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(71) Applicants: **THE REGENTS OF THE UNIVERSITY OF CALIFORNIA** [US/US]; 1111 Franklin Street, Twelfth Floor, Oakland, CA 94607-5200 (US). **UNITED STATES GOVERNMENT AS REPRESENTED BY THE DEPARTMENT OF VETERANS AFFAIRS** [US/US]; 810 Vermont Avenue, Office of the General Counsel, Washington, DC 20420 (US).

(72) Inventors: **JUNG, Michael, E.**; 10889 Wilshire Blvd., Suite 920, Los Angeles, CA 90095-7191 (US). **RETTIG, Matthew**; 10889 Wilshire Blvd., Suite 920, Los Angeles, CA 90095-7191 (US). **AN, Jiabin**; 10889 Wilshire Blvd., Suite 920, Los Angeles, CA 90095-7191 (US). **XIAO, Yonglong**; 10889 Wilshire Blvd., Suite 920, Los Angeles, CA 90095-7191 (US).

(74) Agent: **HALSTEAD, David, P.** et al.; Foley Hoag LLP, 155 Seaport Boulevard, Boston, MA 02210-2600 (US).

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(54) Title: INHIBITORS OF THE N-TERMINAL DOMAIN OF THE ANDROGEN RECEPTOR

(57) Abstract: The present disclosure provides compounds and methods for inhibiting or degrading the N-terminal domain of the androgen receptor, as well as methods for treating cancers such as prostate cancer.

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INHIBITORS OF THE N-TERMINAL DOMAIN OF THE ANDROGEN RECEPTOR

STATEMENT OF GOVERNMENT SUPPORT

This invention was made with government support under CA128611, and CA164331 awarded by the National Institutes of Health. The government has certain rights in the invention. This work was supported by the U.S. Department of Veterans Affairs, and the Federal government has certain rights in the invention.

RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Application No. 63/445,589, filed February 14, 2023; the entire contents of which are incorporated herein by reference.

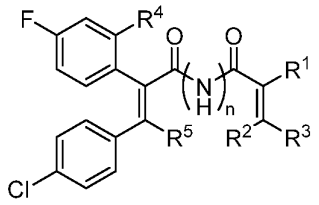
BACKGROUND OF THE INVENTION

Prostate cancer is the most common cancer and the second leading cause of cancer death in Western men. When the cancer is confined locally, the disease can usually be treated by surgery or radiation. However, 30% of prostate cancers treated that way relapse with distant metastatic disease, and some patients have advanced disease at diagnosis. Advanced disease is treated by castration and/or administration of antiandrogens, the so-called androgen deprivation therapy. Castration lowers the circulating levels of androgens and reduces the activity of androgen receptor (AR). Administration of antiandrogens blocks AR function by competing away androgen binding, thereby reducing the AR activity. Although initially effective, these treatments quickly fail and the cancer becomes hormone refractory, or castration resistant.

Castration resistant prostate cancer (CRPC) is typified by persistent expression and transcriptional activity of the androgen receptor (AR). Over the last decade, pre-clinical models, correlative studies involving patient material, and clinical studies have provided the evidence to support the notion that inhibiting the AR represents a viable approach to effectively treat CRPC. Accordingly, improved inhibitors of the AR are needed.

SUMMARY OF THE INVENTION

In certain aspects, the present disclosure provides compounds having the structure of formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, alkyl, aryl, alkynyl, cycloalkyl, or heterocycloalkyl;

R^2 is H, alkyl, or aryl;

or R^1 and R^3 combine to form cycloalkenyl; and

R^3 is H, alkyl, or aryl;

R^4 is H or fluoro;

R^5 is H or alkyl;

n is 1 or 2;

provided that when n is 1:

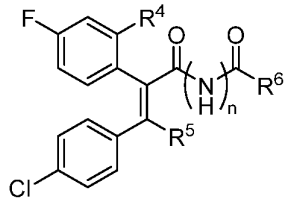
at least one of R^1, R^2, R^3, R^4, and R^5 is not H,

if each of R^2, R^3, and R^5 is H, and R^4 is F, then R^1 is not benzyl,

if each of R^2, R^3, and R^5 is H, then R^1 is not methyl, and

if each of R^1, R^2, and R^5 are H and R^4 is F, then R^3 is not phenyl or trifluoromethyl.

In certain aspects, the present disclosure provides compounds having the structure of formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein:

R^4 is H or fluoro;

R^5 is H or alkyl;

R^6 is haloalkyl, cycloalkyl, or heterocycloalkyl; and

n is 1 or 2,

provided that if R^4 is fluoro, R^5 is H, and n is 1, then R^6 is not cyclopropyl.

In certain aspects, the present disclosure provides pharmaceutical compositions of the subject compounds, as well as methods of using these compounds or compositions in the treatment of cancer, such as prostate cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

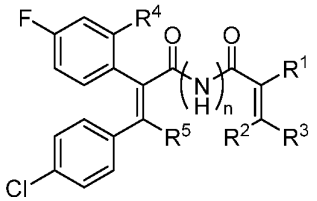
FIG. 1–FIG. 74 each show relative cell viability results in Lncap AR, 22RV1, Lncap95, vCAP, PC3, DU145, and HCT8 cells for the compounds of the disclosure, with control compound JN103. **FIG. 1** shows results for JN182–185. **FIG. 2** shows results for JN182–185. **FIG. 3** shows results for JN182–185. **FIG. 4** shows results for JN182–185 and JN186. **FIG. 5** shows results for JN186. **FIG. 6** show results for JN186. **FIG. 7** shows results for JN187–JN191. **FIG. 8** shows results for JN187–JN191. **FIG. 9** shows results for JN187–JN191. **FIG. 10** shows results for JN187–JN191. **FIG. 11** shows results for JN192. **FIG. 12** shows results for JN192 and JN193. **FIG. 13** shows results for JN193. **FIG. 14** shows results for JN193–JN195. **FIG. 15** shows results for JN194 and JN195. **FIG. 16** shows results for JN194–JN196. **FIG. 17** shows results for JN196. **FIG. 18** shows results for JN196–JN200. **FIG. 19** shows results for JN197–JN200. **FIG. 20** shows results for JN197–JN201. **FIG. 21** shows results for JN202–JN204. **FIG. 22** shows results for JN205–JN206. **FIG. 23** shows results for JN207–JN210. **FIG. 24** shows results for JN207–JN210. **FIG. 25** shows results for JN202 and JN207–JN210. **FIG. 26** shows results for JN211–JN212. **FIG. 27** shows results for JN123. **FIG. 28** shows results for JN214–JN219. **FIG. 29** shows results for JN214–JN220. **FIG. 30** shows results for JN218 and JN220. **FIG. 31** shows results for JN218–JN222. **FIG. 32** shows results for JN221 and JN222. **FIG. 33** shows results for JN221–JN227. **FIG. 34** shows results for JN223–JN231. **FIG. 35** shows results for JN228–JN235. **FIG. 36** shows results for JN233–JN235. **FIG. 37** shows results for JN233–JN238. **FIG. 38** shows results for JN236–JN238. **FIG. 39** shows results for JN236–JN241. **FIG. 40** shows results for JN239–JN243. **FIG. 41** shows results for JN242 and JN243. **FIG. 42** shows results for JN244 and JN245. **FIG. 43** shows results for JN236 and JN247. **FIG. 44** shows results for JN248–JN252. **FIG. 45** shows results for JN253 and JN254. **FIG. 46** shows results for JN255–JN260. **FIG. 47** shows results for JN255–JN260. **FIG. 48** shows results for JN261 and JN262. **FIG. 49** shows results for JN261 and JN262. **FIG. 50** shows results for JN263–JN269. **FIG. 51** shows results for JN271. **FIG. 52** shows results for JN272–JN274. **FIG. 53** shows results for JN275–JN278. **FIG. 54** shows results for JN279–JN281. **FIG. 55** shows results for JN282–JN284. **FIG. 56** shows results for JN282–JN284. **FIG. 57** shows results for JN282–JN284. **FIG. 58**

shows results for JN285–JN288. **FIG. 59** shows results for JN289–JN290. **FIG. 60** shows results for JN291–JN294 and 274-2. **FIG. 61** shows results for JN295–JN297 and JN185. **FIG. 62** shows results for JN298. **FIG. 63** shows results for JN299–JN301. **FIG. 64** shows results for JN299–JN301. **FIG. 65** shows results for JN302–JN304. **FIG. 66** shows results for JN302–JN304. **FIG. 67** shows results for JN302–JN304. **FIG. 68** shows results for JN302–JN304. **FIG. 69** shows results for JN305–JN306. **FIG. 70** shows results for JN305–JN306. **FIG. 71** shows results for JN307–JN308. **FIG. 72** shows results for JN309–JN310. **FIG. 73** shows results for JN311–JN314. **FIG. 74** shows results for JN311–JN314.

FIG. 75–FIG. 86 each show results of the reporter gene assays described in Example 2 for the compounds of the disclosure, with control compound JN103. **FIG. 75** shows results for JN297, JN301, JN308. **FIG. 76** shows results for JN297, JN301, JN185. **FIG. 77** shows results for JN181, JN185, JN281. **FIG. 78** shows results for JN181, JN185, JN272-JN274, JN279, JN281. **FIG. 79** shows results for JN272-274. **FIG. 80** shows results for JN272-JN274. **FIG. 81** shows results for JN185. **FIG. 82** shows results for JN181 and JN185. **FIG. 83** shows results for JN181, JN185, JN186, JN195. **FIG. 84** shows results for JN181, JN185, JN186, JN195. **FIG. 85** shows results for JN181, JN185, JN186, JN195. **FIG. 86** shows results for JN214.

DETAILED DESCRIPTION

In certain aspects, the present disclosure provides compounds having the structure of formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, alkyl, aryl, alkynyl, cycloalkyl, or heterocycloalkyl;

R^2 is H, alkyl, or aryl;

or R^1 and R^3 combine to form cycloalkenyl; and

R^3 is H, alkyl, or aryl;

R^4 is H or fluoro;

R^5 is H or alkyl;

n is 1 or 2;

provided that when n is 1:

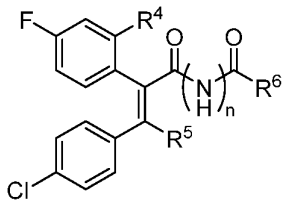
at least one of R^1, R^2, R^3, R^4, and R^5 is not H,

if each of R^2, R^3, and R^5 is H, and R^4 is F, then R^1 is not benzyl,

if each of R^2, R^3, and R^5 is H, then R^1 is not methyl, and

if each of R^1, R^2, and R^5 are H and R^4 is F, then R^3 is not phenyl or trifluoromethyl.

In certain aspects, the present disclosure provides compounds having the structure of formula II:



(II)

or a pharmaceutically acceptable salt thereof, wherein:

R^4 is H or fluoro;

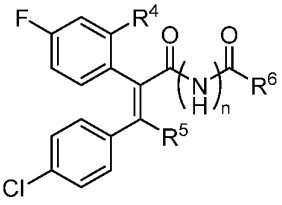
R^5 is H or alkyl;

R^6 is haloalkyl, cycloalkyl, or heterocycloalkyl; and

n is 1 or 2,

provided that if R^4 is fluoro, R^5 is H, and n is 1, then R^6 is not cyclopropyl.

In certain aspects, the present disclosure provides compounds having the structure of formula III:



(III)

or a pharmaceutically acceptable salt thereof, wherein:

R^4 is H or fluoro;

R^5 is H or alkyl;

R^6 is thioalkyl, haloalkyl, cycloalkyl, or heterocycloalkyl; and

n is 1 or 2,

provided that if R^4 is fluoro, R^5 is H, and n is 1, then R^6 is not cyclopropyl.

In certain embodiments, R^1 is alkyl, such as C_1-C_6 alkyl, which can be optionally substituted. For example, R^1 can be methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, or neopentyl, each of which is optionally substituted. In certain preferred embodiments, R^1 is methyl or isopropyl.

In certain embodiments, R^1 is cycloalkyl, such as C_3-C_6 cycloalkyl, which can be optionally substituted. For example, R^1 can be cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is optionally substituted with azido or phenyl, for example. In certain preferred embodiments, R^1 is cyclopropyl or cyclobutyl.

In certain embodiments, R^1 is heterocycloalkyl, such as 3-to 7-membered heterocycloalkyl, which can be optionally substituted. In certain preferred embodiments, R^1 can be a tetrahydropyran, which can be optionally substituted.

In certain embodiments, R^1 is alkynyl, such as C_2-C_6 alkynyl, which can be optionally substituted. For example, R^1 can be propargyl, which can be optionally substituted.

In certain embodiments, R^1 and R^3 combine to form cycloalkenyl, such as C_3-C_7 cycloalkenyl, which can be optionally substituted. For example, R^1 and R^3 combine can combine to form cyclohexenyl, which can be optionally substituted.

In certain embodiments, R^2 is H. Alternatively, in some embodiments R^2 is alkyl, such as C_1-C_6 alkyl, which can be optionally substituted. For example, R^2 can be methyl, which is optionally substituted.

In certain embodiments, R^3 is H. Alternatively, in some embodiments R^3 is alkyl, such as C_1-C_6 alkyl or aryl, such as phenyl, which can be optionally substituted. For example, R^3 can be methyl, which is optionally substituted.

In certain preferred embodiments, each of R^2 and R^3 is H. Alternatively, in some embodiments each of R^2 and R^3 is alkyl, such as C_1-C_6 alkyl, which can be optionally substituted. For example, each of R^2 and R^3 can be methyl, which can be optionally substituted.

In certain preferred embodiments, R^4 is H. Alternatively, in some other preferred embodiments, R^4 is fluoro.

In certain preferred embodiments, each of R^2, R^3, and R^5 are H and R^1 is alkyl, such as C_1-C_6 alkyl, or cycloalkyl, such as C_3-C_6 cycloalkyl.

In certain embodiments, at least one of R^1, R^2, R^3, R^4, and R^5 is not H and preferably, at least one of R^1, R^2, and R^3 is not H.

In certain embodiments, if each of R^2, R^3, and R^5 is H, and R^4 is F, then R^1 is not alkyl aryl such as lower alkyl aryl (e.g., methyl-aryl). For example, in certain embodiments if each of R^2, R^3, and R^5 is H, and R^4 is F, then R^1 is not benzyl.

In certain embodiments, if each of R^2, R^3, and R^5 is H, then R^1 is not alkyl, for example lower alkyl such as methyl, ethyl, or propyl. For example, in certain embodiments if each of R^2, R^3, and R^5 is H, then R^1 is not methyl.

In certain embodiments, if each of R^1, R^2, and R^5 are H and R^4 is F, then R^3 is not aryl, such as C6 aryl, or lower haloalkyl, such as C_1-C_3 haloalkyl or (e.g., halo substituted methyl). For example, in certain embodiments, if each of R^1, R^2, and R^5 are H and R^4 is F, then R^3 is not phenyl or trifluoromethyl.

In certain preferred embodiments, R^5 is H. Alternatively, in some embodiments R^5 is alkyl, such as C_1-C_6 alkyl, which can be optionally substituted. For example, R^5 can methyl, which can be optionally substituted.

In certain embodiments, R^6 is thioalkyl, such as C_1-C_4 thioalkyl.

In certain embodiments, R^6 is haloalkyl, such as C_1-C_3 haloalkyl. For example, R^6 can be methyl or ethyl, which can be substituted by one or more halogens, such as chloro.

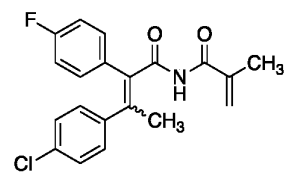
In certain embodiments, R^6 is cycloalkyl, such as C_3-C_6 cycloalkyl, which can be optionally substituted. For example, R^6 can be cyclopropyl, which is optionally substituted.

In certain embodiments, R^6 is heterocycloalkyl, such as C_3-C_6 heterocycloalkyl, which can be optionally substituted. For example, R^6 can be oxirane optionally substituted by alkyl, such as methyl (e.g., ).

In certain preferred embodiments, n is 1. Alternatively, in some embodiments, n is 2.

In certain embodiments, if R^4 is fluoro, R^5 is H, and n is 1, then R^6 is not cycloalkyl. For example, in certain embodiments, if R^4 is fluoro, R^5 is H, and n is 1, then R^6 is not cyclopropyl.

In certain embodiments, the compound is selected from: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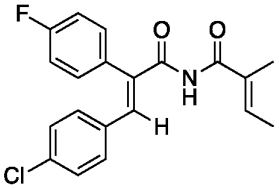
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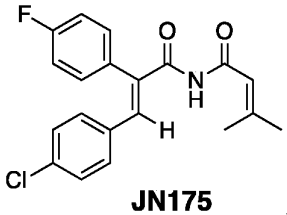
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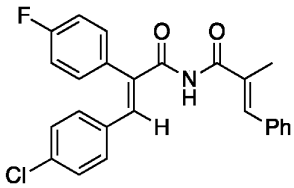
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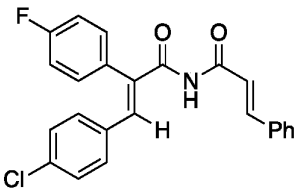
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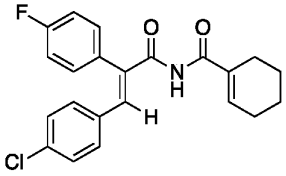
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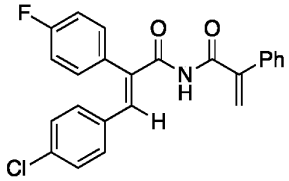
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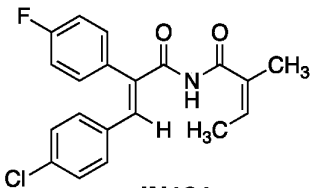
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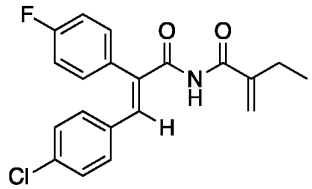
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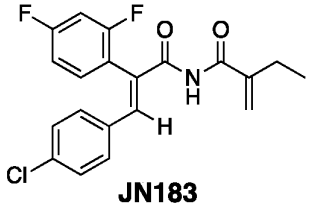
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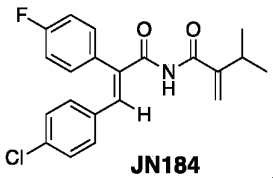
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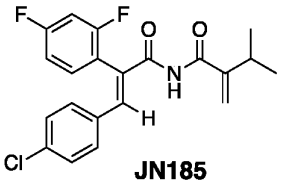
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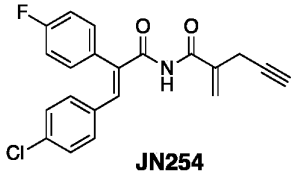
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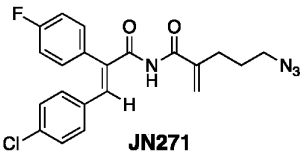
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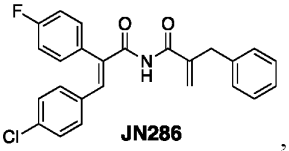
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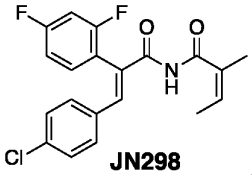
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JN279,


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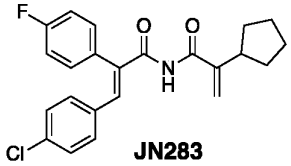
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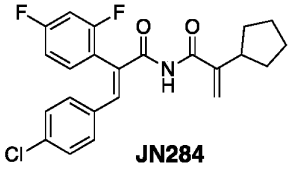
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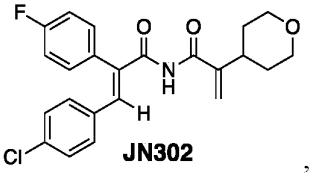
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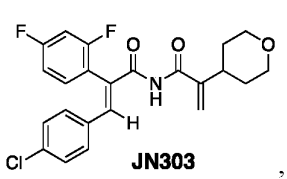
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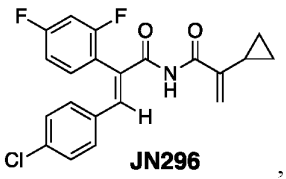
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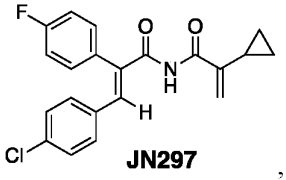
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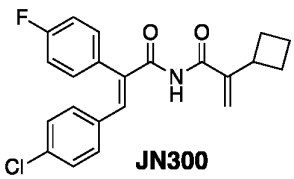
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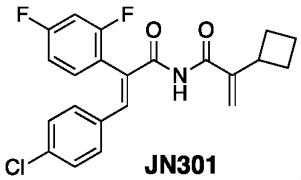
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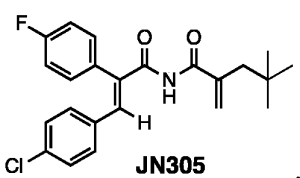
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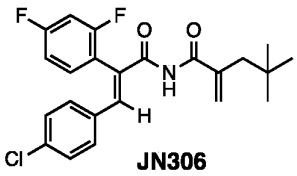
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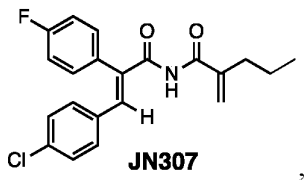
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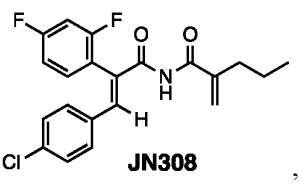
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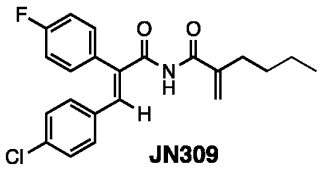
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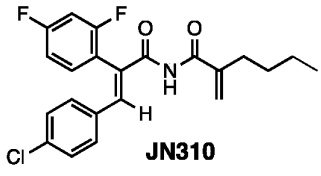
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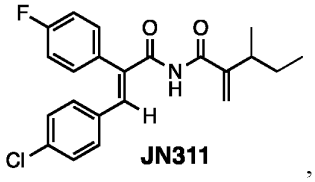
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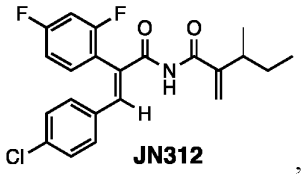
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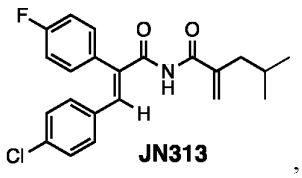
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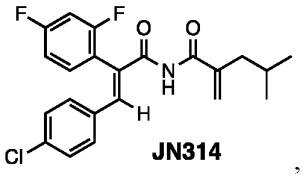
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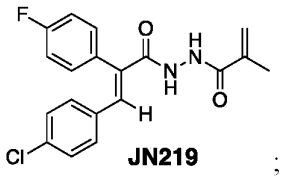
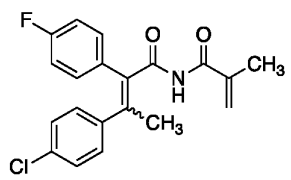

