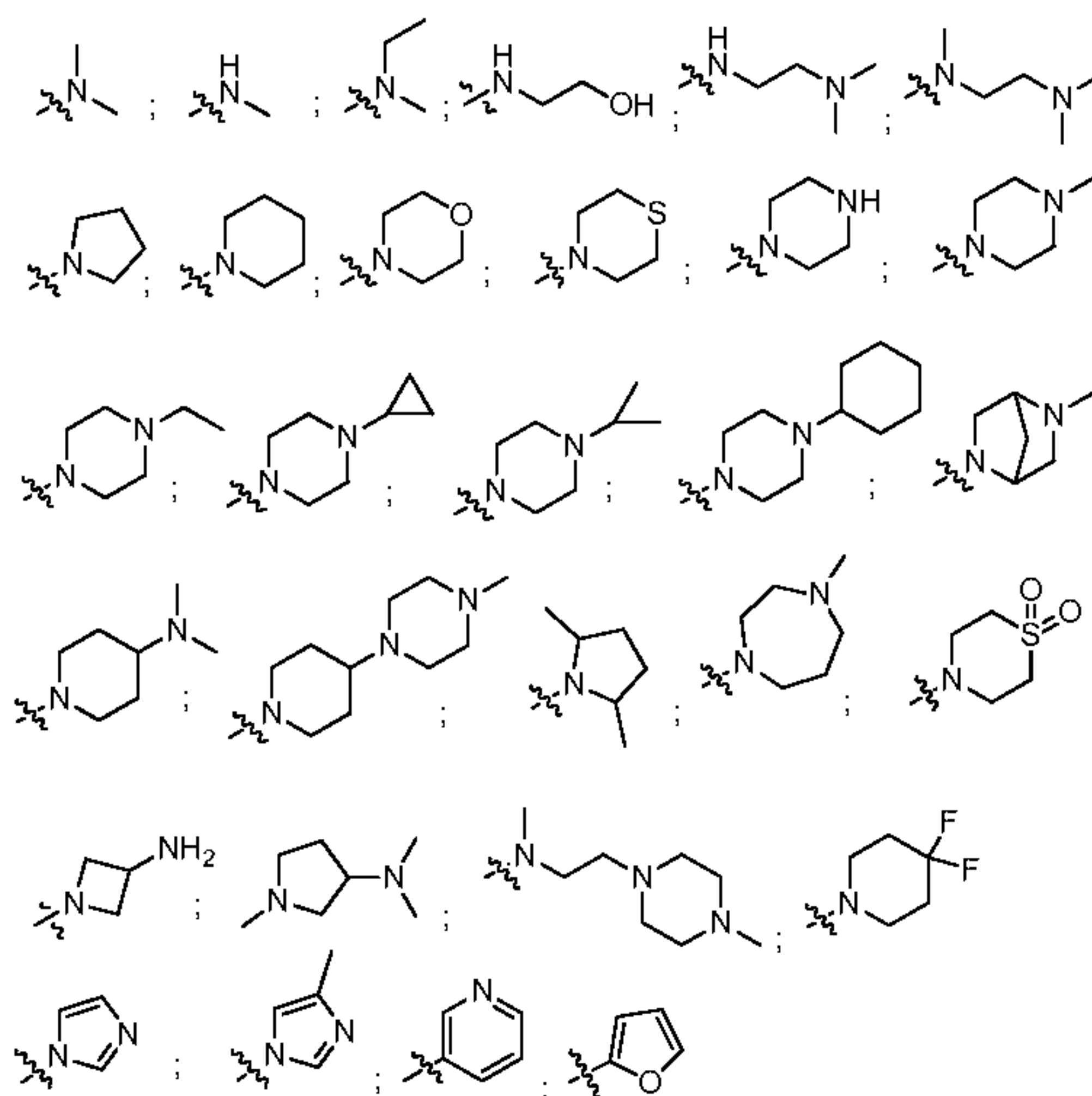
Aryl can be phenyl, or substituted phenyl;

R_5 is independently selected from H, F, Cl, Br, Me, OMe;

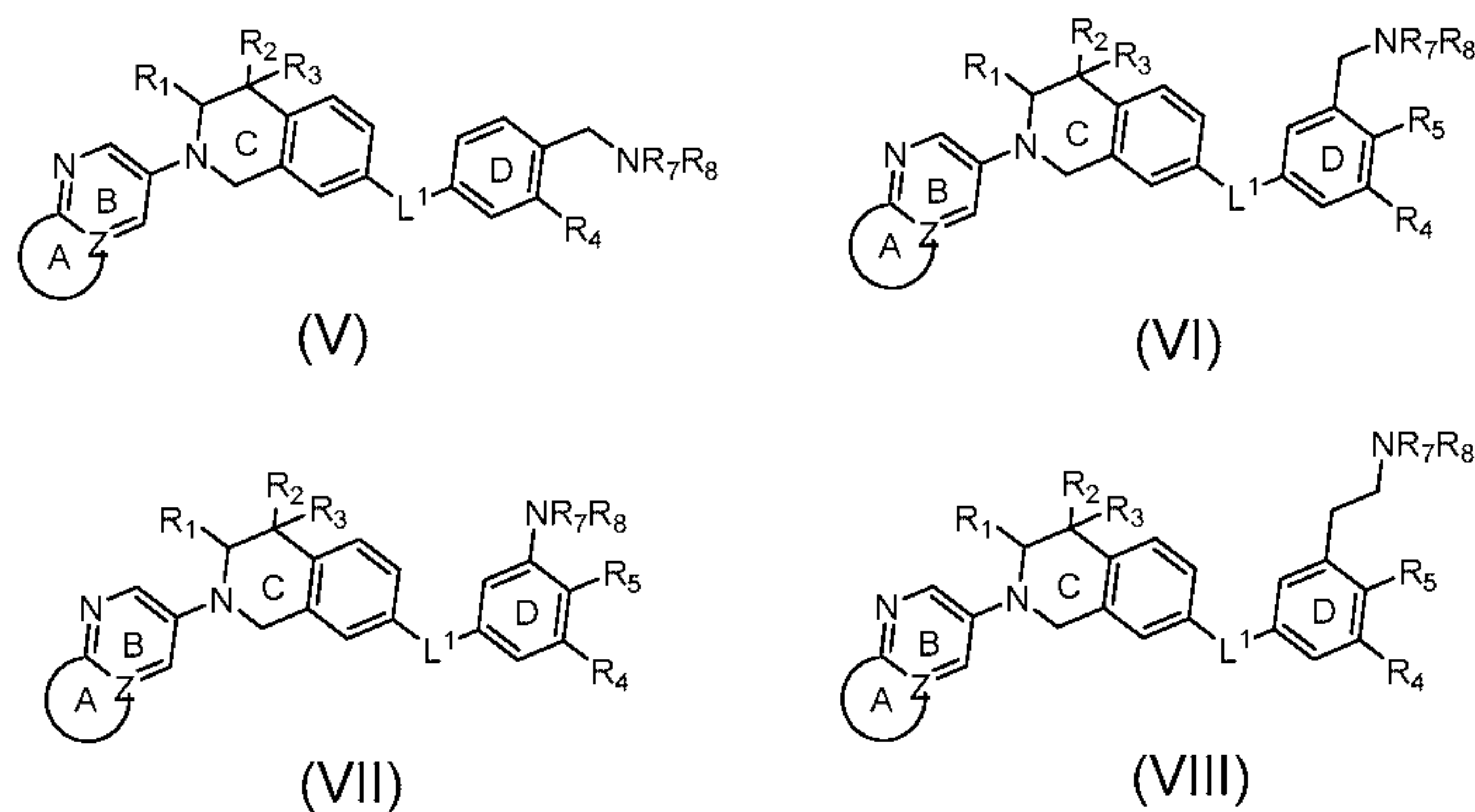
R_7 or R_8 is independently selected from:

- a) H;
- b) C₁~C₃ alkyl;
- c) C₁~C₃ alkyl containing F;
- d) C₃~C₆ cycloalkyl;

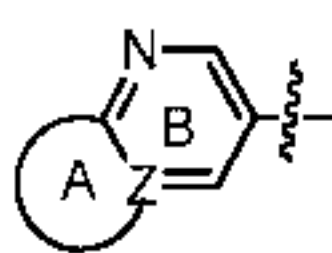
R₇ and R₈ can further form penta-, hexa-, hepta- or octatomic ring structure through C, O, N, S atoms. Alkyl or cycloalkyl will be incorporated into any C or N position in the ring which can be substituted; preferably, $\overset{\text{NR}_7\text{R}_8}{\text{N}}$ is independently selected from:

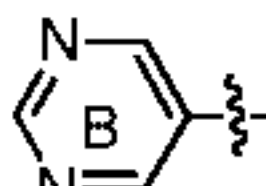
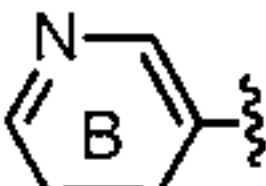
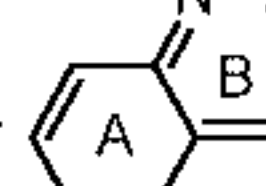
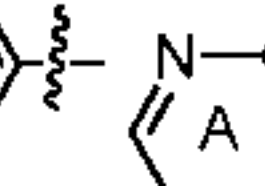
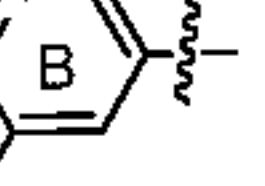
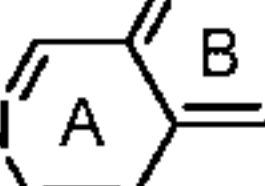
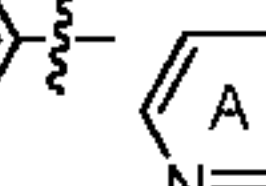
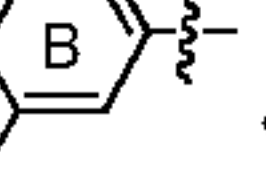
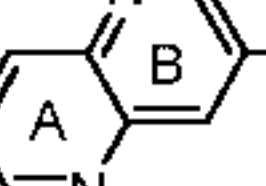
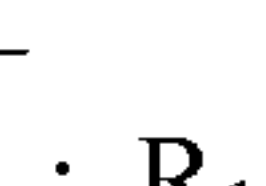


100. The compound according to any one of claims 97-99, wherein the compound of formula (IV) is specially selected from:



wherein

L^1 is independently selected as $-\text{CONH}-$ or $-\text{NHCO}-$;  is independently

selected from:           ; R_1 , R_2 ,

R_3 , R_4 , R_5 , R_7 , R_8 have the same definition as above mentioned.

101. The compound of claim 100, wherein the compound of formula (IV) is specially selected from:

4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)benzamide;

N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(quinolin-3-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4,4-dimethyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(4-chloro-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(4-methyl-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(3-(2-(4-methylpiperazin-1-yl)ethyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(3-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

- 4-methyl-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 4-methyl-2-(pyrimidin-5-yl)-N-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 4-methyl-N-(3-((4-methyl-1,4-diazepan-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- N-(3-ethyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- N-(3-isopropyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- N-(3-((4-ethylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 4-methyl-N-(3-(morpholinomethyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 4-methyl-N-(3-(piperidin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- 4-methyl-2-(pyrimidin-5-yl)-N-(3-(pyrrolidin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- N-(3-((dimethylamino)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- N-(3-cyclohexyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- N-(3-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- N-(3-(((R)-3-(dimethylamino)pyrrolidin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;
- N-(3-(((S)-3-(dimethylamino)pyrrolidin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(4-fluoro-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-tert-butyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-N-(5-((4-methylpiperazin-1-yl)methyl)biphenyl-3-yl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

3-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-cyclopropyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-cyclopentyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

N-(3-((4-cyclohexylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-ethyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

4-methyl-2-(pyrimidin-5-yl)-N-(3-(thiomorpholinomethyl)-5-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

3-((4-methylpiperazin-1-yl)methyl)-N-(2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-(trifluoromethyl)benzamide;

(S)-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

(R)-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide;

(S)-N-(4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)benzamide; and

(R)-N-(4-methyl-2-(pyrimidin-5-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)benzamide.

102. A pharmaceutical composition comprising a compound according to any one of claims 97-101 or a pharmaceutically acceptable salt, stereoisomer or prodrug thereof and a pharmaceutically acceptable carrier, solvent, buffer or diluent.
103. A method of treating a subject having inflammation, liver fibrosis, kidney fibrosis, lung fibrosis, skin scar and atherosclerosis, and cancer comprising administering to said subject a compound according to any one of claims 97-101 or a pharmaceutically acceptable salt, stereoisomer or pro-drug thereof.

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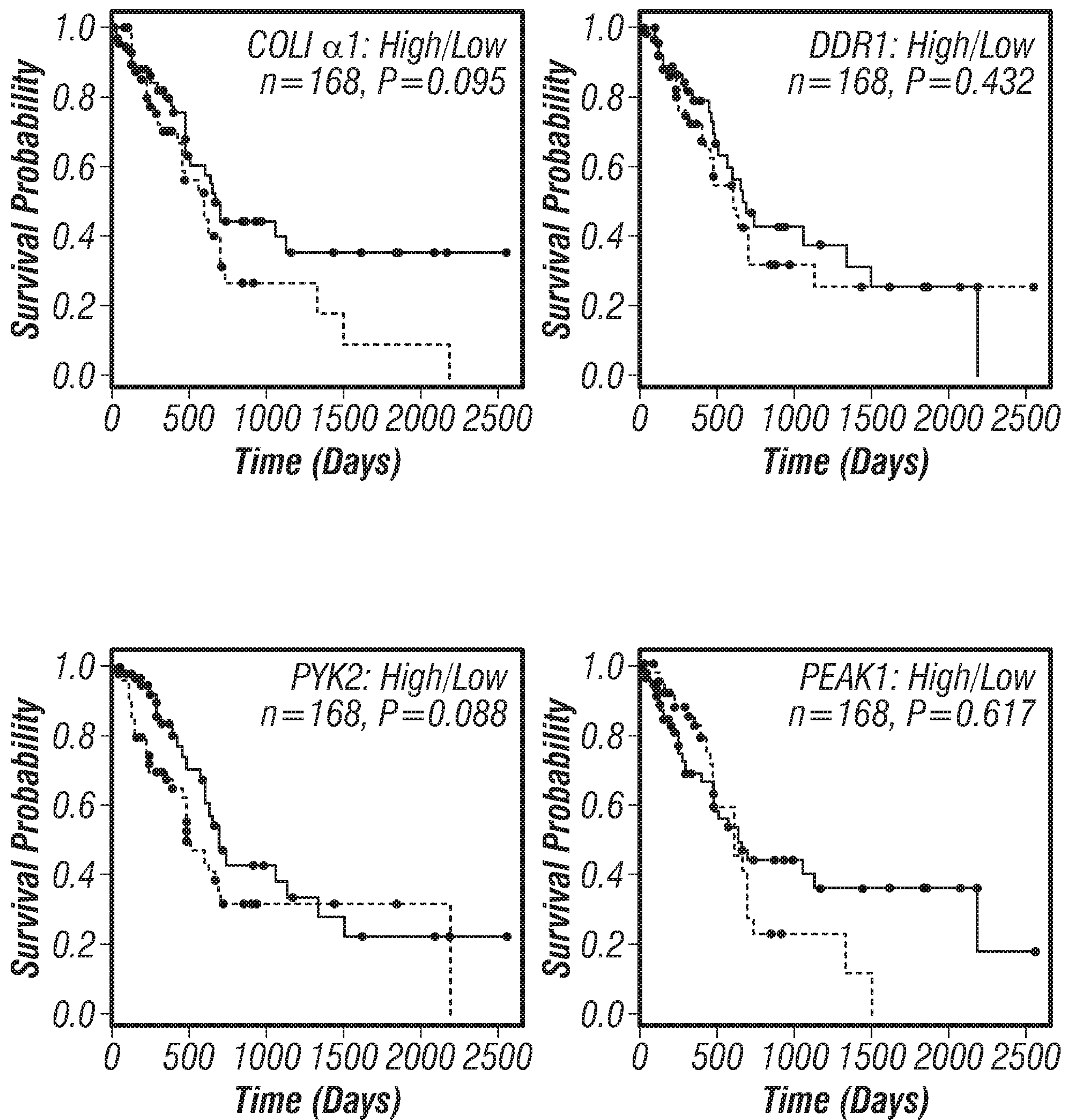


FIG. 1A

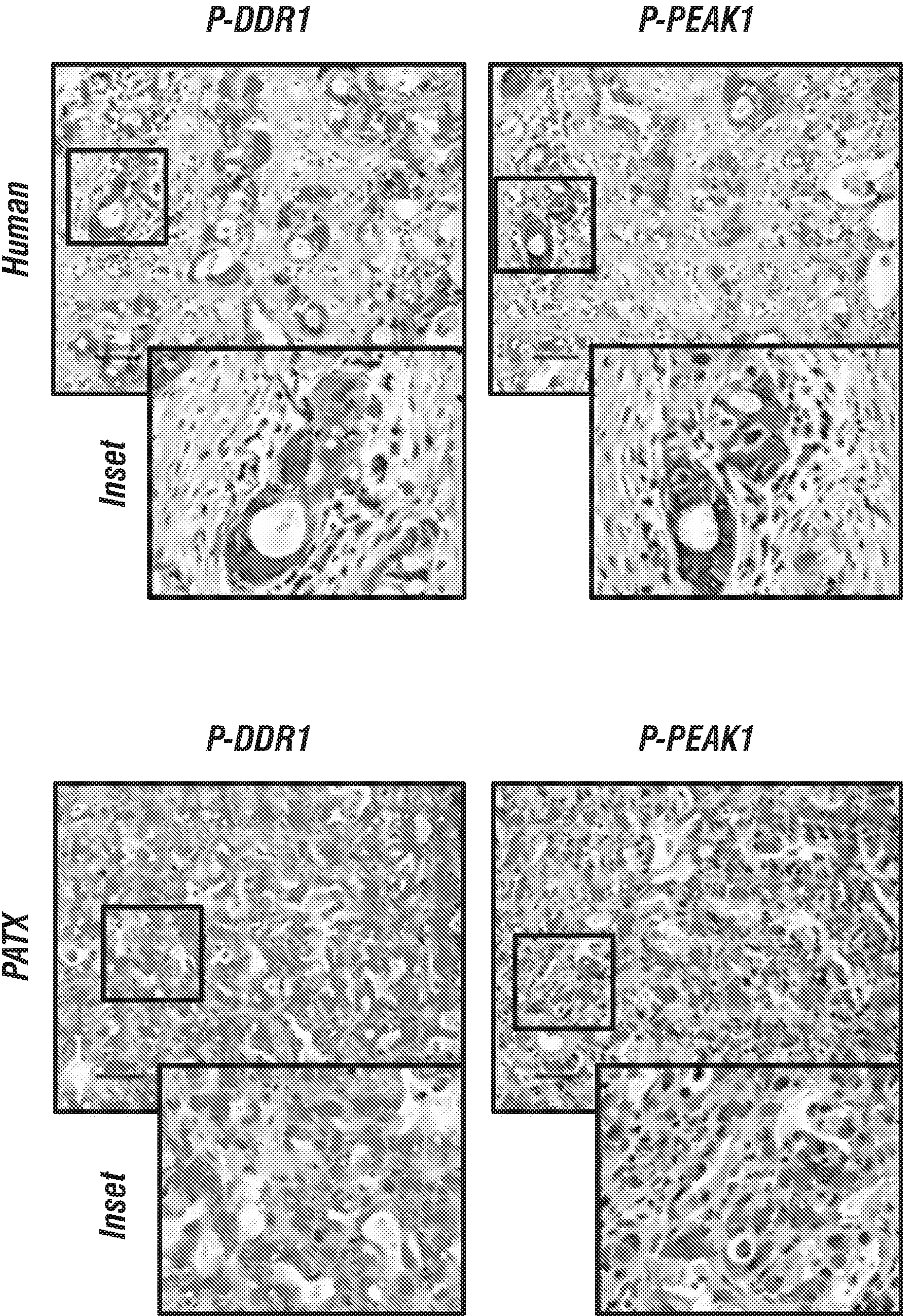


FIG. 1B

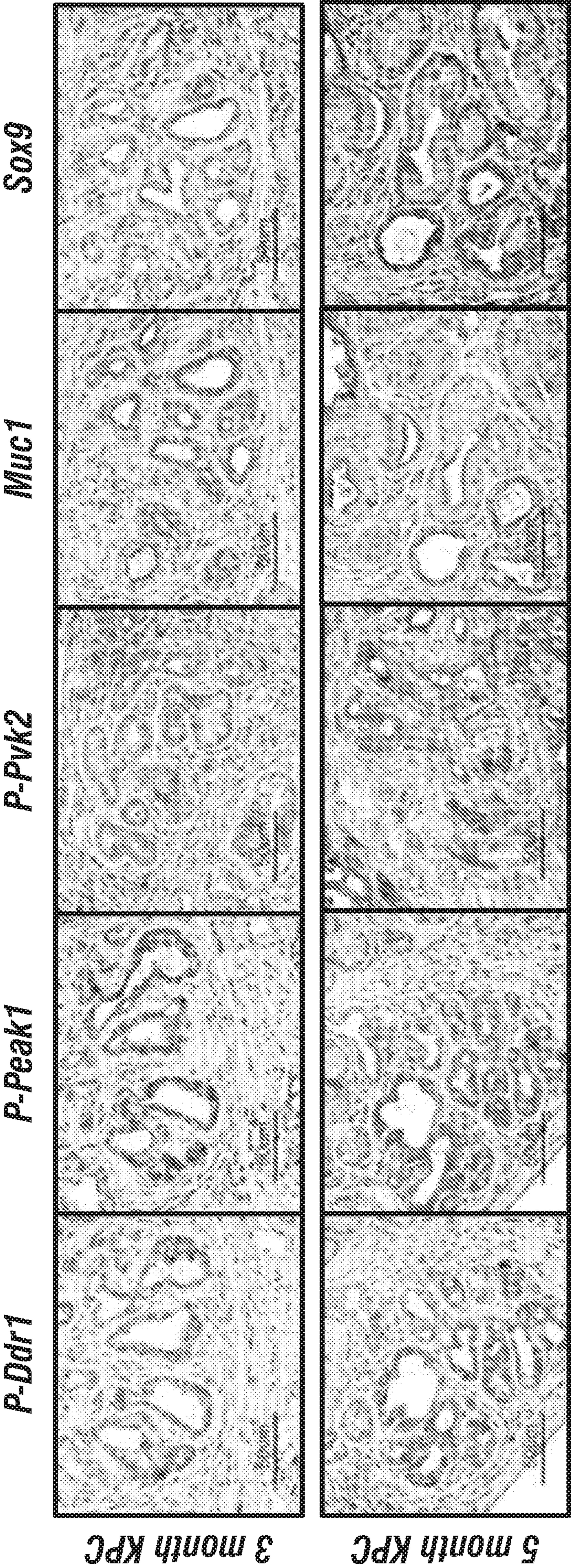


FIG. 1C

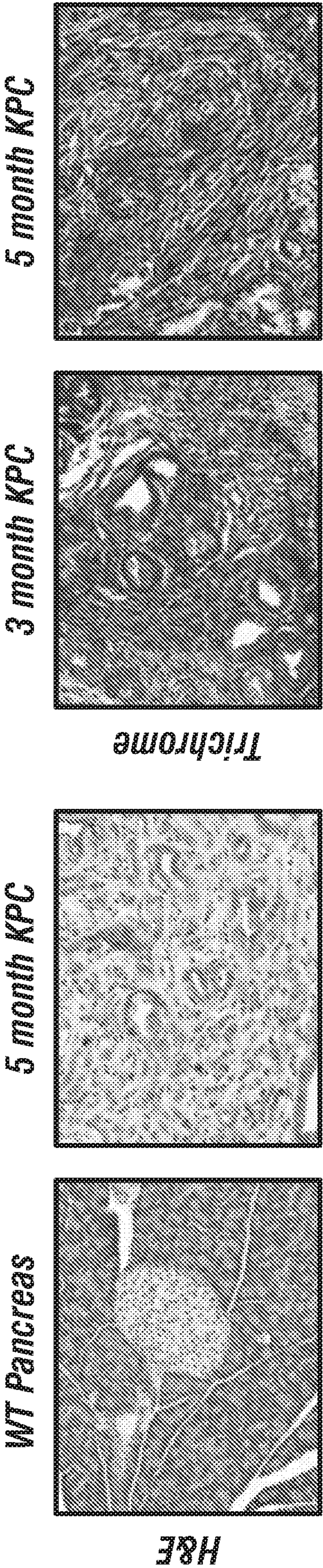


FIG. 1D

FIG. 1E

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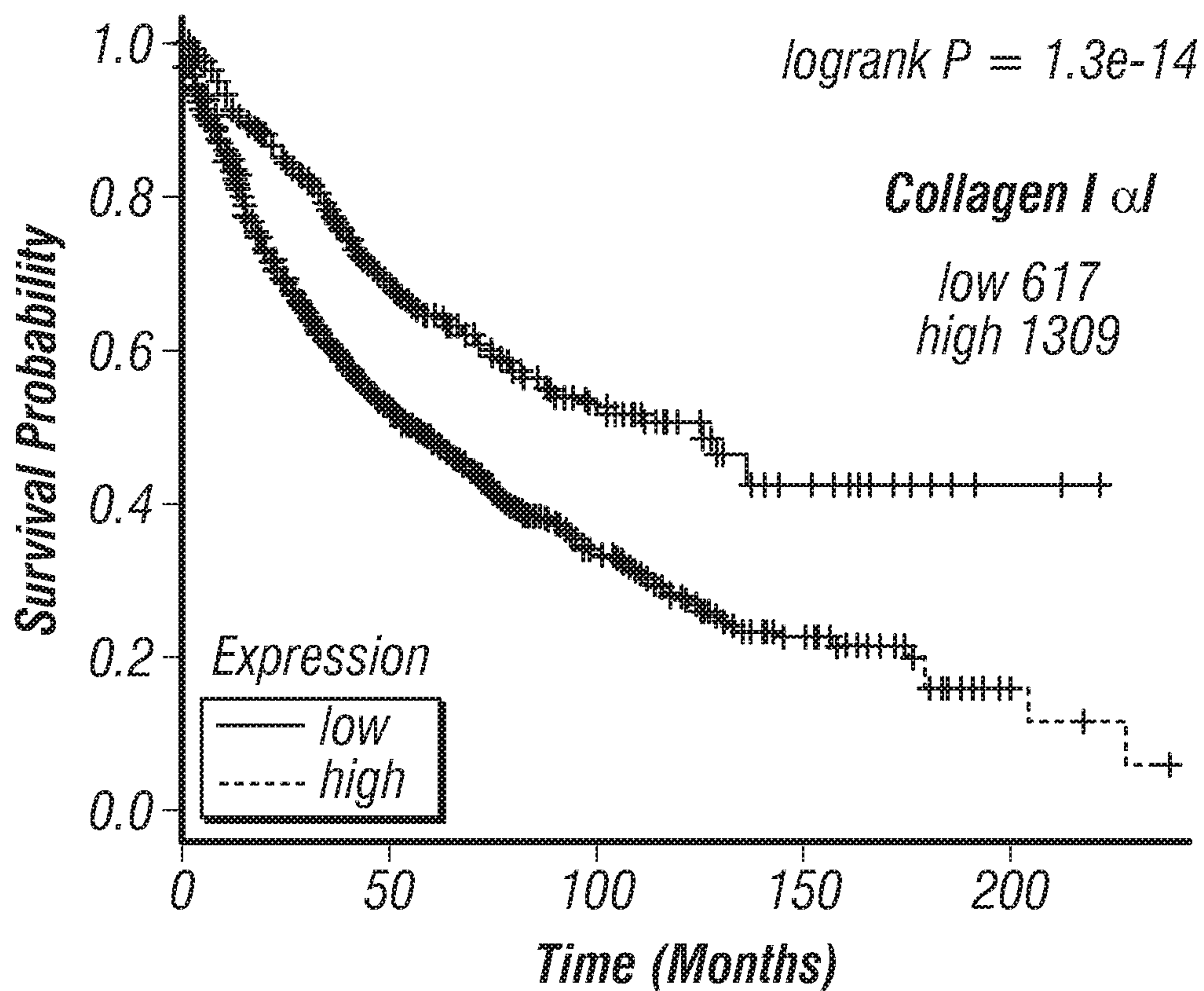
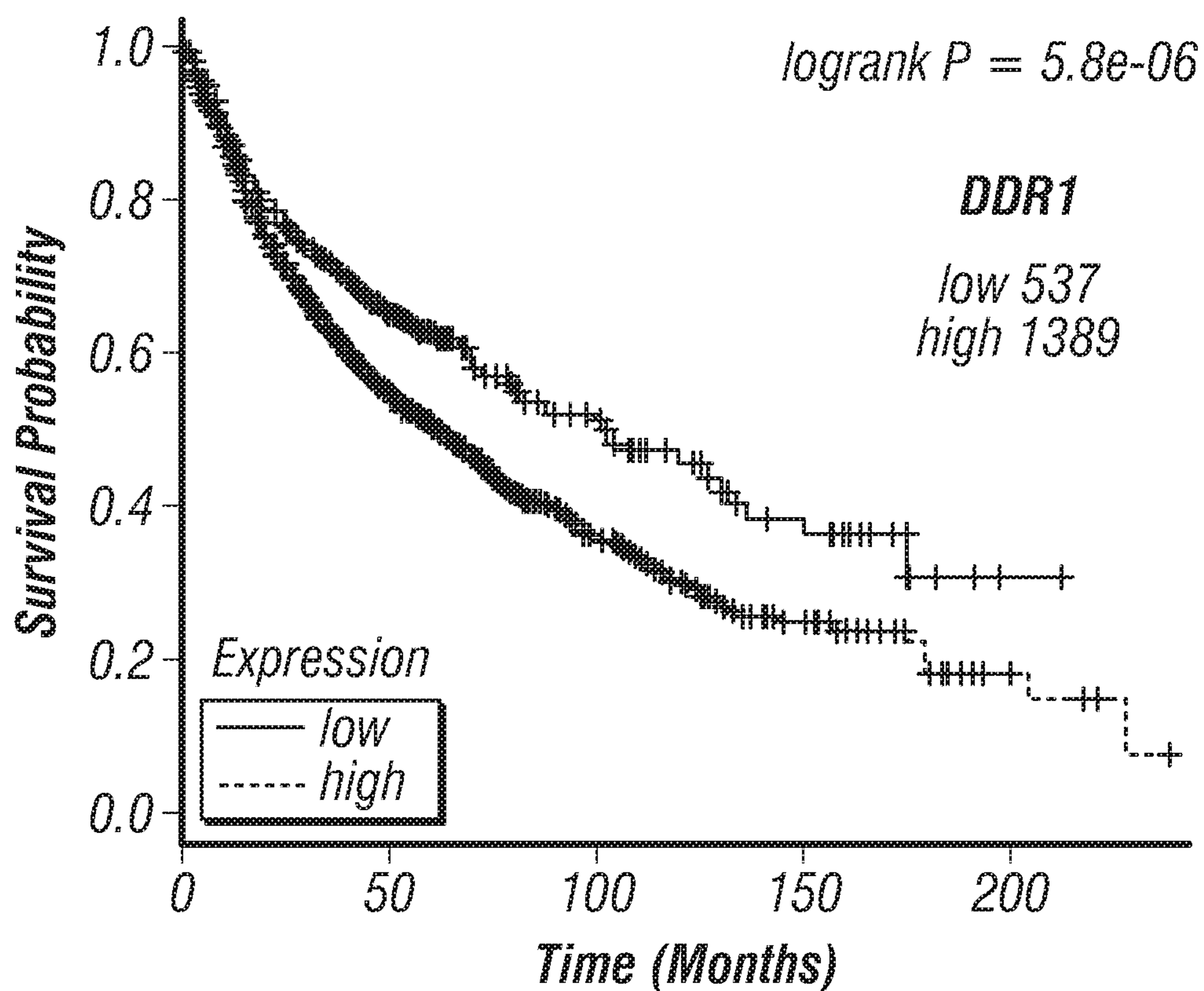


FIG. 2A

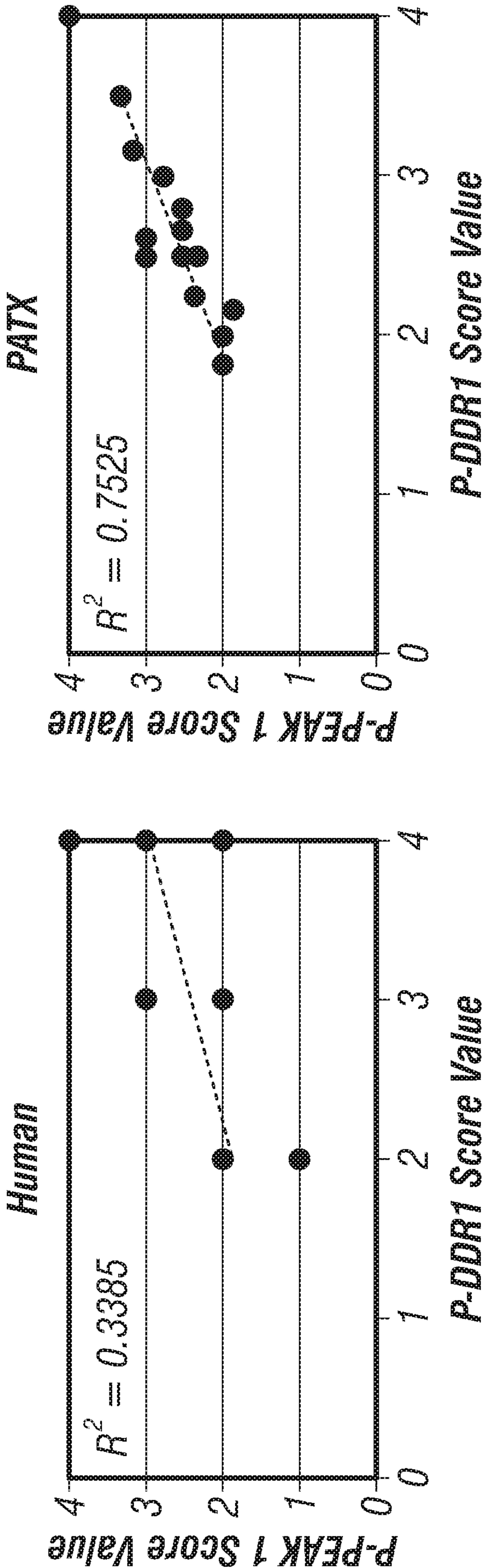


FIG. 2B

	Phospho-DDR1				Phospho-PEAK1			
Score	0-1	2	3	4	0-1	2	3	4
Human (%)	0	31.25	37.5	31.25	3.61	43.7	38.25	14.45
PATX (%)	6.25	53.125	34.38	6.25	13.4	36.5	36.5	13.65