JN219;

or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is selected from: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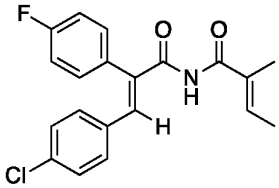
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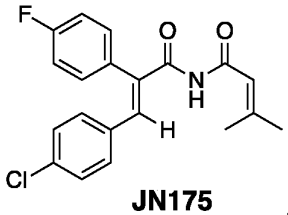
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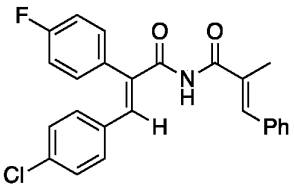
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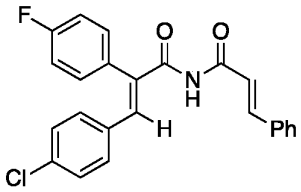
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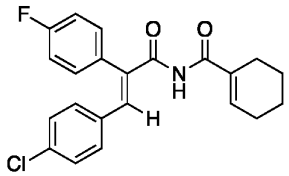
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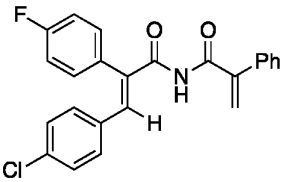
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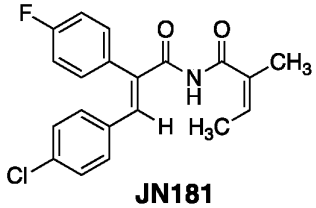
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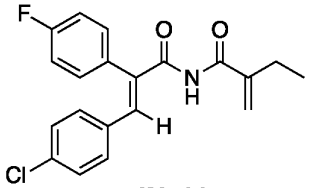
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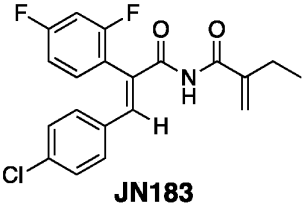
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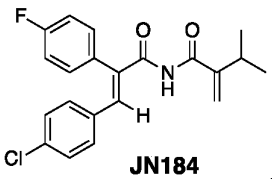
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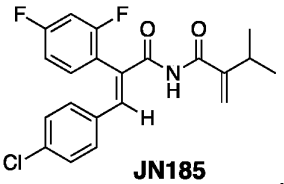
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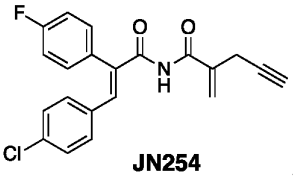
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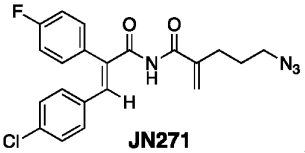
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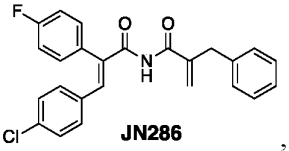
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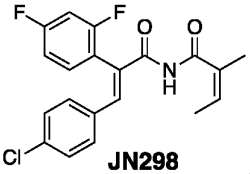
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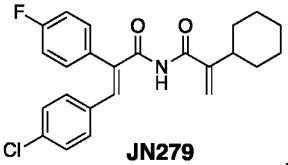
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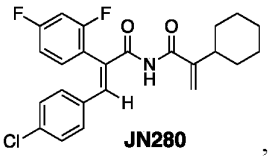
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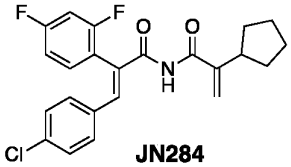
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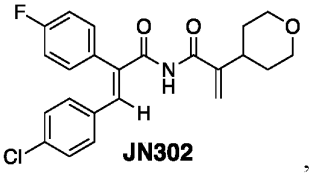
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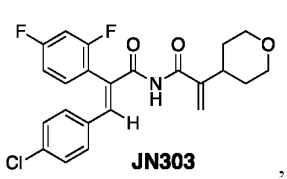
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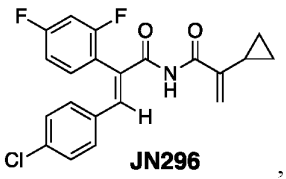
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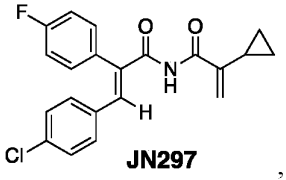
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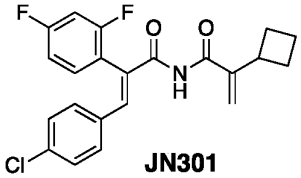
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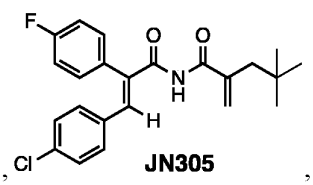
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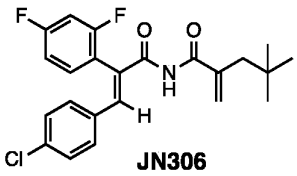
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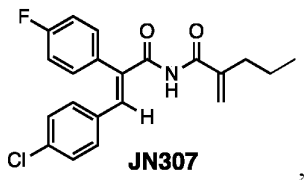
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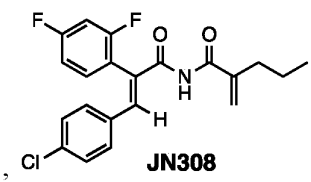
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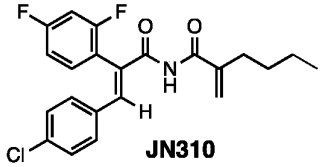
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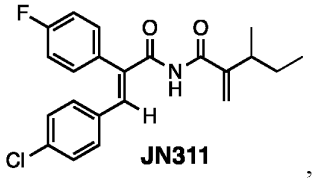
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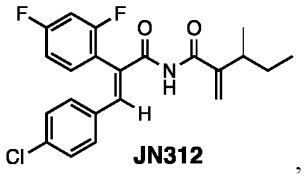
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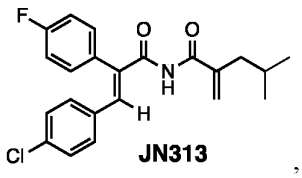
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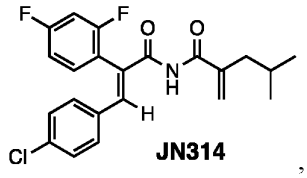
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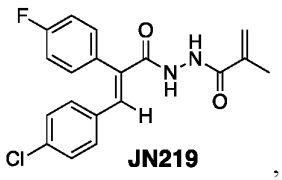
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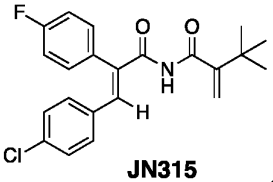
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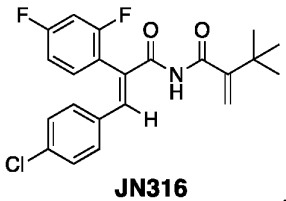
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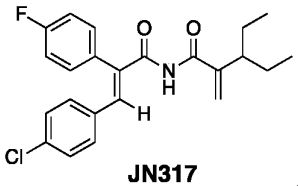
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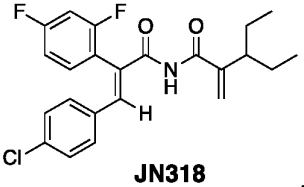
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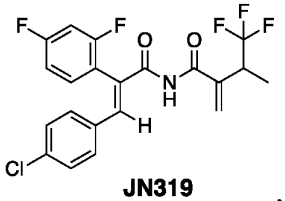
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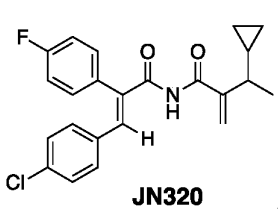
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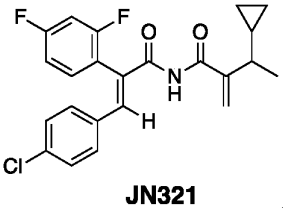
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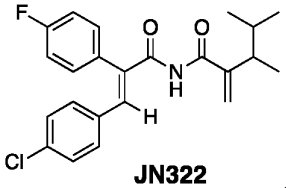
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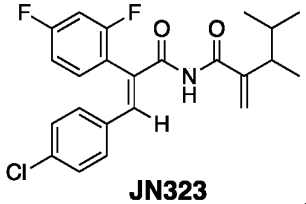
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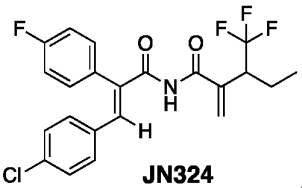
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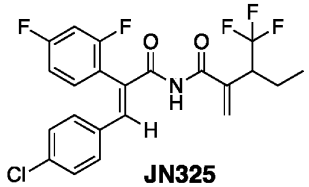
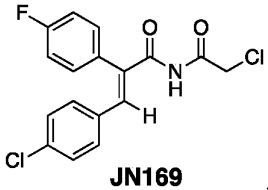

JN325 ; or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is selected from: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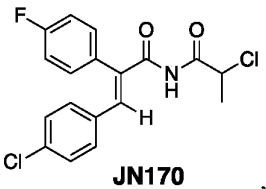
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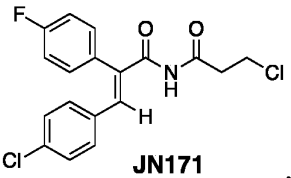
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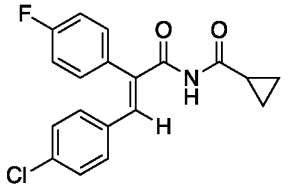
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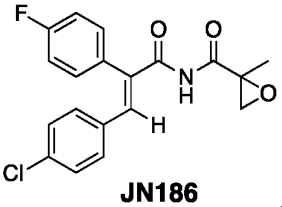
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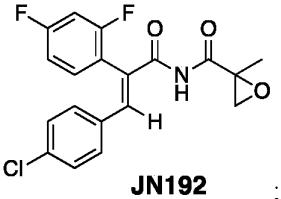
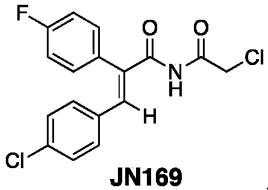

JN192 ; or a pharmaceutically acceptable salt thereof.

In certain embodiments, the compound is selected from: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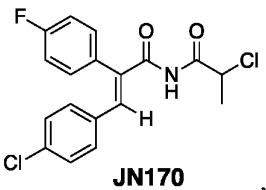
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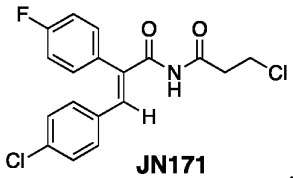
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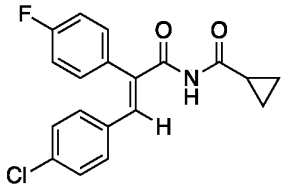
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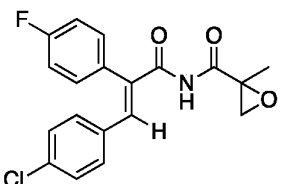
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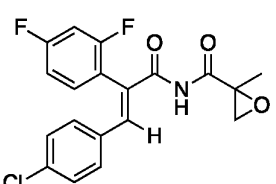
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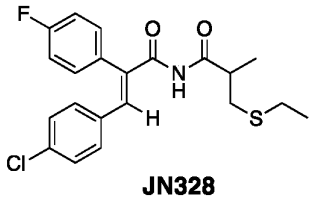
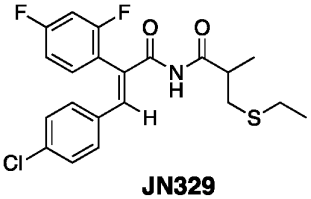


JN328 , and



JN329 ; or a pharmaceutically acceptable salt thereof.

In certain aspects, the present disclosure provides pharmaceutical compositions comprising one of the compounds disclosed herein (such as the solid forms disclosed herein) and a pharmaceutically acceptable excipient.

In certain aspects, the present disclosure provides methods for using of the compounds disclosed herein, for example the solid forms disclosed herein. In certain embodiments, the methods are for inhibiting androgen receptors, and comprise contacting the androgen receptor with a compound or composition disclosed herein. In certain embodiments, the methods are for inducing degradation of an androgen receptor in a cell, comprising contacting the androgen receptor with a compound or composition disclosed herein.

In certain embodiments, the present disclosure provides methods for treating mammals suffering from cancer, comprising administering a compound or composition disclosed herein. In certain embodiments, the cancer is prostate cancer, for example castration-resistant prostate cancer. The cancer may be metastatic or non-metastatic. In certain preferred embodiments, the cancer is resistant to antiandrogen therapy, such as treatment with enzalutamide, bicalutamide, abiraterone, flutamide, nilutamide, darolutamide, or apalutamide. In further embodiments, the cancer is resistant to treatment with enzalutamide, bicalutamide, abiraterone (e.g., abiraterone acetate), flutamide, or nilutamide. In certain such embodiments, the cancer may be resistant to conjoint treatment with abiraterone acetate and prednisone or abiraterone acetate and prednisolone.

In certain aspects, the present disclosure provides compounds as described herein. The compounds described herein are useful, for example, as cancer therapeutics, in particular as AR inhibitors and degraders. In certain aspects, the present disclosure provides methods of treating proliferative diseases, such as prostate cancer, methods of inhibiting AR, and methods of enhancing AR degradation rates using the compounds described herein.

In certain embodiments, compounds of the invention are prodrugs of the compounds described herein. For example, wherein a hydroxyl in the parent compound is present as an ester or a carbonate, or a carboxylic acid present in the parent compound is present as an ester.

In certain such embodiments, the prodrug is metabolized to the active parent compound in vivo (e.g., the ester is hydrolyzed to the corresponding hydroxyl or carboxylic acid).

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

In certain embodiments, the present invention provides pharmaceutical compositions comprising a compound of Formula I or II. In certain embodiments, the pharmaceutical compositions further comprise a pharmaceutically acceptable excipient.

In certain embodiments, the pharmaceutical compositions may be for use in treating or preventing a condition or disease as described herein.

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

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

In certain embodiments, the present invention provides a pharmaceutical preparation suitable for use in a human patient, comprising any of the compounds shown above, and one or more pharmaceutically acceptable excipients.

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

In certain aspects, the compounds of the present disclosure are for use in inhibiting an androgen receptor.

In certain aspects, the compounds of the present disclosure are for use in inducing degradation of an androgen receptor in a cell expressing an androgen receptor.

In certain aspects, the compounds of the present disclosure are for use in treating a mammal suffering from cancer. In certain embodiments, the cancer is prostate cancer. In certain embodiments, the cancer is castration-resistant prostate cancer. In certain embodiments, the cancer is metastatic. In certain embodiments, the cancer is non-metastatic.

In certain embodiments of the above aspects, the cancer is resistant to antiandrogen therapy. In certain embodiments, the cancer is resistant to treatment with enzalutamide, bicalutamide, abiraterone, flutamide, or nilutamide. In certain embodiments, the cancer is resistant to treatment with abiraterone acetate. In certain embodiments, the cancer is resistant to conjoint treatment with abiraterone acetate and prednisone.

In certain aspects, the present disclosure provides methods of inhibiting an androgen receptor, comprising contacting the androgen receptor with a compound or composition of the disclosure.

In certain aspects, the present disclosure provides methods of inducing the degradation of an androgen receptor, comprising contacting the androgen receptor with a compound or composition of the disclosure.

In certain aspects, the present disclosure provides methods of treating a mammal suffering from cancer, comprising administering a compound or composition of the disclosure. In certain embodiments, the cancer is prostate cancer. In certain embodiments, the cancer is castration-resistant prostate cancer. In certain embodiments, the cancer is metastatic. In certain embodiments, the cancer is non-metastatic.

In certain embodiments of the above aspects, the cancer is resistant to antiandrogen therapy. In certain embodiments, the cancer is resistant to treatment with enzalutamide, bicalutamide, abiraterone, flutamide, or nilutamide. In certain embodiments, the cancer is

resistant to treatment with abiraterone acetate. In certain embodiments, the cancer is resistant to conjoint treatment with abiraterone acetate and prednisone.

Discussion

The present disclosure describes compounds that inhibit the AR in novel ways. In mammalian cell systems, the compounds of Formula I or II inhibit ligand-induced and constitutive AR transcriptional activity, and enhance AR degradation.

The compounds disclosed herein target the AR N-terminal TAD. These compounds can be used to treat diseases, the growth of which is driven by the AR or its splice variants. Prostate cancer is an example of one such disease. These compounds offer competitive advantages over existing, approved compounds that target the AR because existing compounds target the LBD of the AR, whereas the compounds disclosed herein are active against full length and constitutively active AR variants that lack a functional LBD. The compounds disclosed herein target the AR N-terminus and inhibits the activity of constitutively active AR variants that lack a functional LBD. These AR variants have been shown to confer resistance to currently approved AR targeting agents. In addition, these compounds induce degradation of the AR including AR splice variants, which is not a known mechanism of any AR targeting agent that has received regulatory approval. These AR variants have been shown to confer resistance to current AR targeting agents.

Compositions and Modes of Administration

The compounds of this invention may be used in treating the conditions described herein, in the form of the free base, salts (preferably pharmaceutically acceptable salts), solvates, hydrates, prodrugs, isomers, or mixtures thereof. All forms are within the scope of the disclosure. Acid addition salts may be formed and provide a more convenient form for use; in practice, use of the salt form inherently amounts to use of the base form. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the subject organism in pharmaceutical doses of the salts, so that the beneficial properties inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of the basic compounds are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt per se is desired only as an intermediate product as, for example, when the salt is formed only for the

purposes of purification and identification, or when it is used as an intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures.

Pharmaceutically acceptable salts within the scope of the disclosure include those derived from the following acids; mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid and sulfamic acid; and organic acids such as acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, quinic acid, and the like.

The compounds of the present invention can be formulated as pharmaceutical compositions and administered to a subject in need of treatment, for example a mammal, such as a human patient, in a variety of forms adapted to the chosen route of administration, for example, orally, nasally, intraperitoneally, or parenterally (e.g., by intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal or topical routes). Parenteral administration may be by continuous infusion over a selected period of time.

In accordance with the methods of the disclosure, the described compounds may be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compositions containing the compounds of the disclosure can be prepared by known methods for the preparation of pharmaceutically acceptable compositions which can be administered to subjects, such that an effective quantity of the active substance is combined in a mixture with a pharmaceutically acceptable vehicle. Suitable vehicles are described, for example, in Remington's Pharmaceutical Sciences (Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., USA 1985). On this basis, the compositions include, albeit not exclusively, solutions of the substances in association with one or more pharmaceutically acceptable vehicles or diluents, and contained in buffered solutions with a suitable pH and iso-osmotic with the physiological fluids.

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

A person skilled in the art would know how to prepare suitable formulations. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (1990 - 18th edition) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19) published in 1999.

Thus, compounds of the invention may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier; or by inhalation or insufflation. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the compounds may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The compounds may be combined with a fine inert powdered carrier and inhaled by the subject or insufflated. Such compositions and preparations should contain at least 0.1% of compounds of formula I or II. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2% to about 60% of the weight of a given unit dosage form. The amount of the compounds in such therapeutically useful compositions is such that an effective dosage level will be obtained.

In certain embodiments of the disclosure, compositions comprising a compound of the present disclosure for oral administration include capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and the like, each containing a predetermined amount of the compound of the present disclosure as an active ingredient.

In solid dosage forms for oral administration (capsules, tablets, troches, pills, dragees, powders, granules, and the like), one or more compositions comprising the compound of the present disclosure may be mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose, gum tragacanth, corn starch, and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain

silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the compounds may be incorporated into sustained-release preparations and devices. For example, the compounds may be incorporated into time release capsules, time release tablets, and time release pills.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the compound of the present disclosure, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol (ethanol), isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming, and preservative agents.

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

In certain embodiments, pharmaceutical compositions suitable for parenteral administration may comprise the compound of the present disclosure in combination with one

or more pharmaceutically acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents. Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the disclosure include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

The compounds may be administered intravenously or intraperitoneally by infusion or injection. Solutions of the compounds or their salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations can contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the compounds which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. 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, buffers 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.

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

For topical administration, the compounds may be applied in pure form. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

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

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the compounds to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508), all of which are hereby incorporated by reference.

Useful dosages of the compounds of formula I or II can be determined by comparing their in vitro activity, and in vivo activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949, which is hereby incorporated by reference.

For example, the concentration of the compounds in a liquid composition, such as a lotion, can be from about 0.1-25% by weight, or from about 0.5-10% by weight. The

concentration in a semi-solid or solid composition such as a gel or a powder can be about 0.1-5% by weight, or about 0.5-2.5% by weight.

The amount of the compounds required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

Effective dosages and routes of administration of agents of the invention are conventional. The exact amount (effective dose) of the agent will vary from subject to subject, depending on, for example, the species, age, weight and general or clinical condition of the subject, the severity or mechanism of any disorder being treated, the particular agent or vehicle used, the method and scheduling of administration, and the like. A therapeutically effective dose can be determined empirically, by conventional procedures known to those of skill in the art. See, e.g., The Pharmacological Basis of Therapeutics, Goodman and Gilman, eds., Macmillan Publishing Co., New York. For example, an effective dose can be estimated initially either in cell culture assays or in suitable animal models. The animal model may also be used to determine the appropriate concentration ranges and routes of administration. Such information can then be used to determine useful doses and routes for administration in humans. A therapeutic dose can also be selected by analogy to dosages for comparable therapeutic agents.

The particular mode of administration and the dosage regimen will be selected by the attending clinician, taking into account the particulars of the case (e.g., the subject, the disease, the disease state involved, and whether the treatment is prophylactic). Treatment may involve daily or multi-daily doses of compound(s) over a period of a few days to months, or even years.

In general, however, a suitable dose will be in the range of from about 0.001 to about 100 mg/kg, e.g., from about 0.01 to about 100 mg/kg of body weight per day, such as above about 0.1 mg per kilogram, or in a range of from about 1 to about 10 mg per kilogram body weight of the recipient per day. For example, a suitable dose may be about 1 mg/kg, 10 mg/kg, or 50 mg/kg of body weight per day.

The compounds of formula I or II are conveniently administered in unit dosage form; for example, containing 0.05 to 10000 mg, 0.5 to 10000 mg, 5 to 1000 mg, or about 100 mg of active ingredient per unit dosage form.

The compounds can be administered to achieve peak plasma concentrations of, for example, from about 0.5 to about 75 μM, about 1 to 50 μM, about 2 to about 30 μM, or about

5 to about 25 μM. Exemplary desirable plasma concentrations include at least or no more than 0.25, 0.5, 1, 5, 10, 25, 50, 75, 100 or 200 μM. For example, plasma levels may be from about 1 to 100 micromolar or from about 10 to about 25 micromolar. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the compounds, optionally in saline, or orally administered as a bolus containing about 1-100 mg of the compounds. Desirable blood levels may be maintained by continuous infusion to provide about 0.00005-5 mg per kg body weight per hour, for example at least or no more than 0.00005, 0.0005, 0.005, 0.05, 0.5, or 5 mg/kg/hr. Alternatively, such levels can be obtained by intermittent infusions containing about 0.0002-20 mg per kg body weight, for example, at least or no more than 0.0002, 0.002, 0.02, 0.2, 2, 20, or 50 mg of the compounds per kg of body weight.

The compounds may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator.

The dosage of the compounds and/or compositions of the disclosure can vary depending on many factors such as the pharmacodynamic properties of the compound, the mode of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the frequency of the treatment and the type of concurrent treatment, if any, and the clearance rate of the compound in the subject to be treated. One of skill in the art can determine the appropriate dosage based on the above factors. The compounds of the disclosure may be administered initially in a suitable dosage that may be adjusted as required, depending on the clinical response. To calculate the human equivalent dose (HED) from a dosage used in the treatment of age-dependent cognitive impairment in rats, the formula HED (mg/kg) = rat dose (mg/kg) x 0.16 may be employed (see Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers, December 2002, Center for Biologics Evaluation and Research). For example, using that formula, a dosage of 10 mg/kg in rats is equivalent to 1.6 mg/kg in humans. This conversion is based on a more general formula HED = animal dose in mg/kg x (animal weight in kg/human weight in kg) 0.33. Similarly, to calculate the HED from a dosage used in the treatment in mouse, the formula HED (mg/kg) = mouse dose (mg/kg) x 0.08 may be employed (see Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers, December 2002, Center for Biologics Evaluation and Research).

The compounds and/or compositions of the disclosure can be used alone or conjointly with other therapeutic agents, or in combination with other types of treatment for treating cell proliferative disorders such as prostate cancer. For example, in some embodiments, the compounds and compositions of the disclosure can be used for treating CRPC or for treating cancers that are resistant to antiandrogen therapies such as enzalutamide, bicalutamide, abiraterone, flutamide, or nilutamide. For example, these other therapeutically useful agents may be administered in a single formulation, simultaneously or sequentially with the compound of the present disclosure according to the methods of the disclosure.

A number of the above-identified compounds exhibit little or no agonistic activities with respect to hormone refractory prostate cancer cells. Because these compounds are strong AR inhibitors, they can be used not only in treating prostate cancer, but also in treating other AR related diseases or conditions such as benign prostate hyperplasia, hair loss, and acne. Because AR belongs to the family of nuclear receptors, these compounds may serve as scaffolds for drug synthesis targeting other nuclear receptors, such as estrogen receptor and peroxisome proliferator-activated receptor. Therefore, they may be further developed for other diseases such as breast cancer, ovarian cancer, diabetes, cardiac diseases, and metabolism related diseases, in which nuclear receptors play a role.

Definitions

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

The methods and techniques of the present disclosure are generally performed, unless otherwise indicated, according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout this specification. See, e.g. “Principles of Neural Science”, McGraw-Hill Medical, New York, N.Y. (2000); Motulsky, “Intuitive Biostatistics”, Oxford University Press, Inc. (1995); Lodish et al., “Molecular Cell Biology, 4th ed.”, W. H. Freeman & Co., New York (2000); Griffiths et al., “Introduction to Genetic Analysis, 7th ed.”, W. H. Freeman & Co., N.Y. (1999); and Gilbert et al., “Developmental Biology, 6th ed.”, Sinauer Associates, Inc., Sunderland, MA (2000).

Chemistry terms used herein are used according to conventional usage in the art, as exemplified by "The McGraw-Hill Dictionary of Chemical Terms", Parker S., Ed., McGraw-Hill, San Francisco, C.A. (1985).

All of the above, and any other publications, patents and published patent applications referred to in this application are specifically incorporated by reference herein. In case of conflict, the present specification, including its specific definitions, will control.

The term "agent" is used herein to denote a chemical compound (such as an organic or inorganic compound, a mixture of chemical compounds), a biological macromolecule (such as a nucleic acid, an antibody, including parts thereof as well as humanized, chimeric and human antibodies and monoclonal antibodies, a protein or portion thereof, e.g., a peptide, a lipid, a carbohydrate), or an extract made from biological materials such as bacteria, plants, fungi, or animal (particularly mammalian) cells or tissues. Agents include, for example, agents whose structure is known, and those whose structure is not known. The ability of such agents to inhibit AR or promote AR degradation may render them suitable as "therapeutic agents" in the methods and compositions of this disclosure.

A "patient," "subject," or "individual" are used interchangeably and refer to either a human or a non-human animal. These terms include mammals, such as humans, primates, livestock animals (including bovines, porcines, etc.), companion animals (e.g., canines, felines, etc.) and rodents (e.g., mice and rats).

"Treating" a condition or patient refers to taking steps to obtain beneficial or desired results, including clinical results. As used herein, and as well understood in the art, "treatment" is an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e. not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

The term "preventing" is art-recognized, and when used in relation to a condition, such as a local recurrence (e.g., pain), a disease such as cancer, a syndrome complex such as heart failure or any other medical condition, is well understood in the art, and includes administration of a composition which reduces the frequency of, or delays the onset of, symptoms of a medical condition in a subject relative to a subject which does not receive the composition. Thus,

prevention of cancer includes, for example, reducing the number of detectable cancerous growths in a population of patients receiving a prophylactic treatment relative to an untreated control population, and/or delaying the appearance of detectable cancerous growths in a treated population versus an untreated control population, e.g., by a statistically and/or clinically significant amount.

"Administering" or "administration of" a substance, a compound or an agent to a subject can be carried out using one of a variety of methods known to those skilled in the art. For example, a compound or an agent can be administered, intravenously, arterially, intradermally, intramuscularly, intraperitoneally, subcutaneously, ocularly, sublingually, orally (by ingestion), intranasally (by inhalation), intraspinally, intracerebrally, and transdermally (by absorption, e.g., through a skin duct). A compound or agent can also appropriately be introduced by rechargeable or biodegradable polymeric devices or other devices, e.g., patches and pumps, or formulations, which provide for the extended, slow or controlled release of the compound or agent. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

Appropriate methods of administering a substance, a compound or an agent to a subject will also depend, for example, on the age and/or the physical condition of the subject and the chemical and biological properties of the compound or agent (e.g. solubility, digestibility, bioavailability, stability and toxicity). In some embodiments, a compound or an agent is administered orally, e.g., to a subject by ingestion. In some embodiments, the orally administered compound or agent is in an extended release or slow release formulation, or administered using a device for such slow or extended release.

As used herein, the phrase "conjoint administration" refers to any form of administration of two or more different therapeutic agents such that the second agent is administered while the previously administered therapeutic agent is still effective in the body (e.g., the two agents are simultaneously effective in the patient, which may include synergistic effects of the two agents). For example, the different therapeutic compounds can be administered either in the same formulation or in separate formulations, either concomitantly or sequentially. Thus, an individual who receives such treatment can benefit from a combined effect of different therapeutic agents.

A "therapeutically effective amount" or a "therapeutically effective dose" of a drug or agent is an amount of a drug or an agent that, when administered to a subject will have the intended therapeutic effect. The full therapeutic effect does not necessarily occur by

administration of one dose, and may occur only after administration of a series of doses. Thus, a therapeutically effective amount may be administered in one or more administrations. The precise effective amount needed for a subject will depend upon, for example, the subject's size, health and age, and the nature and extent of the condition being treated, such as cancer or MDS. The skilled worker can readily determine the effective amount for a given situation by routine experimentation.

As used herein, the terms "optional" or "optionally" mean that the subsequently described event or circumstance may occur or may not occur, and that the description includes instances where the event or circumstance occurs as well as instances in which it does not. For example, "optionally substituted alkyl" refers to the alkyl may be substituted as well as where the alkyl is not substituted.

It is understood that substituents and substitution patterns on the compounds of the present invention can be selected by one of ordinary skilled person in the art to result chemically stable compounds which can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results.

As used herein, the term "optionally substituted" refers to the replacement of one to six hydrogen radicals in a given structure with the radical of a specified substituent including, but not limited to: hydroxyl, hydroxyalkyl, alkoxy, halogen, alkyl, nitro, silyl, acyl, acyloxy, aryl, cycloalkyl, heterocyclyl, amino, aminoalkyl, cyano, haloalkyl, haloalkoxy, -OCO-CH_2-O-alkyl, -OP(O)(O-alkyl)$_2$ or –CH_2-OP(O)(O-alkyl)$_2$. Preferably, "optionally substituted" refers to the replacement of one to four hydrogen radicals in a given structure with the substituents mentioned above. More preferably, one to three hydrogen radicals are replaced by the substituents as mentioned above. It is understood that the substituent can be further substituted.

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

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

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

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

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

The term "alkyl" refers to saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl-substituted cycloalkyl groups, and cycloalkyl-substituted alkyl groups. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C_{1-30} for straight chains, C_{3-30} for branched chains), and more preferably 20 or fewer.

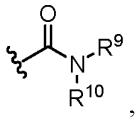
Moreover, the term "alkyl" as used throughout the specification, examples, and claims is intended to include both unsubstituted and substituted alkyl groups, the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc.

The term "C_{x-y}" or "C_x-C_y", when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. C_0alkyl indicates a hydrogen where the group is in a terminal position, a bond if internal. A C_{1-6}alkyl group, for example, contains from one to six carbon atoms in the chain.

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

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

The term "amide", as used herein, refers to a group



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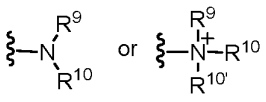
wherein R^9 and R^{10} each independently represent a hydrogen or hydrocarbyl group, or R^9 and R^{10} taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

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



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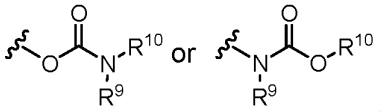
wherein R^9, R^{10}, and $R^{10'}$ each independently represent a hydrogen or a hydrocarbyl group, or R^9 and R^{10} taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

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

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

The term "aryl" as used herein include substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably the ring is a 5- to 7-membered ring, more preferably a 6-membered ring. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like.

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



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wherein R^9 and R^{10} independently represent hydrogen or a hydrocarbyl group.

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

The terms "carbocycle", "carbocyclyl", and "carbocyclic", as used herein, refers to a non-aromatic saturated or unsaturated ring in which each atom of the ring is carbon. Preferably a carbocycle ring contains from 3 to 10 atoms, more preferably from 5 to 7 atoms.

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

The term "carbonate" is art-recognized and refers to a group $-OCO_2-$.

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

The term "ester", as used herein, refers to a group $-C(O)OR^9$ wherein R^9 represents a hydrocarbyl group.

The term "ether", as used herein, refers to a hydrocarbyl group linked through an oxygen to another hydrocarbyl group. Accordingly, an ether substituent of a hydrocarbyl group

may be hydrocarbyl-O-. Ethers may be either symmetrical or unsymmetrical. Examples of ethers include, but are not limited to, heterocycle-O-heterocycle and aryl-O-heterocycle. Ethers include "alkoxyalkyl" groups, which may be represented by the general formula alkyl-O-alkyl.

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

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

The terms "heteroaryl" and "hetaryl" include substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heteroaryl" and "hetaryl" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heteroaromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like.

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

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

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

The term "hydrocarbyl", as used herein, refers to a group that is bonded through a carbon atom that does not have a =O or =S substituent, and typically has at least one carbon-hydrogen bond and a primarily carbon backbone, but may optionally include heteroatoms.

Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and even trifluoromethyl are considered to be hydrocarbyl for the purposes of this application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarbyl groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocycle, alkyl, alkenyl, alkynyl, and combinations thereof.

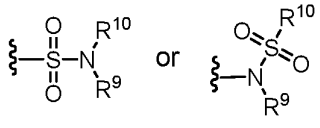
The term "hydroxyalkyl", as used herein, refers to an alkyl group substituted with a hydroxy group.

The term "lower" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups where there are ten or fewer atoms in the substituent, preferably six or fewer. A "lower alkyl", for example, refers to an alkyl group that contains ten or fewer carbon atoms, preferably six or fewer. In certain embodiments, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy substituents defined herein are respectively lower acyl, lower acyloxy, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyalkyl and aralkyl (in which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyl substituent).

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

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

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



wherein R^9 and R^{10} independently represents hydrogen or hydrocarbyl.

The term "sulfoxide" is art-recognized and refers to the group–S(O)-.

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

The term "sulfone" is art-recognized and refers to the group $-S(O)_2-$.

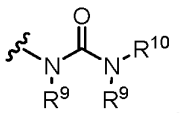
The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate.

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

The term "thioester", as used herein, refers to a group $-C(O)SR^9$ or $-SC(O)R^9$ wherein R^9 represents a hydrocarbyl.

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

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



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wherein R^9 and R^{10} independently represent hydrogen or a hydrocarbyl.

The term "modulate" as used herein includes the inhibition or suppression of a function or activity (such as cell proliferation) as well as the enhancement of a function or activity.

The phrase "pharmaceutically acceptable" is art-recognized. In certain embodiments, the term includes compositions, excipients, adjuvants, polymers and other materials and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

"Pharmaceutically acceptable salt" is used herein to refer to an acid addition salt or a basic addition salt which is suitable for or compatible with the treatment of patients.

The term "pharmaceutically acceptable acid addition salt" as used herein means any non-toxic organic or inorganic salt of any base compounds represented by formula I or II. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulfuric and phosphoric acids, as well as metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic acids that form suitable salts include mono-, di-, and tricarboxylic acids such as glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, benzoic, phenylacetic, cinnamic and salicylic acids, as well as sulfonic acids such as p-toluene sulfonic and methanesulfonic acids. Either the mono or di-acid salts can be formed, and such salts may exist in either a hydrated, solvated or substantially anhydrous form. In general, the acid addition salts of compounds of formula I or II are more soluble in water and various hydrophilic organic solvents, and generally demonstrate higher melting points in comparison to their free base forms. The selection of the appropriate salt will be known to one skilled in the art. Other non-pharmaceutically acceptable salts, e.g., oxalates, may be used, for example, in the isolation of compounds of formula I or II for laboratory use, or for subsequent conversion to a pharmaceutically acceptable acid addition salt.

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

Many of the compounds useful in the methods and compositions of this disclosure have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem. (1976), 45, 11-30. The disclosure contemplates all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds, salts, prodrugs or mixtures thereof (including all possible mixtures of stereoisomers). See, e.g., WO 01/062726.

Furthermore, certain compounds which contain alkenyl groups may exist as Z (zusammen) or E (entgegen) isomers. In each instance, the disclosure includes both mixture and separate individual isomers.

Some of the compounds may also exist in tautomeric forms. Such forms, although not explicitly indicated in the formulae described herein, are intended to be included within the scope of the present disclosure.

"Prodrug" or "pharmaceutically acceptable prodrug" refers to a compound that is metabolized, for example hydrolyzed or oxidized, in the host after administration to form the compound of the present disclosure (e.g., compounds of formula I or II). Typical examples of prodrugs include compounds that have biologically labile or cleavable (protecting) groups on a functional moiety of the active compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, or dephosphorylated to produce the active compound. Examples of prodrugs using ester or phosphoramidate as biologically labile or cleavable (protecting) groups are disclosed in U.S. Patents 6,875,751, 7,585,851, and 7,964,580, the disclosures of which are incorporated herein by reference. The prodrugs of this disclosure are metabolized to produce a compound of formula I or II. The present disclosure includes within its scope, prodrugs of the compounds described herein. Conventional procedures for the selection and preparation of suitable prodrugs are described, for example, in "Design of Prodrugs" Ed. H. Bundgaard, Elsevier, 1985.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filter, diluent, excipient, solvent or encapsulating material useful for formulating a drug for medicinal or therapeutic use.

The term "Log of solubility", "LogS" or "logS" as used herein is used in the art to quantify the aqueous solubility of a compound. The aqueous solubility of a compound significantly affects its absorption and distribution characteristics. A low solubility often goes

along with a poor absorption. LogS value is a unit stripped logarithm (base 10) of the solubility measured in mol/liter.

Discussion

Adenocarcinoma of the prostate (PCa) is the most common non-cutaneous solid tumor diagnosed in men in the U.S. and represents the second leading cause of cancer-related mortality in men, second only to lung cancer. PCa is initially androgen dependent (AD), and androgen deprivation therapy (ADT), which is delivered by surgical or chemical castration in the form of luteinizing hormone releasing hormone (LHRH) analogues (Figure 1A), results in apoptosis and growth arrest of AD PCa cells and induces a clinical response in virtually all patients. Unfortunately, castration resistant prostate cancer (CRPC) inevitably develops and not only represents the terminal phase of the disease with a median survival of approximately 12-15 months, but also is associated with profound morbidity. Until recently, the chemotherapeutic agent, docetaxel, was the only systemic therapy for CRPC that prolonged median overall survival, albeit by a modest two to three months. In 2010, another cytotoxic chemotherapeutic, cabazitaxel, was also granted regulatory approval for docetaxel-resistant patients based on a three month improvement in survival, as was the cellular vaccine, Provenge, which extended survival by four months in a highly select sub-group of patients with excellent performance status. Thus, despite these modest, incremental advances, novel treatment approaches based on an understanding of the biology behind castration resistance are required to more substantially improve the outcomes of CRPC patients.

A large body of experimental and clinical evidence has established that restoration of AR activity underlies therapeutic resistance in the vast majority of CRPC patients. Although the AR has non-genotropic effects, reactivation of AR transcriptional activity represents the principal biochemical driving force that is necessary and sufficient for castration resistance. Cellular adaptations, including 1) AR gene amplification, 2) intratumoral steroidogenesis, 3) gain-of-function AR gene mutations that allow for ligand promiscuity, 4) somatic mosaicism of the AR, 5) heightened expression of AR transcriptional coactivators, 6) as well as truly ligand-independent AR activation mediated by growth factors, cytokines, and AR phosphorylation, are mutually non-exclusive mechanisms that drive AR transcriptional activity despite castrate serum levels of androgens. Activating mutations of the AR signaling axis has been identified in nearly all cases of CRPC in a recent integrative genomic analysis of over 200 CRPC patients.

Based on these observations, drugs that target the AR signaling axis through novel approaches, including pure AR antagonists (e.g., enzalutamide) and CYP17 inhibitors aimed at inhibiting intratumoral steroidogenesis (e.g., abiraterone acetate) have made their way through the clinic (Figure 1B). Abiraterone acetate and enzalutamide have both been approved for the treatment of metastatic CRPC (mCRPC). However, primary resistance to these agents occurs in roughly one third of patients, while the remaining patients develop secondary resistance manifested by progression of disease after an initial period of response of variable duration.

The phase 3 studies that demonstrated the clinical success of abiraterone acetate and enzalutamide in chemotherapy naïve and post-chemotherapy patients confirmed the pathophysiologic relevance of the AR as a driver of castration resistance. Cross-resistance between abiraterone and enzalutamide is the norm as evidenced by the low response rate when one of these agents is used subsequent to progression on the other. Since the clinical implementation of these second-generation endocrine therapies, pre-clinical models as well as sequencing studies of cohorts of mCRPC patients have demonstrated ongoing AR expression and signaling in post-abiraterone/post-enzalutamide mCRPC. In fact, the AR is the most frequently mutated gene, and an AR-dependent transcriptional program is reactivated in this context. Thus, the AR represents a key driver of castration resistant growth in both newly developed CRPC and post-abiraterone/post-enzalutamide CRPC.