FIG. 2C

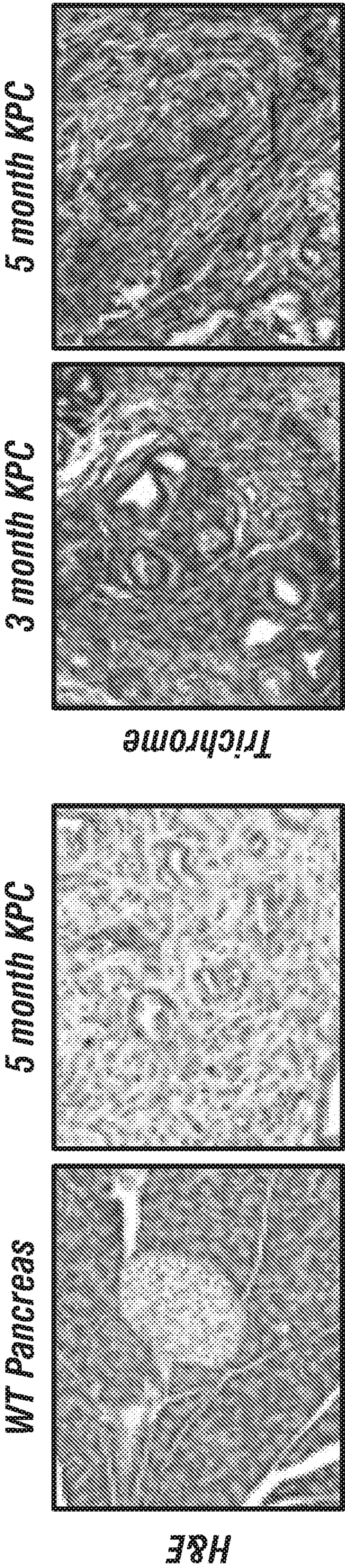
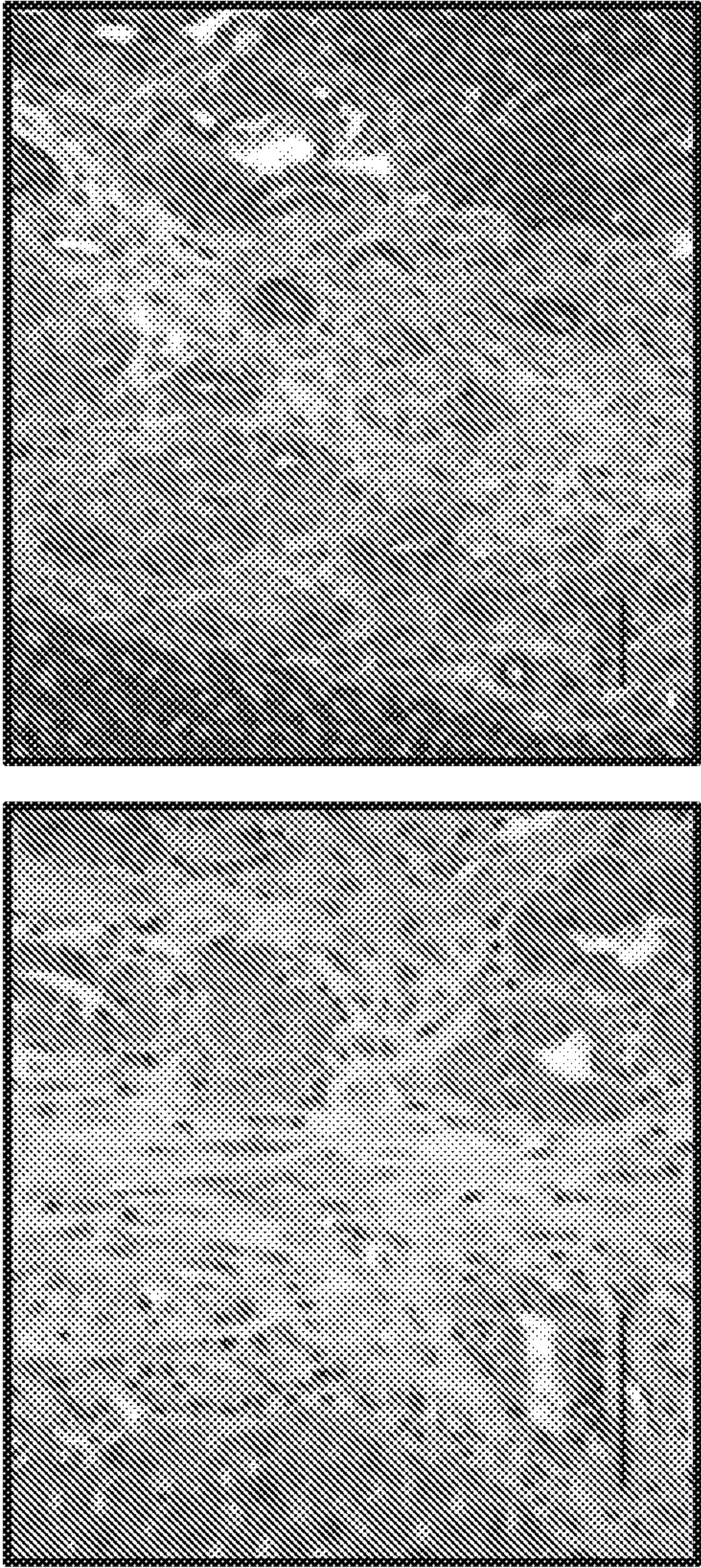


FIG. 3D



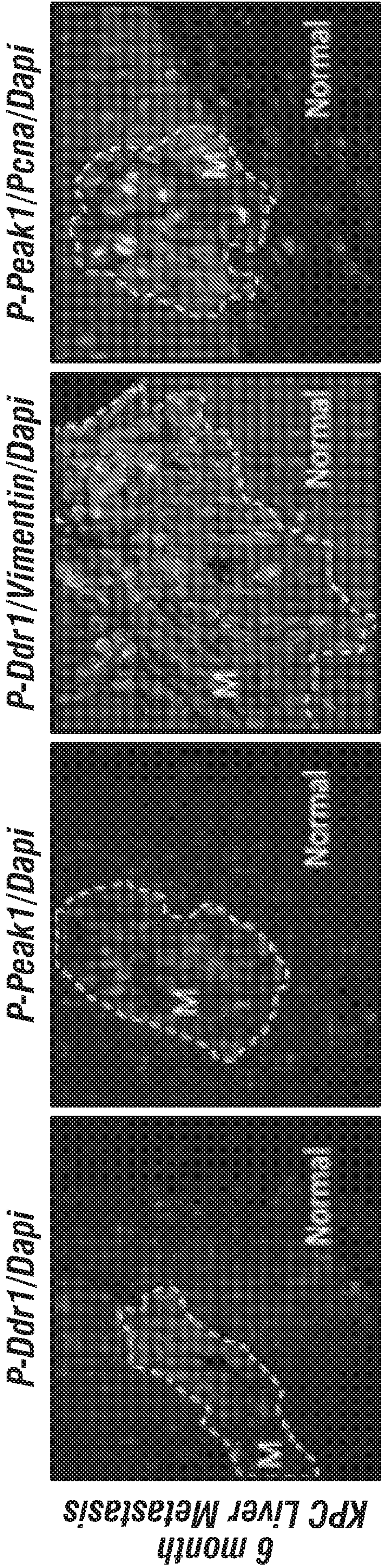


FIG. 3G

FIG. 3H

FIG. 3I

FIG. 3J

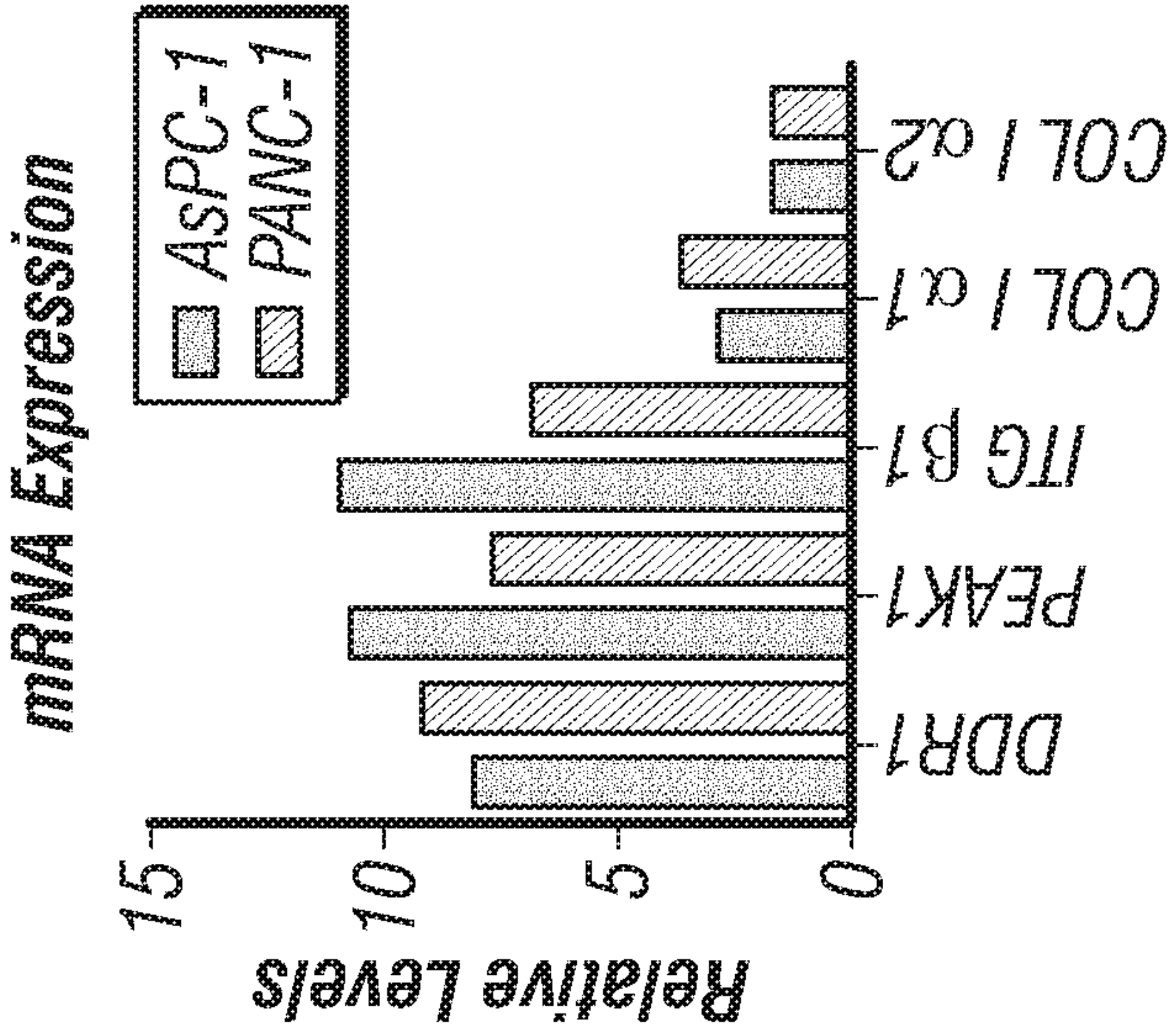
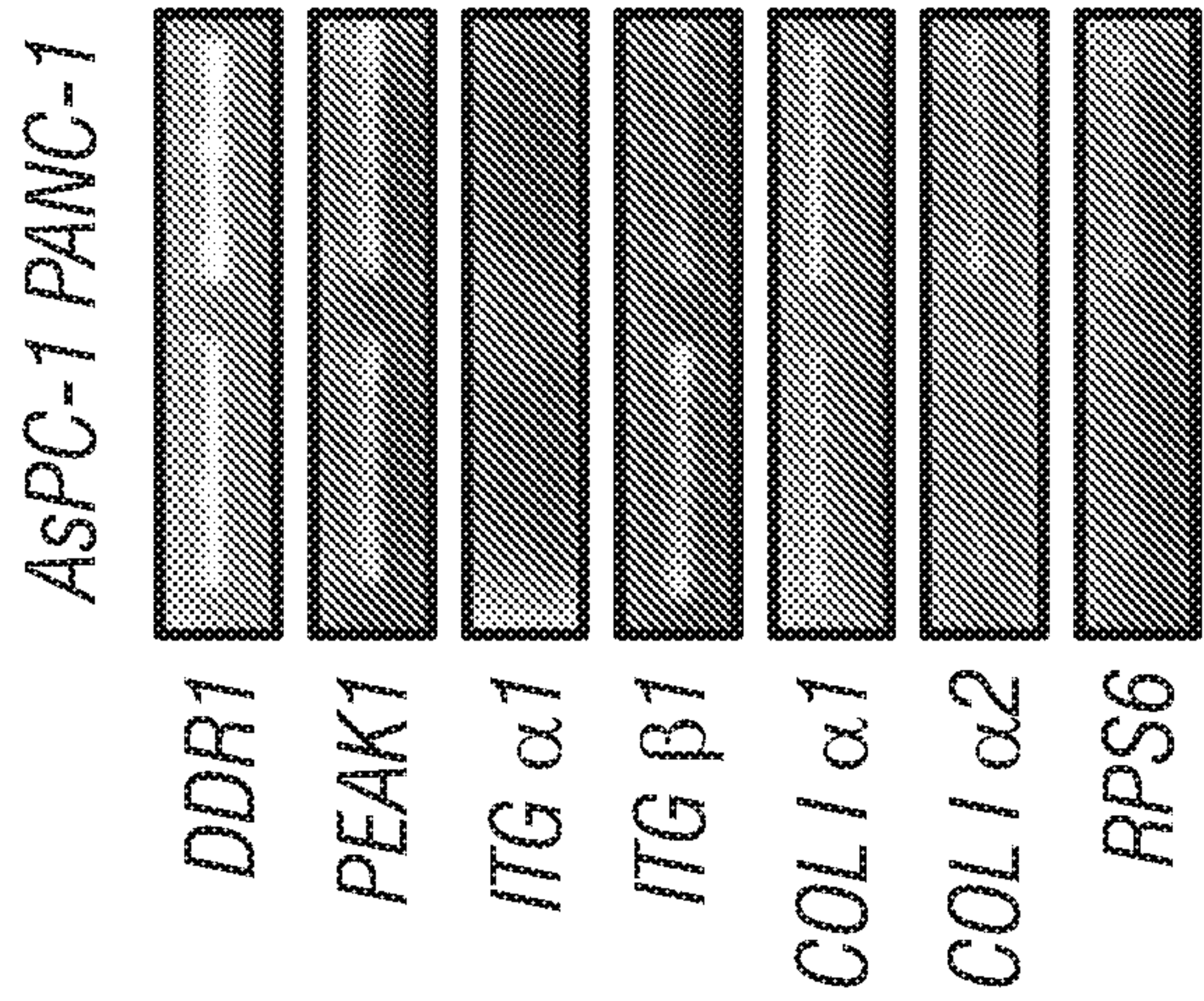


FIG. 4A

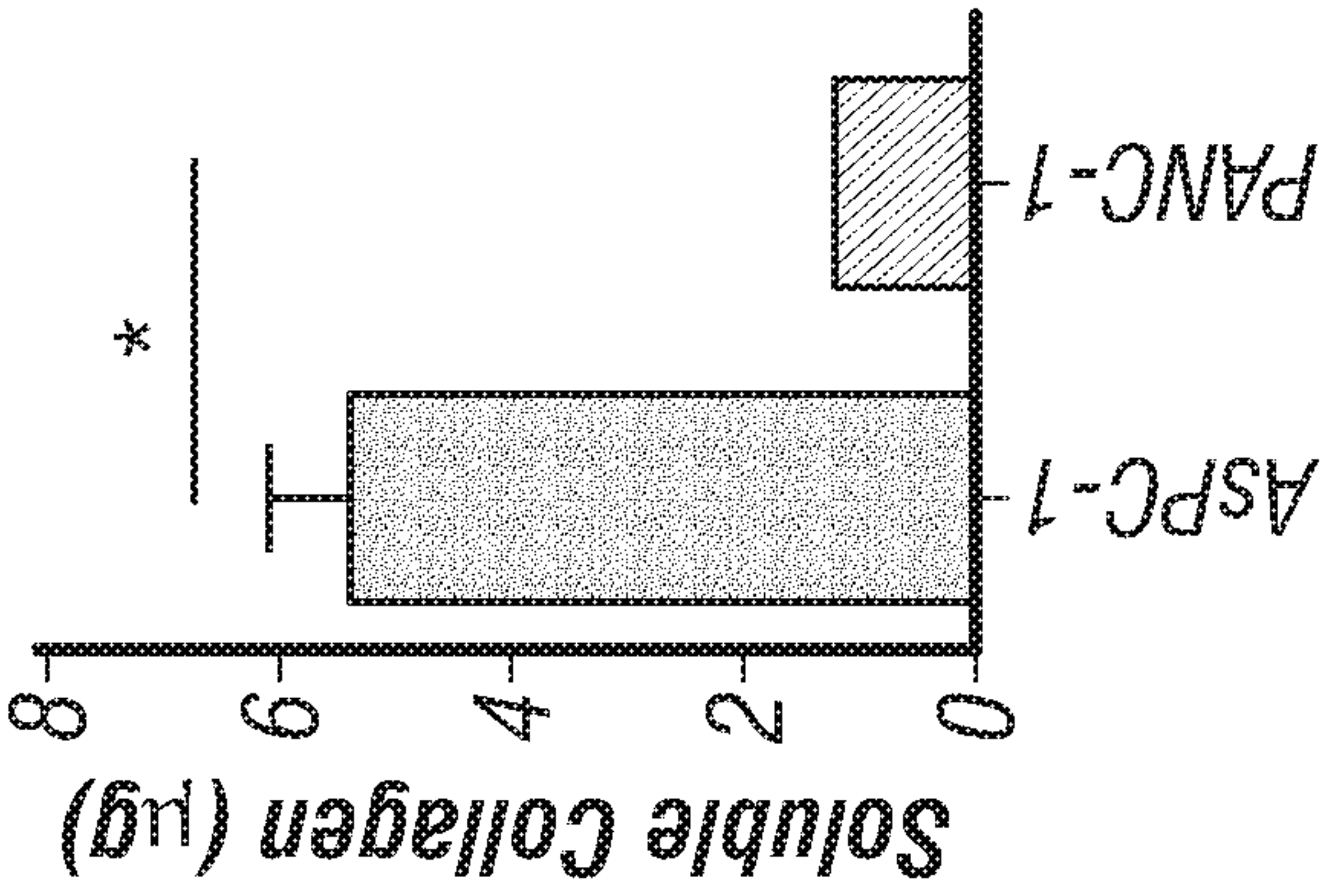


FIG. 4B

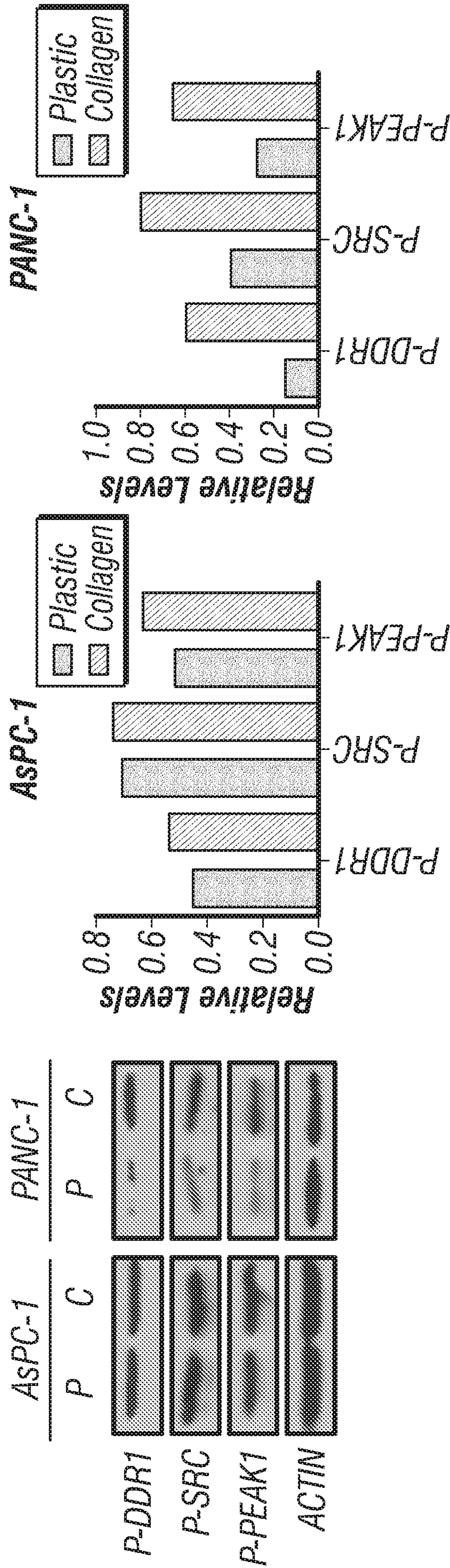


FIG. 4C

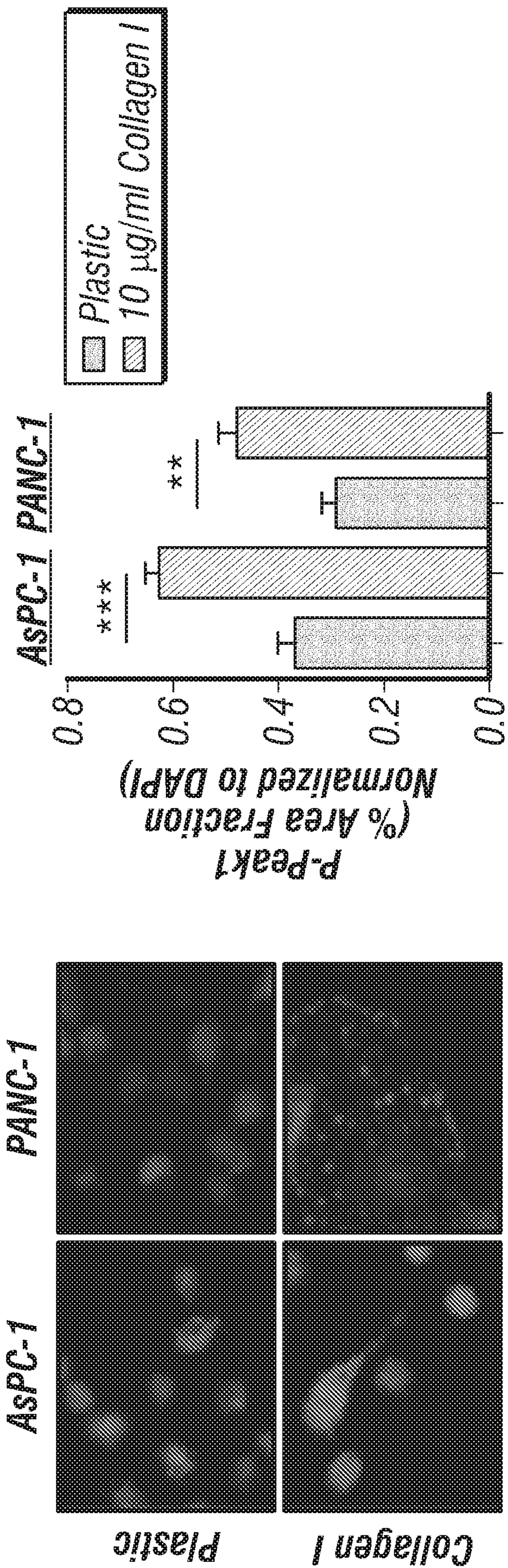


FIG. 4D

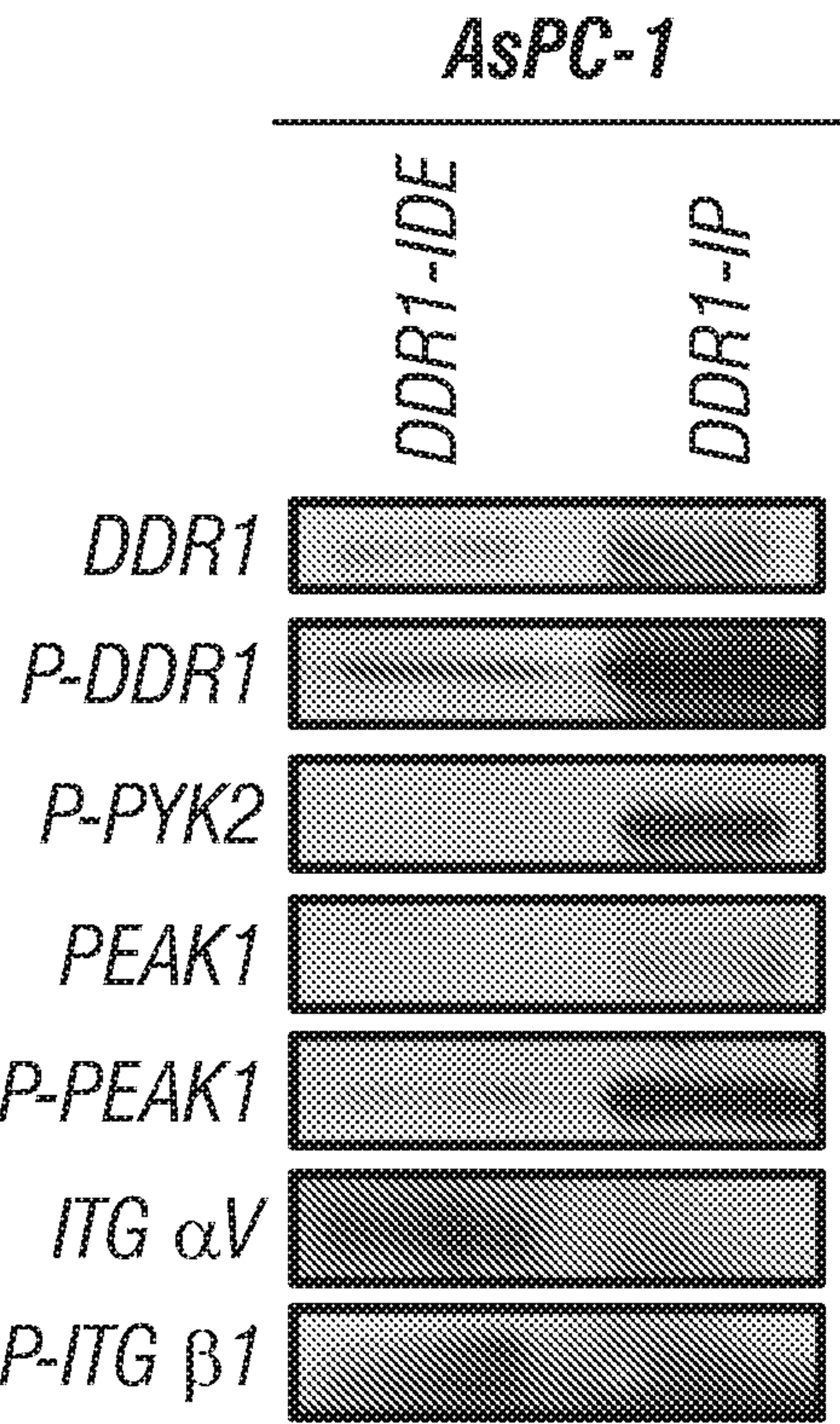


FIG. 4E

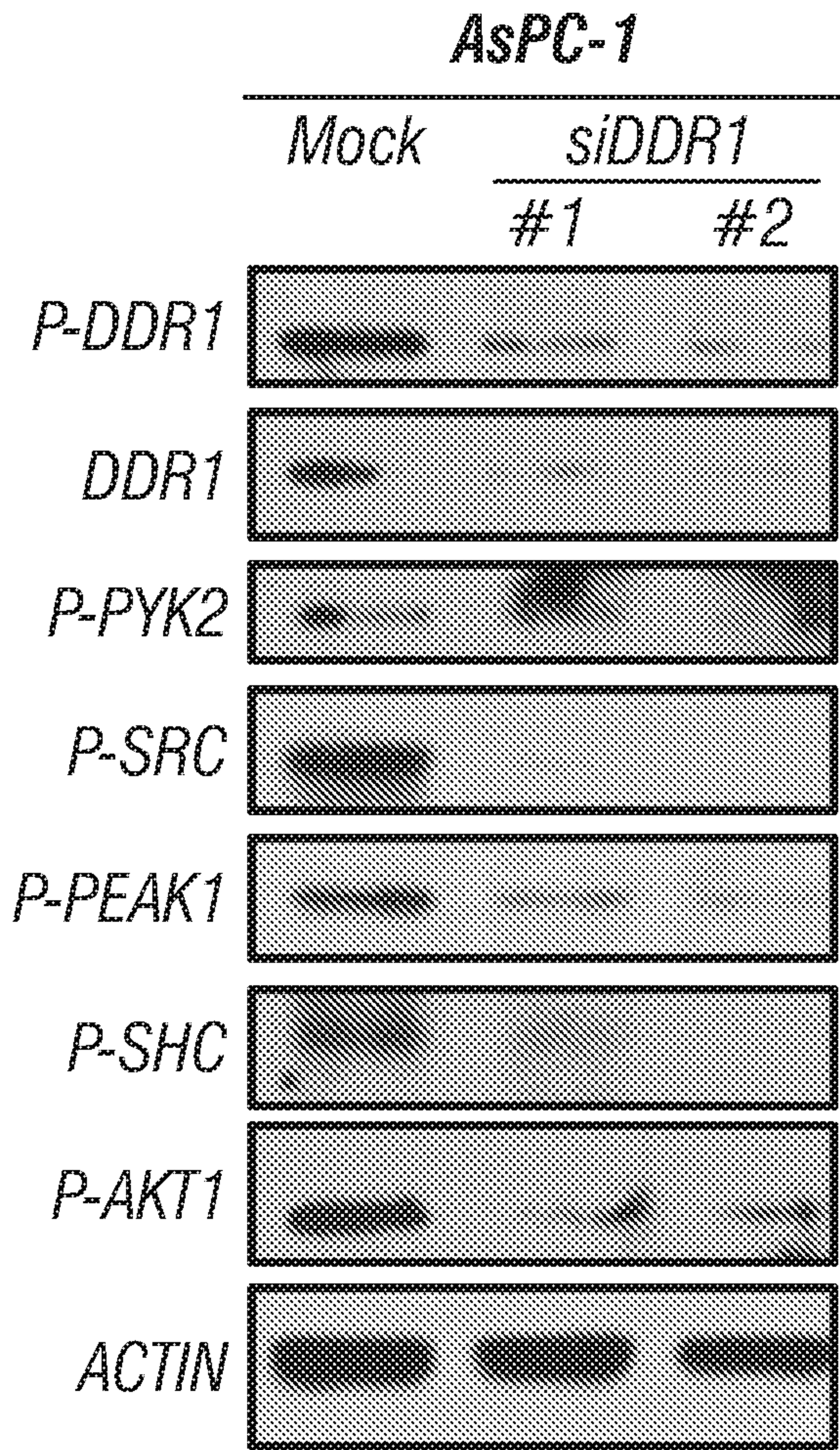


FIG. 4F

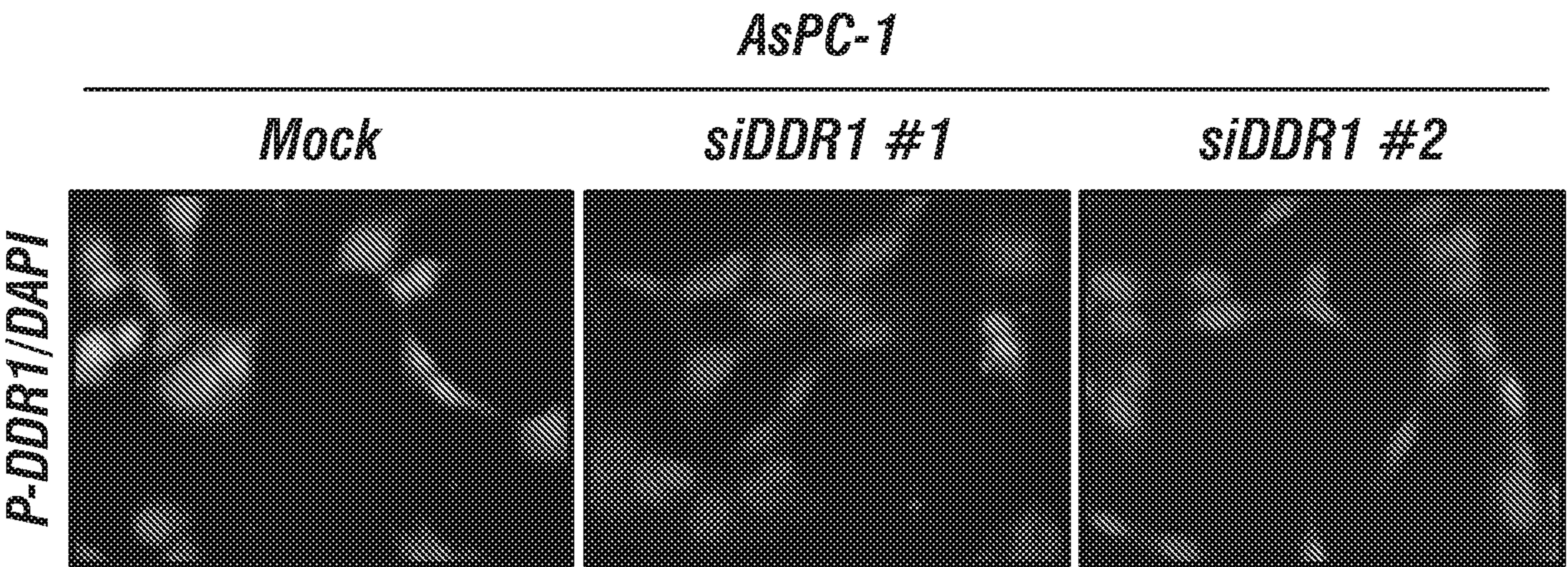


FIG. 4G

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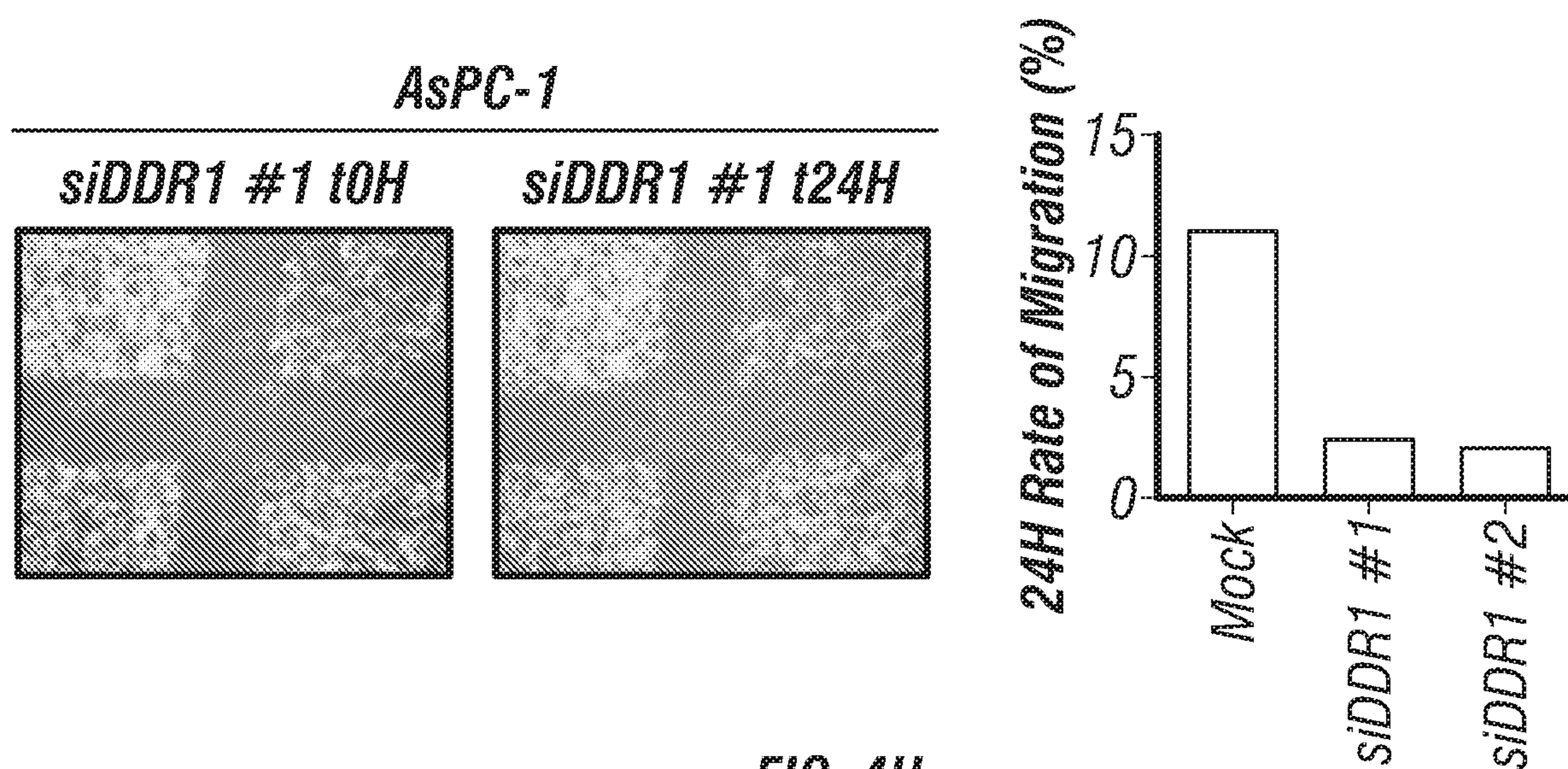


FIG. 4H

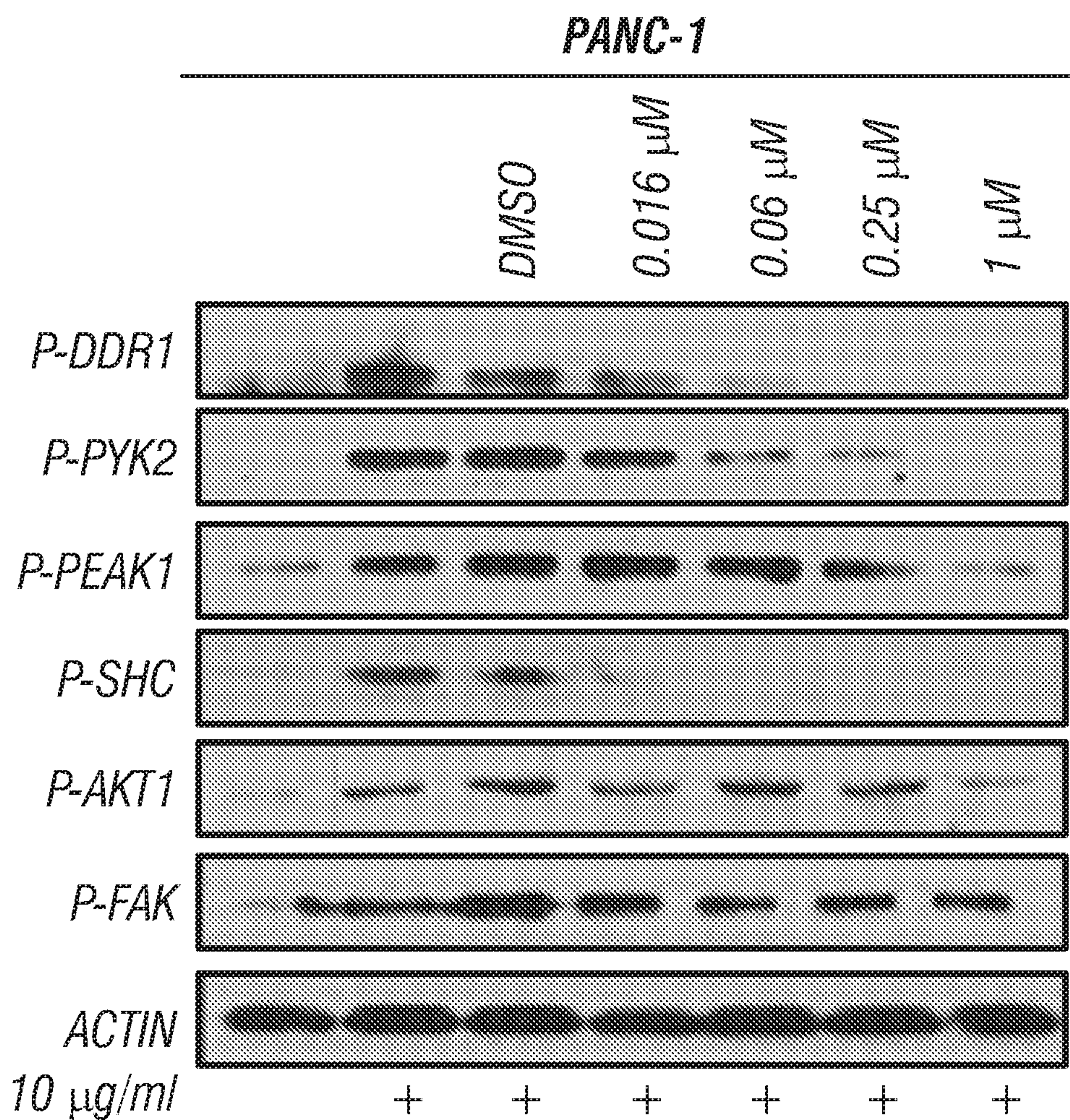


FIG. 5A

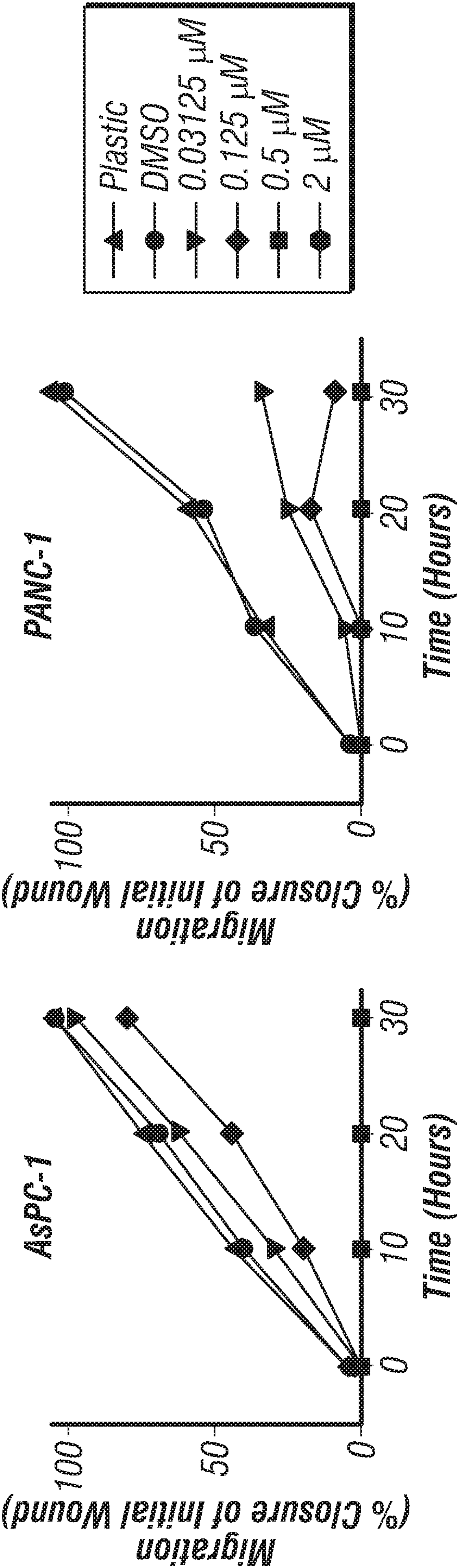


FIG. 5B

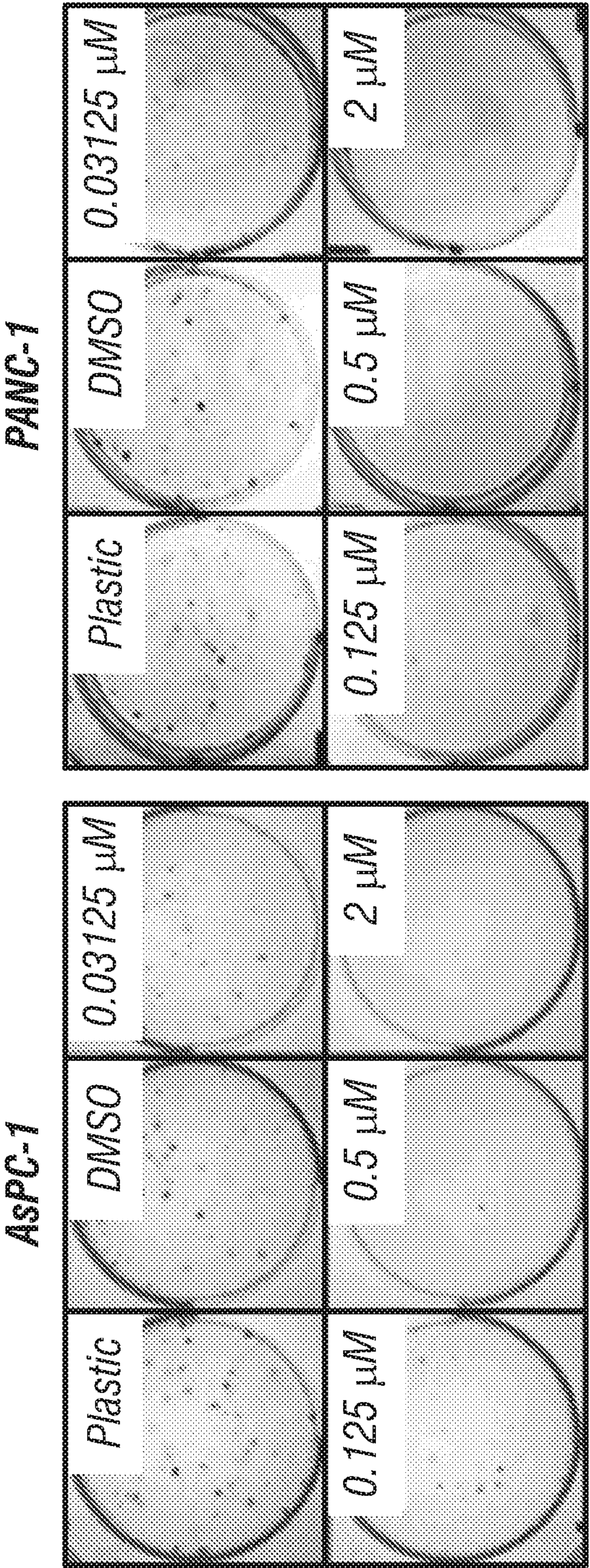


FIG. 5C

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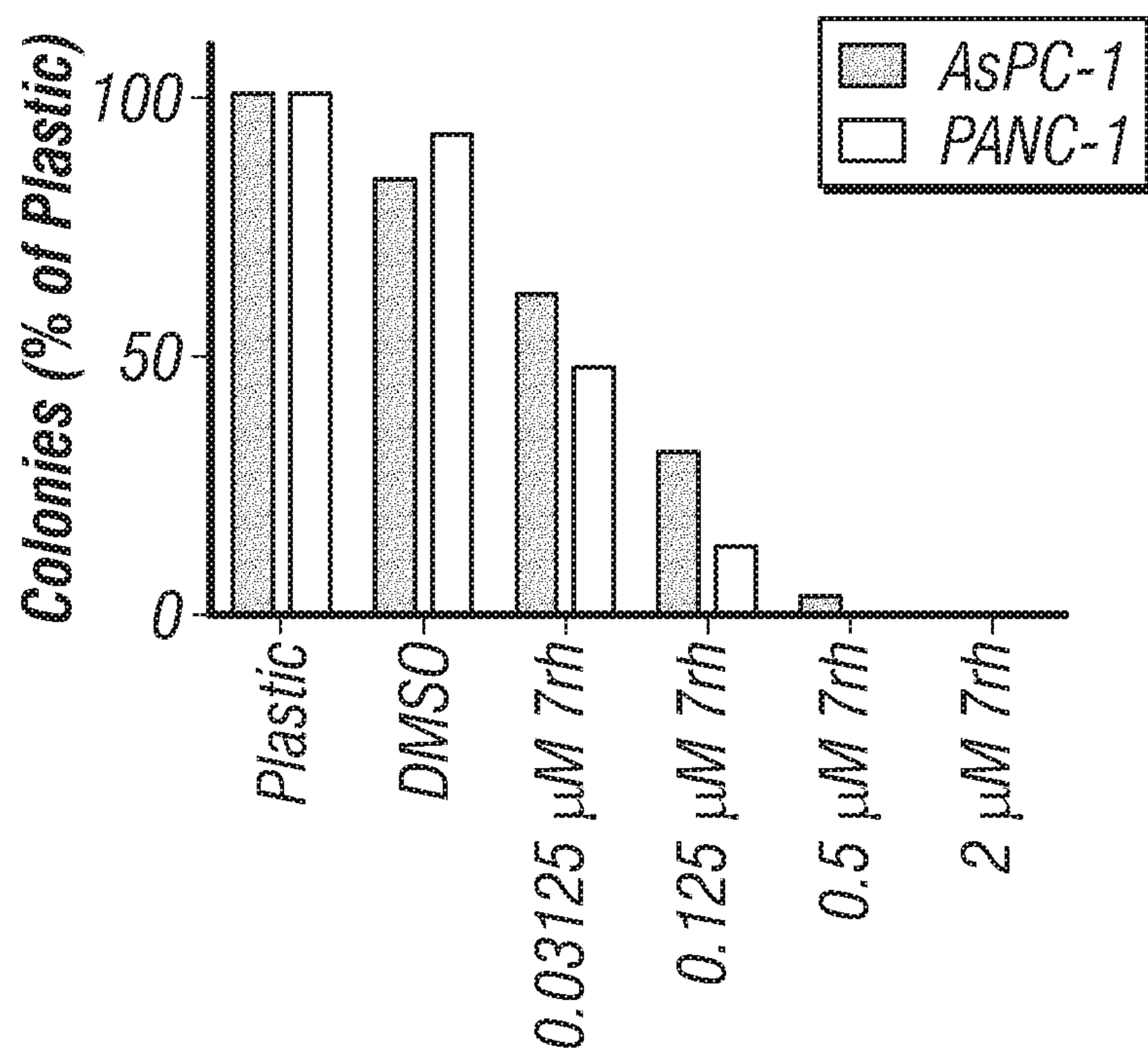
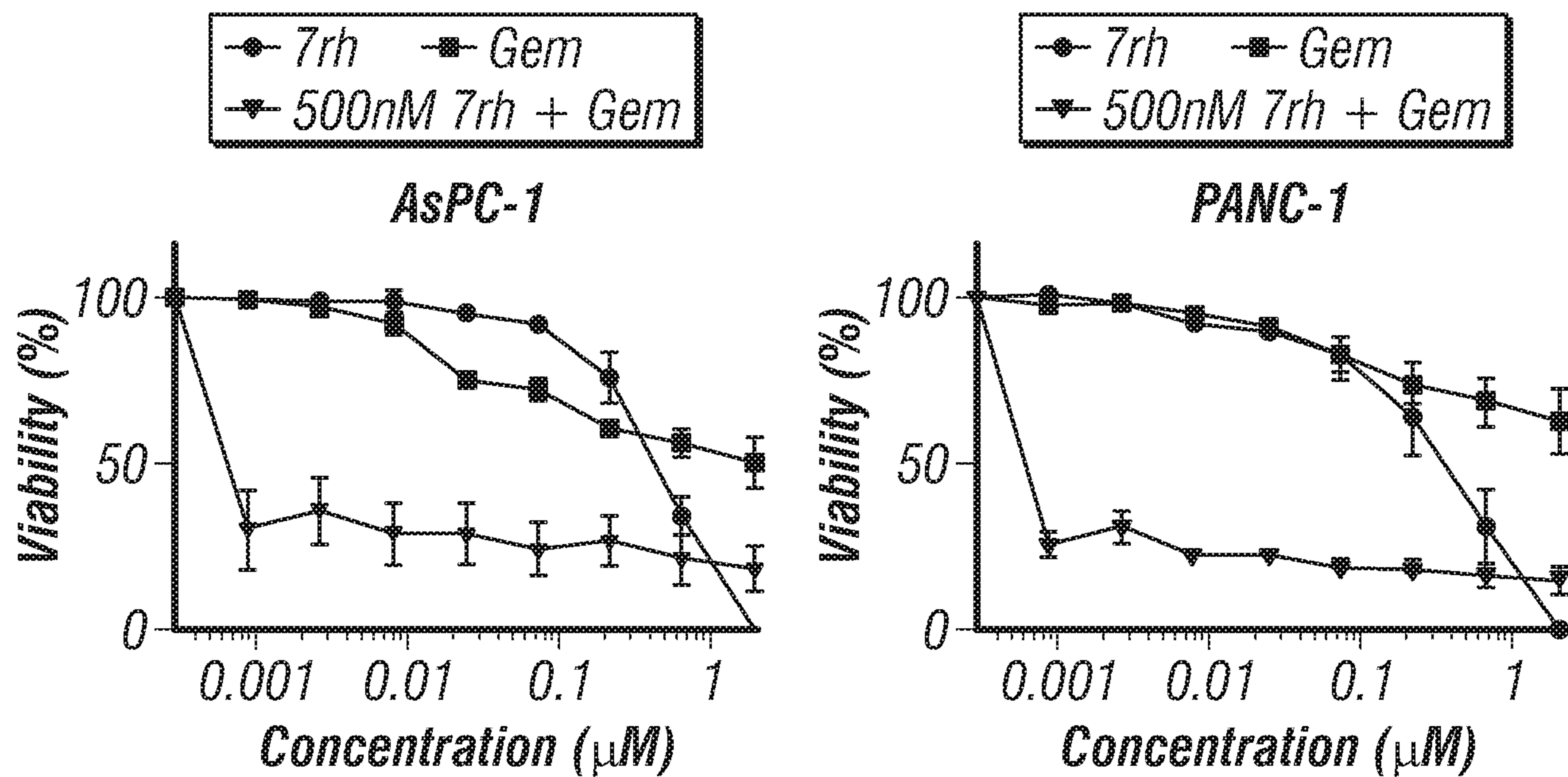
FIG. 5C
(Cont'd)

FIG. 5D

	<i>AsPC-1</i>	<i>PANC-1</i>
<i>7rh (nM)</i> <i>Avg IC₅₀</i>	490 (6)	380 (4)
<i>Gemcitabine (nM)</i> <i>Avg IC₅₀</i>	2000 (3)	2000 (4)
<i>250 nM 7rh + Gem</i> <i>Avg IC₅₀</i>	1725 (3)	16.4 (3)
<i>500 nM 7rh + Gem</i> <i>Avg IC₅₀</i>	2.05 (2)	0.035 (3)

FIG. 5D
(Cont'd)

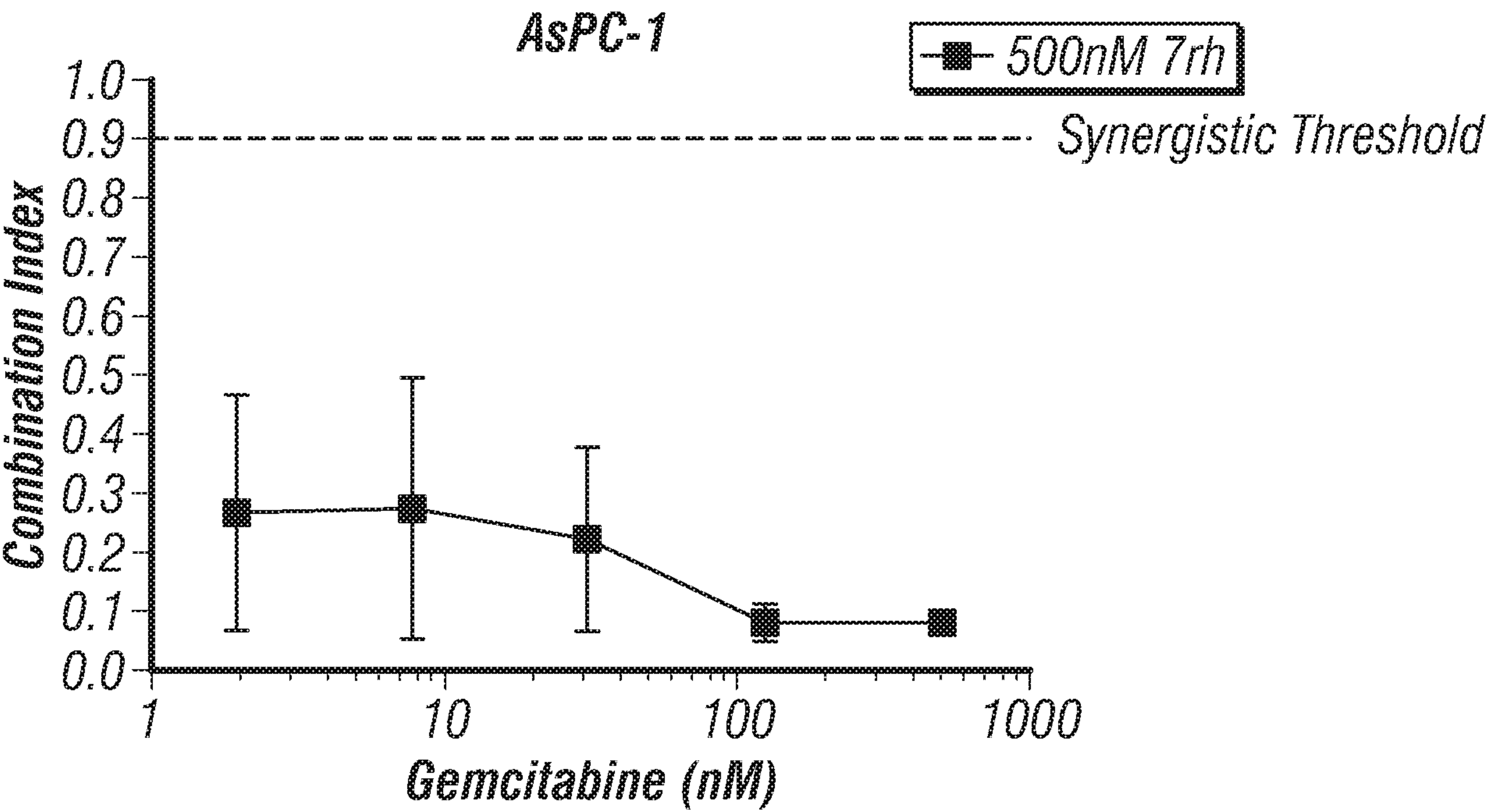


FIG. 6

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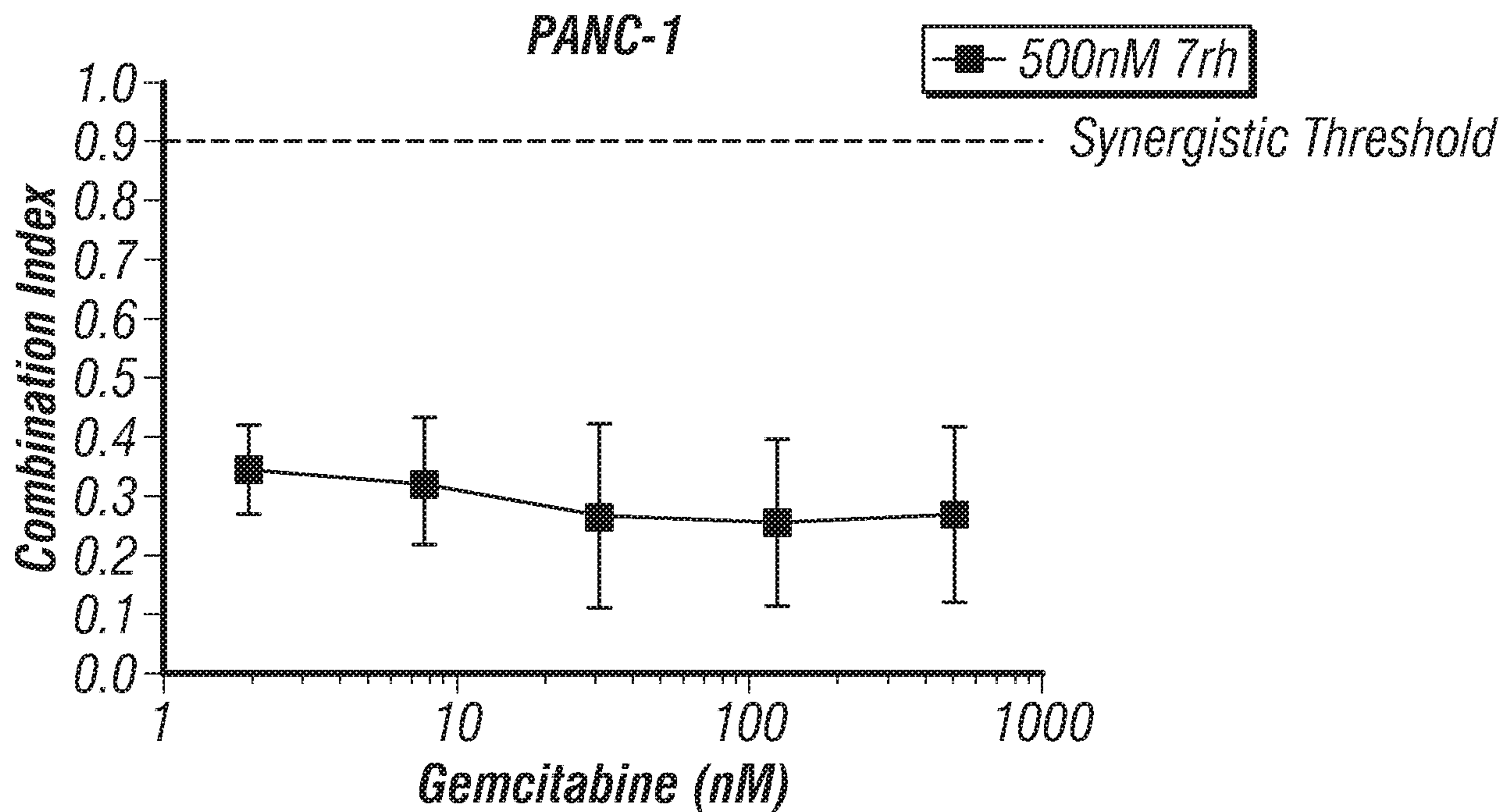


FIG. 6
(Cont'd)