Constitutively active variants of the AR that lack a functional LBD have recently been shown to be expressed in prostate cancer specimens with increasing frequency in mCRPC specimens. These constitutively active variants confer resistance to abiraterone acetate and enzalutamide; in fact, these variants would not be expected to respond to any existing drug that directly or indirectly targets the LBD. Given the inevitable development of primary or secondary resistance to abiraterone and enzalutamide and the pathophysiologic relevance of the AR throughout the natural and treated history of the castration resistant state, there is an unmet need to develop novel AR targeting agents to improve the clinical outcomes of patients with metastatic CRPC.

All existing endocrine therapies in clinical use for the treatment of PCa, including but not limited to abiraterone and enzalutamide, directly or indirectly target the C-terminal ligand binding domain (LBD) of the AR. The C-terminal LBD of the AR represents the direct or indirect molecular target of new AR targeting agents in development as well as those that have long been employed, including luteinizing hormone releasing hormone (LHRH) analogues

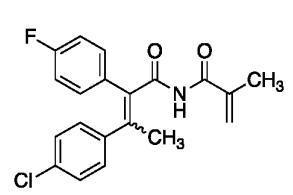
(e.g., leuprolide, a "chemical castration") and partial AR antagonists (e.g., bicalutamide) (Figure 1C). The other major domains of the AR, including the centrally located DNA binding domain (DBD) and N-terminal transactivation domain (TAD), have yet to be directly targeted and exploited for therapeutic benefit. These domains are required for AR transcriptional activity, yet no drug that targets either of these domains has been successfully brought to the point of regulatory approval to date. The centrally located DBD shares significant homology with other members of the nuclear steroid receptor family (e.g., glucocorticoid receptor [GR], progesterone receptor [PR]), whereas the N-terminally located AR TAD shares the least homology with that of other members of this family and accordingly could be selectively targeted.

The AR TAD is an intrinsically disordered protein that has not been amenable to crystallization. Hence, its structure has not been resolved, and, by extension, the AR TAD does not lend itself to structure based drug design. Proof-of-principle support for the notion of targeting the TAD has come from studies in which TAD decoy molecules inhibited AR-dependent growth.

Proof-of-principle support for the notion of targeting the TAD has come from recent studies by a group that identified TAD decoy molecules as well as a marine sponge extract that selectively targets the AR TAD. Importantly, this marine sponge extract, known as EPI-001, inhibited CRPC growth through interaction with the AF1 region of the TAD. EPI-001 was not identified through a high throughput screen, and is likely to have been absorbed by marine sponges in vivo as an industrial compound. Other compounds have been shown to have an inhibitory effect on constitutively active AR splice variants. Galeterone binds to the AR LBD but was reported to induce degradation of AR splice variants. Galeterone entered into clinical trials, but a phase 3 studied was recently discontinued at an interim analysis due to futility. Niclosamide, an anti-fungal agent, also inhibits AR splice variants and has entered into early phase clinical trials. Other AR TAD inhibitors include those described in International Publication No. WO 2018/136792, which is fully incorporated herein by reference.

The compounds disclosed herein have been prepared and tested for activity against AR, as listed in Table 1:

Table 1. Exemplary Compounds of the Disclosure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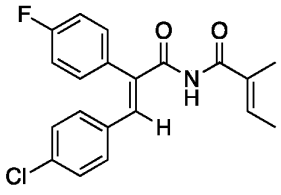
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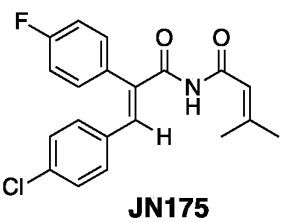
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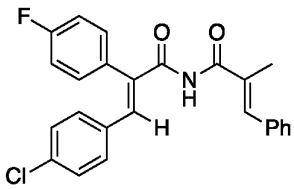
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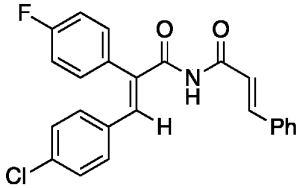
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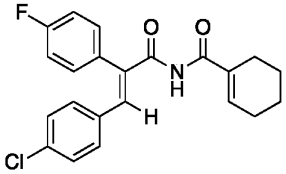
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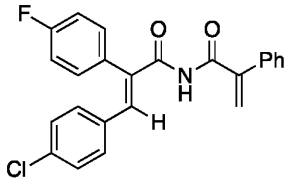
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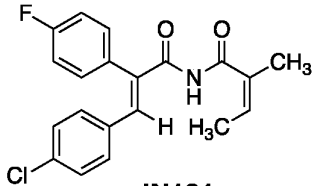
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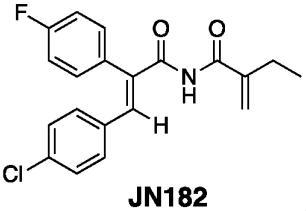
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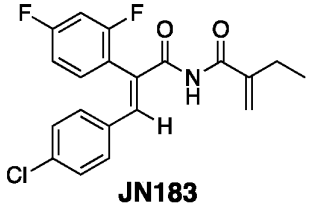
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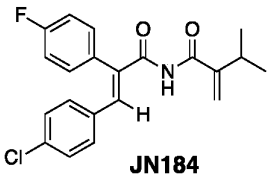
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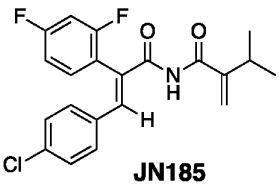
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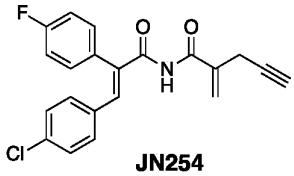
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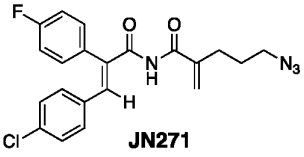
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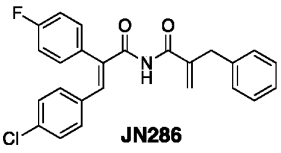
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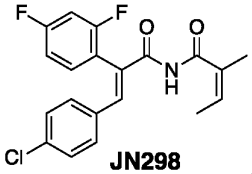
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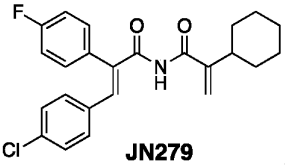
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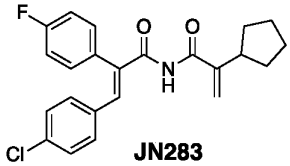
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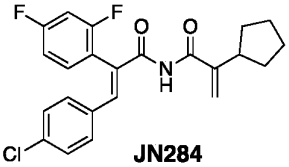
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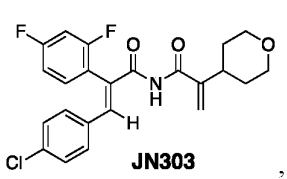
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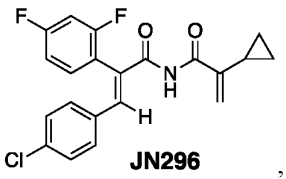
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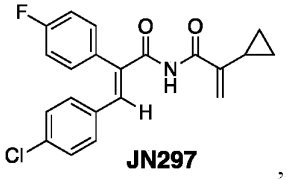
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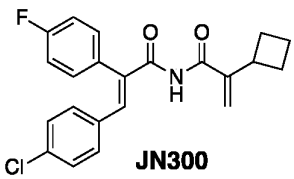
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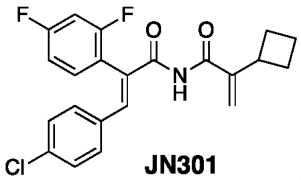
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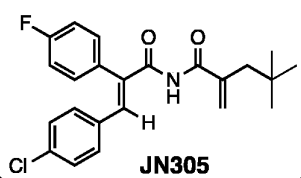
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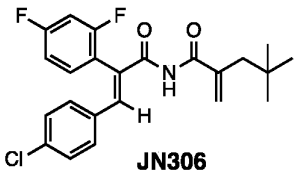
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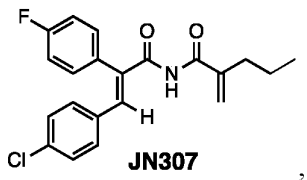
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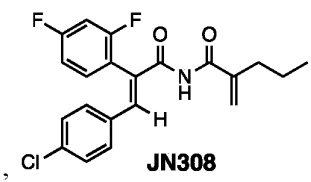
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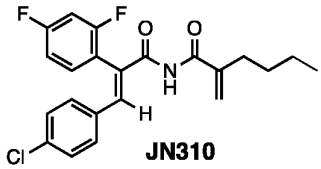
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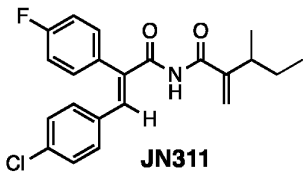
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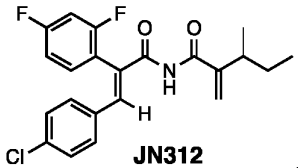
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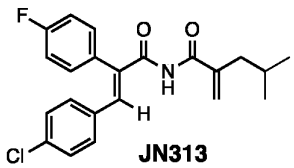
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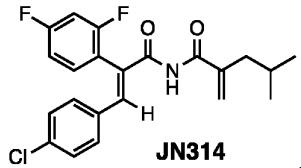
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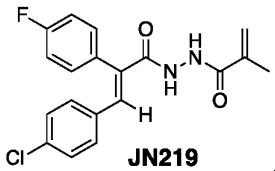
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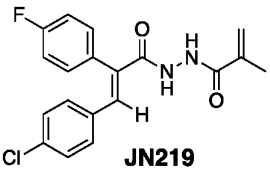
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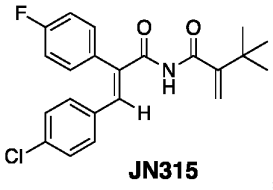
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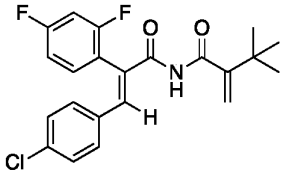
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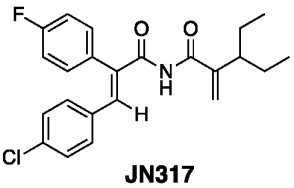
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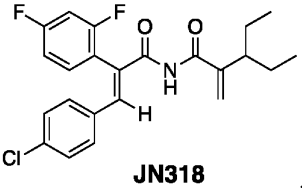
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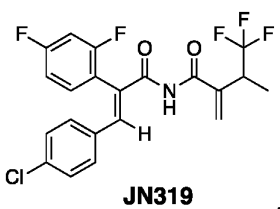
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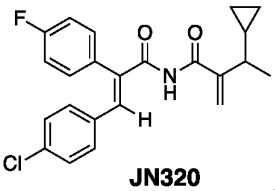
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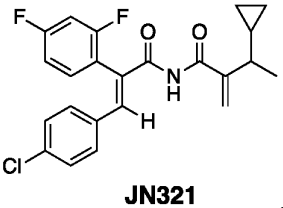
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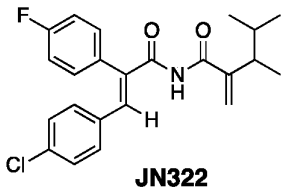
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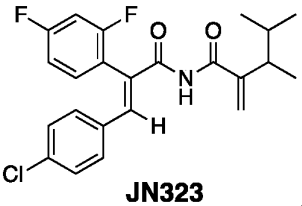
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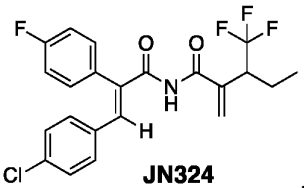
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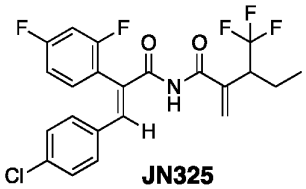
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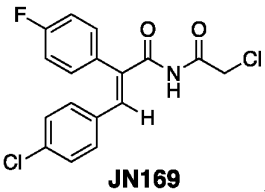
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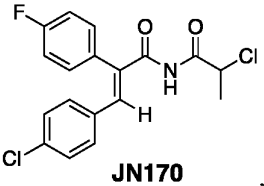
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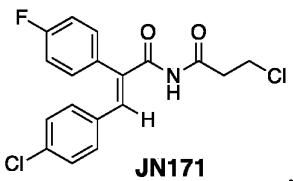
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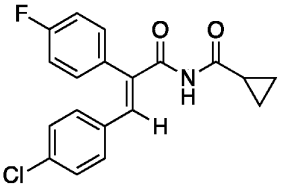
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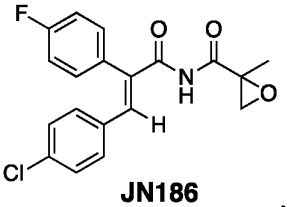
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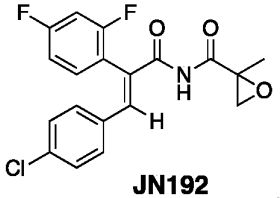
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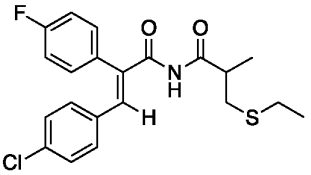
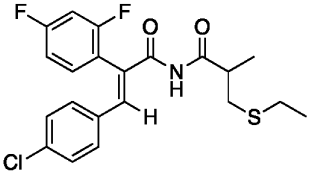

JN328 , and


JN329 .

The compounds disclosed herein are believed to AR degraders that directly target the TAD. By targeting the AR and its splice variants, these compounds offer the promise of overcoming AR-dependent castration resistance irrespective of the underlying molecular mechanism(s), including but not limited to the expression of constitutively active ARSVs that lack a functional C-terminal LBD.

In certain aspects, the present disclosure comprises a compound of the disclosure and a pharmaceutically acceptable excipient.

EXAMPLES

The invention now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

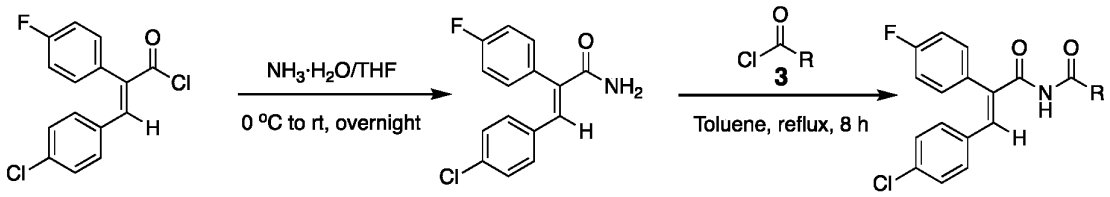
Chemistry

General Materials and Methods

All solvents and reagents were purchased from commercial sources and used without further purification unless otherwise noted. Dichloromethane (calcium hydride), diethyl ether (sodium), and tetrahydrofuran (sodium) used for the reactions were dried by distillation over the indicated drying agents. All reactions were performed under an inert atmosphere of dry argon and monitored by thin layer chromatography (TLC) on pre-coated EMD silica gel 60 F_{254} TLC aluminum sheets and visualized with a UV lamp. Flash column chromatography was performed on SiliaFlash P60 (SiliCycle Inc.) silica gel (40−63 μm, 60 Å pore size). Preparative scale thin layer chromatography was performed on glass-backed 20 × 20 cm (1500 μm thickness) preparative TLC plates (Analtech, Z513040). NMR spectra were obtained on a Bruker AV500 instrument at the UCLA MIC Magnetic Resonance Laboratory. NMR data were analyzed using the MestReNova NMR software (Mestrelab Research S. L., version 11.0.2). Chemical shifts (δ) are expressed in ppm and are internally referenced for ^{1}H NMR ($CHCl_3$ 7.26 ppm, DMSO-d_6 2.50 ppm) and ^{13}C NMR ($CDCl_3$ 77.16 ppm, DMSO-d_6 39.52 ppm). DART-MS spectra were collected on a Thermo Exactive Plus MSD (Thermo Scientific) equipped with an ID-CUBE ion source and a Vapur Interface (IonSense). Both the source and MSD were controlled by Excalibur, version 3.0. The analyte was spotted onto OpenSpot sampling cards (IonSense) using dichloromethane or chloroform as the solvent. Ionization was accomplished using He plasma with no additional ionization agents. Melting points were recorded on a Büchi® B-545 melting point apparatus. Analytical HPLC was performed on a 2.0 × 50 mm Waters Corp. 1.5 μm C_{18} analytical HPLC column. A linear gradient of mobile phase was used over 5 min from 5 – 95% MeCN/water containing 0.2% HCOOH. The flow rate was 0.4 mL/min and the peaks were detected by a LCT-Premier ESI-TOF mass spectrometer in the positive ion mode.

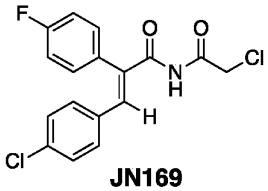
Example 1: Chemical Synthesis

Preparation of Imides JN169 to JN171.



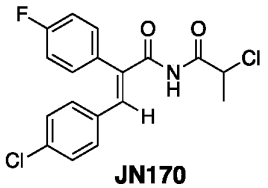
The acid chloride **1** (1 eq) was dissolved in THF (100 mL) and the resulting solution was cooled to 0 °C. Aqueous ammonia ($NH_3 \cdot H_2O$, 40.0 mL, 28-30%) was added slowly under vigorous stirring. The mixture was warmed to room temperature and stirred overnight. The solvent was removed, water (50 mL) was added and the resulting mixture was extracted with ethyl acetate (50 mL x 3). Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford the amide **2** as a white solid. The crude material was used for next step without purification.

The amide **2** (1 eq) was dissolved in dry toluene (30 mL) and the substituted acyl chloride **3** was added. The mixture was heated up to reflux and stirred for 8 h under Ar. The solvent was removed, the crude residue was purified by column chromatography on silica gel (eluent: hexanes: ethyl acetate = 1:8) to yield the desired product **3** as a white solid.



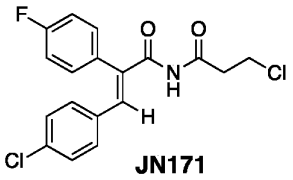
JN169

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.89 (s, 1H), 7.27 – 7.20 (m, 4H), 7.20 – 7.14 (m, 2H), 6.96 – 6.89 (m, 2H), 4.64 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.87, 164.98, 163.49 (d, J = 252.5 Hz), 141.18, 136.29, 132.27, 132.20, 132.10, 131.88 (d, J = 8.1 Hz), 129.76 (d, J = 4.0 Hz), 129.03, 117.88 (d, J = 21.2 Hz), 45.28.



JN170

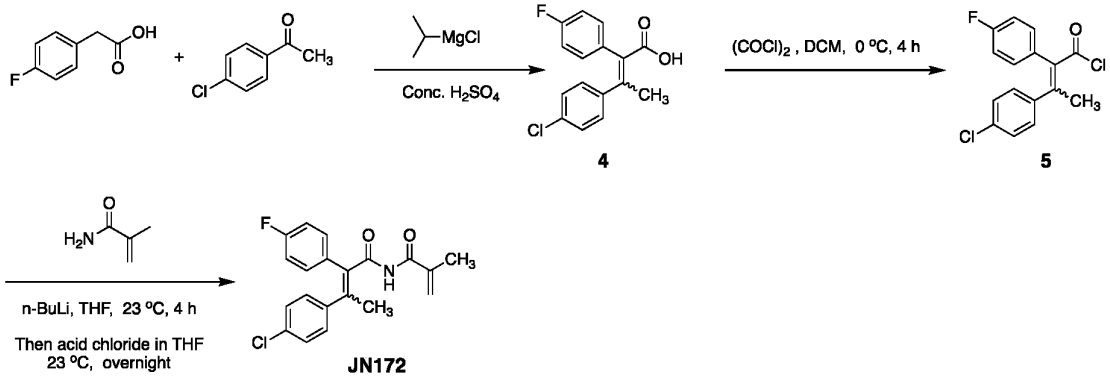
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.91 (s, 1H), 7.33 – 7.20 (m, 4H), 7.20 – 7.14 (m, 2H), 6.99 – 6.91 (m, 2H), 4.99 (q, J = 6.9 Hz, 1H), 1.68 (d, J = 6.9 Hz, 3H).



JN171

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.86 (s, 1H), 7.28 – 7.10 (m, 6H), 6.97 – 6.89 (m, 2H), 3.44 (t, J = 6.4 Hz, 2H), 3.11 (t, J = 6.4 Hz, 2H).

Preparation of Imide JN172.



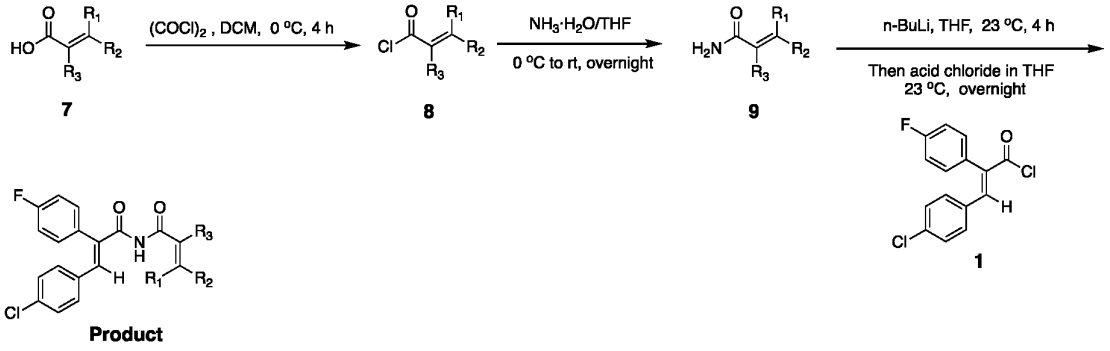
A solution of 4-fluorophenylacetic acid (1 eq) in dry tetrahydrofuran (THF, 50 mL) was added to the solution of isopropylmagnesium chloride in THF (2 eq, 2 M) at room temperature. The resulting thick suspension was stirred at 40 °C for 1 h, treated with ketone (1.5 eq) at 25 °C and stirred at 40 °C for another hour. Addition of a 14.2% aqueous solution of sulfuric acid (50 mL) with ice cooling, extraction of the aqueous phase with ethyl acetate and evaporation of the organic phase afforded crude hydroxyacid as a dark oil. To a solution of the hydroxyacid in dichloromethane (50 mL) was added with stirring sulfuric acid (20 mL) at room temperature. The dichloromethane was evaporated, the yellow solution was stirred for 45 min at room temperature and then poured into ice water. The precipitate was filtered off, washed with water, and dried to yield the desired product **4**, which was used without any further purification.