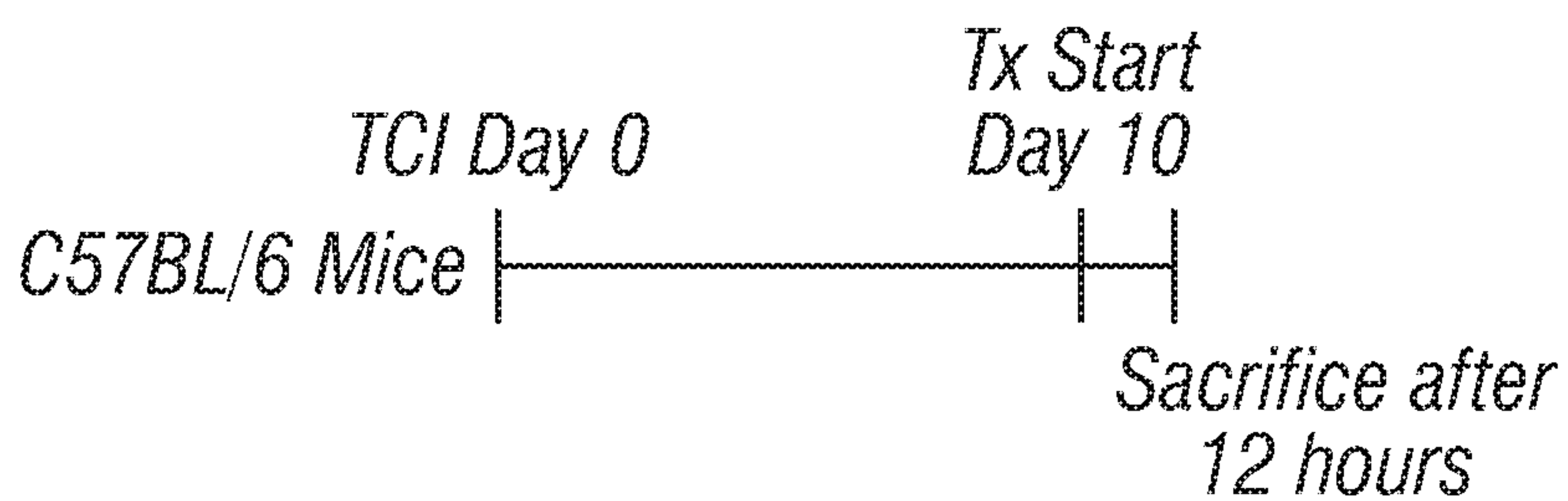


FIG. 7A

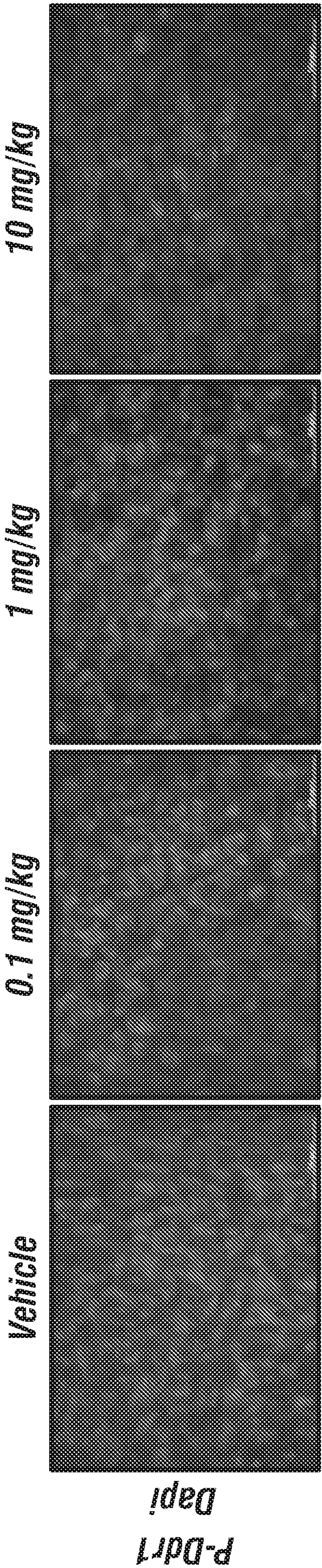


FIG. 7B

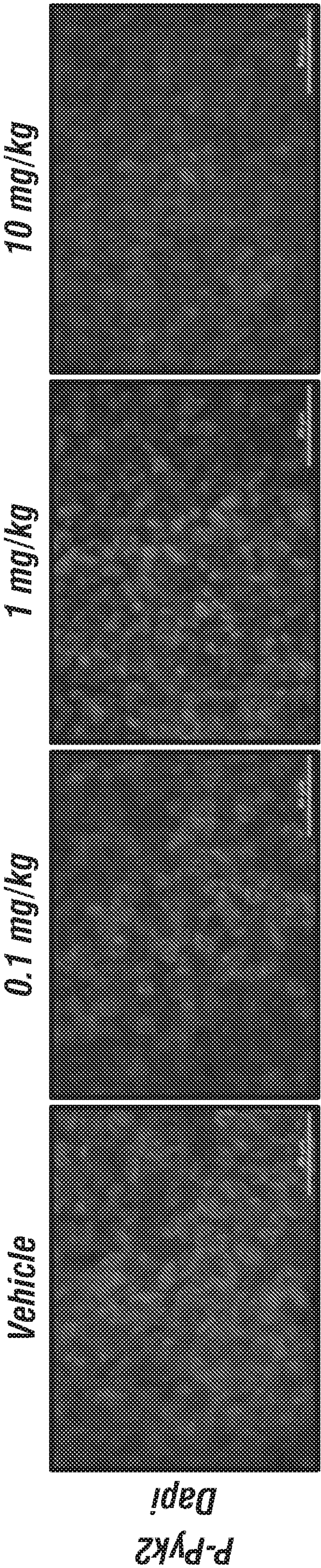


FIG. 7C

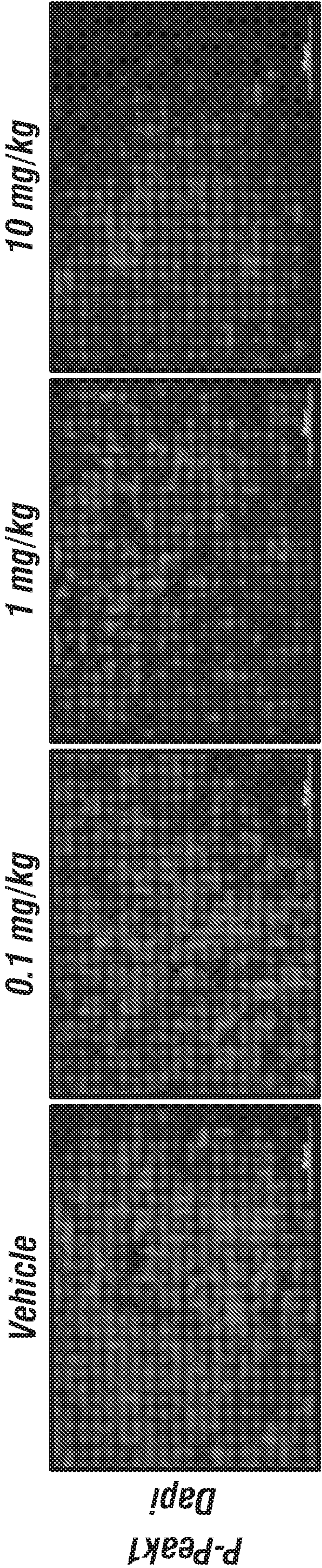


FIG. 7D

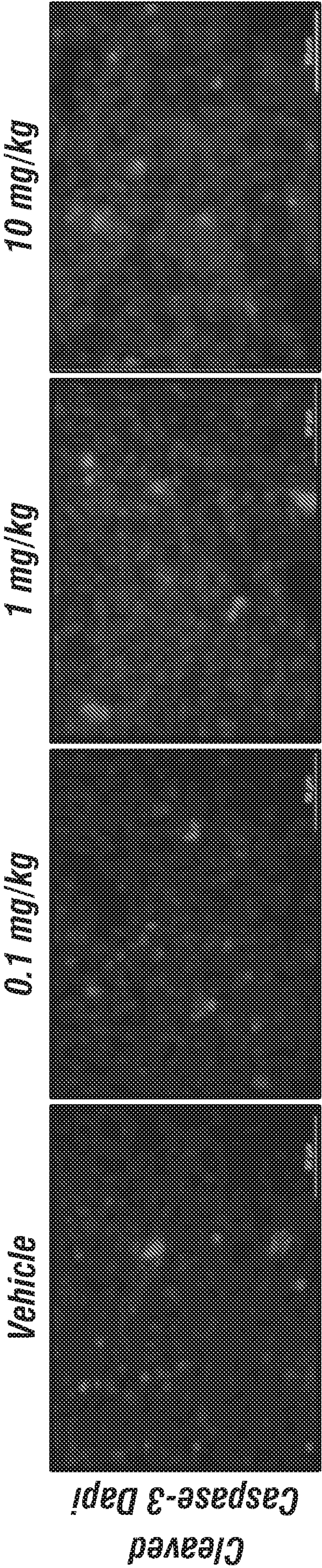


FIG. 7E

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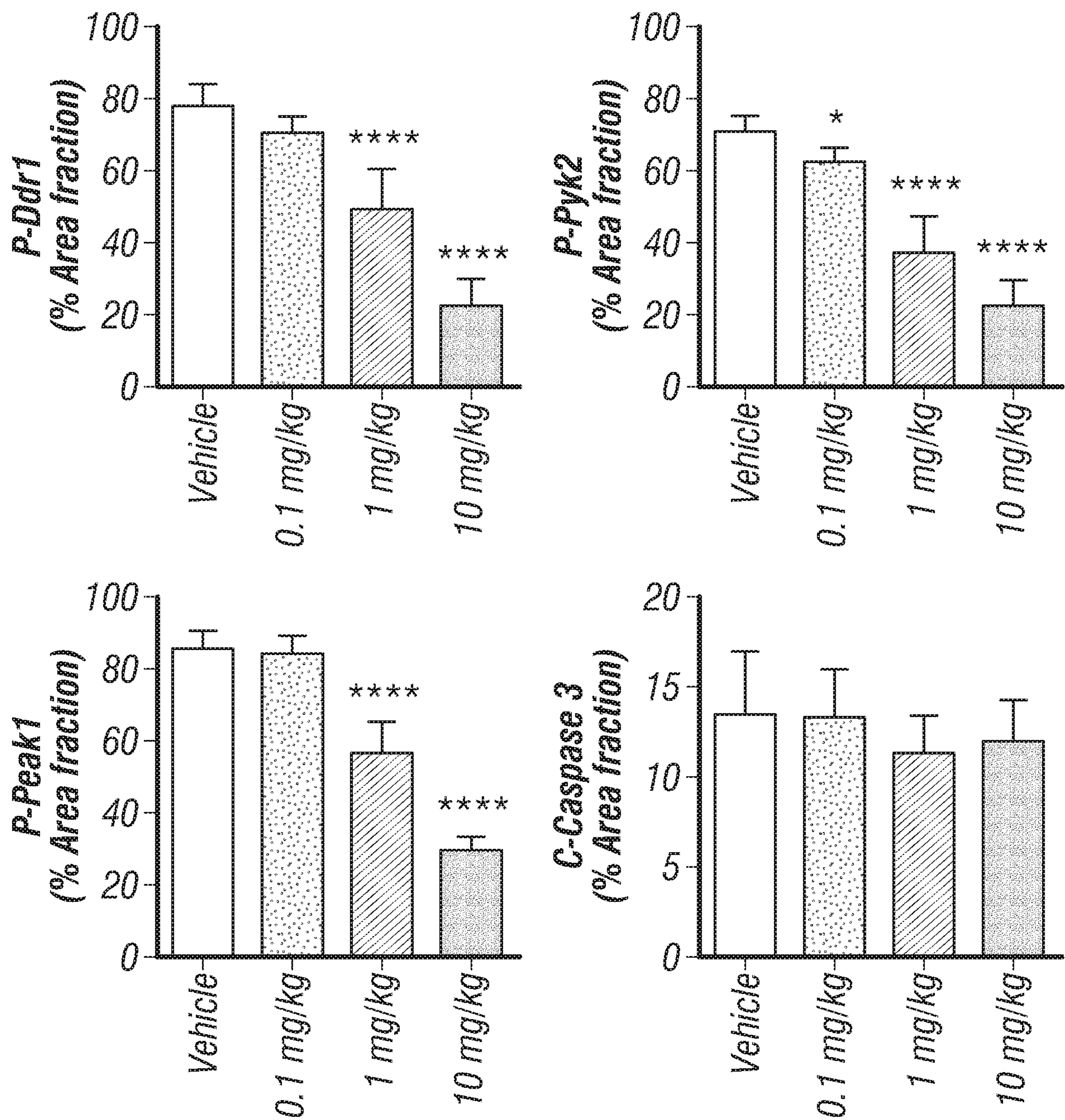


FIG. 7E
(Cont'd)

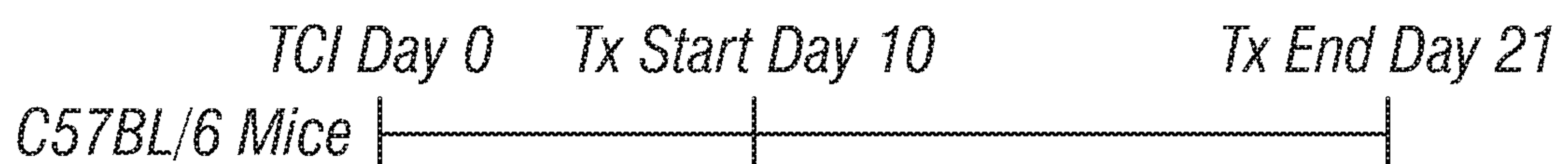


FIG. 8A

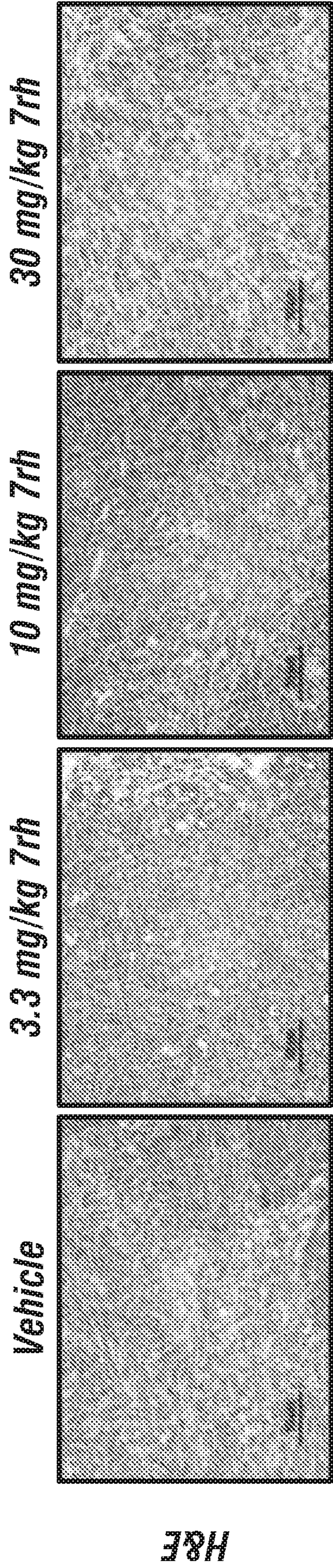


FIG. 8B

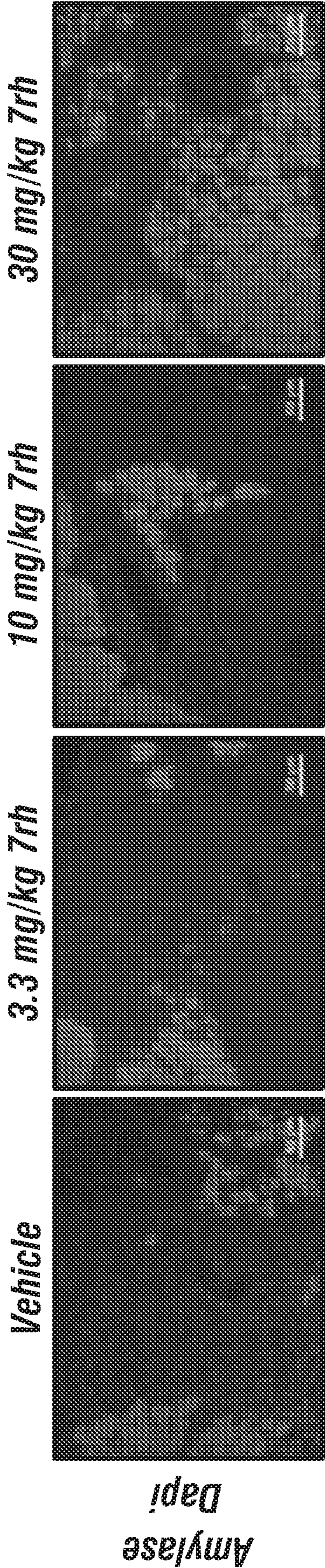


FIG. 8C

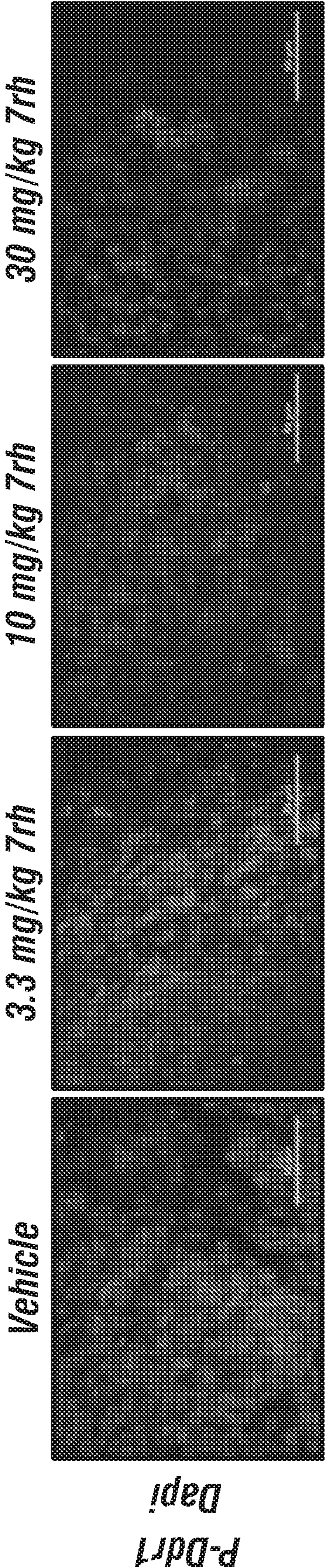


FIG. 8D

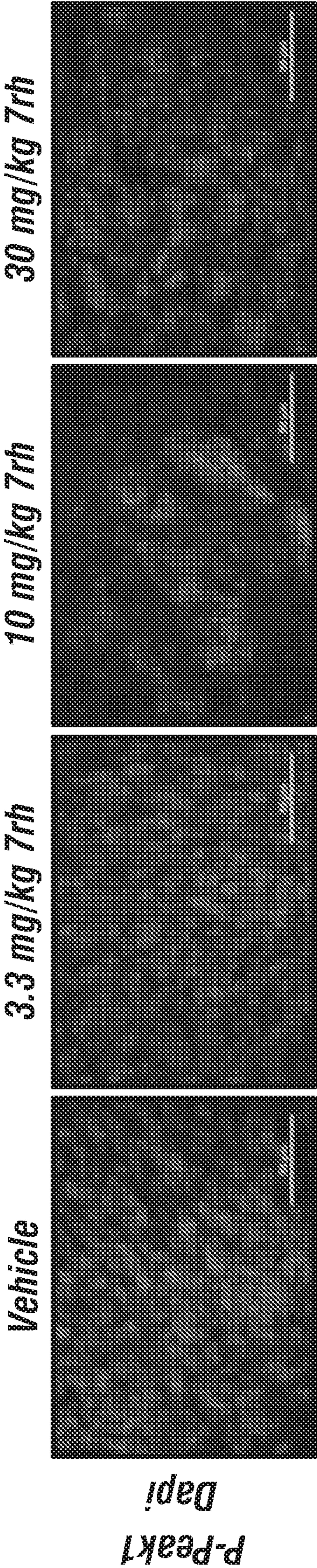


FIG. 8E

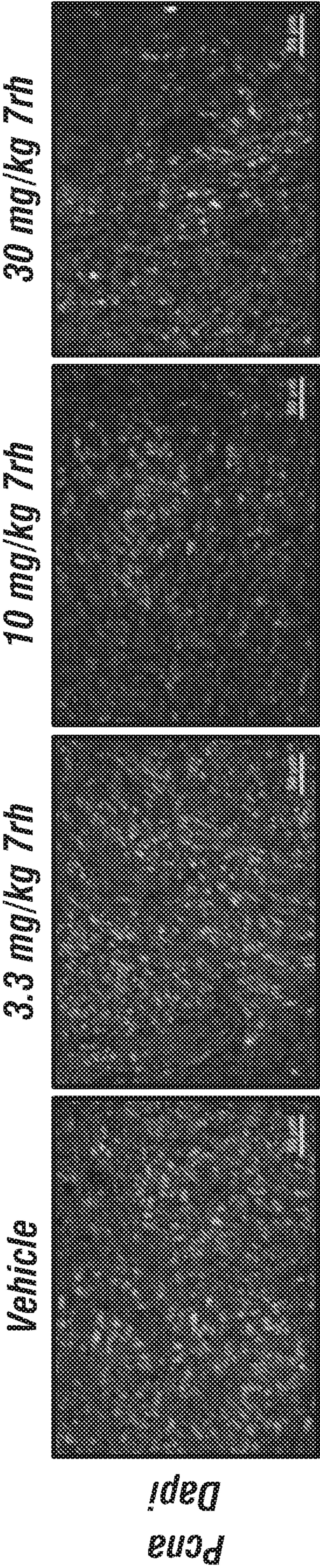
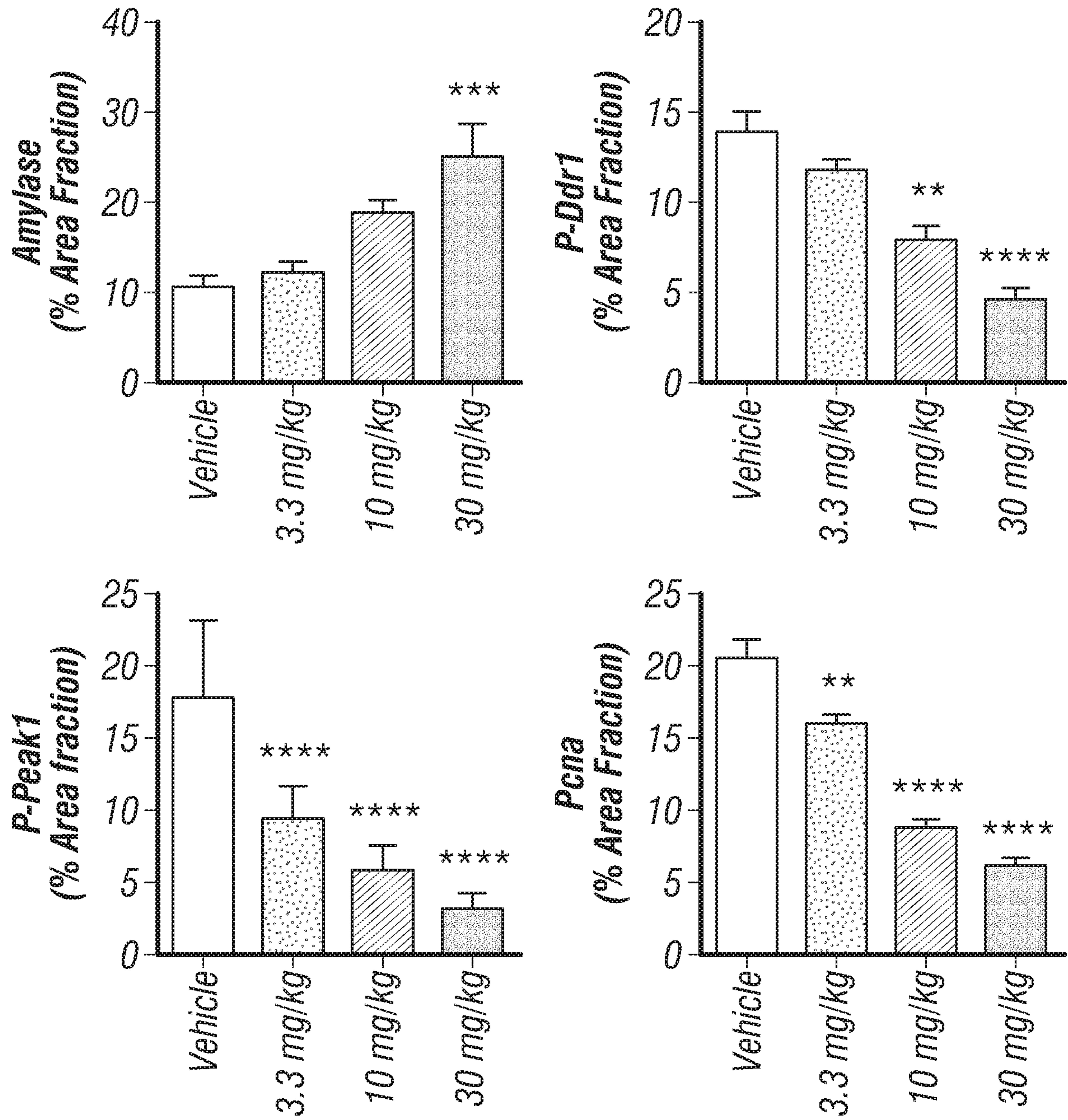


FIG. 8F

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FIG. 8F
(Cont'd)

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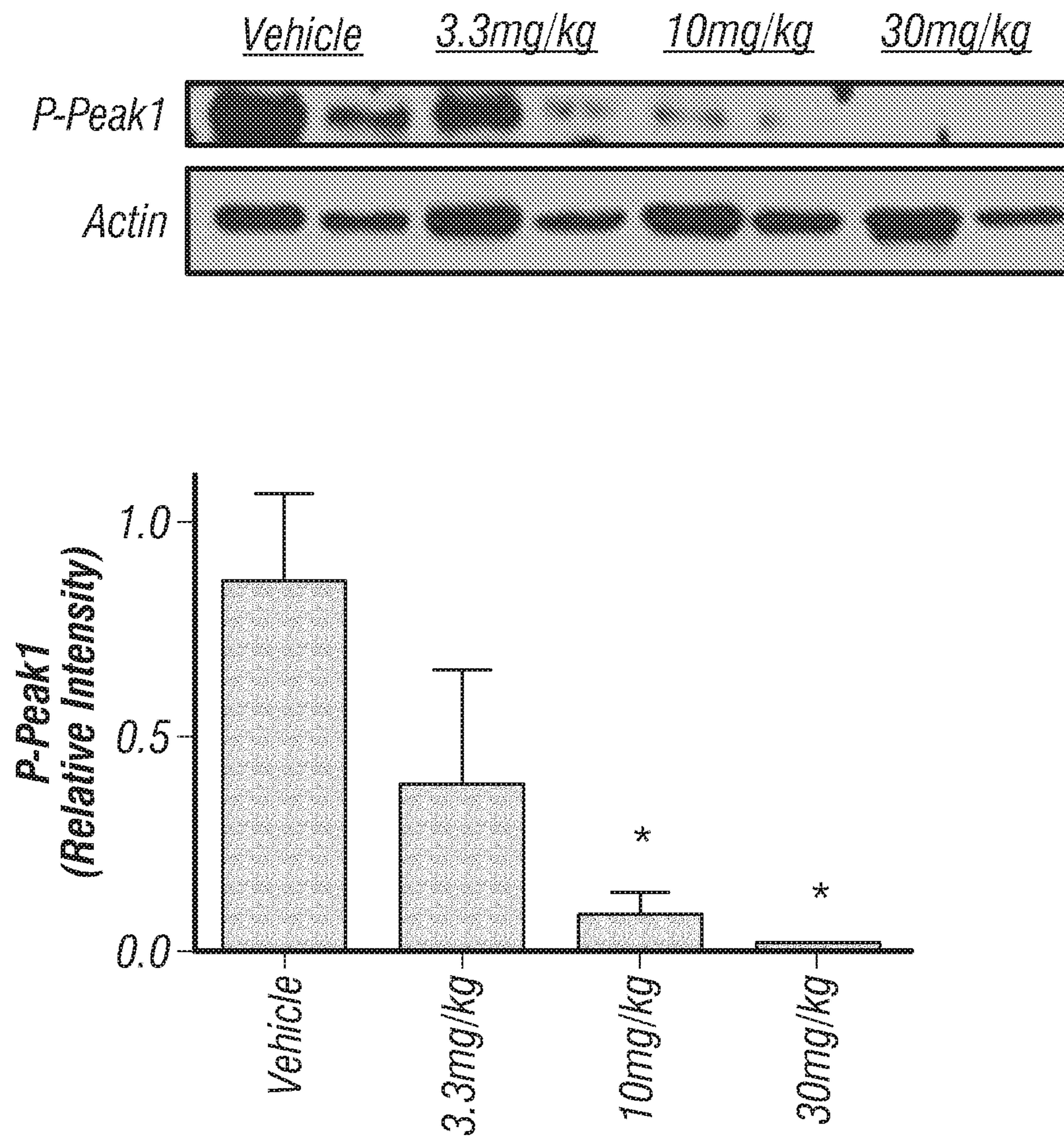


FIG. 8G

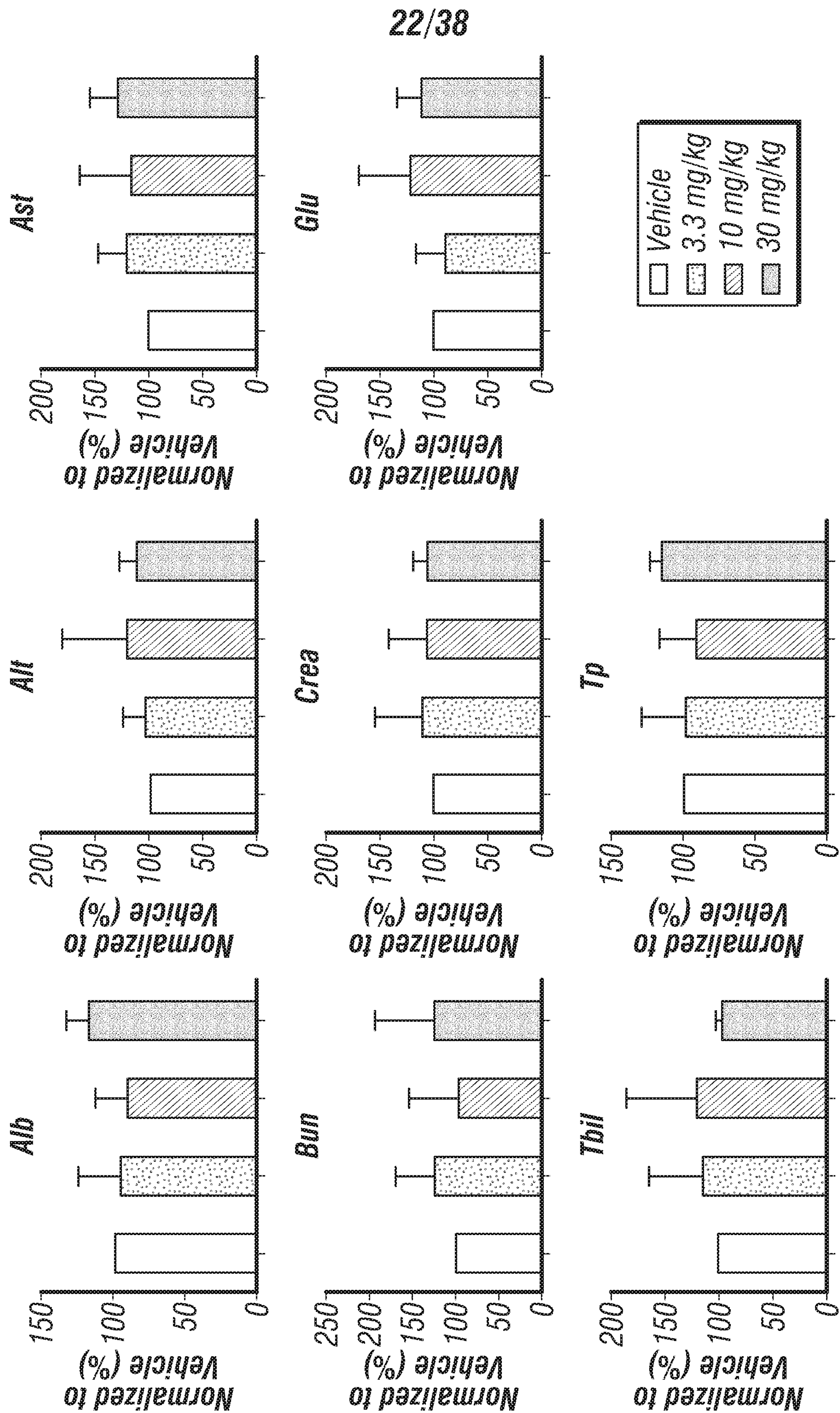


FIG. 9A

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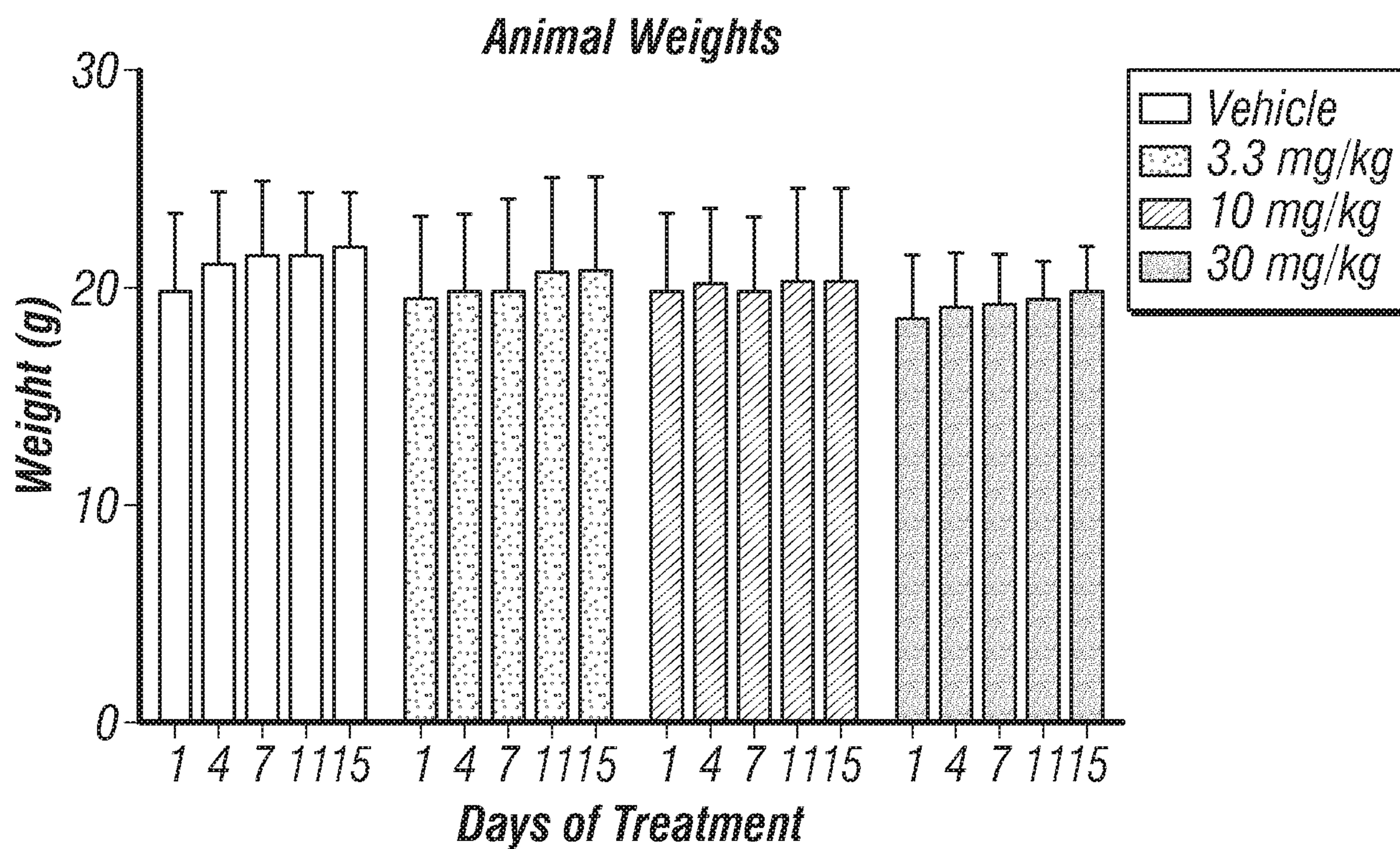