The acrylic acid **4** was suspended in dichloromethane (100 mL) and the flask cooled to 0 °C. To this was added oxalyl chloride (1.2 eq) followed by anhydrous DMF (1.0 mL, slowly),

and the solution left to stir at 0 °C for 4 h. Then the volatiles were removed in vacuo to yield the crude acid chloride **5** as a dark liquid, which was used without any further purification.

In a flask cooled in a Dry Ice-acetone bath, *n*-BuLi (2.50 M solution in hexanes, 0.95 eq) was added to a suspension of methacrylamide (0.95 eq) in THF (75 mL), and stirring continued for further 4 h at 23 °C. Then the acid chloride **5** (1.0 eq) was slowly added to the flask as a solution in THF (50 mL). The resultant mixture was stirred overnight at 23 °C, and then partitioned between ethyl acetate(150 mL) and saturated NH_4Cl (150 mL). The organic layer was separated and washed sequentially with saturated $NaHCO_3$ (150 mL) and brine (150 mL). Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. the crude residue was purified by column chromatography on silica gel (eluent: hexanes : ethyl acetate = 1:8) to yield the desired product **JN172** as a brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.19 – 7.11 (m, 2H), 7.11 – 7.03 (m, 2H), 7.02 – 6.95 (m, 2H), 6.90 – 6.80 (m, 2H), 5.64 (q, J = 0.9 Hz, 1H), 5.55 (q, J = 1.6 Hz, 1H), 2.25 (s, 3H), 1.92 (dd, J = 1.6, 0.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.19, 165.23, 162.20 (d, J = 249.5 Hz), 140.18, 139.74, 139.66, 133.36, 133.17, 132.07 (d, J = 8.1 Hz), 131.76 (d, J = 3.0 Hz), 130.11, 128.52, 122.85, 115.51 (d, J = 21.2 Hz), 22.70, 18.42.

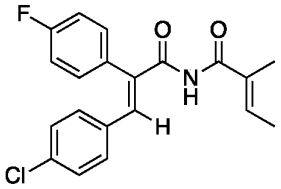
Preparation of Imides JN174 to JN181.



The substituted acrylic acid **7** (1.0 eq) was suspended in dichloromethane (100 mL) and the flask cooled to 0 °C. To this was added oxalyl chloride (1.2 eq) followed by anhydrous DMF (1.0 mL, slowly), and the solution left to stir at 0 °C for 4 h. Then the volatiles were removed in vacuo to yield the crude acid chloride **8** as a light yellow liquid. It was used in the next step without any further purification.

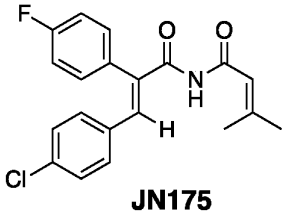
The material **8** was dissolved in THF (100 mL) and the resulting solution was cooled to 0 °C. Aqueous ammonia ($NH_3 \cdot H_2O$, 40.0 mL, 28-30%) was added slowly under vigorous stirring. The mixture was warmed to room temperature and stirred overnight. The solvent was removed, water (50 mL) was added and the resulting mixture was extracted with ethyl acetate (50 mL x 3). Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford the amide **9** as a white solid. The crude material was used for next step without purification.

In a flask cooled in a Dry Ice-acetone bath, *n*-BuLi (2.50 M solution in hexanes, 0.95 eq) was added to a suspension of amide **9** (0.95 eq) in THF (75 mL), and stirring continued for further 4 h at 23 °C. Then the acid chloride **1** (1.0 eq) was slowly added to the flask as a solution in THF (50 mL). The resultant mixture was stirred overnight at 23 °C, and then partitioned between ethyl acetate(150 mL) and saturated NH_4Cl (150 mL). The organic layer was separated and washed sequentially with saturated $NaHCO_3$ (150 mL) and brine (150 mL). Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel using a mobile phase gradient of 0-20% ethyl acetate/hexanes, followed by a gradient of 15-20% ethyl acetate/hexanes containing 2% triethylamine additive. The isolated pale-yellow solid was then further purified by recrystallization in dichloromethane/hexanes to yield the desired product as a white solid.



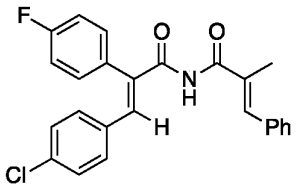
JN174

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.84 (s, 1H), 7.36 - 7.18 (m, 4H), 7.18 - 7.10 (m, 2H), 7.01 - 6.88 (m, 2H), 6.21 (qq, *J* = 6.9, 1.2 Hz, 1H), 1.71 (dq, *J* = 6.9, 1.2 Hz, 3H), 1.66 (dq, *J* = 1.2, 1.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.69, 164.43, 163.26 (d, *J* = 251.5 Hz), 139.64, 135.71, 134.99, 133.56, 132.72, 132.28, 131.92, 131.91 (d, *J* = 8.1 Hz), 130.88 (d, *J* = 4.0 Hz), 128.91, 117.57 (d, *J* = 22.2 Hz), 14.56, 12.14.



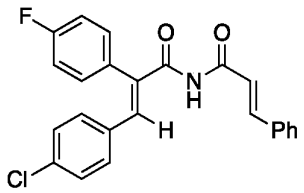
JN175

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.56 (s, 1H), 7.25 – 7.10 (m, 6H), 6.97 – 6.84 (m, 2H), 6.78 (qq, *J* = 1.3, 1.3 Hz, 1H), 2.15 (d, *J* = 1.3 Hz, 3H), 1.99 (d, *J* = 1.3 Hz, 3H).



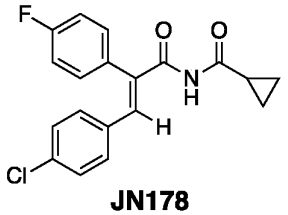
JN176

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.90 (s, 1H), 7.44 – 7.29 (m, 5H), 7.29 – 7.21 (m, 4H), 7.19 – 7.13 (m, 2H), 7.06 (d, *J* = 1.4 Hz, 1H), 7.01 – 6.92 (m, 2H), 1.94 (d, *J* = 1.4 Hz, 3H).



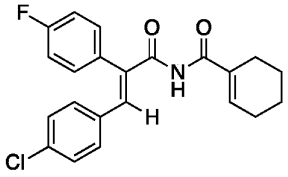
JN177

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.83 (m, 2H), 7.80 – 7.75 (m, 1H), 7.66 – 7.60 (m, 2H), 7.44 – 7.38 (m, 3H), 7.30 – 7.21 (m, 4H), 7.19 – 7.15 (m, 2H), 6.97 – 6.90 (m, 2H).



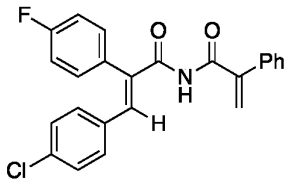
JN178

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.75 (s, 1H), 7.26 – 7.12 (m, 6H), 6.99 – 6.85 (m, 2H), 3.03 (tt, *J* = 7.9, 4.6 Hz, 1H), 1.19 – 1.12 (m, 2H), 1.06 – 0.99 (m, 2H).



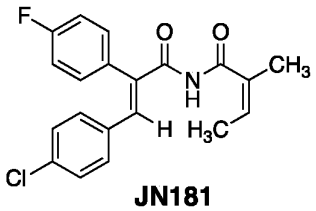
JN179

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.86 (s, 1H), 7.33 – 7.19 (m, 4H), 7.19 – 7.12 (m, 2H), 6.99 – 6.90 (m, 2H), 6.40 – 6.36 (m, 1H), 2.14 – 2.08 (m, 2H), 2.05 – 1.96 (m, 2H), 1.64 – 1.49 (m, 4H).



JN180

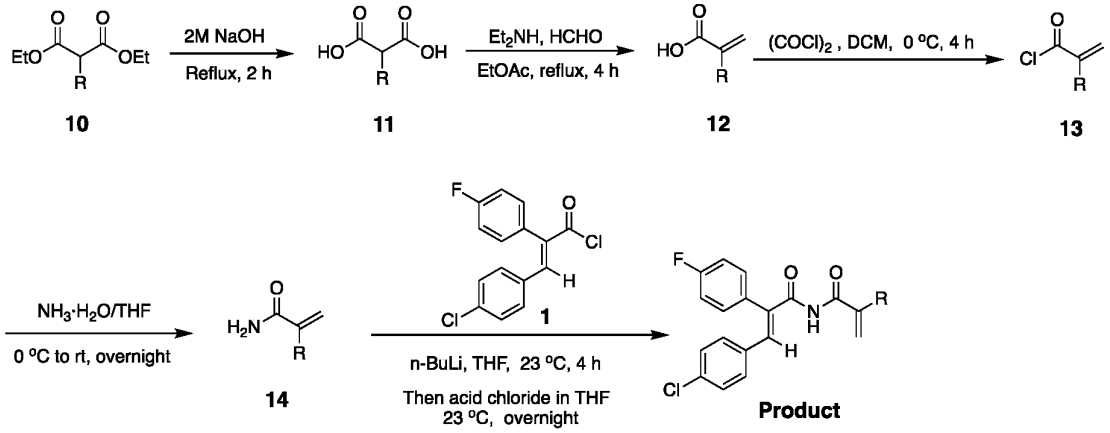
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.83 (s, 1H), 7.38 – 7.29 (m, 1H), 7.23 (t, *J* = 7.7 Hz, 2H), 7.16 – 7.08 (m, 2H), 7.05 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.00 – 6.90 (m, 4H), 6.89 – 6.82 (m, 2H), 6.40 – 6.24 (m, 1H), 5.64 (d, *J* = 1.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.42, 164.00, 163.03 (d, *J* = 250.5 Hz), 144.07, 140.20, 135.84, 135.64, 133.08, 132.56, 131.97, 131.28 (d, *J* = 8.1 Hz), 130.04 (d, *J* = 4.0 Hz), 129.19, 128.94, 128.88, 128.07, 126.97, 117.54 (d, *J* = 22.2 Hz).



JN181

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), δ 7.86 (s, 1H), 7.29 – 7.18 (m, 4H), 7.18 – 7.12 (m, 2H), 6.98 – 6.88 (m, 2H), 5.71 (qq, *J* = 7.2, 1.6 Hz, 1H), 1.81 (dq, *J* = 1.6, 1.6 Hz, 3H), 1.69 (dq, *J* = 7.2, 1.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.55, 164.11, 163.35 (d, *J* = 251.5 Hz), 140.17, 135.89, 133.13, 132.61, 131.98, 131.89 (d, *J* = 8.1 Hz), 131.82, 130.80, 130.49 (d, *J* = 4.0 Hz), 128.95, 117.68 (d, *J* = 22.2 Hz), 20.02, 15.28.

Preparation of Imides JN182 to JN185.



A solution of 2 M NaOH (40 mL) was added to the substituted malonate **10** (5 g) at room temperature. The resulting mixture was refluxed in an oil bath for 2 h. Then the resulting solution was cooled to room temperature, extracted with hexane and the aqueous layer was acidified to pH 1 with concentrated HCl. The resulting solution was extracted with ethyl acetate (20 mL x 3), the organic phase was dried over anhydrous $MgSO_4$ and the solvent removed by evaporation to afford the corresponding diacid **11**, which was used without further purification in the next step.

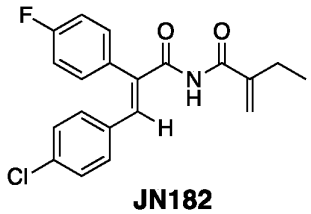
Diethylamine (1.1 eq) was added dropwise to a solution of the crude diacid **11** in ethyl acetate(100 mL) at 0 °C, with subsequent addition of paraformaldehyde (1.5 eq). The resulting suspension was refluxed in an oil bath for 2 h. Then the resulting solution was cooled to room temperature and quenched with H_2O, then acidified to pH to 1with concentrated HCl. The aqueous layer was then extracted with ethyl acetate (50mL x 3),the organic phase was dried over anhydrous $MgSO_4$ and the solvent removed by evaporation to afford the corresponding acrylic acid **12**. The resulting crude acrylic acid **12** was used without further purification in the next step.

The acrylic acid **12** was suspended in dichloromethane (100 mL) and the flask cooled to 0 °C. To this was added oxalyl chloride (1.2 eq) followed by anhydrous DMF (1.0 mL, slowly), and the solution left to stir at 0 °C for 4 h. Then the volatiles were removed in vacuo to yield the crude acid chloride **13** as a light yellow liquid. This was used for next step without purification.

The residue was dissolved in THF (100 mL) and the resulting solution was cooled to 0 °C. Aqueous ammonia ($NH_3·H_2O$, 40.0 mL, 28-30%) was added slowly with vigorous stirring. The mixture was warmed to room temperature and stirred overnight. The solvent was removed,

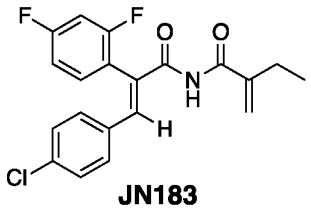
water (50 mL) was added and the resulting mixture was extracted with ethyl acetate (50 mL x 3). Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford the amide **14** as a white solid. The crude material was used for next step without purification.

In a flask cooled in a Dry Ice-acetone bath, *n*-BuLi (2.50 M solution in hexanes, 0.95 eq) was added to a suspension of amide **14** (0.95 eq) in THF (75 mL), and stirring continued for further 4 h at 23 °C. Then the acid chloride **1** (1.0 eq) was slowly added to the flask as a solution in THF (50 mL). The resultant mixture was stirred overnight at 23 °C, and then partitioned between ethyl acetate (150 mL) and saturated NH_4Cl (150 mL). The organic layer was separated and washed sequentially with saturated $NaHCO_3$ (150 mL) and brine (150 mL). Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel using a mobile phase gradient of 0-20% ethyl acetate/hexanes, followed by a gradient of 15-20% ethyl acetate/hexanes containing 2% triethylamine additive. The isolated pale-yellow solid was then further purified by recrystallization in dichloromethane/hexanes to yield the desired product as a white solid.



JN182

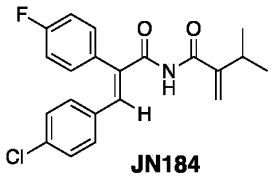
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.79 (s, 1H), 7.26 – 7.10 (m, 4H), 7.10 – 7.04 (m, 2H), 6.90 – 6.81 (m, 2H), 5.25 (d, *J* = 1.7 Hz, 1H), 5.19 (s, 1H), 2.13 (q, *J* = 7.4 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.02, 164.22, 163.30 (d, *J* = 251.5 Hz), 146.47, 140.02, 135.83, 133.29, 132.63, 131.97, 131.88 (d, *J* = 8.1 Hz), 130.77 (d, *J* = 4.0 Hz), 128.94, 119.45, 117.69 (d, *J* = 22.2 Hz), 24.86, 12.43.



JN183

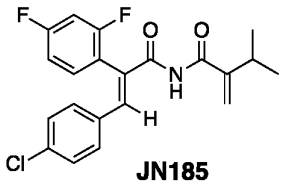
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.88 (s, 1H), 7.26 – 7.09 (m, 3H), 7.03 – 6.88 (m, 4H), 5.39 – 5.25 (m, 2H), 2.28 – 2.13 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.66, 164.08, 163.97 (dd, *J* = 254.5, 12.1 Hz), 160.42 (dd, *J* = 254.5, 14.1 Hz),

146.53, 142.06, 136.14, 133.02 (dd, J = 9.1, 4.0 Hz), 132.53, 131.43, 129.11, 127.47, 119.49, 118.38 (dd, J = 16.2, 4.0 Hz), 113.43 (dd, J = 21.2, 4.0 Hz), 105.76 (t, J = 25.8 Hz), 24.96, 12.39.



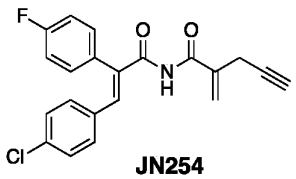
JN184

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.75 (s, 1H), 7.21 – 7.14 (m, 2H), 7.14 – 7.08 (m, 2H), 7.07 – 7.02 (m, 2H), 6.90 – 6.74 (m, 2H), 5.17 (d, J = 1.4 Hz, 1H), 5.07 (s, 1H), 2.60 (heptet, d, J = 6.8, 1.4 Hz, 1H), 0.90 (d, J = 6.8 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.83, 164.38, 163.30 (d, J = 251.5 Hz), 151.80, 139.97, 135.81, 133.36, 132.66, 131.95, 131.87 (d, J = 9.1 Hz), 130.74 (d, J = 4.0 Hz), 128.94, 117.65 (d, J = 21.2 Hz), 116.96, 29.69, 21.50.



JN185

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.92 (s, 1H), 7.25 – 7.17 (m, 3H), 7.07 – 6.95 (m, 4H), 5.34 (d, J = 1.5 Hz, 1H), 5.31 (s, 1H), 2.82 – 2.66 (m, 1H), 1.04 (d, J = 6.8 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.53, 164.28, 163.97 (dd, J = 255.5, 12.1 Hz), 160.46 (dd, J = 253.5, 12.1 Hz), 151.81, 141.95, 136.12, 133.04 (dd, J = 9.1, 4.0 Hz), 132.56, 131.41, 129.10, 127.62, 118.38 (dd, J = 16.2, 4.0 Hz), 117.03, 113.37 (dd, J = 21.2, 4.0 Hz), 105.71(t, J = 25.3 Hz), 29.84, 21.45.

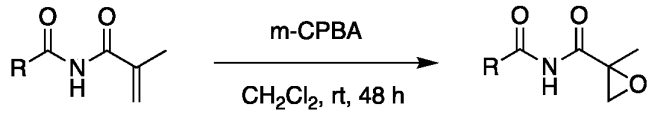


JN254

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.83 (s, 1H), 7.28 – 7.23 (m, 2H), 7.22 – 7.15 (m, 2H), 7.15 – 7.09 (m, 2H), 6.92 – 6.86 (m, 2H), 5.80 (td, J = 1.9, 0.7 Hz, 1H), 5.32 (td, J = 1.3, 1.3 Hz, 1H), 3.17 (dt, J = 2.8, 1.6 Hz, 2H), 2.11 (t, J = 2.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.53, 164.13, 163.37 (d, J = 251.5 Hz), 140.34, 139.52, 135.96, 133.10, 132.57,

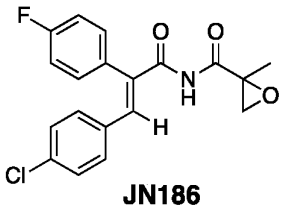
132.00, 131.94 (d, J = 8.1 Hz), 130.64 (d, J = 4.0 Hz), 128.99, 121.96, 117.77 (d, J = 22.2 Hz), 79.41, 72.90, 21.63.

Preparation of Imides JN186, JN192 and JN209.



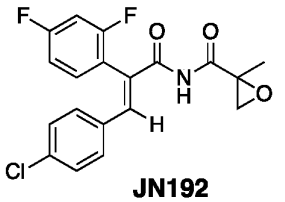
15 **Product**

m-CPBA (2 eq) was added to a solution of compound **15** (1 eq) in dichloromethane (30 ml) at 0 °C. The reaction mixture was stirred at room temperature for 48 h. The reaction mixture was quenched with water, extracted with dichloromethane, washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude desired product, which was purified by column chromatography (eluent: hexanes:ethyl acetate = 1:8) to obtain the desired product as a white solid.



JN186

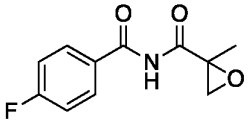
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.84 (s, 1H), 7.22 (d, J = 6.8 Hz, 4H), 7.19 – 7.13 (m, 2H), 6.97 – 6.91 (m, 2H), 2.77 (d, J = 4.7 Hz, 1H), 2.61 (d, J = 4.7 Hz, 1H), 1.53 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.74, 164.13, 163.35 (d, J = 251.5 Hz), 140.35, 135.97, 133.22, 132.56, 132.04, 131.66 (d, J = 8.1 Hz), 130.41 (d, J = 3.0 Hz), 128.97, 117.66 (d, J = 22.2 Hz), 56.59, 53.54, 16.36.



JN192

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.92 (s, 1H), 7.22 – 7.12 (m, 3H), 7.09 – 6.89 (m, 4H), 2.82 (d, J = 4.7 Hz, 1H), 2.72 (d, J = 4.7 Hz, 1H), 1.55 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.64, 164.04 (dd, J = 255.5, 12.1 Hz), 163.38, 160.35 (dd, J = 252.5, 12.1 Hz),

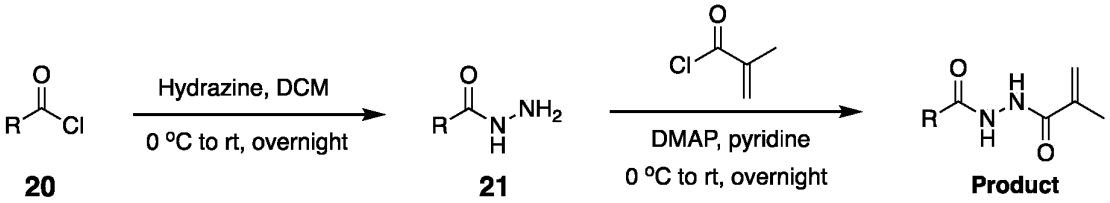
142.40, 136.25, 132.86 (dd, J = 10.1, 4.0 Hz), 132.39, 131.51, 129.11, 127.25, 118.00 (dd, J = 17.2, 4.0 Hz), 113.51 (dd, J = 21.2, 3.0 Hz), 105.70 (t, J = 25.3 Hz), 56.65, 53.59, 16.31.