FIG. 9B

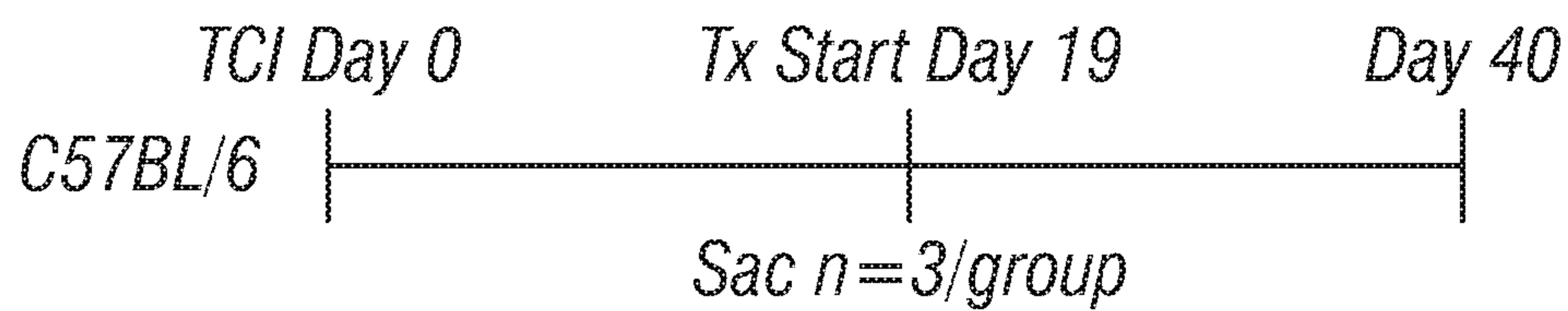


FIG. 10A

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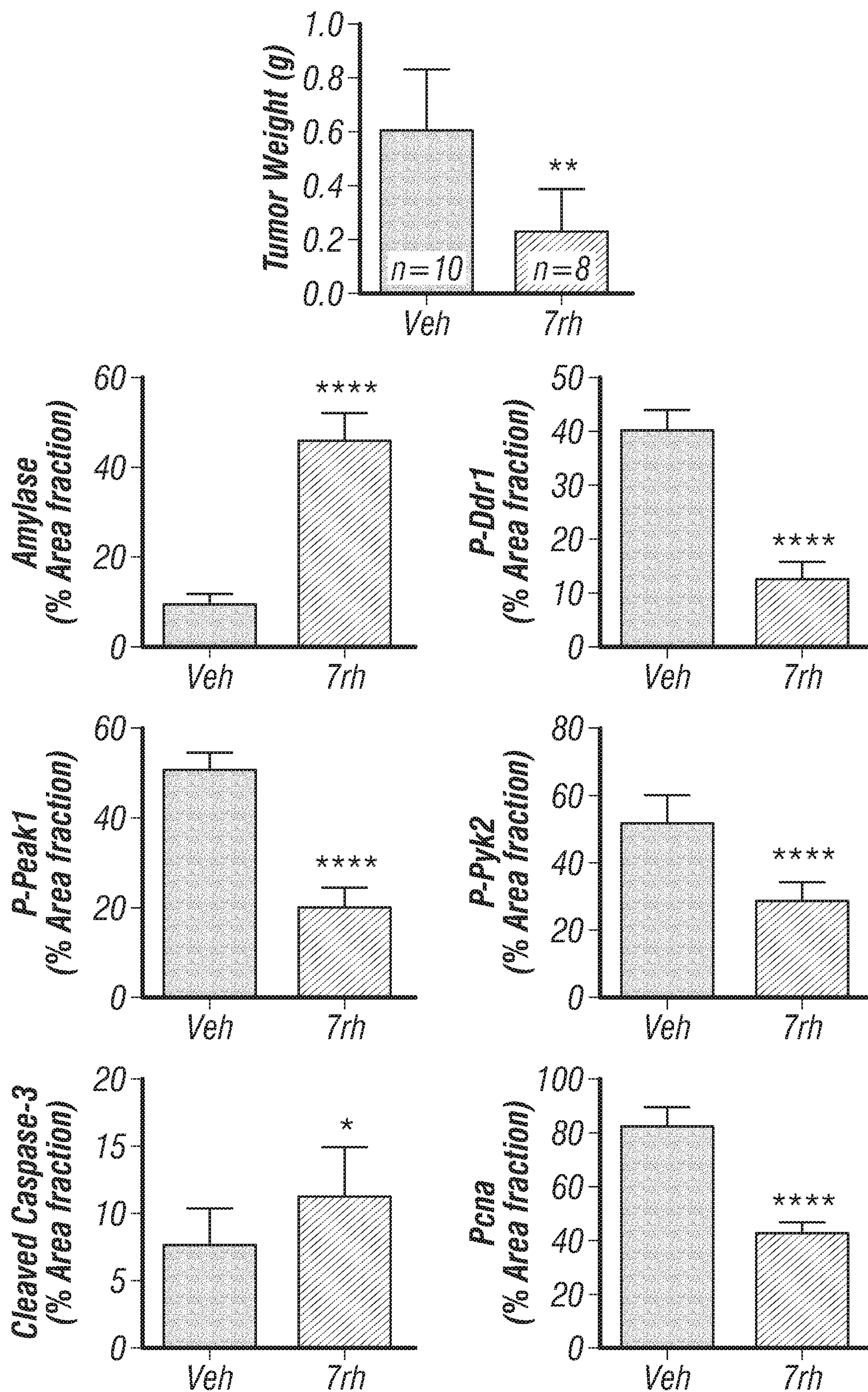


FIG. 10B

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H&E

Vehicle

7rh

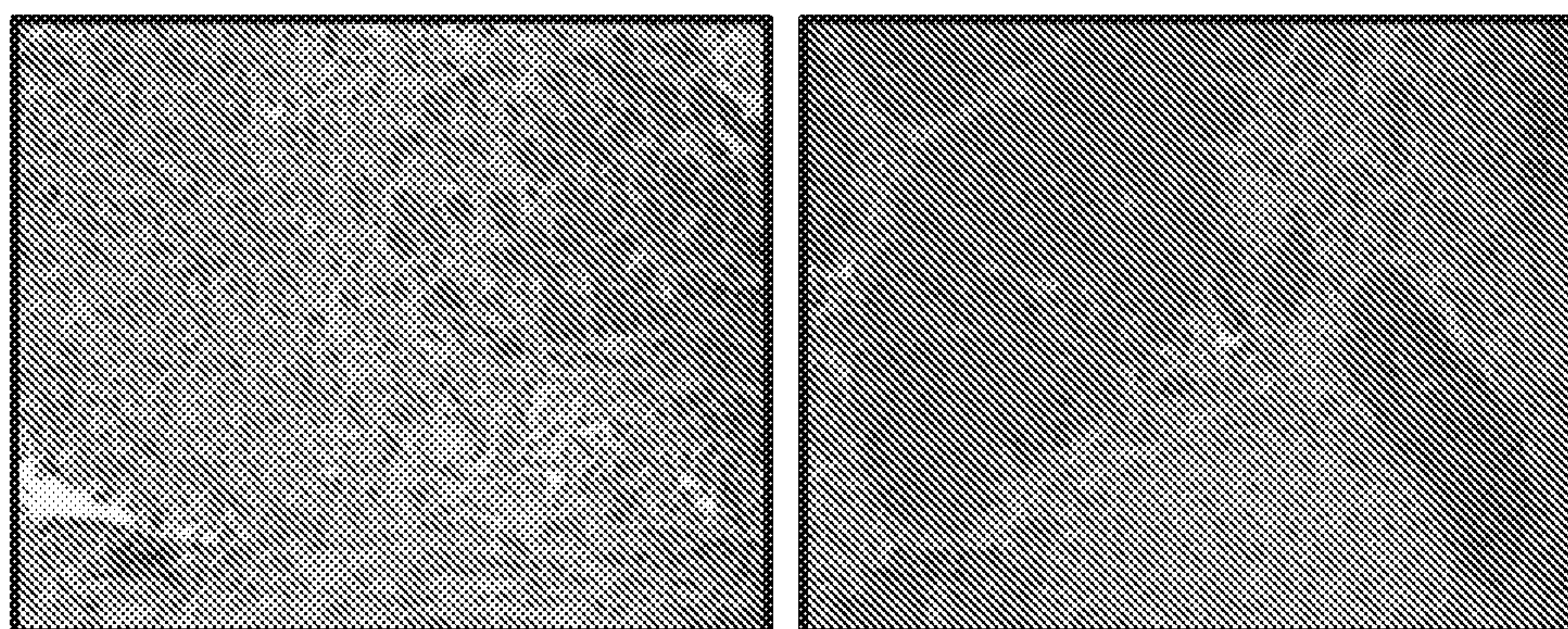


FIG. 10C

Amylase

Dapi

Vehicle

7rh

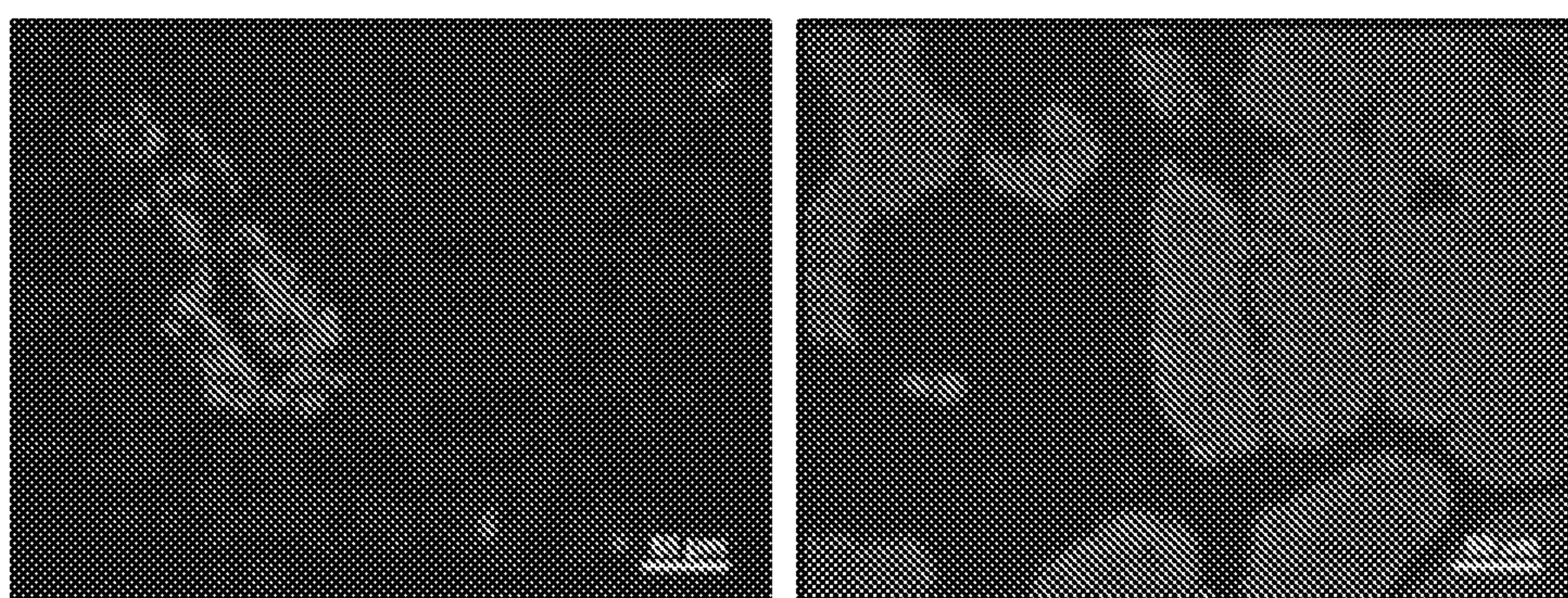


FIG. 10D

P-Ddr1

Dapi

Vehicle

7rh

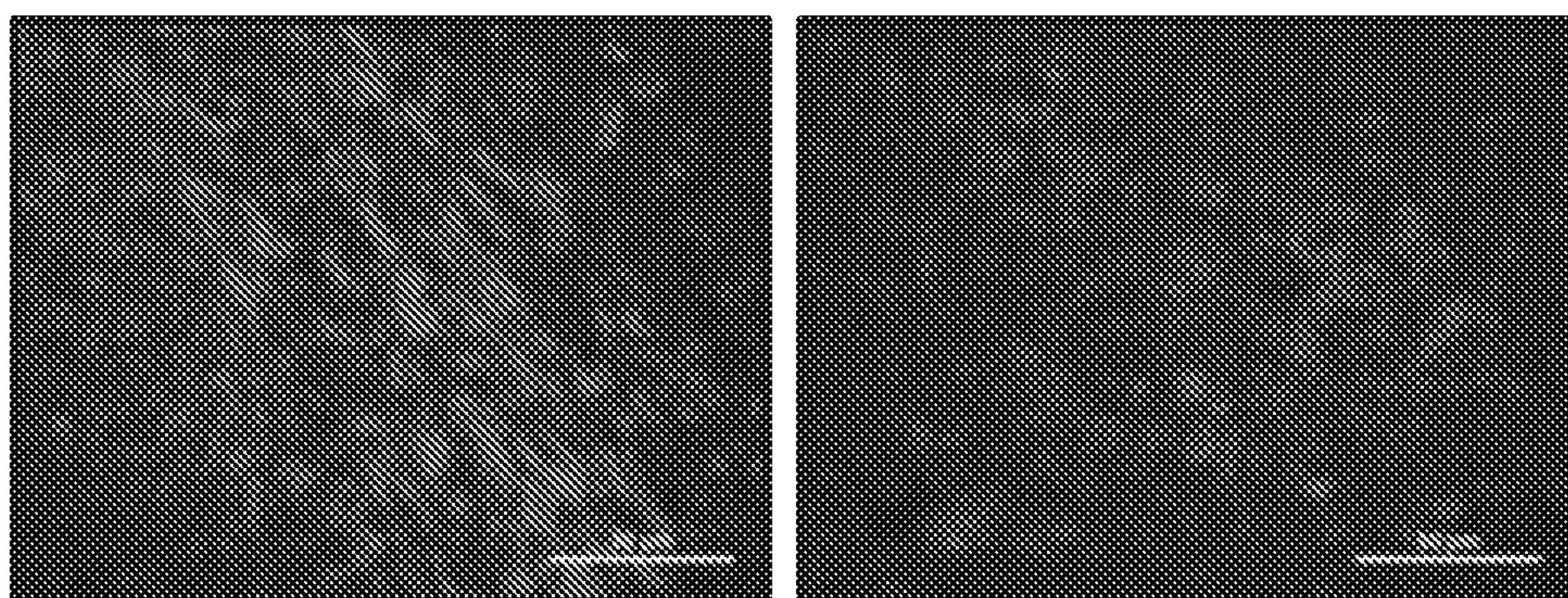


FIG. 10E

P-Peak1

Dapi

Vehicle

7rh

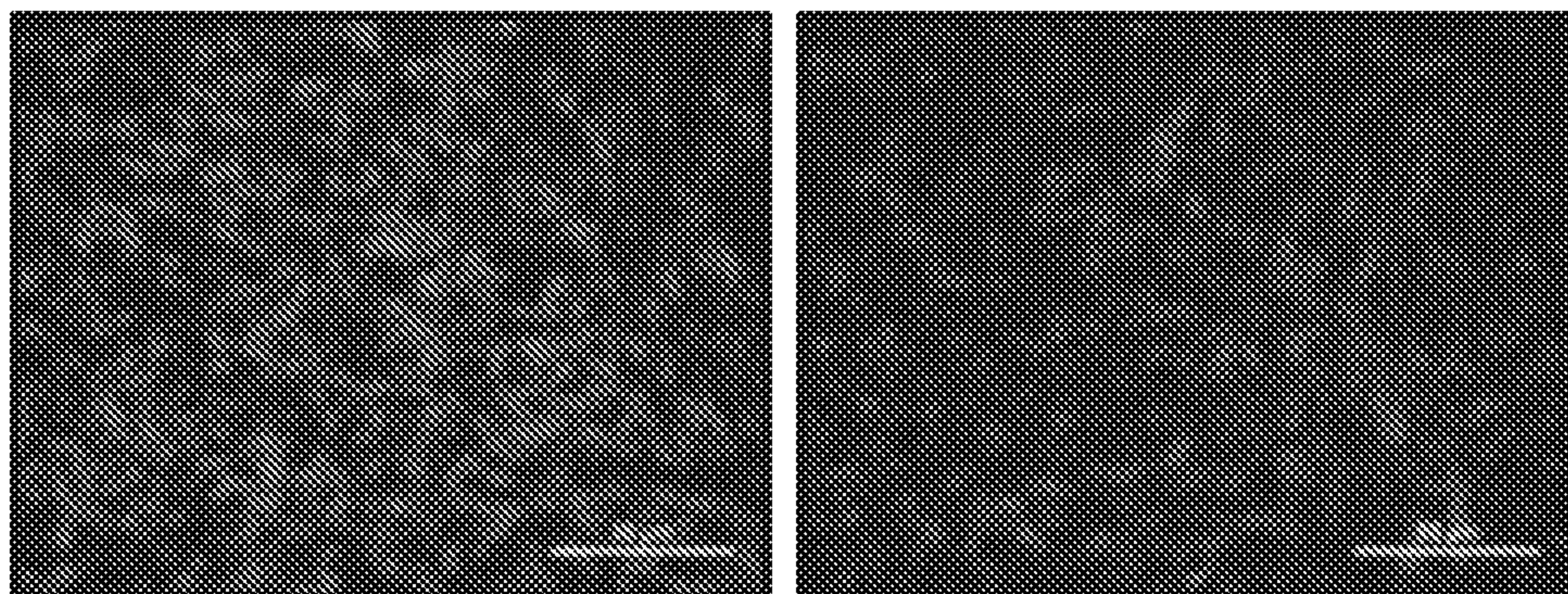


FIG. 10F

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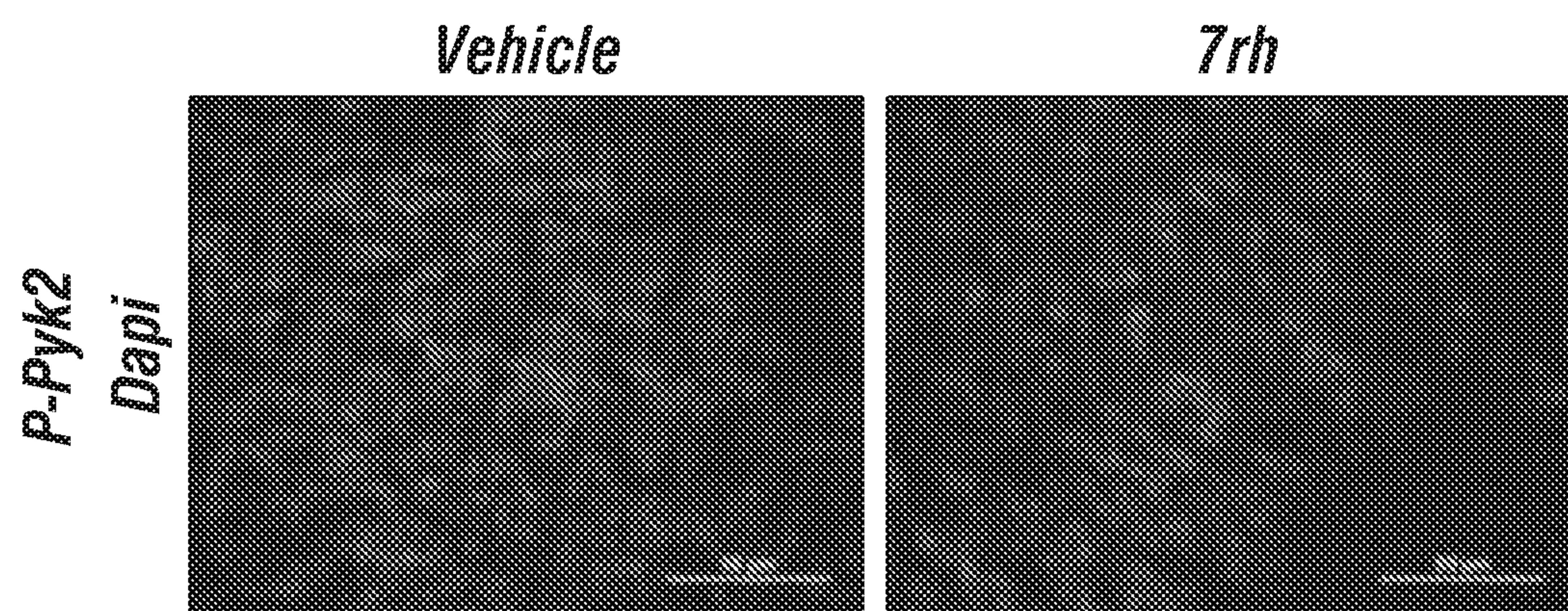


FIG. 10G

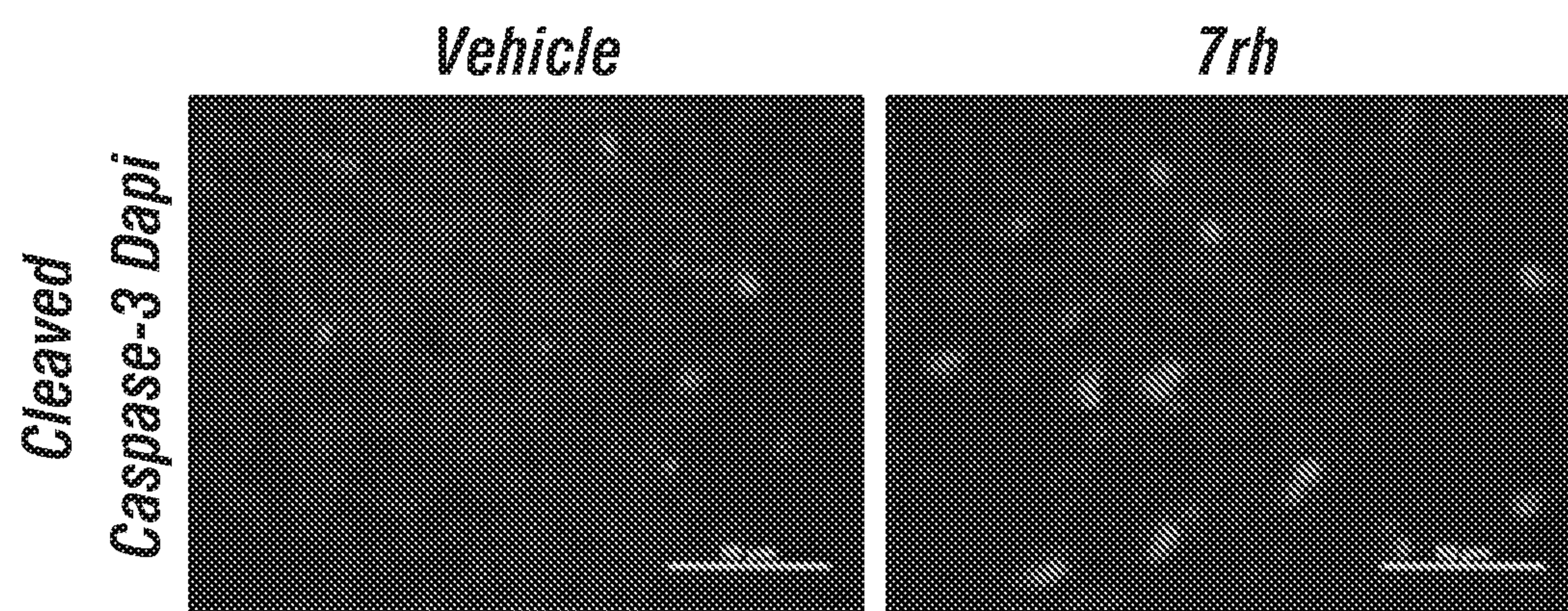


FIG. 10H

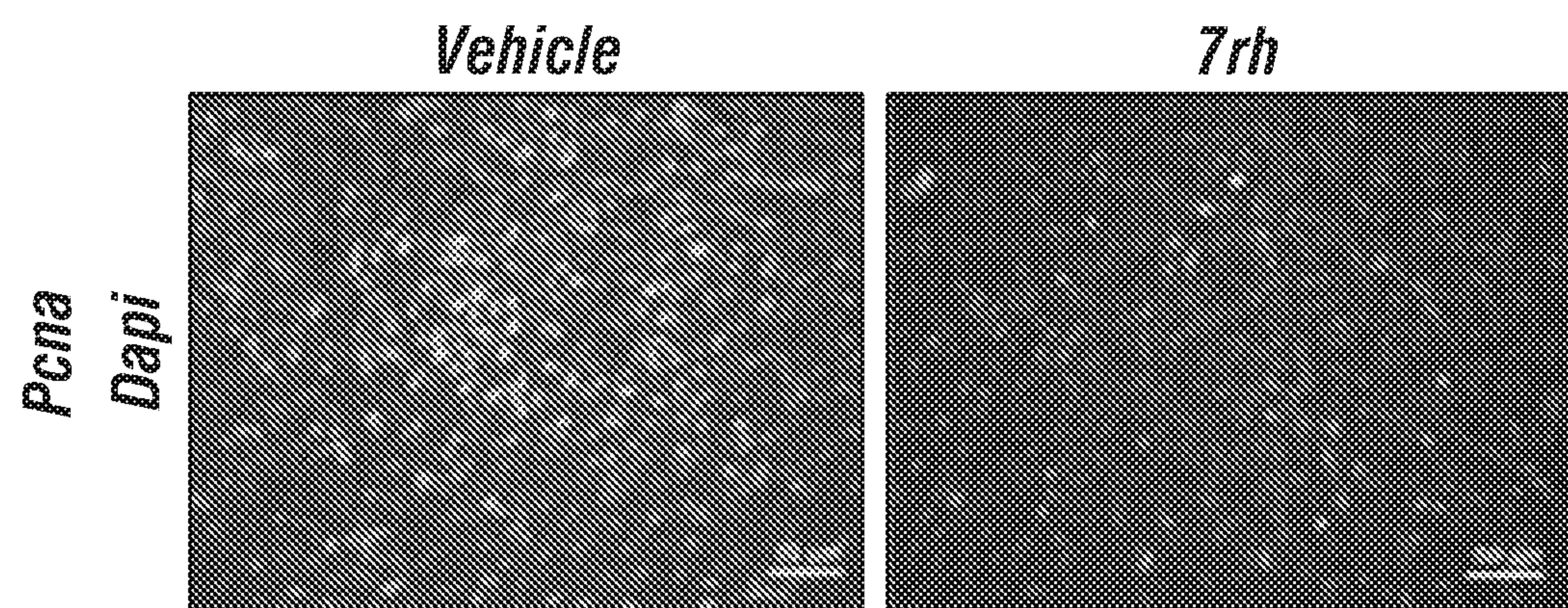


FIG. 10I

Timeline diagram showing experimental stages: TCI Day 0, Tx Start Day 27, and Survival. The timeline is marked with vertical lines and includes the label *Nod Scid* and *Sac n=12*.

Percent survival

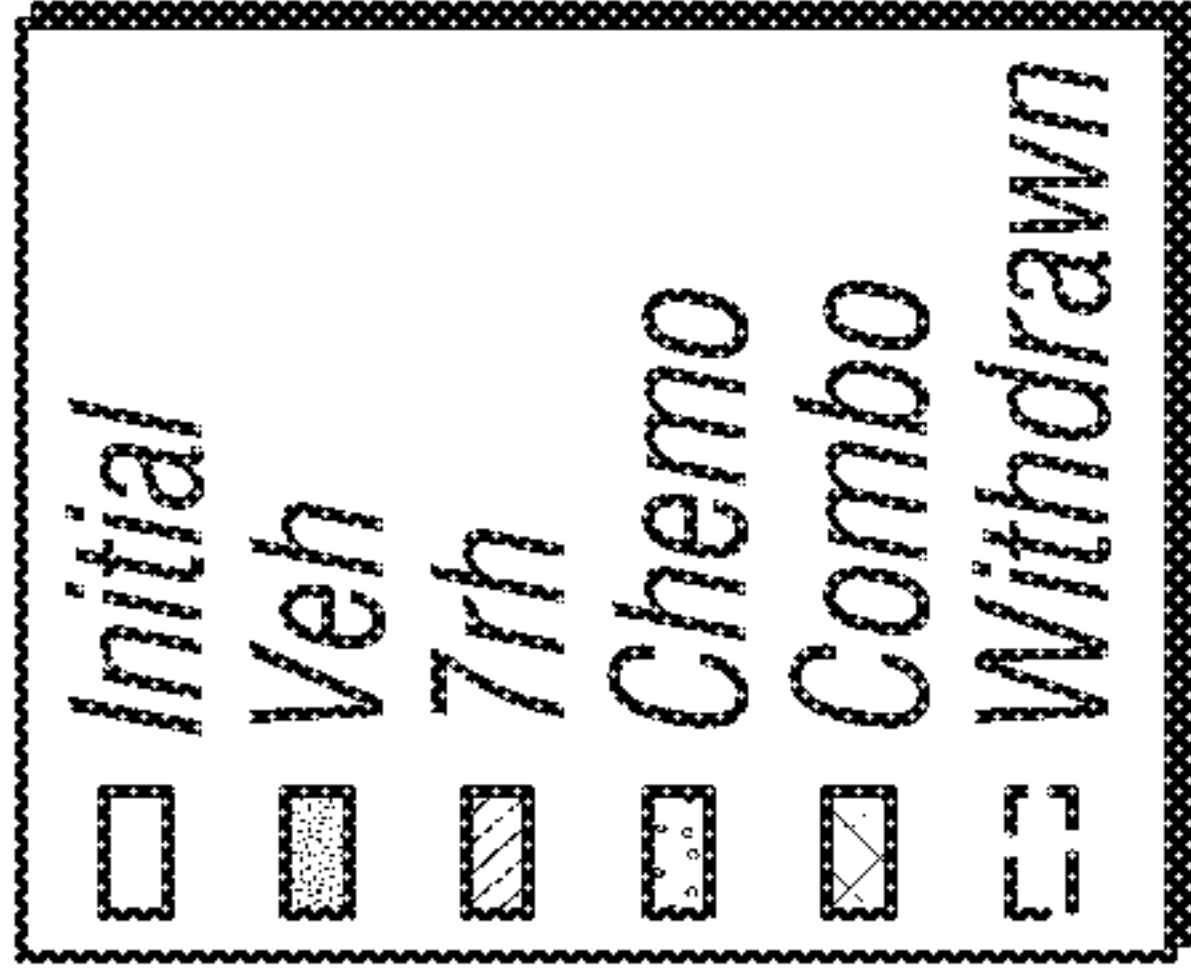
Days Post Tumor Cell Injection
(Tx Start: Day 27)

— Veh $n=12$
 ---- 7rh $n=12$
 Chemo $n=12$
 -.-.- Combo $n=12$

* = Tx withdrawn day 102

<i>Group</i>	<i>n</i>	<i>Median survival</i>	<i>p value vs vehicle</i>	<i>p value vs combo</i>
7rh	12	57	none	0.0011
Chemo	12	73	0.0006	<0.0001
Combo	12	98	< 0.0001	

SUBSTITUTE SHEET (RULE 26)