JN209

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 7.90 – 7.72 (m, 2H), 7.21 – 7.08 (m, 2H), 3.04 (d, J = 4.6 Hz, 1H), 3.00 (d, J = 4.6 Hz, 1H), 1.67 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.93, 165.93 (d, J = 256.5 Hz), 163.90, 130.61 (d, J = 9.1 Hz), 129.14 (d, J = 3.0 Hz), 116.32 (d, J = 22.2 Hz), 57.04, 53.84, 16.58.

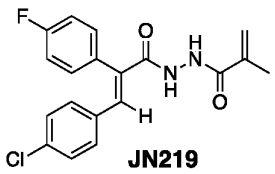
Preparation of Diacylhydrazide JN219



20 **21** **Product**

The acyl chloride **20** (1 eq) was dissolved in dichloromethane (15 mL) and the mixture was cooled to 0°C. Hydrazine hydrate 99% (2 mL) was added slowly. The resulting solution was stirred at 23 °C for 12ch. The crude solution was diluted with 20 mL of dichloromethane and washed with a solution of NaOH 10% (15mL). The organic phase was concentrated under reduce pressure to afford the acyl hydrazide **21**.

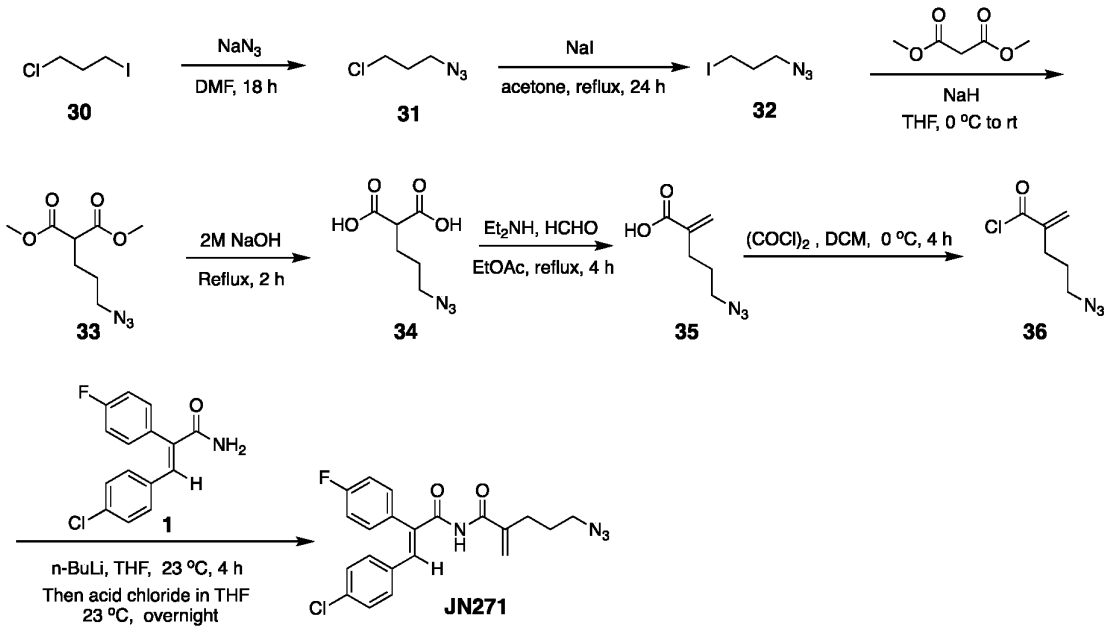
Methacryloyl chloride (1.1 eq) in dichloromethane (20 mL) was added dropwise to a dried round bottom flask containing the substituted acyl hydrazide **21** (1 eq), pyridine (2.0 mL) and *N*,*N*-dimethyl-4-aminopyridine (DMAP; 120 mg) in dichloromethane (30 mL). The mixture was stirred at 23 °C for 6 h and then washed with dilute aqueous HCl (1M , 3 x 10 mL) and water (3 x 10 mL), and dried over sodium sulfate. filtered, and concentrated. Purification by silica gel column chromatography gave the desired products.



JN219

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.39 (s, 1H), 7.78 (s, 1H), 7.34 – 7.24 (m, 2H), 7.23 – 7.10 (m, 4H), 7.01 – 6.85 (m, 2H), 5.87 (q, J = 1.0 Hz, 1H), 5.46 (dq, J = 2.2, 1.0 Hz, 1H), 1.98 (app t, J = 1.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.35, 163.31 (d, J = 250.5 Hz), 163.04, 137.97, 136.84, 135.40, 132.84, 131.89 (d, J = 8.1 Hz), 131.77, 131.42, 130.03 (d, J = 4.0 Hz), 128.86, 122.36, 117.38 (d, J = 21.2 Hz), 18.25.

Preparation of Azidopropyl Imide JN271.



Sodium azide (1 eq) was added to a solution of 1-iodo-3-chloropropane **30** (1 eq) in DMF (20 mL) at room temperature. The resulting mixture was stirred for 18 h and then extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with water (3 x 10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford the azidochloride **31** as a colorless oil. The crude material was approximately 90% pure by NMR and was used without further purification.

A mixture of the azidochloride **31** (1 eq) and sodium iodide (2 eq) in acetone (30 mL) was heated at reflux for 18 h. The reaction was cooled to room temperature, saturated aqueous $Na_2S_2O_3$ (10 mL) was added and the mixture extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification via flash chromatography (hexanes : diethyl ether = 99:1) afforded the azidoiodide **32** as a pale yellow oil. It was used in the next step without further purification.

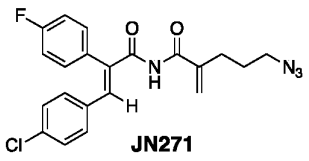
To a solution of dimethyl malonate (1 eq) in THF (30.0 ml) was slowly added NaH (60% in mineral oil, 1 eq) at 0 °C. After vigorous evolution of hydrogen gas, the reaction mixture was treated with azidoiodide **32** (2 eq) and warmed to room temperature. After stirring for 12 h, the reaction mixture was quenched by careful addition of H_2O, extracted with ethyl acetate, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography provided compound **33** as a light yellow oil. It was used in the next step without further purification.

2 M NaOH (40 mL) was added to compound **33** at room temperature. The resulting mixture was refluxed in an oil bath for 2 h. Then the resulting solution was cooled to room temperature, extracted with hexane and the aqueous layer was acidified to pH 1 with concentrated HCl. The resulting solution was extracted with ethyl acetate (20 mL x 3), the organic phase was dried over anhydrous $MgSO_4$ and the solvent removed by evaporation to afford the corresponding diacid **34** which was used without further purification in the next step.

Diethylamine (1.1 eq) was added dropwise to a solution of the crude diacid **34** in ethyl acetate (100 mL) at 0 °C, with subsequent addition of paraformaldehyde (1.5 eq). The resulting suspension was refluxed in an oil bath for 2 h. Then the resulting solution was cooled to room temperature and quenched with H_2O, and acidified to pH to 1with concentrated HCl. The aqueous layer was then extracted with ethyl acetate (50mL x 3), the organic phase was dried over anhydrous $MgSO_4$ and the solvent removed by evaporation to afford the acrylic acid **35**. The crude acrylic acid **35** was used without further purification in the next step.

The acrylic acid **35** was suspended in dichloromethane (100 mL) and the flask cooled to 0 °C. To this was added oxalyl chloride (1.2 eq) followed by anhydrous DMF (1.0 mL, slowly), and the solution left to stir at 0 °C for 4 h. Then the volatiles were removed in vacuo to yield the crude acid chloride **36** as a light yellow liquid. The crude acid chloride **36** was used without further purification in the next step.

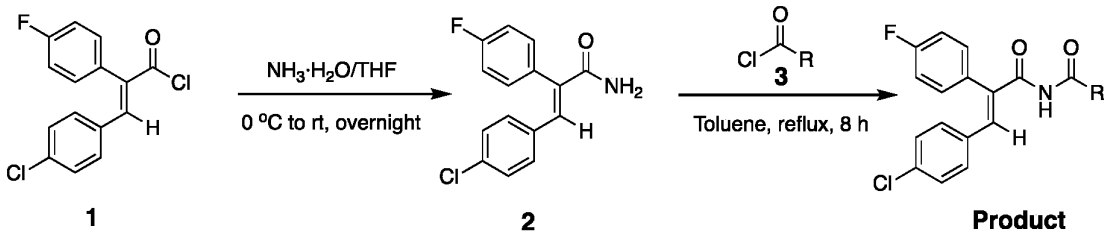
In a flask cooled in a Dry Ice-acetone bath, *n*-BuLi (2.50 M solution in hexanes, 0.95 eq) was added to a suspension of amide **1** (0.95 eq) in THF (75 mL), and stirring continued for further 4 h at 23 °C. Then the acid chloride **36** (1.0 eq) was slowly added to the flask as a solution in THF (50 mL). The resultant mixture was stirred overnight at 23 °C, and then partitioned between ethyl acetate (150 mL) and saturated NH_4Cl (150 mL). The organic layer was separated and washed sequentially with saturated $NaHCO_3$ (150 mL) and brine (1500 mL). Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel using a mobile phase gradient of 0-20% ethyl acetate/hexanes, followed by a gradient of 15-20% ethyl acetate/hexanes containing 2% triethylamine additive to yield **JN271** as a yellow solid.



JN271

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.86 (s, 1H), 7.32 – 7.27 (m, 2H), 7.26 – 7.22 (m, 2H), 7.18 – 7.14 (m, 2H), 6.97 – 6.92 (m, 2H), 5.40 (d, *J* = 1.4 Hz, 1H), 5.26 (s, 1H), 3.26 (t, *J* = 6.7 Hz, 2H), 2.33 (td, *J* = 7.5, 1.2 Hz, 2H), 1.78 – 1.66 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.96, 164.33 (d, *J* = 252.5 Hz), 164.30, 144.00, 140.15, 135.91, 133.19, 132.58, 131.97, 131.88 (d, *J* = 8.1 Hz), 130.69 (d, *J* = 4.0 Hz), 128.96, 120.82, 117.71 (d, *J* = 21.2 Hz), 50.83, 29.41, 27.54, .

Preparation of Imides JN286.

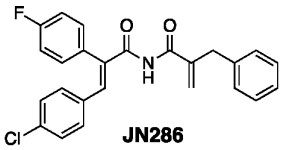


1 **2** **Product**

The acid chloride **1** (1 eq) was dissolved in THF (100 mL) and the resulting solution was cooled to 0 °C. Aqueous ammonia ($NH_3 \cdot H_2O$, 40.0 mL, 28-30%) was added slowly under vigorous stirring. The mixture was warmed to room temperature and stirred overnight. The

solvent was removed, water (50 mL) was added and the resulting mixture was extracted with ethyl acetate (50 mL x 3). Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford the amide **2** as a white solid. The crude material was used for next step without purification.

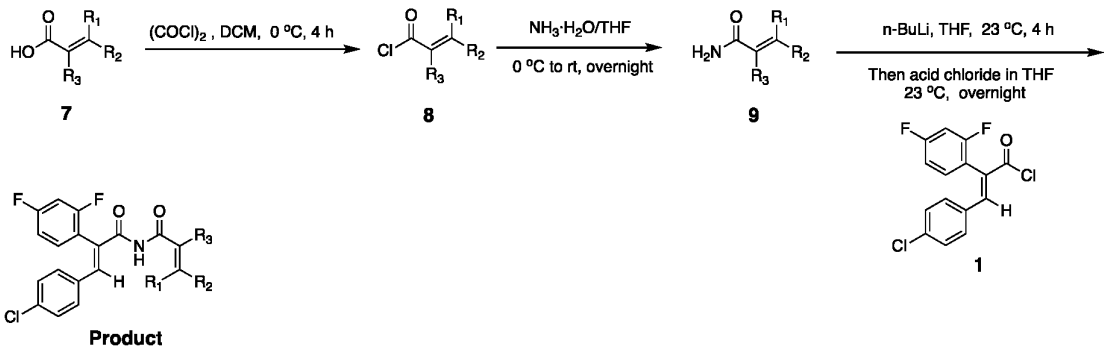
To a suspension of amide **2** (0.95 eq) in tetrahydrofuran (75 mL) in a flask cooled in a Dry Ice-acetone bath, was added *n*-BuLi (2.50 M solution in hexanes, 0.95 eq), and stirring continued for further 4 h at 23 °C. Then the acid chloride **3**(1.0 eq) was slowly added to the flask as a solution in tetrahydrofuran (50 mL). The resultant mixture was stirred overnight at 23 °C, and then partitioned between ethyl acetate (150 mL) and saturated NH_4Cl (150 mL). The organic layer was separated and washed sequentially with saturated $NaHCO_3$ (150 mL) and brine (150 mL). Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel using a mobile phase gradient of 0-20%. ethyl acetate/hexanes, followed by a gradient of 15-20% ethyl acetate/hexanes containing 2% triethylamine additive. The isolated pale-yellow solid was then further purified by recrystallization from dichloromethane/hexanes to yield the desired product as a white solid.



JN286

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.80 (s, 1H), 7.29 – 7.24 (m, 2H), 7.23 – 7.17 (m, 4H), 7.17 – 7.12 (m, 3H), 7.11 – 7.05 (m, 2H), 6.93 – 6.88 (m, 2H), 5.43 (s, 1H), 5.29 (t, J = 1.5 Hz, 1H), 3.57 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.57, 164.31, 163.24 (d, J = 252.5 Hz), 144.15, 139.99, 137.55, 135.80, 133.32, 132.62, 131.92, 131.85 (d, J = 8.1 Hz), 130.53 (d, J = 4.0 Hz), 129.07, 128.91, 128.81, 126.90, 122.49, 117.58 (d, J = 21.2 Hz), 37.98.

Preparation of Imide JN298.

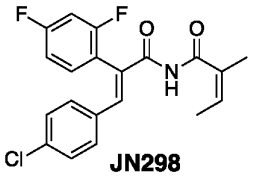


The substituted acrylic acid **7** (1.0 eq) was suspended in dichloromethane (100 mL) and the flask cooled to 0 °C. To this was added oxalyl chloride (1.2 eq) followed by anhydrous DMF (1.0 mL, slowly), and the solution left to stir at 0 °C for 4 h. Then the volatiles were removed in vacuo to yield the crude acid chloride **8** as a light yellow liquid. It was used in the next step without any further purification.

The acid chloride **8** was dissolved in THF (100 mL) and the resulting solution was cooled to 0 °C. Aqueous ammonia ($NH_3 \cdot H_2O$, 40.0 mL, 28-30%) was added slowly under vigorous stirring. The mixture was warmed to room temperature and stirred overnight. The solvent was removed, water (50 mL) was added and the resulting mixture was extracted with ethyl acetate (50 mL x 3). Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford the amide **9** as a white solid. The crude material was used for next step without purification.

In a flask cooled in a Dry Ice-acetone bath, *n*-BuLi (2.50 M solution in hexanes, 0.95 eq) was added to a suspension of amide **9** (0.95 eq) in THF (75 mL), and stirring continued for further 4 h at 23 °C. Then the acid chloride **1** (1.0 eq) was slowly added to the flask as a solution in THF (50 mL). The resultant mixture was stirred overnight at 23 °C, and then partitioned between ethyl acetate(150 mL) and saturated NH_4Cl (150 mL). The organic layer was separated and washed sequentially with saturated $NaHCO_3$ (150 mL) and brine (150 mL). Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel using a mobile phase gradient of 0-20% ethyl acetate/hexanes, followed by a gradient of 15-20% ethyl acetate/hexanes containing 2% triethylamine additive. The isolated pale-yellow solid was

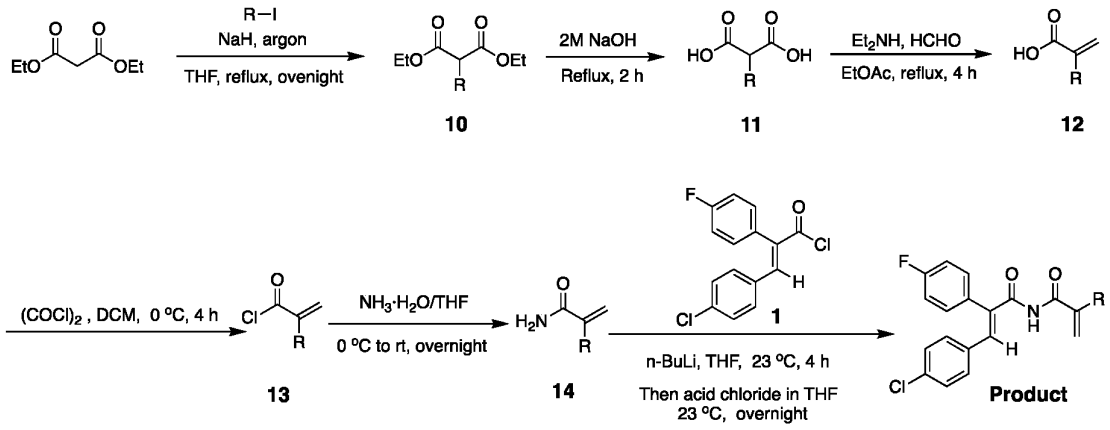
then further purified by recrystallization in dichloromethane/hexanes to yield the desired product as a white solid.



JN298

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.89 (s, 1H), 7.27 – 7.12 (m, 3H), 7.08 – 6.91 (m, 4H), 6.41 – 6.20 (m, 1H), 1.75 (bd, J = 6 Hz, 3H), 1.72 (bs, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.36, 164.35, 163.92 (dd, J = 254.5, 11.1 Hz), 160.44 (dd, J = 252.5, 12.1 Hz), 141.63, 136.01, 135.14, 133.05 (dd, J = 10.1, 4.0 Hz), 132.63, 132.39, 131.37, 129.07, 127.80, 118.53 (dd, J = 17.2, 4.0 Hz), 113.30 (dd, J = 21.2, 4.0 Hz), 105.66 (dd, J = 25.3, 25.3 Hz), 14.56, 12.28.

Preparation of Imides JN279, JN280, JN283, JN284, JN302, JN303.



To a stirred suspension of NaH (60% in mineral oil, 1 eq) in dry THF (70 mL) at room temperature, a solution of diethyl malonate (1 eq) in THF (10 mL)was added. The solution was stirred at room temperature for 1h,andthen a solution of alkyl iodide (1 eq) in THF (10 mL) was added dropwise. The reaction mixture was refluxed by oil bath for 24 h. Upon completion, the reaction was cooled to room temperature and quenched with saturated NH_4Cl (15mL), extracted with ethyl acetate (30 mL x 3).The organic phase was dried over anhydrous $MgSO_4$ and the solvent removed by evaporation. The resulting crude product was purified by flash

chromatography on silica gel (eluent: hexanes : ethyl acetate = 5:1) to give the substituted malonate **10** as a colorless oil.

A solution of 2 M NaOH (40 mL) was added to the substituted malonate **10** (5 g) at room temperature. The resulting mixture was refluxed in an oil bath for 2 h. Then the resulting solution was cooled to room temperature, extracted with hexane and the aqueous layer was acidified to pH 1 with concentrated HCl. The resulting solution was extracted with ethyl acetate (20 mL x 3), the organic phase was dried over anhydrous $MgSO_4$ and the solvent removed by evaporation to afford the corresponding diacid **11**, which was used without further purification in the next step.

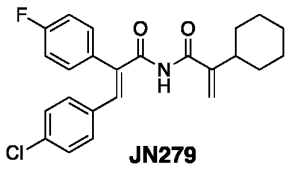
Diethylamine (1.1 eq) was added dropwise to a solution of the crude diacid **11** in ethyl acetate(100 mL) at 0 °C, with subsequent addition of paraformaldehyde (1.5 eq). The resulting suspension was refluxed in an oil bath for 2 h. Then the resulting solution was cooled to room temperature and quenched with H_2O, then acidified to pH to 1with concentrated HCl. The aqueous layer was then extracted with ethyl acetate (50mL x 3),the organic phase was dried over anhydrous $MgSO_4$ and the solvent removed by evaporation to afford the corresponding acrylic acid **12**. The resulting crude acrylic acid **12** was used without further purification in the next step.

The acrylic acid **12** was suspended in dichloromethane (100 mL) and the flask cooled to 0 °C. To this was added oxalyl chloride (1.2 eq) followed by anhydrous DMF (1.0 mL, slowly), and the solution left to stir at 0 °C for 4 h. Then the volatiles were removed in vacuo to yield the crude acid chloride **13** as a light yellow liquid. This was used for next step without purification.

The residue was dissolved in THF (100 mL) and the resulting solution was cooled to 0 °C. Aqueous ammonia ($NH_3 \cdot H_2O$, 40.0 mL, 28-30%) was added slowly with vigorous stirring. The mixture was warmed to room temperature and stirred overnight. The solvent was removed, water (50 mL) was added and the resulting mixture was extracted with ethyl acetate (50 mL x 3). Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford the amide **14** as a white solid. The crude material was used for next step without purification.

In a flask cooled in a Dry Ice-acetone bath, *n*-BuLi (2.50 M solution in hexanes, 0.95 eq) was added to a suspension of amide **14** (0.95 eq) in THF (75 mL), and stirring continued for further 4 h at 23 °C. Then the acid chloride **1** (1.0 eq) was slowly added to the flask as a solution in THF (50 mL). The resultant mixture was stirred overnight at 23 °C, and then partitioned between ethyl acetate (150 mL) and saturated NH_4Cl (150 mL). The organic layer

was separated and washed sequentially with saturated $NaHCO_3$ (150 mL) and brine (150 mL). Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel using a mobile phase gradient of 0-20% ethyl acetate/hexanes, followed by a gradient of 15-20% ethyl acetate/hexanes containing 2% triethylamine additive. The isolated pale-yellow solid was then further purified by recrystallization in dichloromethane/hexanes to yield the desired product as a white solid.



JN279

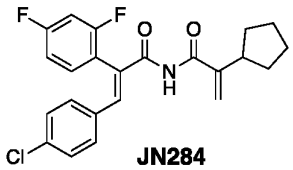
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.86 (s, 1H), 7.31 – 7.26 (m, 2H), 7.25 – 7.19 (m, 2H), 7.19 – 7.13 (m, 2H), 7.00 – 6.90 (m, 2H), 5.24 (d, J = 1.4 Hz, 1H), 5.23 (s, 1H), 2.29 (tt, J = 11.7, 3.3 Hz, 1H), 1.78 – 1.56 (m, 6H), 1.32 – 1.18 (m, 2H), 1.17 – 0.97 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.00, 164.42, 163.32 (d, J = 251.5 Hz), 150.87, 139.99, 135.83, 133.40, 132.68, 131.96, 131.88 (d, J = 8.1 Hz), 130.76 (d, J = 4.0 Hz), 128.95, 117.67 (d, J = 21.2 Hz), 117.49, 39.40, 32.19, 26.51, 26.17.

JN280

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.89 (s, 1H), 7.27 – 7.12 (m, 3H), 7.06 – 6.95 (m, 4H), 5.34 (s, 1H), 5.29 (d, J = 1.5 Hz, 1H), 2.33 (tt, J = 11.8, 3.0 Hz, 1H), 1.89 – 1.68 (m, 6H), 1.44 – 1.19 (m, 2H), 1.16 – 1.01 (m, 2H).

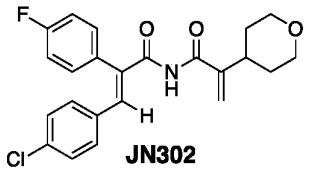
JN283

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.87 (s, 1H), 7.37 – 7.19 (m, 4H), 7.19 – 7.08 (m, 2H), 6.99 – 6.85 (m, 2H), 5.32 (d, J = 1.6 Hz, 1H), 5.30 (d, J = 0.8 Hz, 1H), 2.64 (pentet, J = 8.3 Hz, 1H), 1.84 – 1.71 (m, 2H), 1.70 – 1.58 (m, 2H), 1.59 – 1.46 (m, 2H), 1.38 – 1.21 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.76, 164.32, 163.31 (d, J = 251.5 Hz), 148.82, 139.98, 135.82, 133.38, 132.67, 131.95, 131.90 (d, J = 8.1 Hz), 130.79 (d, J = 3.0 Hz), 128.94, 117.86, 117.65 (d, J = 21.2 Hz), 41.60, 31.75, 24.89.



JN284

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.92 (s, 1H), 7.30 – 7.08 (m, 3H), 7.08 – 6.90 (m, 4H), 5.39 (d, *J* = 0.9 Hz, 1H), 5.36 (d, *J* = 1.6 Hz, 1H), 2.71 (pentet, *J* = 8.4 Hz, 1H), 1.96 – 1.75 (m, 2H), 1.70 – 1.62 (m, 2H), 1.60 – 1.51 (m, 2H), 1.44 – 1.15 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.44, 164.19, 163.98 (dd, *J* = 254.5, 11.1 Hz), 160.69 (dd, *J* = 253.5, 11.1 Hz), 148.91, 142.01, 136.12, 133.05 (dd, *J* = 19.1, 4.0 Hz), 132.56, 131.42, 129.10, 127.57, 118.40 (dd, *J* = 16.2, 4.0 Hz), 117.81, 113.33 (dd, *J* = 32.3, 4.0 Hz), 105.72 (dd, *J* = 25.3, 25.3 Hz), 41.70, 31.68, 24.91.



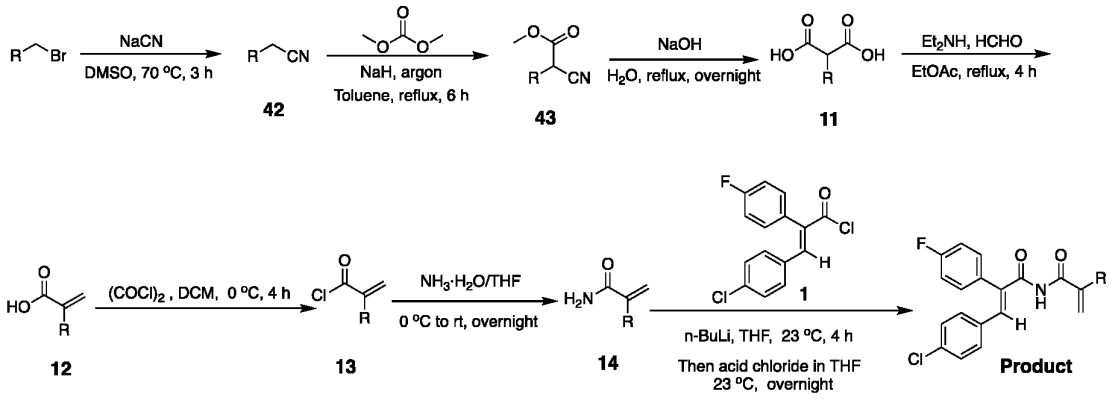
JN302

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.87 (s, 1H), 7.32 – 7.27 (m, 2H), 7.25 – 7.20 (m, 2H), 7.18 – 7.08 (m, 2H), 6.99 – 6.87 (m, 2H), 5.42 – 5.25 (m, 1H), 5.20 (s, 1H), 4.04 – 3.89 (m, 2H), 3.42 (td, *J* = 11.8, 2.0 Hz, 2H), 2.67 (tt, *J* = 11.8, 3.6 Hz, 1H), 1.68 – 1.63 (m, 2H), 1.44 (tt, *J* = 11.8, 4.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.54, 164.37, 163.34 (d, *J* = 252.5 Hz), 149.31, 140.23, 135.96, 133.17, 132.58, 131.98, 131.88 (d, *J* = 8.1 Hz), 130.68 (d, *J* = 4.0 Hz), 128.99, 117.76, 117.74 (d, *J* = 22.2 Hz), 68.04, 36.53, 31.78.

JN303

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.90 (s, 1H), 7.25 – 7.11 (m, 3H), 7.08 – 6.87 (m, 4H), 5.35 (d, *J* = 1.1 Hz, 1H), 5.33 (d, *J* = 1.1 Hz, 1H), 4.09 – 3.87 (m, 2H), 3.43 (tt, *J* = 11.9, 2.0 Hz, 2H), 2.69 (tt, *J* = 11.9, 3.6 Hz, 1H), 1.71 – 1.64 (m, 2H), 1.53 – 1.41 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.37, 164.31, 164.01 (dd, *J* = 254.5, 11.1 Hz), 160.46 (dd, *J* = 253.5, 11.1 Hz), 149.28, 142.18, 136.24, 133.03 (dd, *J* = 10.1, 4.0 Hz), 132.46, 131.45, 129.14, 127.43, 118.30 (dd, *J* = 17.2, 4.0 Hz), 117.84, 113.44 (dd, *J* = 22.2, 4.0 Hz), 105.77 (d, *J* = 25.3, 25.3 Hz), 68.04, 36.66, 31.71.

Preparation of Imides JN296, JN297, JN300, JN301.



Sodium cyanide (1.5 eq), 50 mL dimethylsulfoxide were charged in two necked round bottom flask fitted with magnetic bar at 60 °C. The reaction mixture was stirred at 60 °C followed by drop wise addition of alkyl bromide (1 eq). The reaction mixture was stirred at 70 °C for 3 h. The reaction mixture was cooled to room temperature and poured it in 500 mL of crushed ice. Stirred the reaction mixture in ice for 30 min and product was extracted with ether (50 mL x 3). The organic layer was washed with 6N HCl (200 mL), saturated sodium bicarbonate solution (200 mL) and brine (200 mL). After drying organic layer over anhydrous sodium sulphate, the solvent was evaporated under reduced pressure to yield product as colorless liquid of **42**.

Compound **42** (1 eq) and dimethyl carbonate (2 eq) were dissolved in anhydrous toluene under argon, then NaH (2 eq) was added slowly. The mixture was brought to reflux for 6 h and cooled to rt. The reaction was quenched with acetic acid (10 mL) and then water (100 mL) was added. Separate the organic phase and extract aqueous phase with DCM. The combined organic phase was washed with brine, dried over anhydrous Na_2SO4, filtered, and concentrated. The residue was purified by flash chromatography (hexane: ethyl acetate = 5:1 as the eluent) to get the product **43**.

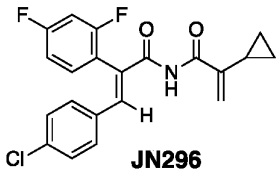
To the cyano ester **43** (1 eq) was added NaOH (10 eq) in 50 mL deionized water and the mixture was heated to reflux overnight. Then reaction mixture was washed with ethyl acetate (50 mL × 3). The remaining aqueous fraction was acidified with 1M HCl (pH = 1) and extracted with ethyl acetate and the combined organic fraction was concentrated in a rotatory evaporator to give the product **11**.

Diethylamine (1.1 eq) was added dropwise to a solution of the crude diacid **11** in ethyl acetate(100 mL) at 0 °C, with subsequent addition of paraformaldehyde (1.5 eq). The resulting suspension was refluxed in an oil bath for 2 h. Then the resulting solution was cooled to room temperature and quenched with H_2O, then acidified to pH to 1with concentrated HCl. The aqueous layer was then extracted with ethyl acetate (50mL x 3),the organic phase was dried over anhydrous $MgSO_4$ and the solvent removed by evaporation to afford the corresponding acrylic acid **12**. The resulting crude acrylic acid **12** was used without further purification in the next step.

The acrylic acid **12** was suspended in dichloromethane (100 mL) and the flask cooled to 0 °C. To this was added oxalyl chloride (1.2 eq) followed by anhydrous DMF (1.0 mL, slowly), and the solution left to stir at 0 °C for 4 h. Then the volatiles were removed in vacuo to yield the crude acid chloride **13** as a light yellow liquid. This was used for next step without purification.

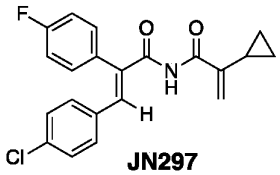
The residue was dissolved in THF (100 mL) and the resulting solution was cooled to 0 °C. Aqueous ammonia ($NH_3 \cdot H_2O$, 40.0 mL, 28-30%) was added slowly with vigorous stirring. The mixture was warmed to room temperature and stirred overnight. The solvent was removed, water (50 mL) was added and the resulting mixture was extracted with ethyl acetate (50 mL x 3). Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford the amide **14** as a white solid. The crude material was used for next step without purification.

In a flask cooled in a Dry Ice-acetone bath, *n*-BuLi (2.50 M solution in hexanes, 0.95 eq) was added to a suspension of amide **14** (0.95 eq) in THF (75 mL), and stirring continued for further 4 h at 23 °C. Then the acid chloride **1** (1.0 eq) was slowly added to the flask as a solution in THF (50 mL). The resultant mixture was stirred overnight at 23 °C, and then partitioned between ethyl acetate (150 mL) and saturated NH_4Cl (150 mL). The organic layer was separated and washed sequentially with saturated $NaHCO_3$ (150 mL) and brine (150 mL). Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel using a mobile phase gradient of 0-20% ethyl acetate/hexanes, followed by a gradient of 15-20% ethyl acetate/hexanes containing 2% triethylamine additive. The isolated pale-yellow solid was then further purified by recrystallization in dichloromethane/hexanes to yield the desired product as a white solid.



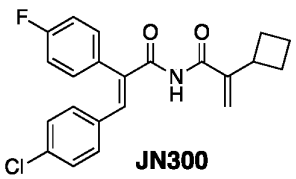
JN296

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.99 (s, 1H), 7.34 – 7.13 (m, 3H), 7.12 – 6.91 (m, 4H), 6.07 (s, 1H), 5.35 (dd, *J* = 1.3, 1.3 Hz, 1H), 1.29 – 1.11 (m, 1H), 0.51 – 0.39 (m, 2H), 0.39 – 0.29 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.59, 164.04 (dd, *J* = 254.5, 12.1 Hz), 163.64, 160.62 (dd, *J* = 253.5, 11.1 Hz), 143.13, 142.49, 136.15, 133.25 (dd, *J* = 9.1, 4.0 Hz), 132.57, 131.44, 129.11, 127.39, 124.24, 118.50 (dd, *J* = 17.2, 4.0 Hz), 113.45 (dd, *J* = 21.2, 4.0 Hz), 105.75 (dd, *J* = 25.3, 25.3 Hz), 12.14, 6.06.



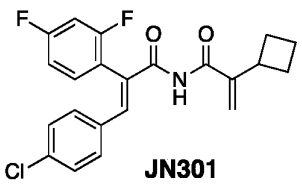
JN297

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.92 (s, 1H), 7.34 – 7.28 (m, 2H), 7.25 – 7.18 (m, 2H), 7.18 – 7.12 (m, 2H), 7.00 – 6.85 (m, 2H), 6.05 (t, *J* = 1.0 Hz, 1H), 5.32 (dd, *J* = 1.7, 1.0 Hz, 1H), 1.13 – 1.04 (m, 1H), 0.51 – 0.32 (m, 2H), 0.34 – 0.23 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.45, 164.17, 163.36 (d, *J* = 252.5 Hz), 143.18, 140.42, 135.84, 133.41, 132.68, 132.13 (d, *J* = 9.1 Hz), 131.98, 130.91 (d, *J* = 4.0 Hz), 128.94, 124.16, 117.62 (d, *J* = 22.2 Hz), 12.10, 6.03.



JN300

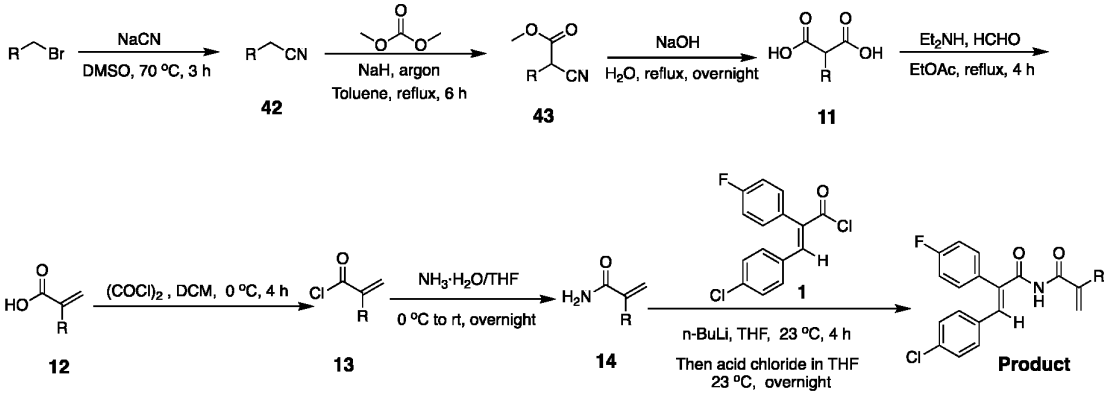
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.87 (s, 1H), 7.35 – 7.20 (m, 4H), 7.20 – 7.09 (m, 2H), 6.99 – 6.87 (m, 2H), 5.56 (d, *J* = 1.4 Hz, 1H), 5.32 (d, *J* = 1.9 Hz, 1H), 3.11 – 2.88 (m, 1H), 1.97 – 1.88 (m, 2H), 1.87 – 1.75 (m, 3H), 1.74 – 1.68 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.32, 164.21, 163.36 (d, *J* = 251.5 Hz), 147.49, 140.10, 135.82, 133.32, 132.65, 132.97 (d, *J* = 8.1 Hz), 131.95, 130.79 (d, *J* = 4.0 Hz), 128.93, 119.81, 117.65 (d, *J* = 22.2 Hz), 36.64, 27.84, 18.10.



JN301

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.92 (s, 1H), 7.31 – 7.08 (m, 3H), 7.09 – 6.87 (m, 4H), 5.62 (d, *J* = 1.4 Hz, 1H), 5.36 (d, *J* = 1.9 Hz, 1H), 3.16 – 2.96 (m, 1H), 2.11 – 1.95 (m, 2H), 1.92 – 1.78 (m, 3H), 1.77 – 1.69 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.90, 164.04, 164.00 (dd, *J* = 11.1, 254.5 Hz), 160.48 (dd, *J* = 252.5, 11.1 Hz), 147.63, 142.06, 136.10, 133.09 (dd, *J* = 10.1, 4.0 Hz), 132.55, 131.40, 129.08, 127.50, 119.68, 118.40 (dd, *J* = 17.2, 4.0 Hz), 113.38 (dd, *J* = 21.2, 4.0 Hz), 105.72 (dd, *J* = 25.3, 25.3 Hz), 36.67, 27.83, 18.13.

Preparation of Imides JN305 to JN314



Sodium cyanide (1.5 eq) and 50 mL dimethyl sulfoxide were added to a two-necked round bottom flask fitted with magnetic bar at 60 °C. The reaction mixture was stirred at 60 °C followed by dropwise addition of the alkyl bromide (1 eq). The reaction mixture was stirred at 70 °C for 3 h. The reaction mixture was cooled to 21 °C and poured into 500 mL of crushed ice. The reaction mixture was stirred in ice for 30 min and the product was extracted with ether (50 mL x 3). The organic layer was washed with 6N HCl (200 mL), saturated sodium bicarbonate solution (200 mL) and brine (200 mL). After drying the organic layer over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure to yield the desired product **42** as a colorless liquid.

Compound **42** (1 eq) and dimethyl carbonate (2 eq) were dissolved in anhydrous toluene under argon, and then NaH (2 eq) was added slowly. The mixture was brought to reflux for 6 h and cooled to 21 °C. The reaction was quenched with acetic acid (10 mL) and then water (100 mL) was added. The organic phase was separated and the aqueous phase

extracted with dichloromethane. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexane: ethyl acetate = 5:1 as the eluent) to obtain the desired product **43**.

To compound **43** (1 eq) was added NaOH (10 eq) in 50 mL deionized water and the mixture was heated to reflux overnight. The reaction mixture was washed with ethyl acetate (50 mL × 3). The remaining aqueous fraction was acidified with 1M HCl (pH = 1) and extracted with ethyl acetate. The combined organic fraction was concentrated in a rotatory evaporator to give the crude product **11**, which was used in the next step without further purification.

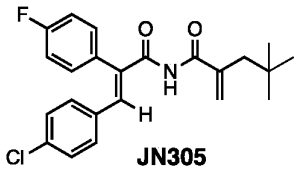
Diethylamine (1.1 eq) was added dropwise to a solution of the crude diacid **11** in ethyl acetate (100 mL) at 0 °C, with subsequent addition of paraformaldehyde (1.5 eq). The resulting suspension was refluxed in an oil bath for 2 h. Then the resulting solution was cooled to 21 °C and quenched with H_2O, then acidified to pH = 1with concentrated HCl. The aqueous layer was then extracted with ethyl acetate (50mL x 3), the organic phase was dried over anhydrous $MgSO_4$, and the solvent removed by evaporation to afford the corresponding acrylic acid **12**. The resulting crude acrylic acid **12** was used in the next step without further purification.

The acrylic acid **12** was suspended in dichloromethane (100 mL) and the flask cooled to 0 °C. To this was added oxalyl chloride (1.2 eq) followed by anhydrous dimethylformamide (DMF, 1.0 mL, slowly), and the solution left to stir at 0 °C for 4 h. Then the volatiles were removed in vacuo to yield the crude acid chloride **13** as a light yellow liquid. This was used for next step without any further purification.

The crude acid chloride **13** was dissolved in THF (100 mL) and the resulting solution was cooled to 0 °C. Aqueous ammonia ($NH_3 \cdot H_2O$, 40.0 mL, 28-30%) was added slowly with vigorous stirring. The mixture was warmed to 21 °C and stirred overnight. The solvent was removed, water (50 mL) was added, and the resulting mixture was extracted with ethyl acetate (50 mL x 3). Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford the amide **14** as a white solid. The crude material was used for next step without further purification.

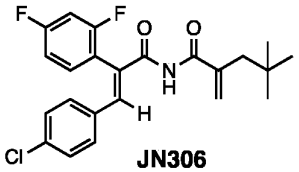
In a flask cooled in a Dry Ice-acetone bath, *n*-butyllithium (*n*-BuLi, 2.50 M solution in hexanes, 0.95 eq) was added to a suspension of the amide **14** (0.95 eq) in THF (75 mL), and stirring was continued for a further 4 h at 21 °C. Then the acid chloride **1** (1.0 eq) was slowly added to the flask as a solution in THF (50 mL). The resulting mixture was stirred overnight at 21 °C, and then partitioned between ethyl acetate (150 mL) and saturated NH_4Cl (150 mL).

The organic layer was separated and washed sequentially with saturated $NaHCO_3$ (150 mL) and brine (150 mL). Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel using a mobile phase gradient of 0-20% ethyl acetate/hexanes, followed by a gradient of 15-20% ethyl acetate/hexanes containing 2% triethylamine additive. The isolated pale-yellow solid was then further purified by recrystallization in dichloromethane/hexanes to yield the desired product as a white solid.



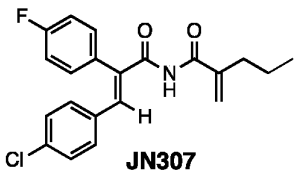
JN305

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.84 (s, 1H), 7.34 – 7.19 (m, 4H), 7.18 – 7.07 (m, 2H), 7.03 – 6.85 (m, 2H), 5.39 (s, 1H), 5.29 (s, 1H), 2.18 (s, 2H), 0.81 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.26, 164.47, 163.31 (d, J = 251.5 Hz), 143.38, 139.89, 135.81, 133.39, 132.67, 131.94, 131.87 (d, J = 8.1 Hz), 130.78 (d, J = 3.0 Hz), 128.94, 123.28, 117.63 (d, J = 21.2 Hz), 45.38, 31.54, 29.31.