* = compared to initial
^ = compared to vehicle

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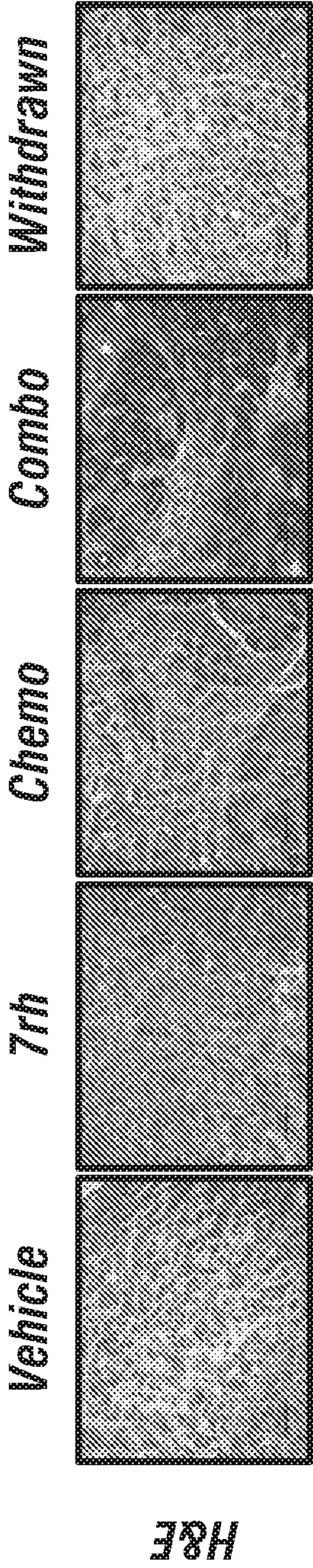
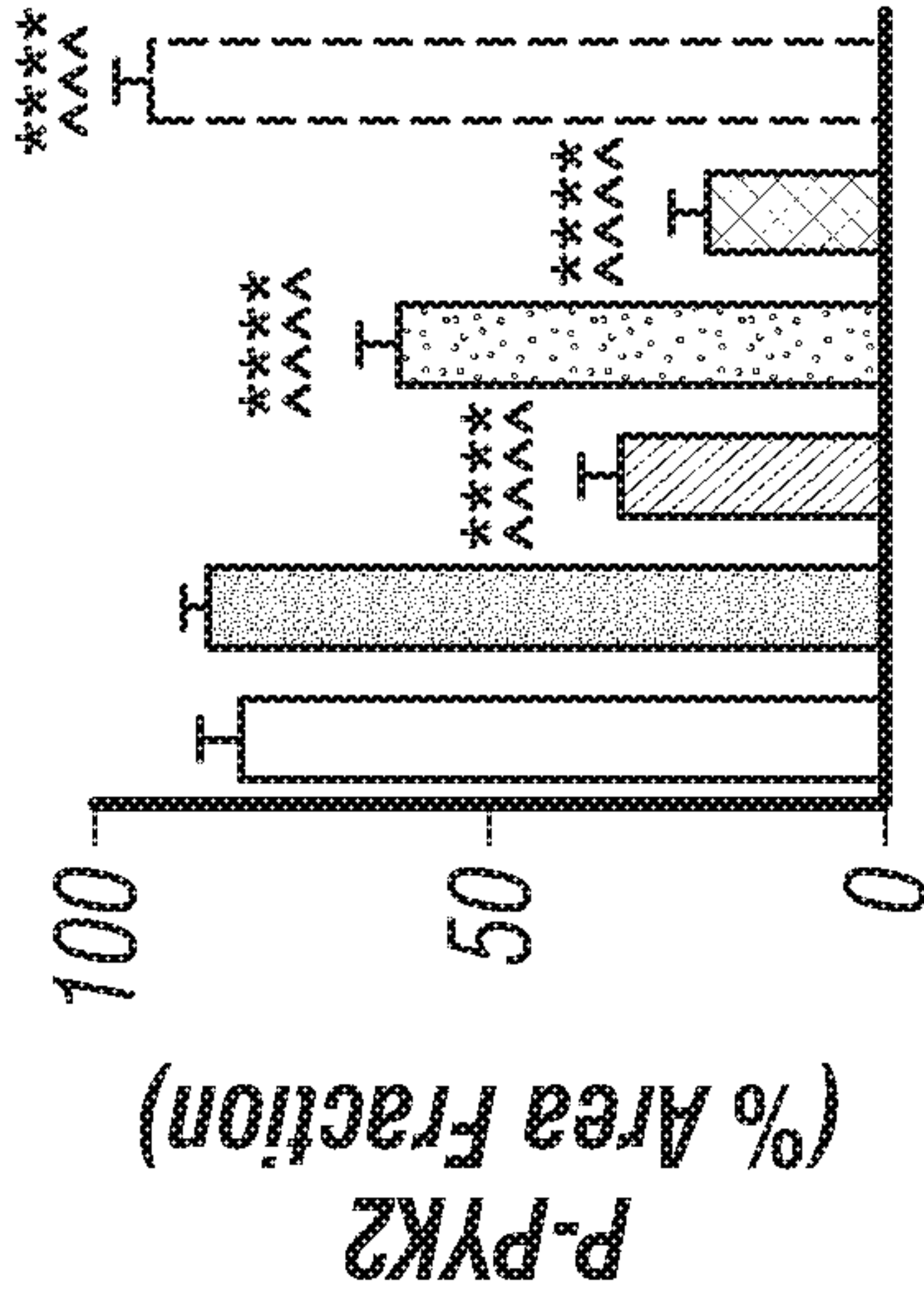
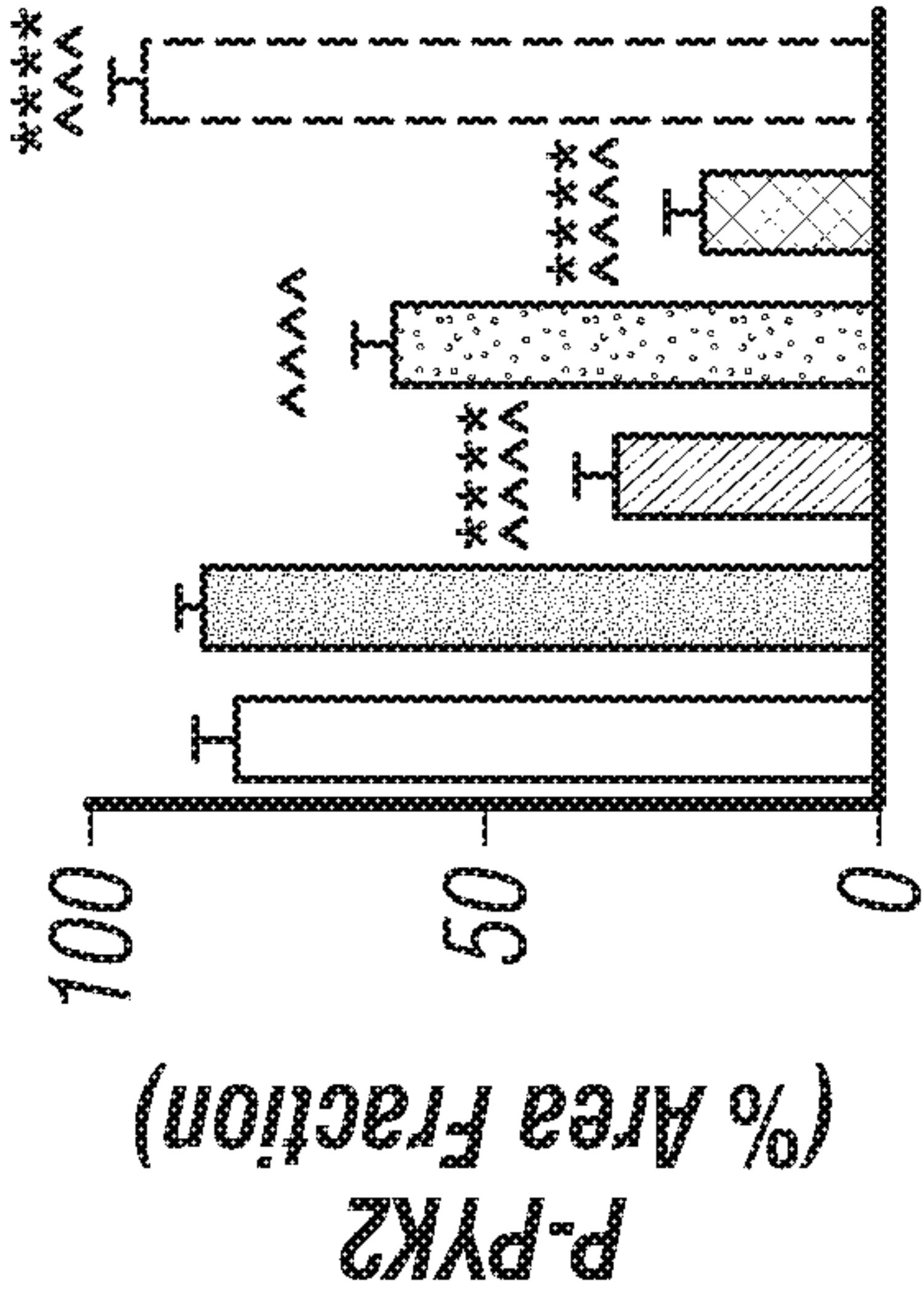


FIG. 11D

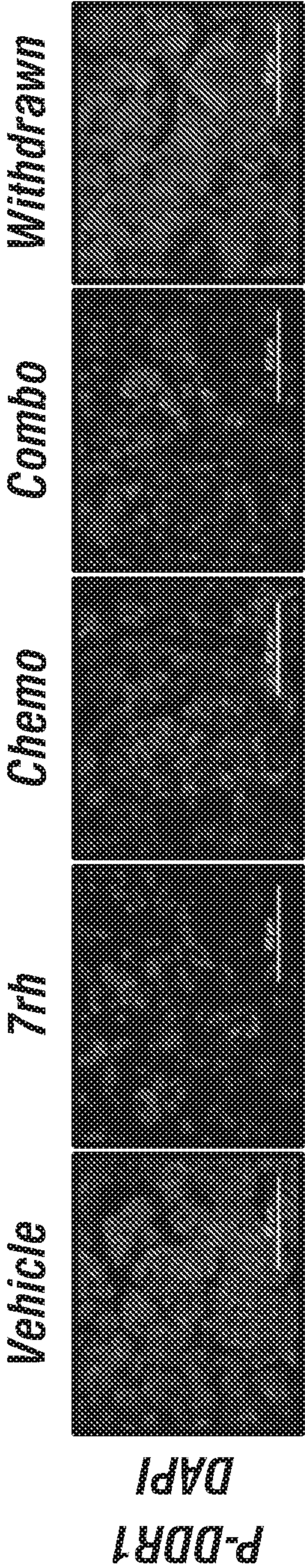


FIG. 11E

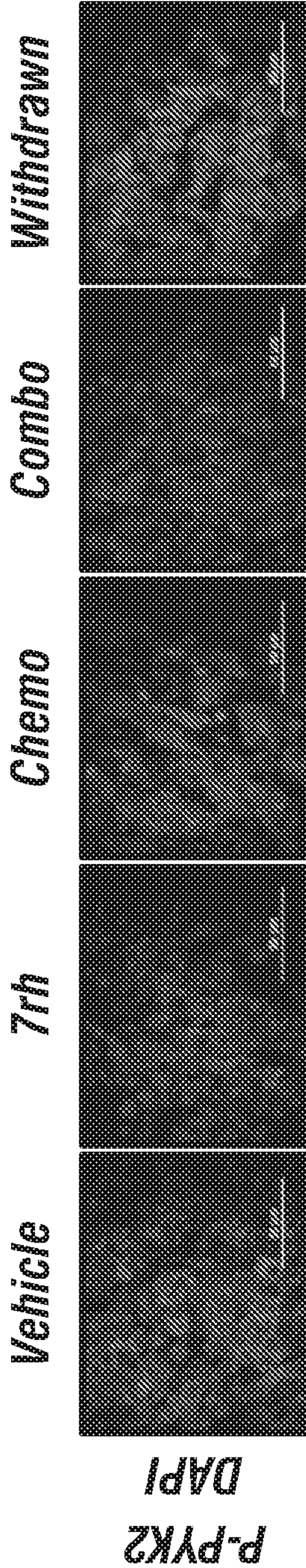


FIG. 11F

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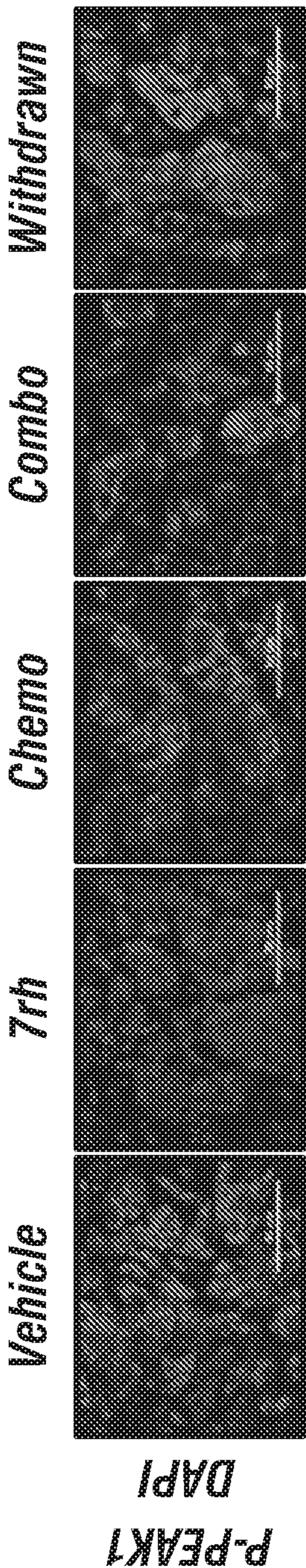
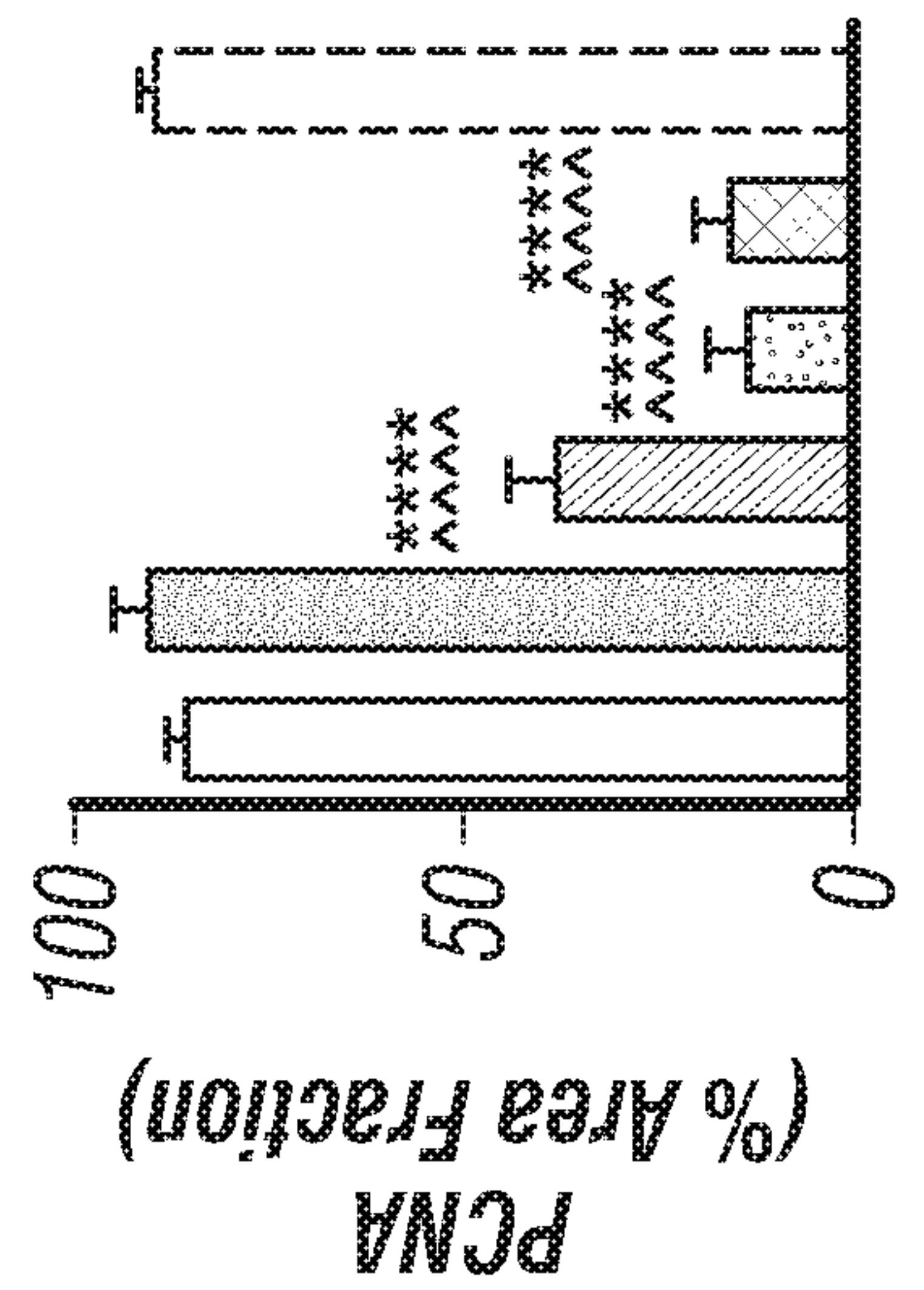
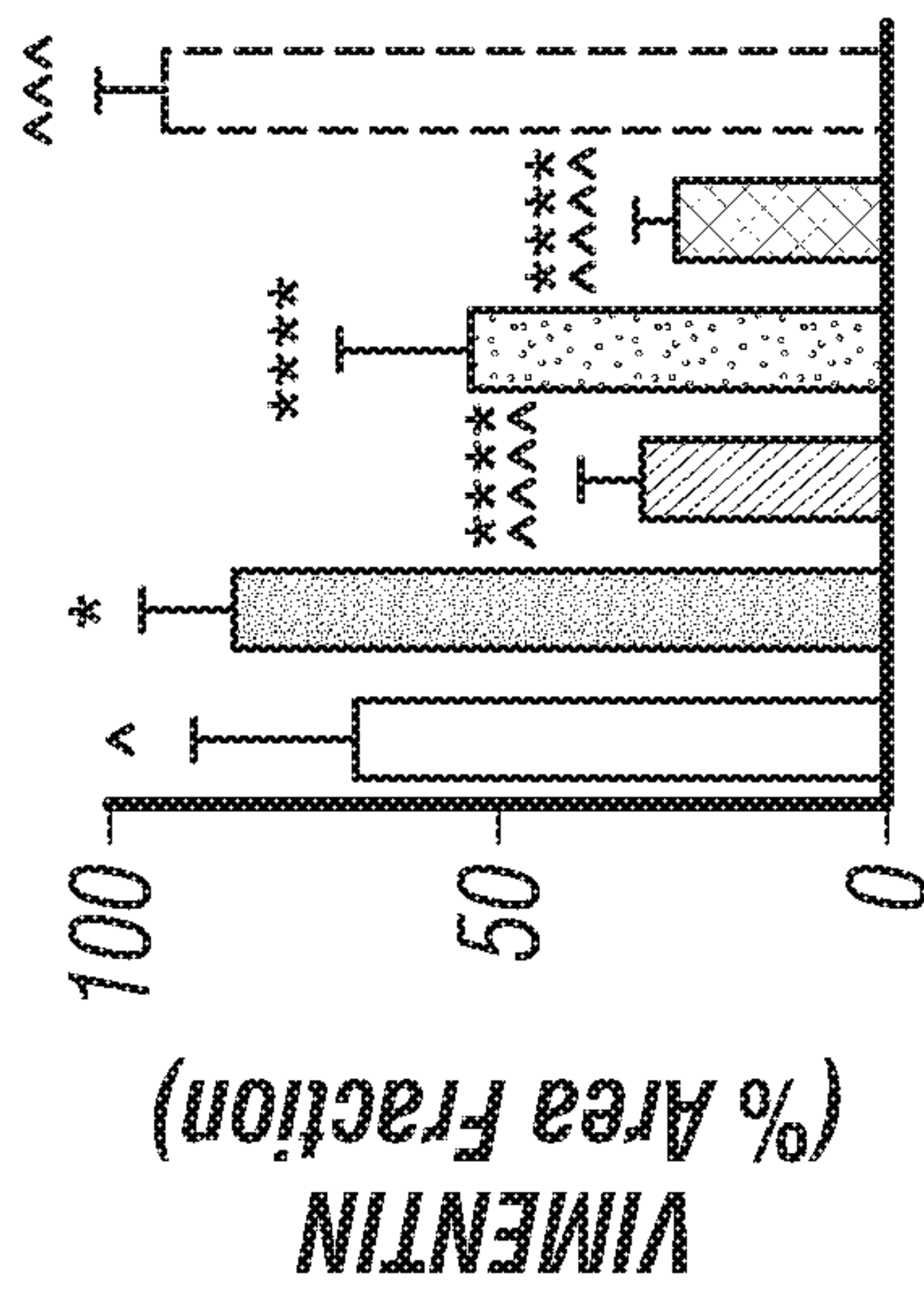
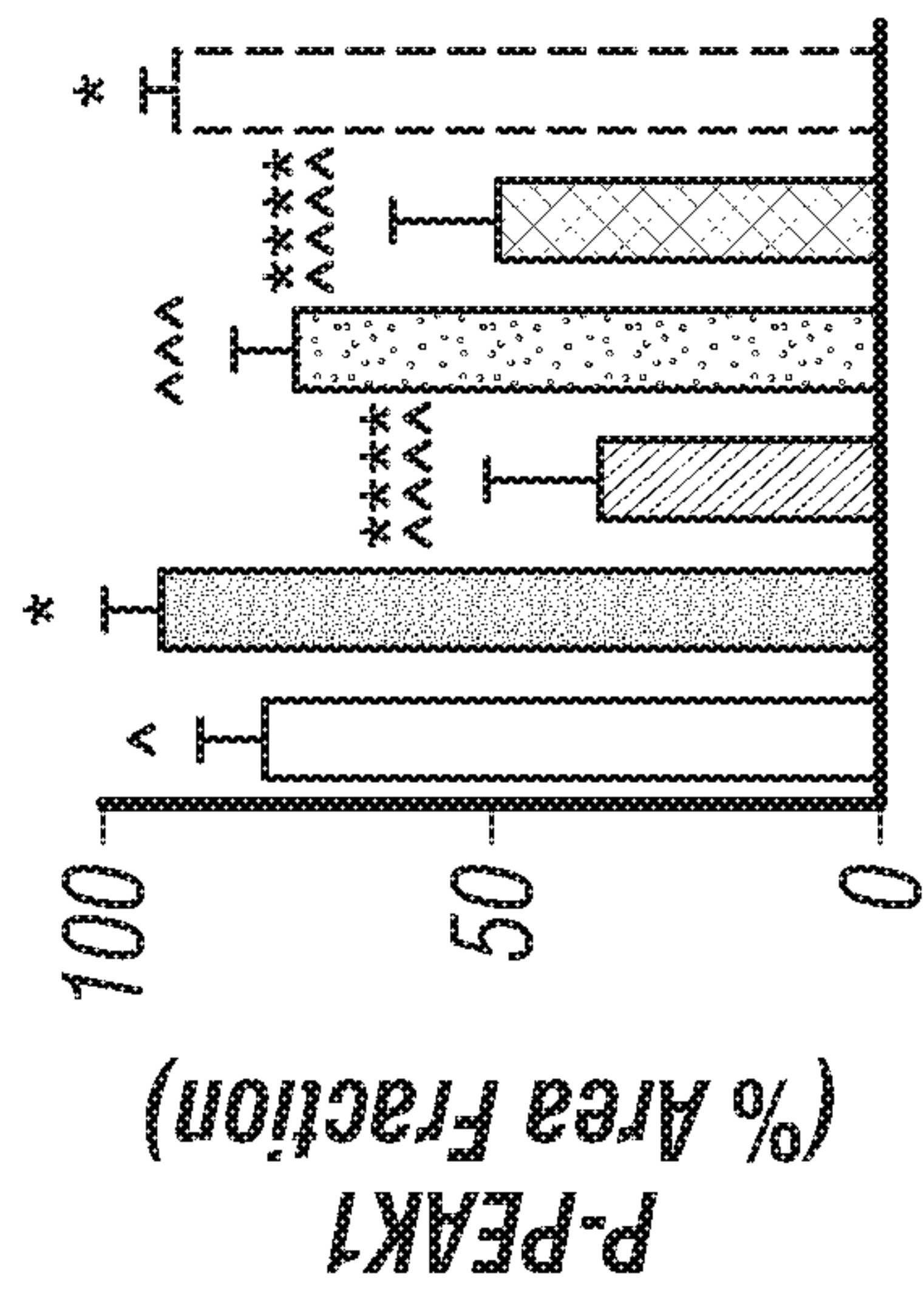


FIG. 11G

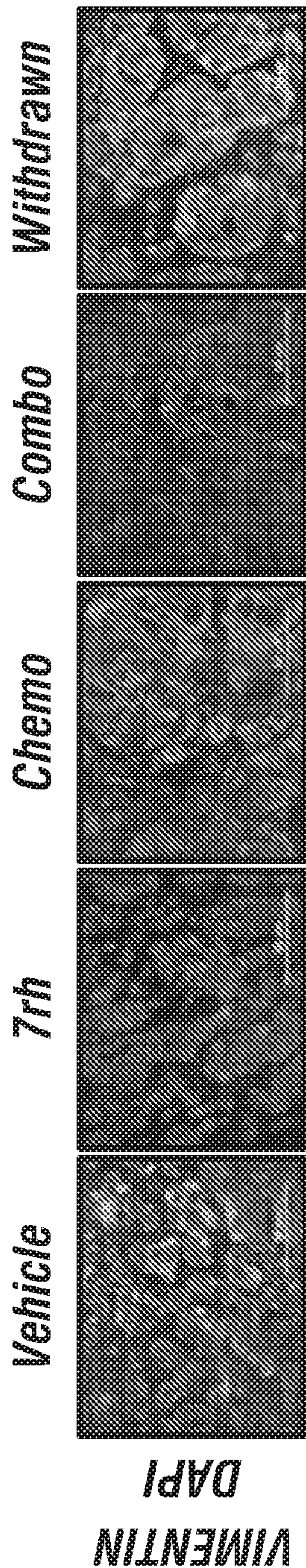


FIG. 11I

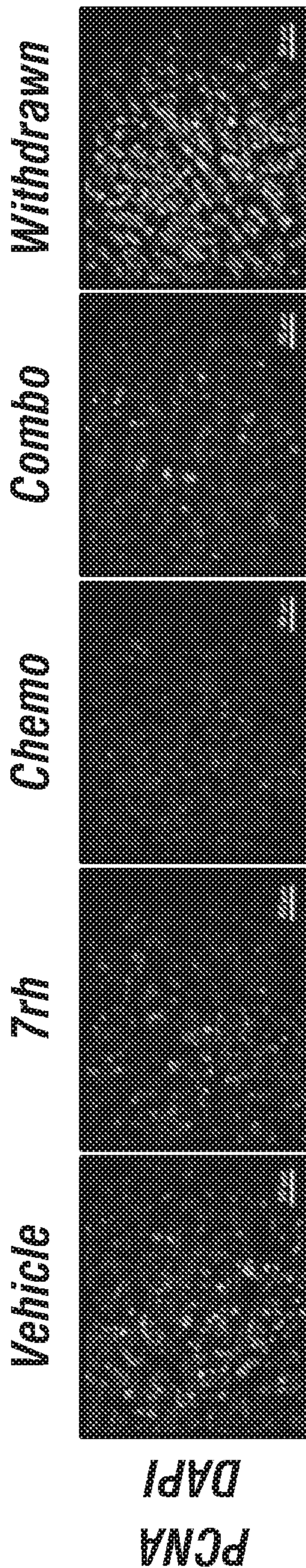


FIG. 11J

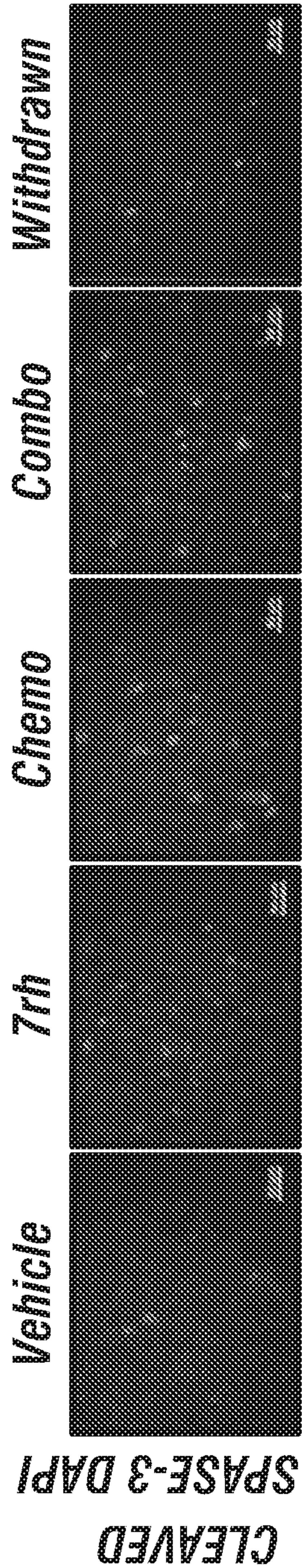
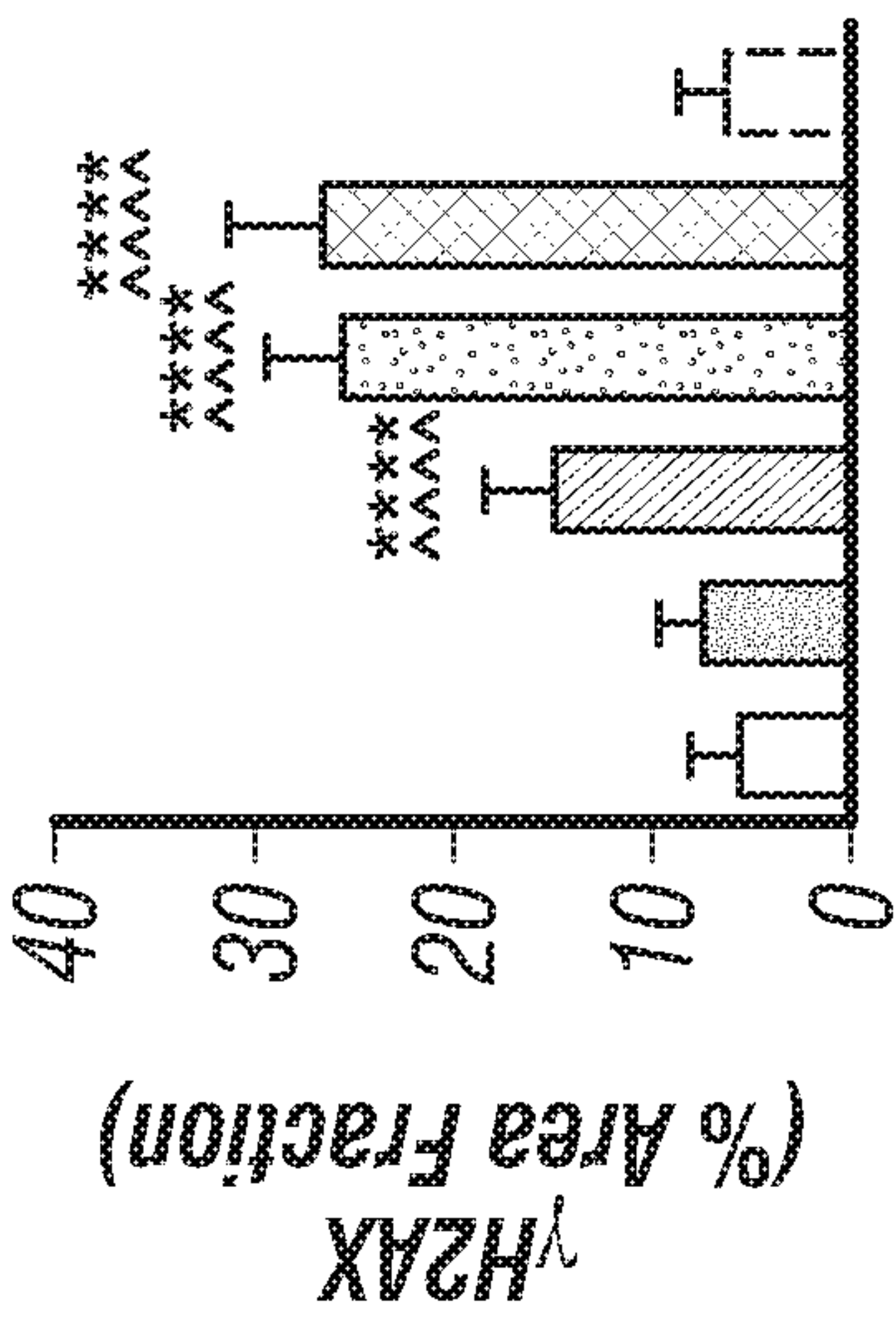
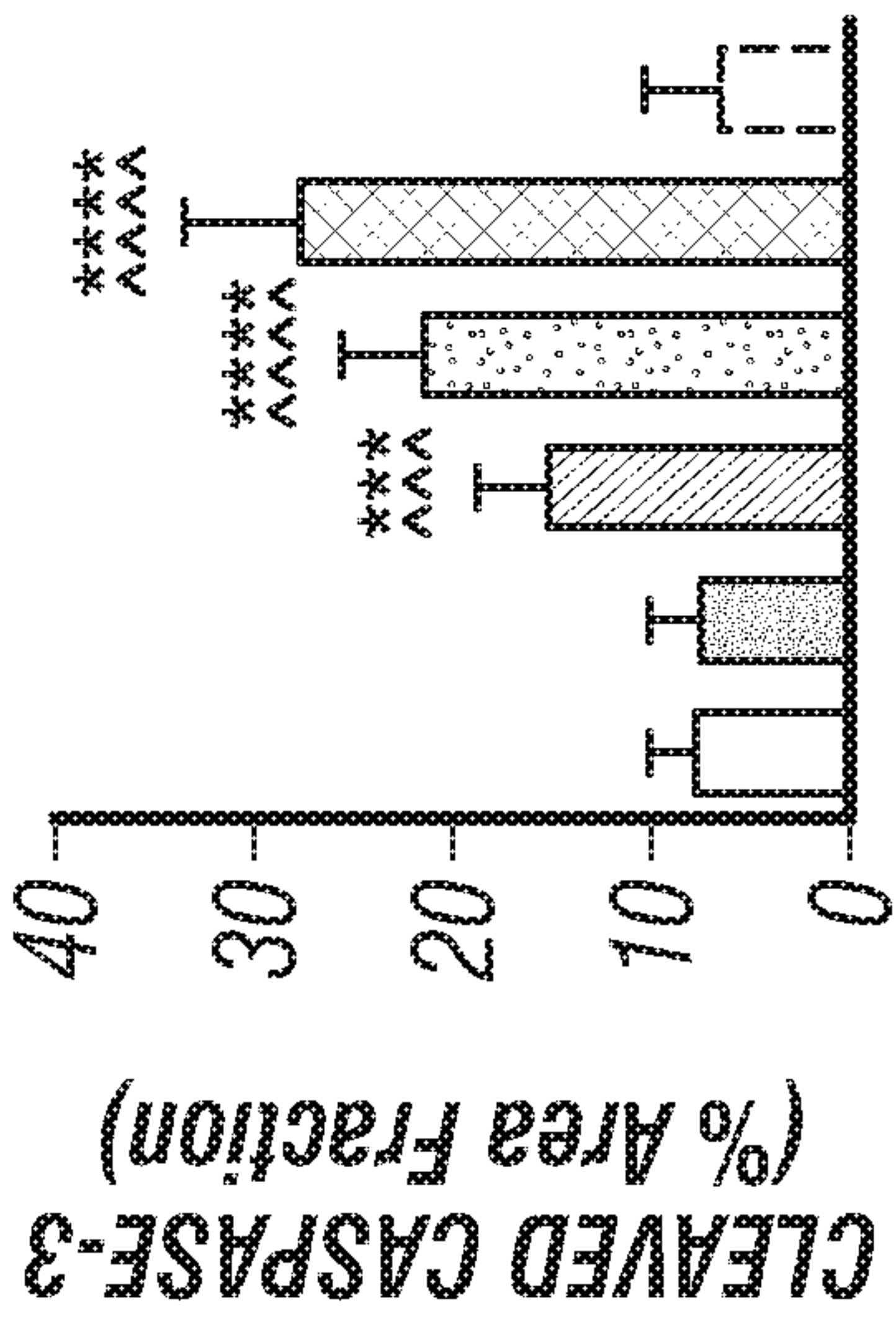


FIG. 11K

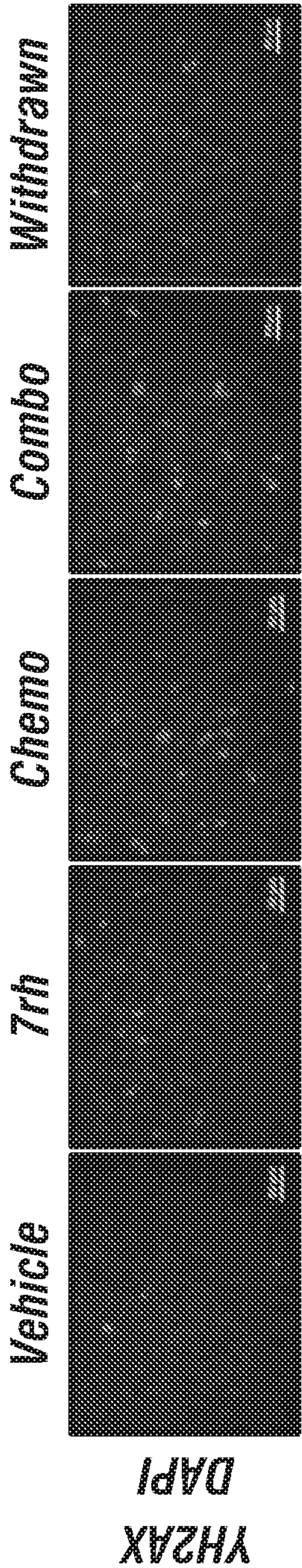


FIG. 11L

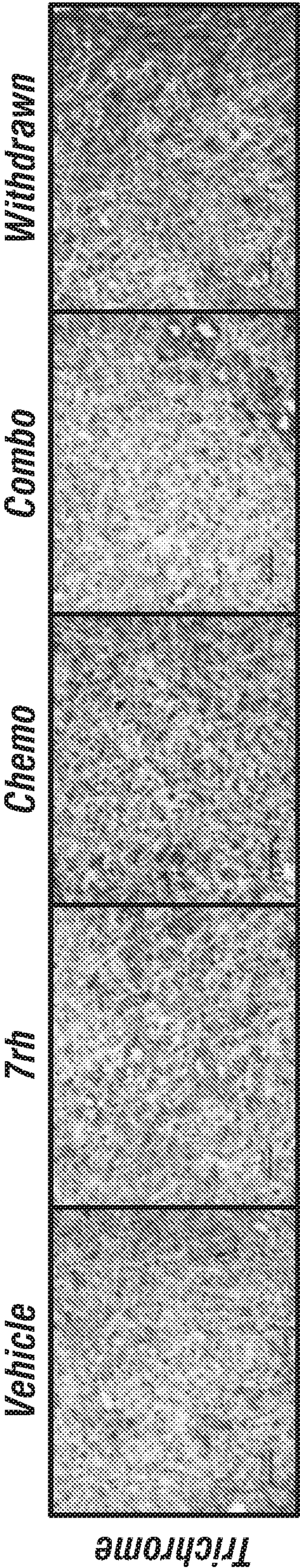
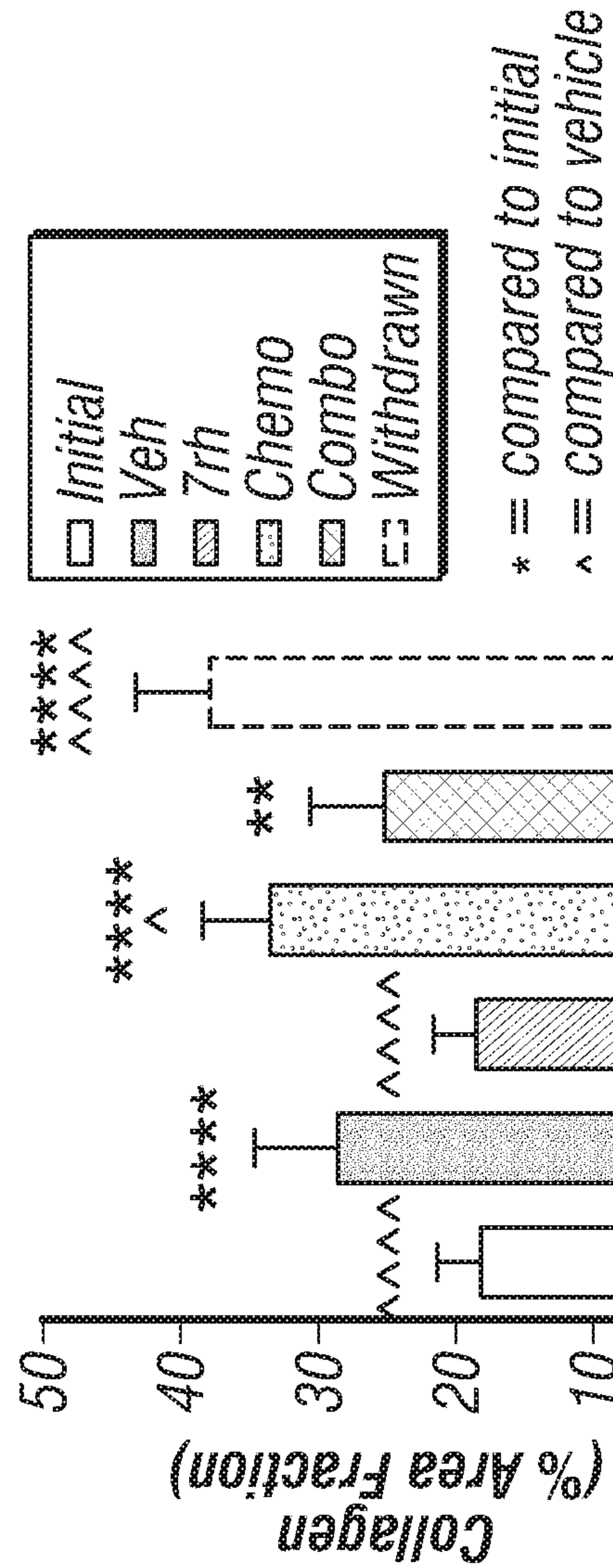


FIG. 12A

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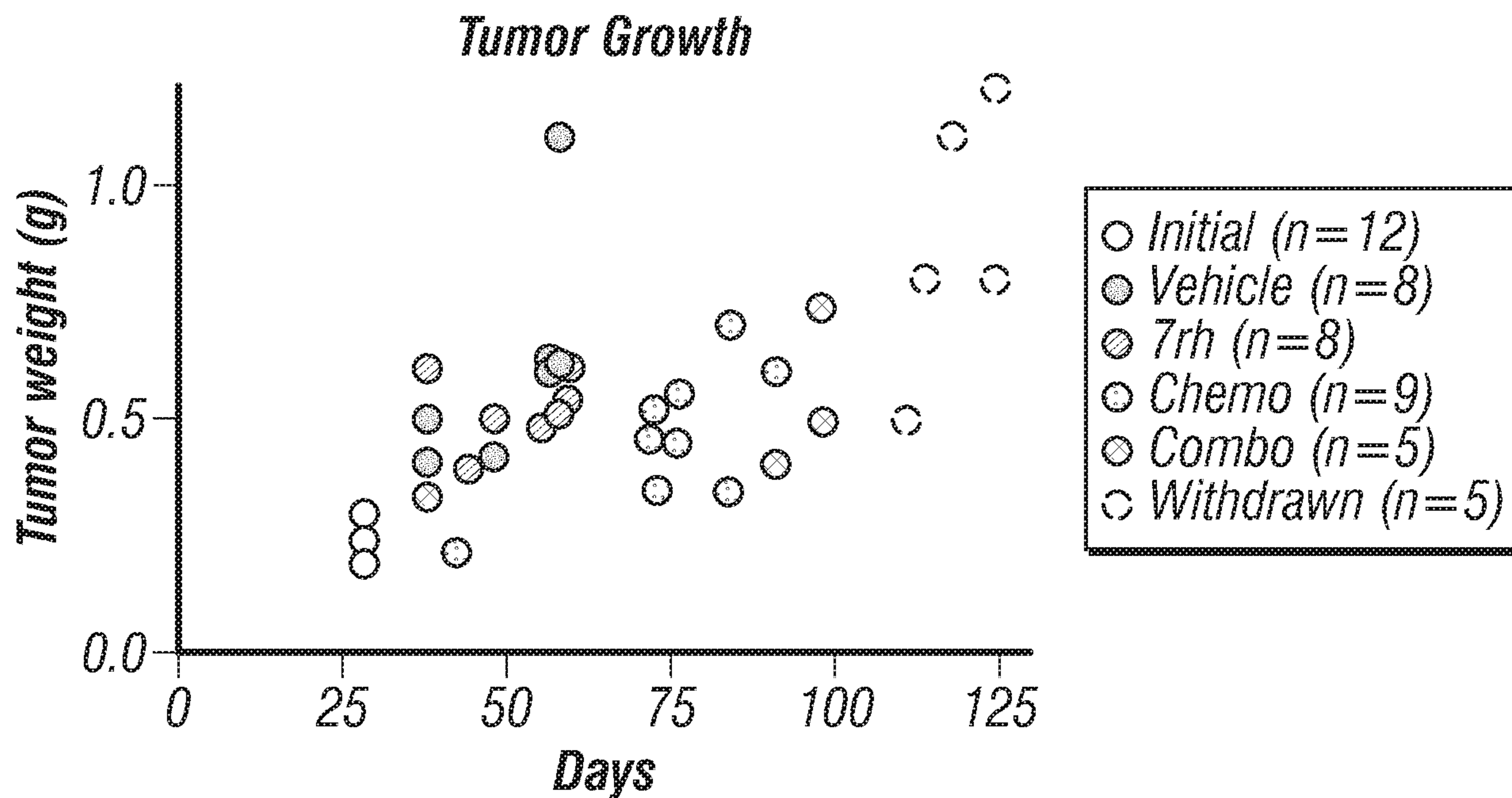


FIG. 12B

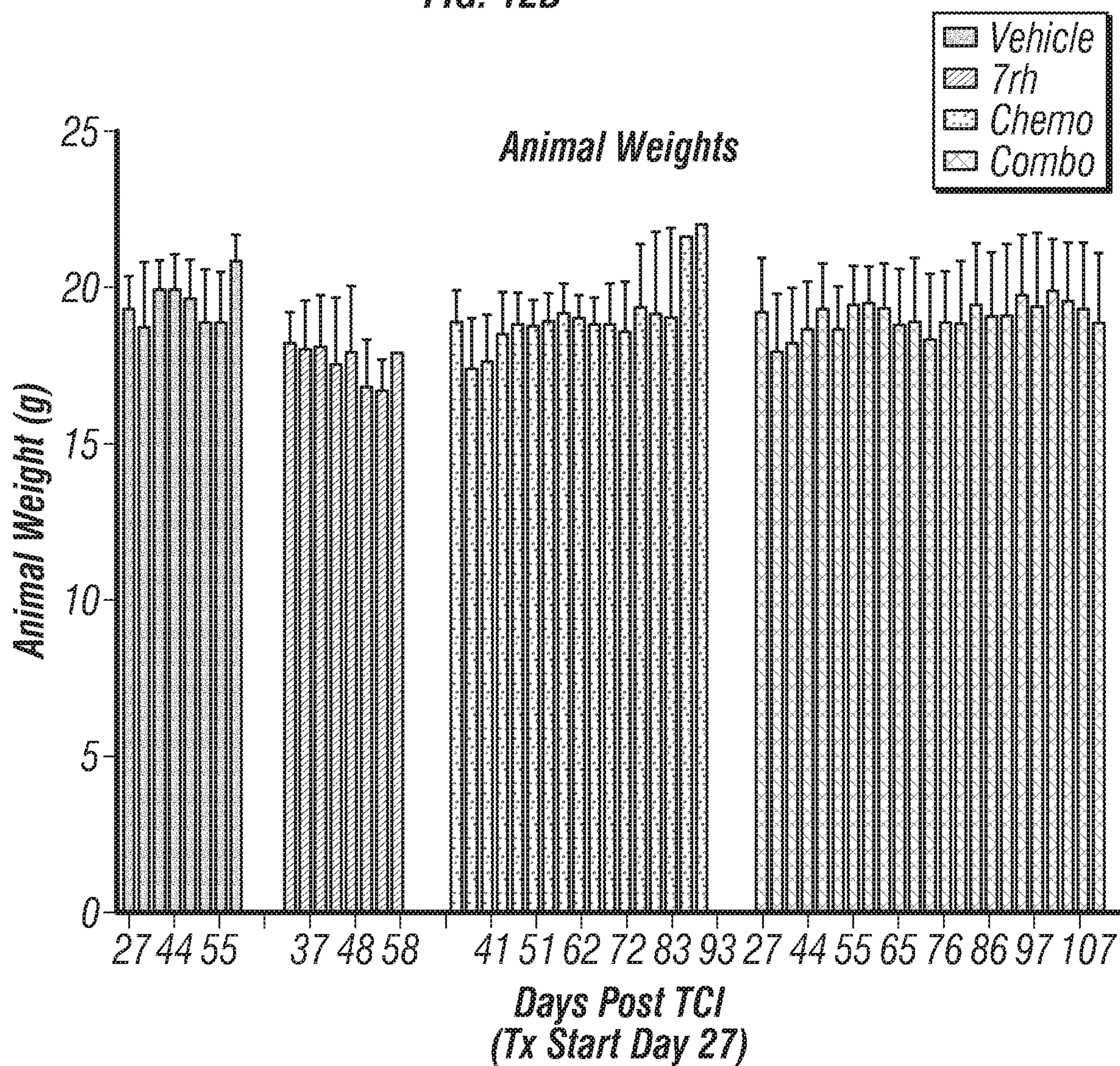


FIG. 12C

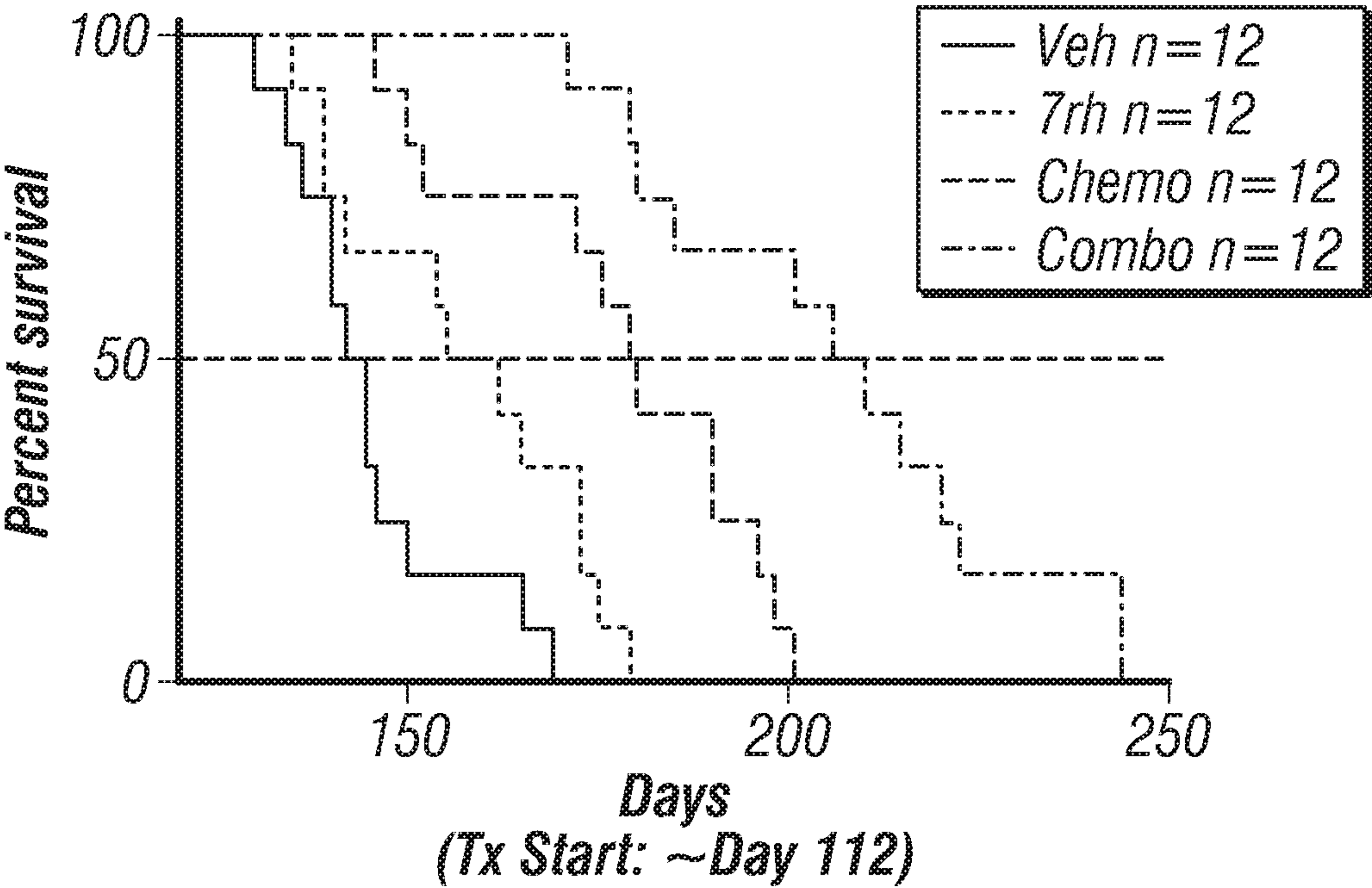
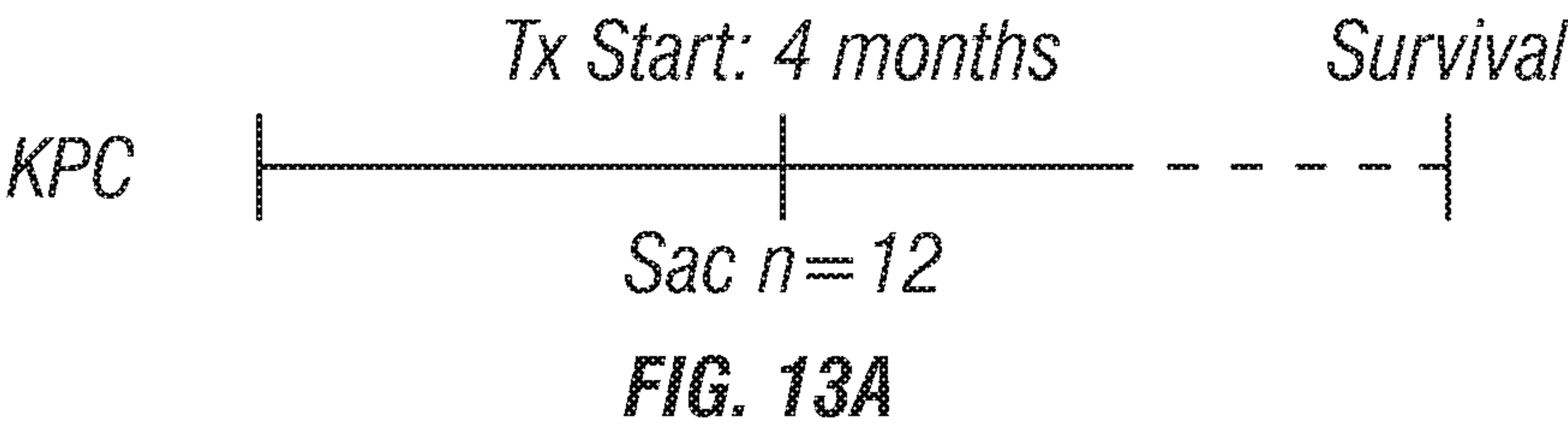


FIG. 13B

<i>Group</i>	<i>n</i>	<i>Median survival</i>	<i>p value vs vehicle</i>	<i>p value vs combo</i>
<i>7rh</i>	<i>12</i>	<i>159</i>	<i>none</i>	<i><0.0001</i>
<i>Chemo</i>	<i>12</i>	<i>180</i>	<i><0.0001</i>	<i>0.0012</i>
<i>Combo</i>	<i>12</i>	<i>208</i>	<i><0.0001</i>	

FIG. 13C

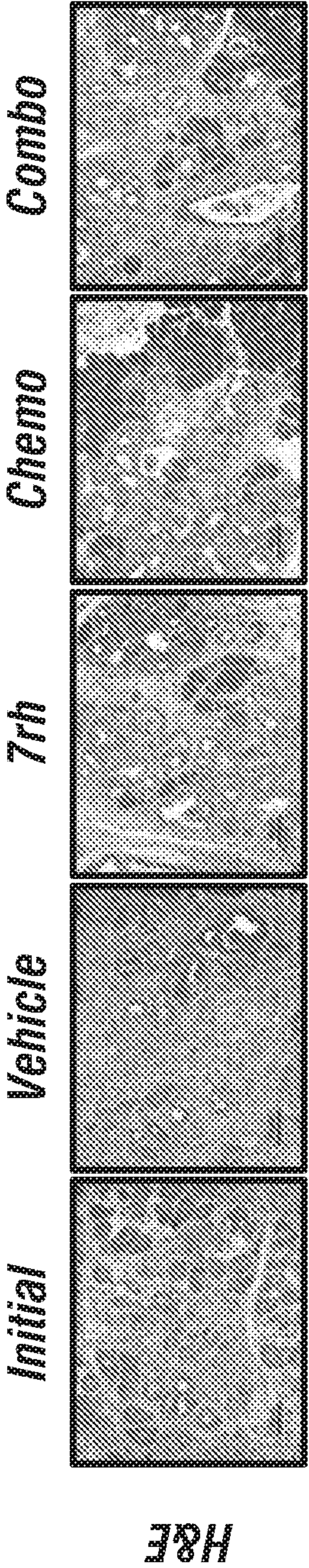
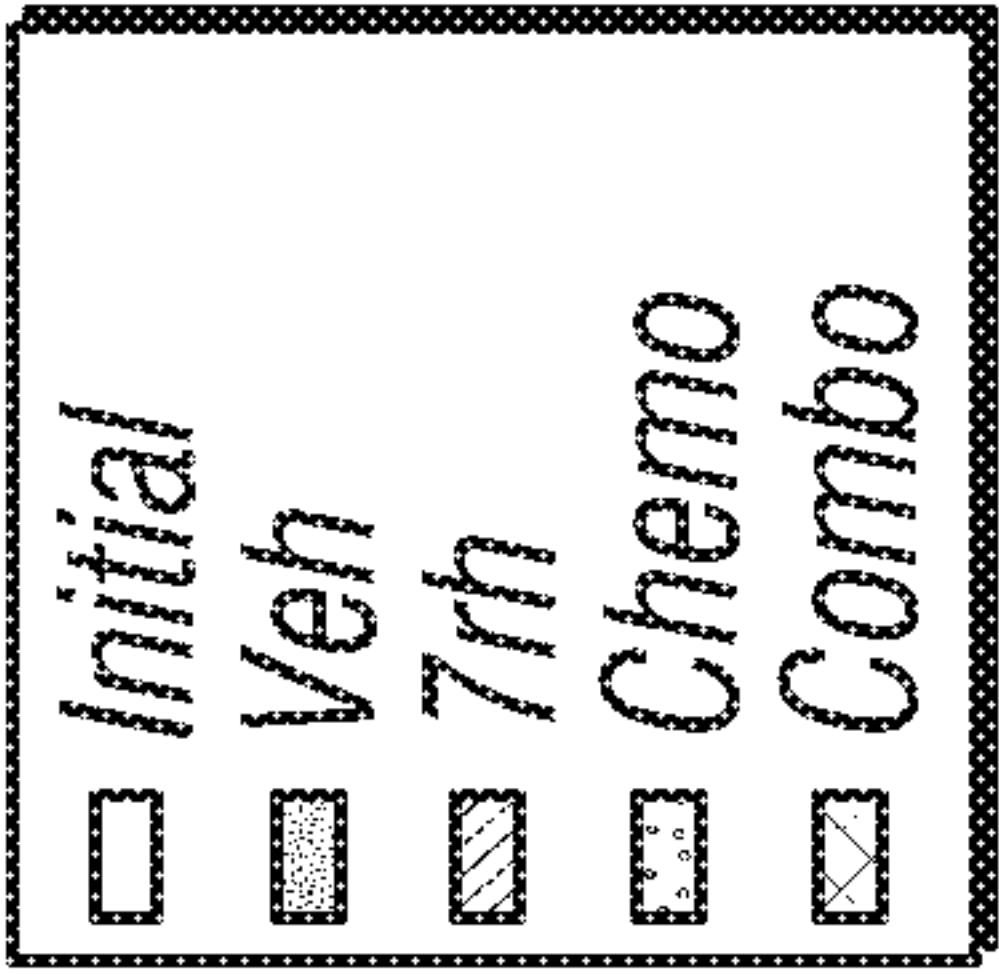
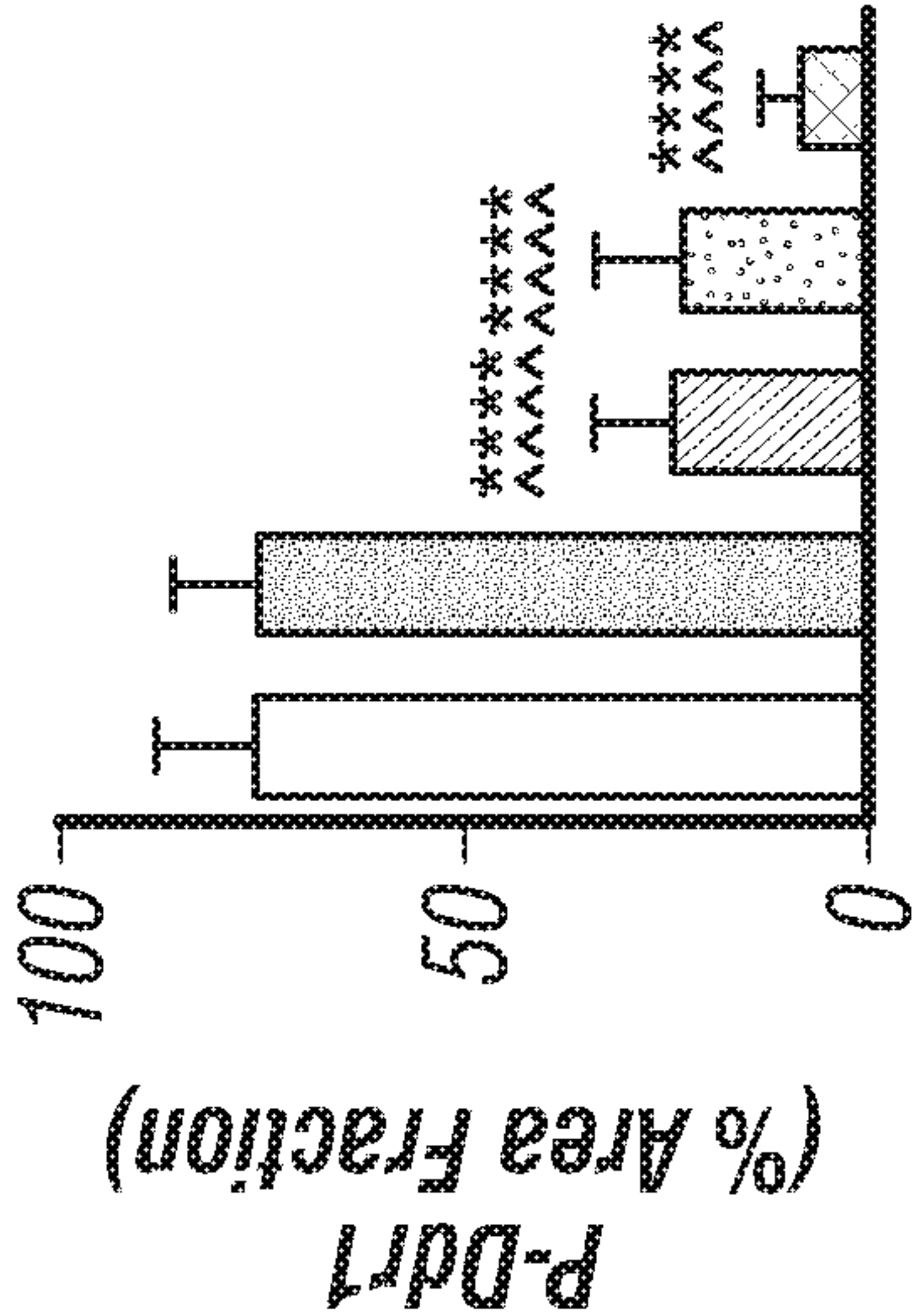


FIG. 13D

* = compared to initial
^ = compared to vehicle



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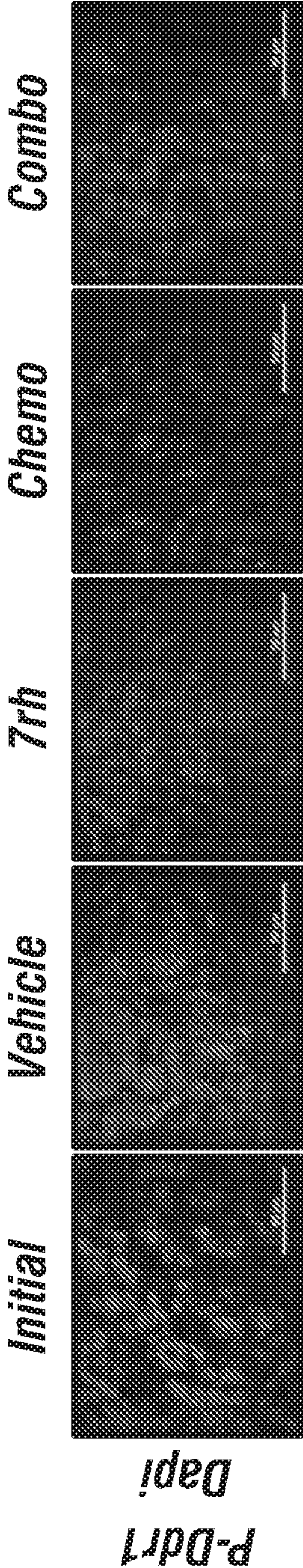


FIG. 13E

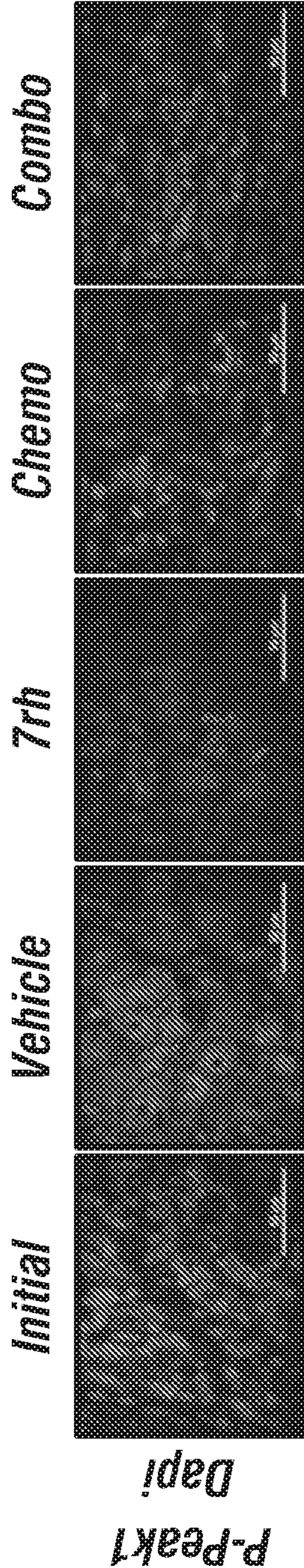
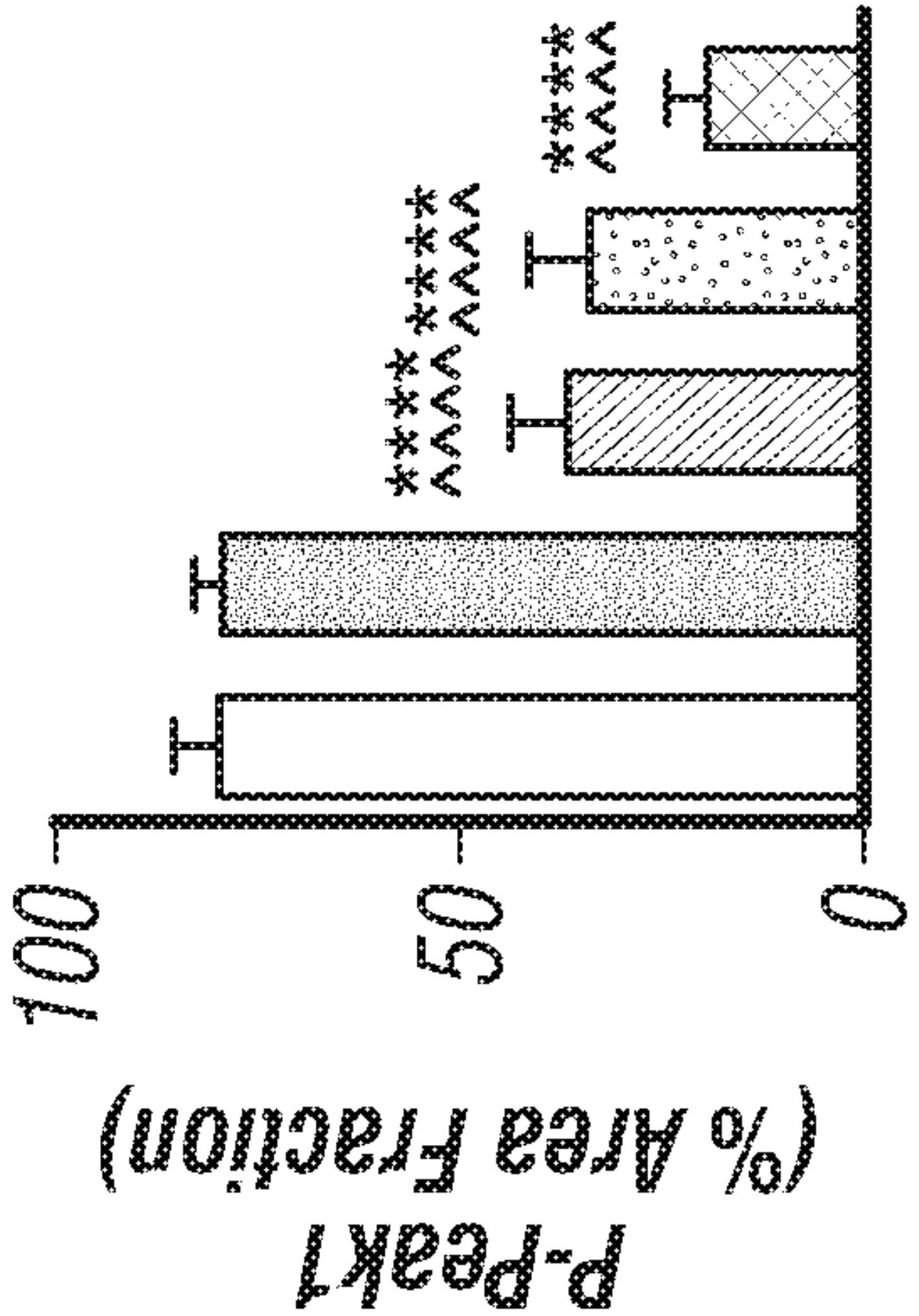


FIG. 13F

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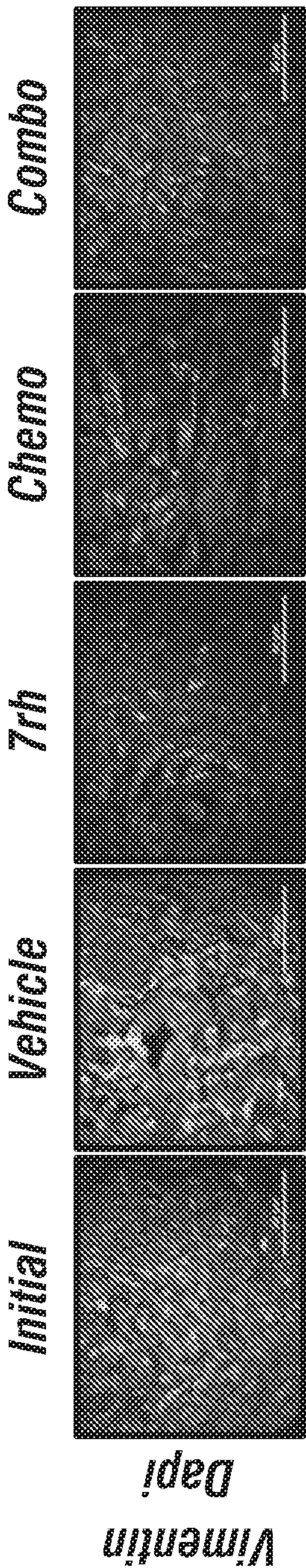
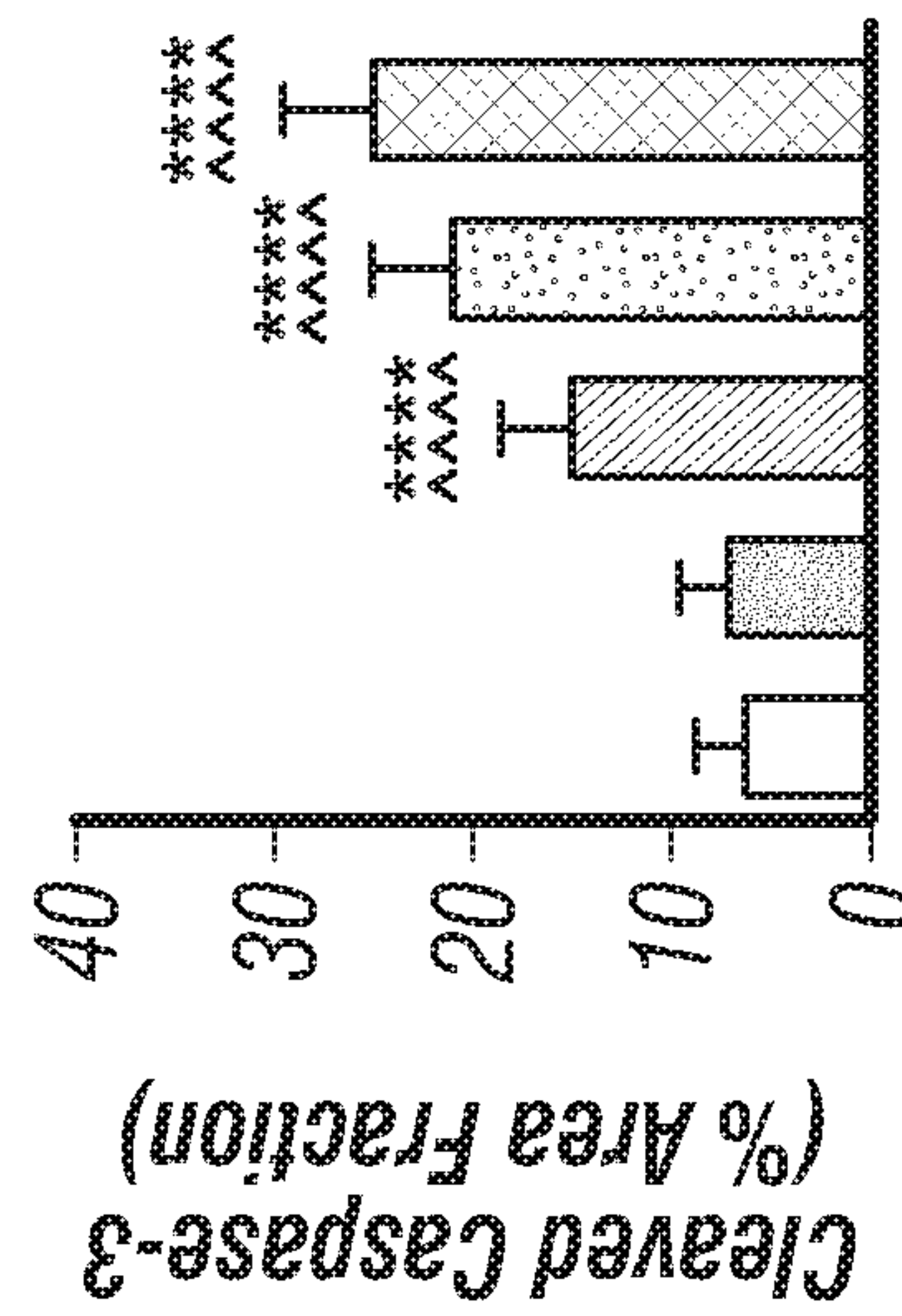
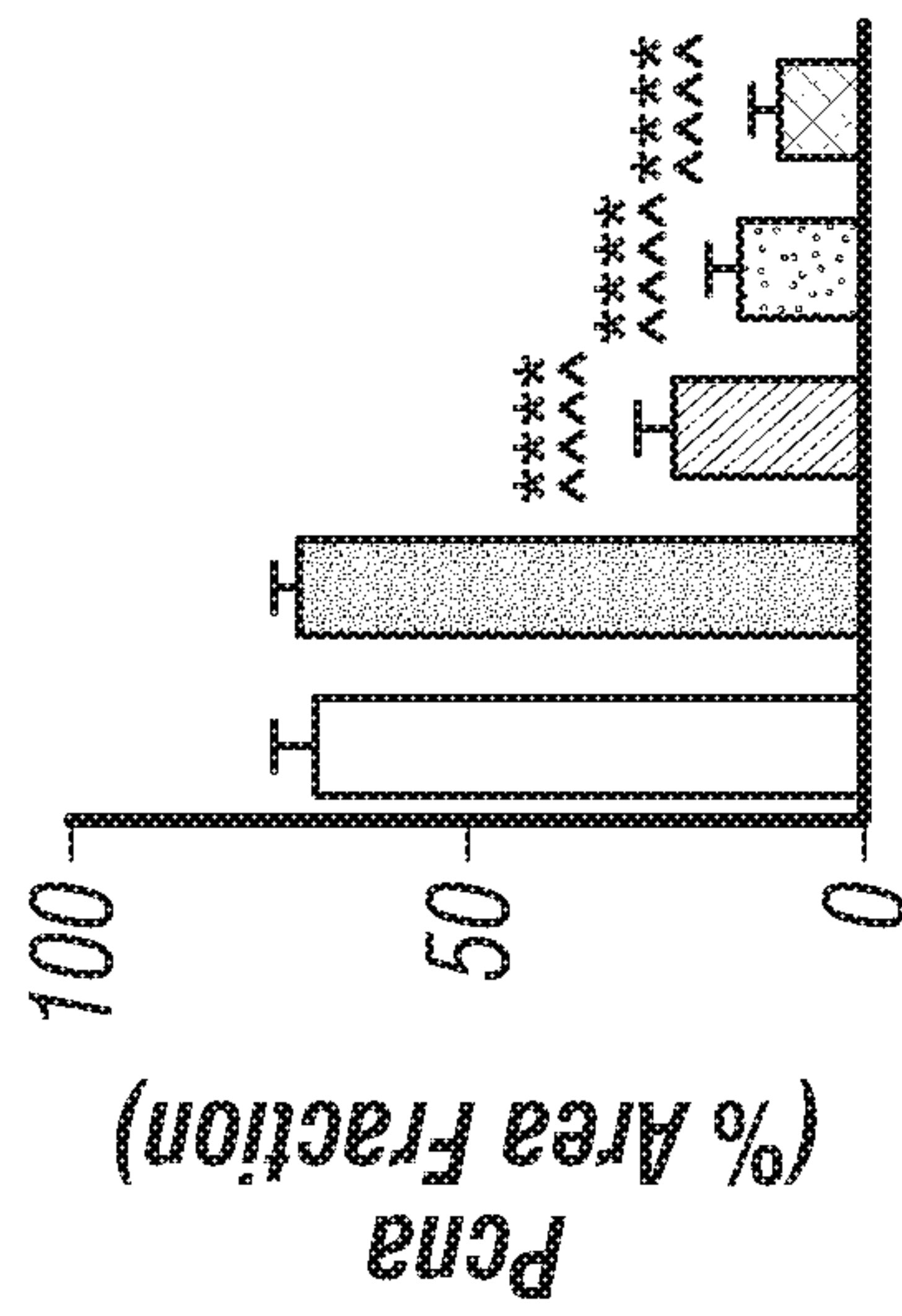
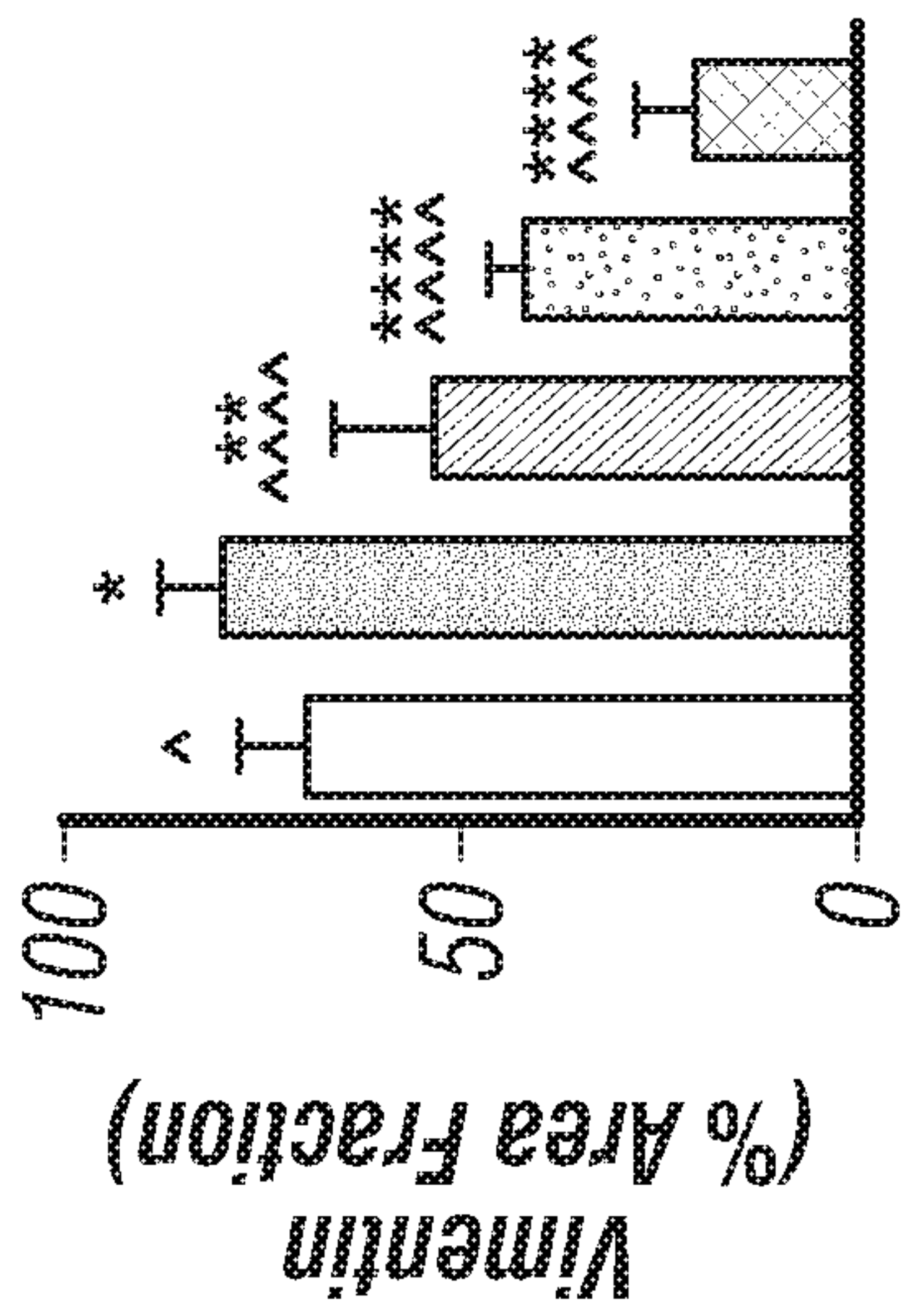


FIG. 13G

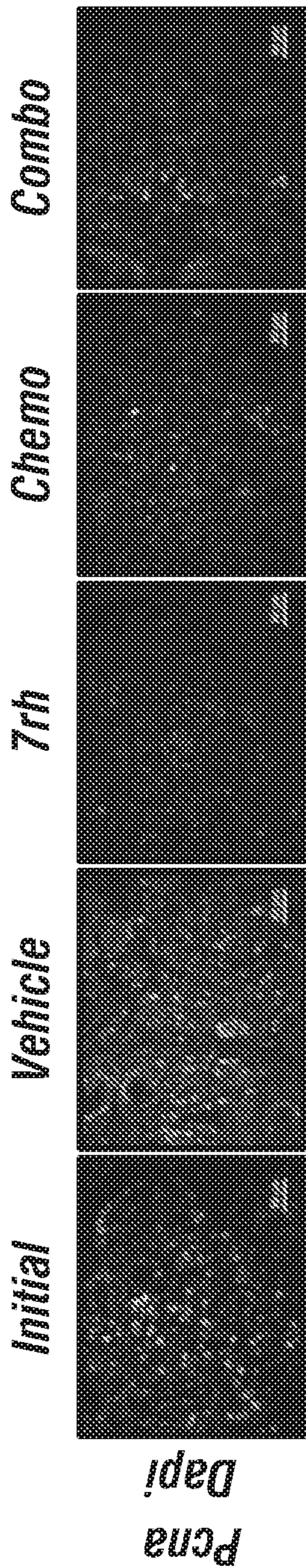


FIG. 13H

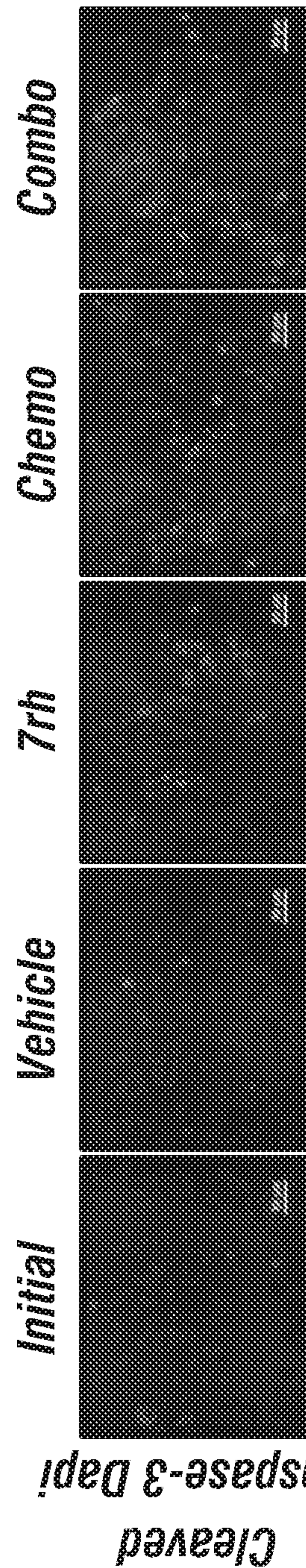
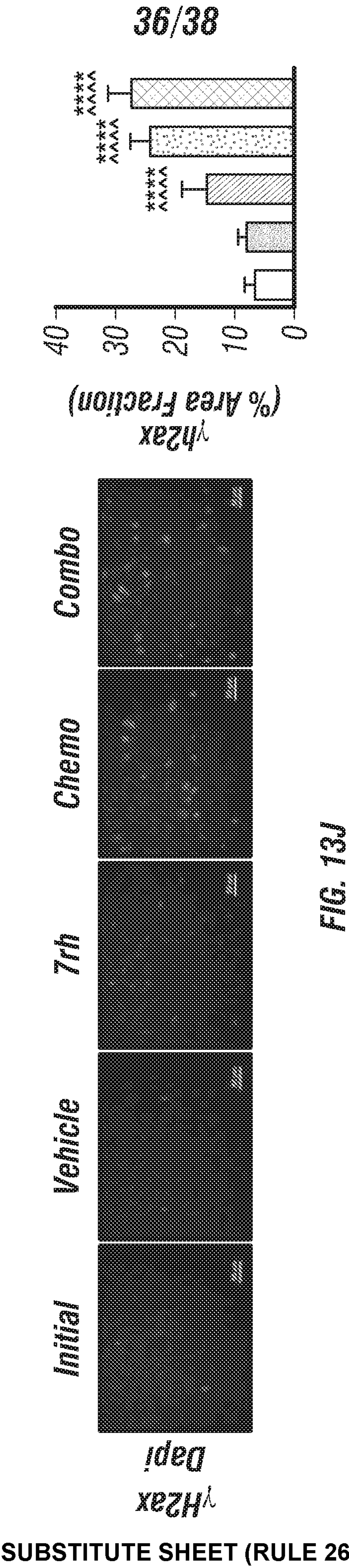


FIG. 13I



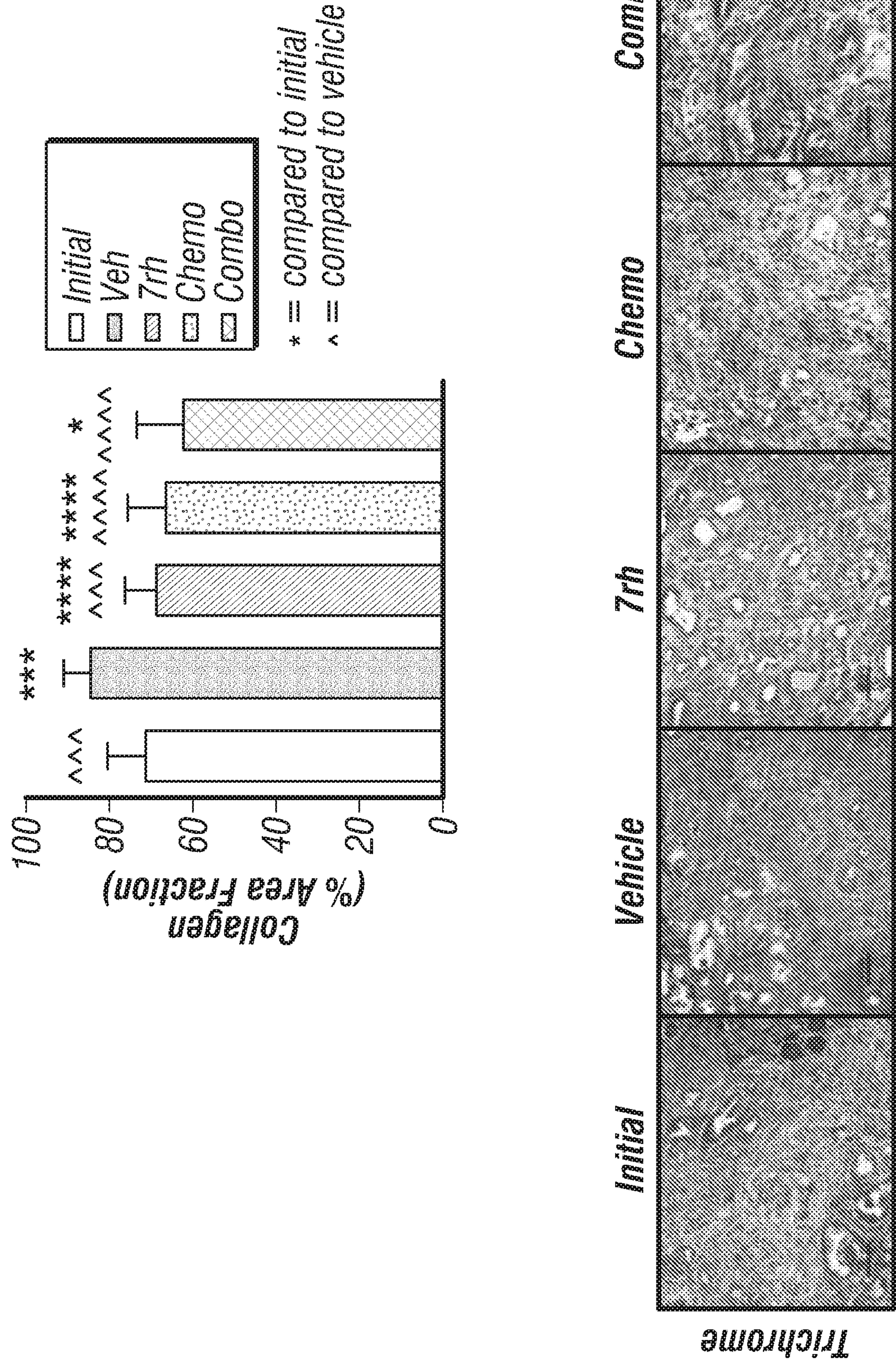
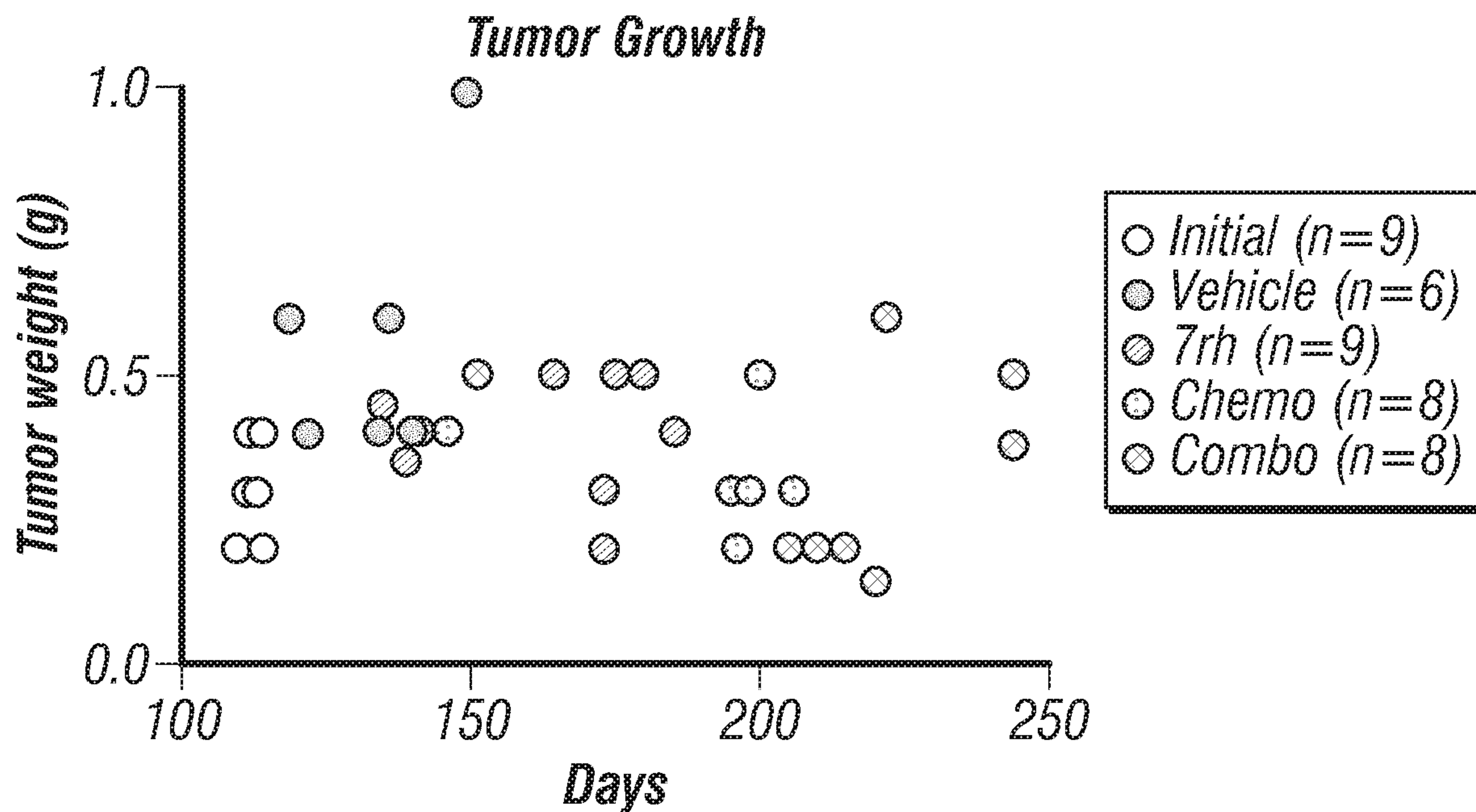
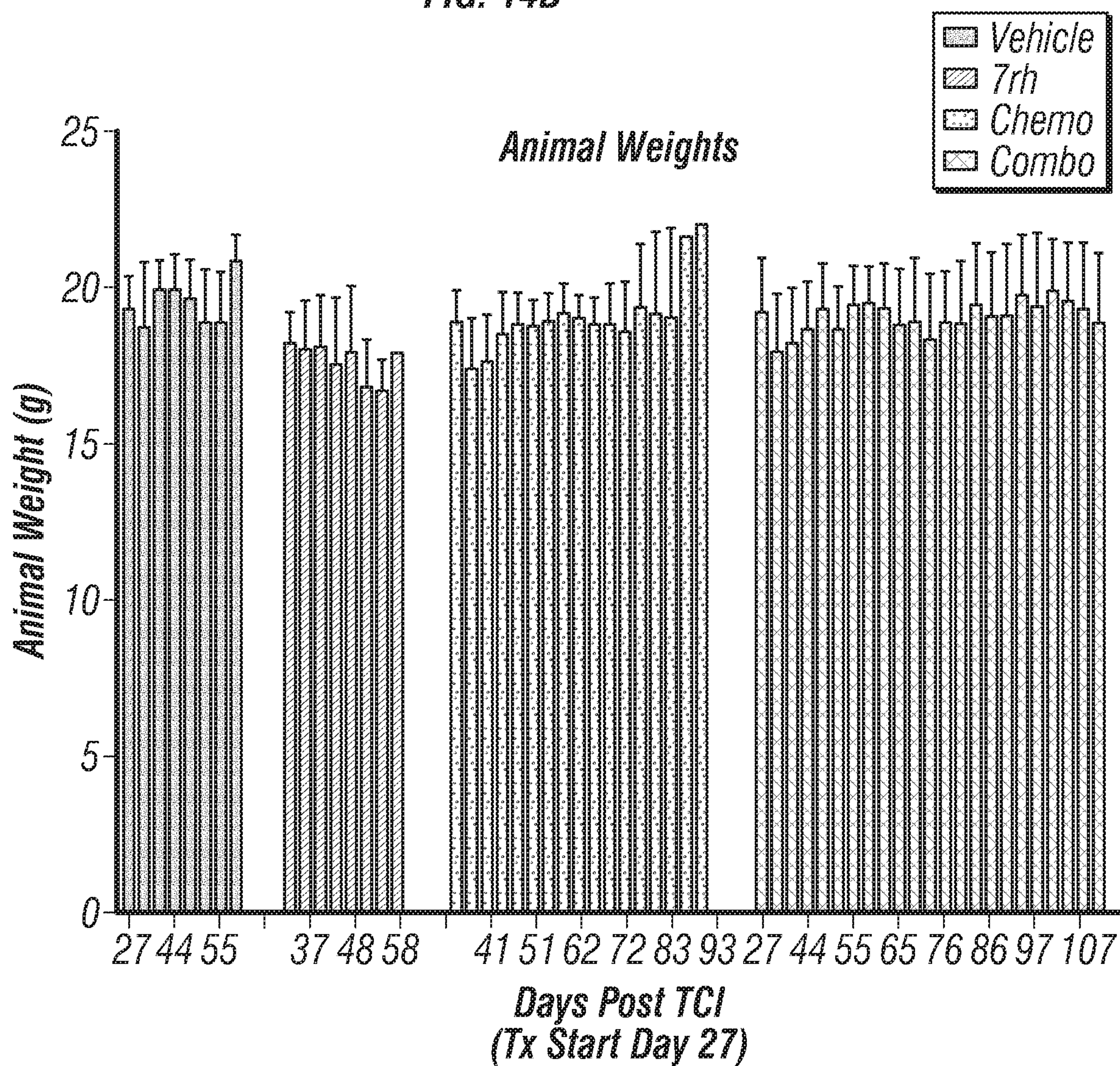
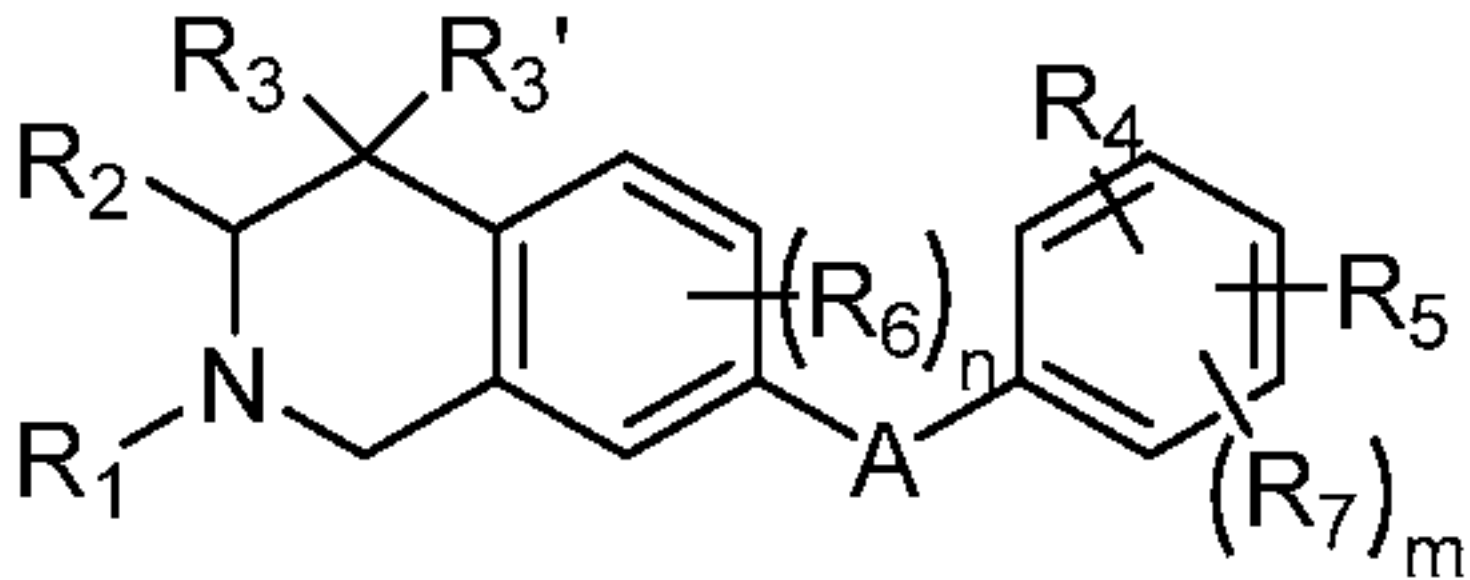


FIG. 14A

38/38**FIG. 14B****FIG. 14C**



(I)