JN306

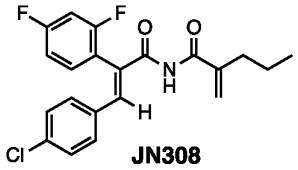
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.88 (s, 1H), 7.25 – 7.11 (m, 3H), 7.07 – 6.88 (m, 4H), 5.52 (s, 1H), 5.35 (s, 1H), 2.22 (s, 2H), 0.83 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.02, 164.48, 163.96 (dd, J = 254.5, 11.1 Hz), 160.47 (dd, J = 252.5, 12.1 Hz), 143.31, 141.85, 136.08, 133.04 (dd, J = 10.1, 4.0 Hz), 132.56, 131.41, 129.08, 127.69, 123.56, 118.41(dd, J = 16.2, 4.0 Hz) , 113.32 (dd, J = 21.2, 4.0 Hz), 105.66 (t, J = 26.3 Hz), 45.59, 31.58, 29.29.



JN307

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.86 (s, 1H), 7.37 – 7.17 (m, 4H), 7.17 – 7.06 (m, 2H), 6.98 – 6.84 (m, 2H), 5.34 (s, 1H), 5.33 (t, J = 1.4 Hz, 1H), 2.14 (td, J = 7.3, 1.4 Hz, 2H),

1.48 – 1.28 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.94, 164.26, 163.30 (d, J = 251.5 Hz), 144.77, 139.94, 135.81, 133.35, 132.65, 131.95, 131.88 (d, J = 8.1 Hz), 130.79 (d, J = 4.0 Hz), 128.93, 120.79, 117.65 (d, J = 22.2 Hz), 33.99, 21.40, 13.71.

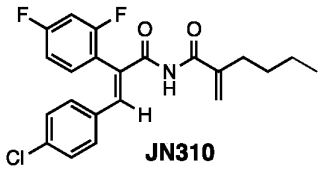


JN308

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.92 (s, 1H), 7.27 – 7.11 (m, 3H), 7.07 – 6.92 (m, 4H), 5.44 (s, 1H), 5.38 (t, J = 1.4 Hz, 1H), 2.26 – 2.11 (m, 2H), 1.47 – 1.32 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.60, 164.13, 163.98 (dd, J = 254.5, 12.1 Hz), 160.45 (dd, J = 252.5, 12.1 Hz), 144.89, 142.03, 136.14, 133.04 (dd, J = 9.1, 4.0 Hz), 132.55, 131.42, 129.11, 127.53, 120.78, 118.42 (dd, J = 17.2, 4.0 Hz), 113.40 (dd, J = 21.2, 4.0 Hz), 105.74 (t, J = 25.3 Hz), 34.10, 21.40, 13.74.

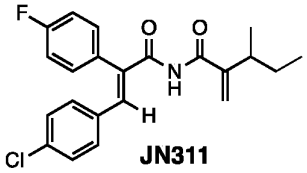
JN309

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.86 (s, 1H), 7.37 – 7.17 (m, 4H), 7.17 – 7.07 (m, 2H), 7.01 – 6.81 (m, 2H), 5.34 – 5.31 (m, 2H), 2.26 – 2.04 (m, 2H), 1.40 – 1.12 (m, 4H), 0.85 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.95, 164.52, 163.28 (d, J = 251.5 Hz), 145.00, 139.92, 135.79, 133.36, 132.64, 131.93, 131.87 (d, J = 8.1 Hz), 130.78 (d, J = 3.0 Hz), 128.91, 120.58, 117.63 (d, J = 21.2 Hz), 31.66, 30.29, 22.36, 13.91.



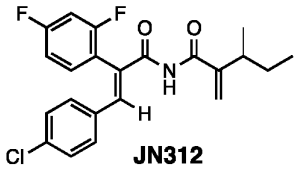
JN310

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.91 (s, 1H), 7.30 – 7.15 (m, 3H), 7.08 – 6.91 (m, 4H), 5.43 (s, 1H), 5.38 (t, J = 1.4 Hz, 1H), 2.30 – 2.12 (m, 2H), 1.41 – 1.17 (m, 4H), 0.87 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.61, 164.15, 163.97 (dd, J = 254.5, 11.1 Hz), 160.44 (dd, J = 252.5, 12.1 Hz), 145.12, 142.01, 136.12, 133.03 (dd, J = 10.1, 4.0 Hz), 132.55, 131.41, 129.10, 127.54, 120.58, 118.41 (dd, J = 16.2, 4.0 Hz), 113.38 (dd, J = 22.2, 4.0 Hz), 105.72 (t, J = 25.3 Hz), 31.79, 30.29, 22.40, 13.94.



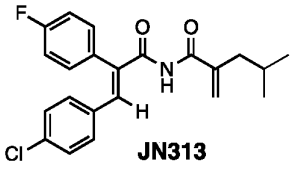
JN311

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.85 (s, 1H), 7.35 – 7.20 (m, 4H), 7.17 – 7.02 (m, 2H), 7.05 – 6.86 (m, 2H), 5.26 (d, *J* = 1.2 Hz, 1H), 5.23 (s, 1H), 2.53 – 2.47 (m, 1H), 1.54 – 1.31 (m, 1H), 1.38 – 1.19 (m, 1H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.79 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.76, 164.40, 163.29 (d, *J* = 251.5 Hz), 150.60, 139.92, 135.80, 133.40, 132.67, 131.94, 131.86 (d, *J* = 8.1 Hz), 130.77 (d, *J* = 4.0 Hz), 128.93, 118.06, 117.63 (d, *J* = 21.2 Hz), 36.55, 28.48, 18.92, 11.63.



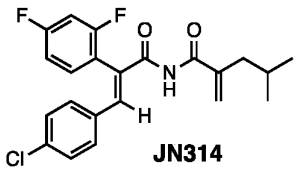
JN312

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.90 (s, 1H), 7.25 – 7.07 (m, 3H), 7.08 – 6.86 (m, 4H), 5.36 (s, 1H), 5.31 (d, *J* = 1.2 Hz, 1H), 2.63 – 2.43 (m, 1H), 1.54 – 1.41 (m, 1H), 1.36 – 1.27 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.81 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.42, 164.33, 163.95 (dd, *J* = 254.5, 11.1 Hz), 160.44 (dd, *J* = 252.5, 12.1 Hz), 150.59, 141.90, 136.09, 133.04 (dd, *J* = 10.1, 4.0 Hz), 132.57, 131.40, 129.08, 127.65, 118.40 (dd, *J* = 16.2, 4.0 Hz), 118.17, 113.34 (dd, *J* = 22.2, 12.1 Hz), 105.68 (t, *J* = 25.3 Hz), 36.69, 28.48, 18.84, 11.64.



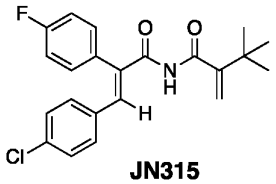
JN313

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.86 (s, 1H), 7.34 – 7.19 (m, 4H), 7.18 – 7.07 (m, 2H), 7.00 – 6.76 (m, 2H), 5.38 (s, 1H), 5.31 (d, *J* = 1.2 Hz, 1H), 2.05 (dd, *J* = 7.3, 1.2 Hz, 2H), 1.66 – 1.56 (m, 1H), 0.79 (d, *J* = 6.6 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.01, 164.31, 163.30 (d, *J* = 252.5 Hz), 143.88, 139.97, 135.81, 133.36, 132.65, 131.94, 131.88 (d, *J* = 8.1 Hz), 130.78 (d, *J* = 4.0 Hz), 128.93, 122.05, 117.65 (d, *J* = 21.2 Hz), 41.49, 27.17, 22.32.



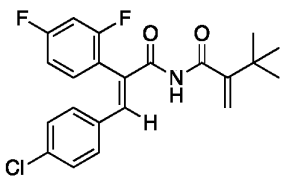
JN314

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.91 (s, 1H), 7.33 – 7.14 (m, 3H), 7.07 – 6.91 (m, 4H), 5.48 (s, 1H), 5.36 (d, *J* = 1.2 Hz, 1H), 2.10 (dd, *J* = 7.2, 1.2 Hz, 2H), 1.71 – 1.64 (m, 1H), 0.82 (d, *J* = 6.6 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.68, 164.23, 163.98 (dd, *J* = 254.5, 12.1 Hz), 160.46 (dd, *J* = 252.5, 11.1 Hz), 144.00, 142.03, 136.13, 133.05 (dd, *J* = 10.1, 4.0 Hz), 132.56, 131.42, 129.10, 127.57, 122.08, 118.41 (dd, *J* = 16.2, 4.0 Hz), 113.38 (dd, *J* = 22.2, 4.0 Hz), 105.72 (t, *J* = 25.3 Hz), 41.61, 27.26, 22.35.The preparation of the imides **JN315** and **JN316** was the same as for the preparation of the imides **JN296, JN297, JN300,** and **JN301**.



JN315

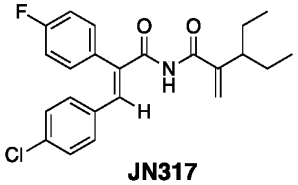
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 2H), 7.30 – 7.19 (m, 4H), 7.19 – 7.13 (m, 2H), 6.97 – 6.87 (m, 2H), 5.27 (s, 1H), 5.05 (s, 1H), 1.15 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.83, 164.72, 163.47 (d, *J* = 252.5 Hz), 155.25, 140.14, 135.99, 133.58, 132.85, 132.11, 132.00 (d, *J* = 8.1 Hz), 130.81(d, *J* = 4.0 Hz), 129.11, 117.78 (d, *J* = 22.2 Hz), 115.25, 35.76, 29.54.



JN316

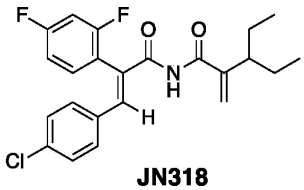
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.82 (s, 1H), 7.23 – 7.15 (m, 3H), 7.06 – 6.91 (m, 4H), 5.32 (s, 1H), 5.15 (s, 1H), 1.16 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.20, 164.32, 163.98 (dd, *J* = 254.5, 11.1 Hz), 160.47 (dd, *J* = 252.5, 12.1 Hz), 154.93, 141.90, 136.12, 133.02 (dd, *J* = 10.1, 4.0 Hz), 132.55, 131.42, 129.10, 127.71, 118.31 (dd, *J* = 16.2, 4.0 Hz), 115.18, 113.35 (dd, *J* = 21.2, 4.0 Hz), 105.70 (t, *J* = 25.3 Hz), 35.58, 29.39.

The preparation of the imides **JN317, JN318** and **JN326** was the same as for the preparation of the imides **JN182** to **JN185)**



JN317

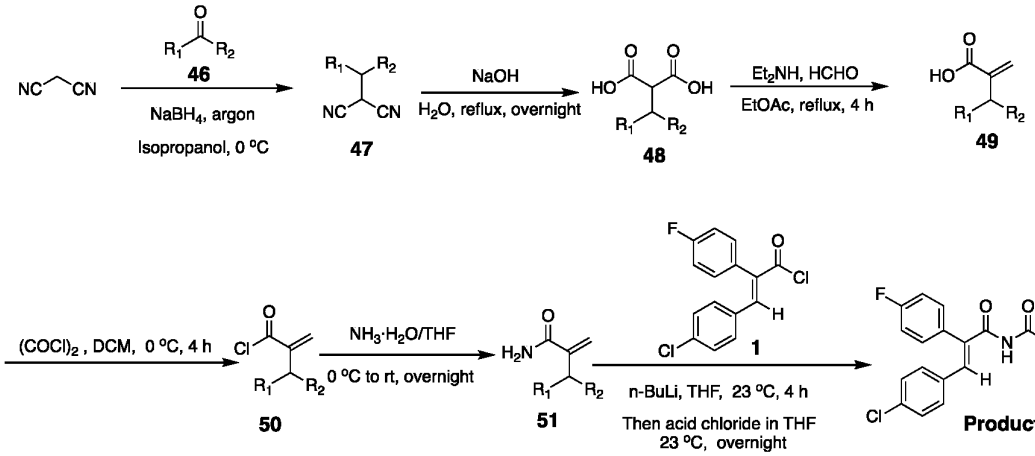
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.85 (s, 1H), 7.32 – 7.25 (m, 2H), 7.25 – 7.18 (m, 2H), 7.18 – 7.11 (m, 2H), 7.03 – 6.84 (m, 2H), 5.31 (s, 1H), 5.23 (d, *J* = 0.9 Hz, 1H), 2.31 – 2.22 (m, 5.7 Hz, 1H), 1.50 – 1.29 (m, 4H), 0.74 (t, *J* = 7.4 Hz, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.63, 164.47, 163.34 (d, *J* = 252.5 Hz), 148.55, 139.93, 135.83, 133.51, 132.74, 131.99, 131.92 (d, *J* = 8.1 Hz), 130.88 (d, *J* = 4.0 Hz), 128.98, 119.60, 117.67 (d, *J* = 21.2 Hz), 44.48, 26.40, 11.63.



JN318

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.90 (s, 1H), 7.24 – 7.08 (m, 3H), 7.08 – 6.90 (m, 4H), 5.44 (s, 1H), 5.29 (d, *J* = 0.9 Hz, 1H), 2.36 – 2.19 (m, 1H), 1.52 – 1.33 (m, 4H), 0.76 (t, *J* = 7.4 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.10, 164.36, 163.95 (dd, *J* = 254.5, 11.1 Hz), 160.45 (dd, *J* = 252.5, 12.1 Hz), 148.46, 141.88, 136.08, 133.06 (dd, *J* = 10.1, 4.0 Hz), 132.60, 131.41, 129.08, 127.71, 119.75, 118.47 (dd, *J* = 17.2, 4.0 Hz), 113.32 (dd, *J* = 21.2, 4.0 Hz), 105.65 (t, *J* = 25.3 Hz), 44.55, 29.23, 11.58.

The preparation of the imides **JN319** to **JN325**:



A solution of malononitrile (1.0 eq) and the ketone **46** (2.0 eq) in isopropanol (2 mL/mmol of malononitrile) was cooled to 0 °C. Sodium borohydride (ca. 1 eq) was added and the mixture was stirred until the reaction was complete according to TLC. On several occasions, if any intermediate olefin was present or remaining ketone required reducing, more borohydride (up to 0.6 eq) was added. The reaction was carefully quenched with water and 1M HCl solution, extracted with dichloromethane, filtered, and concentrated. The crude product could be purified by column chromatography to give the product **47**.

To the dintirile **47** (1 eq) was added NaOH (10 eq) in 50 mL deionized water and the mixture was heated to reflux overnight. Then the mixture was washed with ethyl acetate (50 mL × 3). The remaining aqueous fraction was acidified with 1M HCl (pH = 1) and extracted with ethyl acetate and the combined organic fraction was concentrated in a rotatory evaporator to give the diacid **48**.

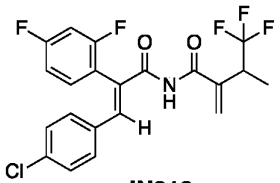
Diethylamine (1.1 eq) was added dropwise to a solution of the crude diacid 48 in ethyl acetate (100 mL) at 0 °C, with subsequent addition of paraformaldehyde (1.5 eq). The resulting suspension was refluxed in an oil bath for 2 h. Then the resulting solution was cooled to 22 °C and quenched with water, then acidified to pH to 1with concentrated HCl. The aqueous layer was then extracted with ethyl acetate (50. mL x 3), the organic phase was dried over anhydrous $MgSO_4$ and the solvent removed by evaporation to afford the corresponding acrylic acid **49**. The resulting crude acrylic acid **49** was used without further purification in the next step.

The acrylic acid **49** was suspended in dichloromethane (100 mL) and the flask was cooled to 0 °C. To this was added oxalyl chloride (1.2 eq) followed by anhydrous DMF (1.0 mL, slowly), and the solution left to stir at 0 °C for 4 h. Then the volatiles were removed in vacuo to yield the crude acid chloride **50** as a light yellow liquid. This was used for next step without further purification.

The material from the last step was dissolved in THF (100 mL) and the resulting solution was cooled to 0 °C. Aqueous ammonia ($NH_3 \cdot H_2O$, 40.0 mL, 28-30%) was added slowly with vigorous stirring. The mixture was warmed to 22 °C and stirred overnight. The solvent was removed in vacuo, water (50 mL) was added and the resulting mixture was extracted with ethyl acetate (50 mL x 3). It was then dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford the amide **51** as a white solid. The crude material was used for next step without purification.

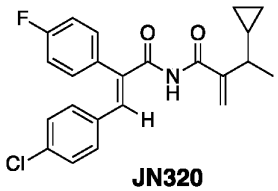
In a flask cooled in a Dry Ice-acetone bath, *n*-butyllithium (*n*-BuLi, 2.50 M solution in hexanes, 0.95 eq) was added to a suspension of the amide **51** (0.95 eq) in THF (75 mL), and

stirring was continued for a further 4 h at 22 °C. Then the acid chloride **1** (1.0 eq) was slowly added to the flask as a solution in THF (50 mL). The resultant mixture was stirred overnight at 22 °C, and then partitioned between ethyl acetate (150 mL) and saturated NH_4Cl (150 mL). The organic layer was separated and washed sequentially with saturated $NaHCO_3$ (150 mL) and brine (150 mL). Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel using a mobile phase gradient of 0-20% ethyl acetate/hexanes, followed by a gradient of 15-20% ethyl acetate/hexanes containing 2% triethylamine additive. The isolated pale-yellow solid was then further purified by recrystallization in dichloromethane/hexanes to yield the desired product as a white solid.



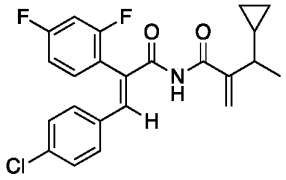
JN319

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.90 (s, 1H), 7.26 – 7.13 (m, 3H), 7.08 – 6.92 (m, 4H), 5.83 – 5.72 (m, 1H), 5.67 (t, *J* = 1.0 Hz, 1H), 3.68 – 3.55 (m, 1H), 1.32 (d, *J* = 7.2 Hz, 3H).



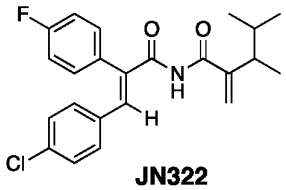
JN320

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.86 (s, 1H), 7.35 – 7.27 (m, 2H), 7.25 – 7.19 (m, 2H), 7.19 – 7.11 (m, 2H), 7.01 – 6.89 (m, 2H), 5.43 (d, *J* = 1.3 Hz, 1H), 5.20 (s, 1H), 1.95 – 1.77 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.68 – 0.60 (m, 1H), 0.52 – 0.43 (m, 1H), 0.46 – 0.35 (m, 1H), 0.16 – 0.01 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.29, 164.54, 163.46 (d, *J* = 202 Hz), 150.87, 140.16, 135.98, 133.51, 132.81, 132.12, 132.04 (d, *J* = 7.1 Hz), 130.91 (d, *J* = 3.0 Hz), 129.11, 117.90, 117.74 (d, *J* = 4.0 Hz), 40.51, 19.54, 16.66, 4.81, 4.60.



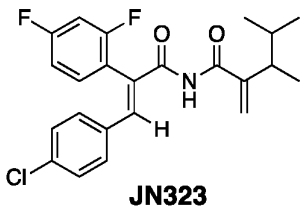
JN321

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.90 (s, 1H), 7.24 – 7.09 (m, 3H), 7.06 – 6.91 (m, 4H), 5.47 (d, *J* = 1.4 Hz, 1H), 5.32 (s, 1H), 1.98 – 1.78 (m, 1H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.71 – 0.61 (m, 1H), 0.56 – 0.46 (m, 1H), 0.45 – 0.36 (m, 1H), 0.18 – 0.06 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.76, 164.14, 163.87 (dd, *J* = 253.3, 11.3 Hz), 160.36 (dd, *J* = 252, 12.6 Hz), 150.60, 141.89, 136.02, 132.93 (dd, *J* = 8.8, 3.8 Hz), 132.44, 131.32, 129.00, 127.47, 118.27 (dd, *J* = 16.4, 3.8 Hz) , 117.52, 113.28 (dd, *J* = 21.4, 3.8 Hz), 105.62 (t, *J* = 25.2 Hz), 40.36, 19.16, 16.43, 4.51, 4.36.



JN322

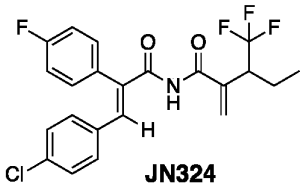
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.86 (s, 1H), 7.33 – 7.27 (m, 2H), 7.25 – 7.19 (m, 2H), 7.19 – 7.13 (m, 2H), 7.03 – 6.87 (m, 2H), 5.28 (s, 1H), 5.24 (d, *J* = 1.2 Hz, 1H), 2.47 – 2.40 (m, 1H), 1.67 – 1.59 (m, 2H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H), 0.74 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.10, 164.59, 163.44 (d, *J* = 201 Hz), 150.31, 140.10, 135.97, 133.54, 132.82, 132.11, 132.02 (d, *J* = 7.1 Hz), 130.95 (d, *J* = 3.0 Hz), 129.10, 119.05, 117.80 (d, *J* = 17.2 Hz), 41.47, 31.63, 21.33, 18.64, 15.34.



JN323

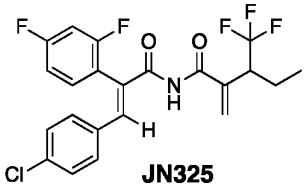
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.89 (s, 1H), 7.24 – 7.12 (m, 3H), 7.06 – 6.94 (m, 4H), 5.40 (s, 1H), 5.29 (d, *J* = 1.2 Hz, 1H), 2.53 – 2.37 (m, 1H), 1.64 (h, *J* = 6.7 Hz, 1H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.75 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.48, 164.30, 163.84 (dd, *J* = 254.5, 12.6 Hz), 160.34 (dd, *J* = 252.0, 12.6 Hz),

149.97, 141.81, 135.98, 132.94 (dd, J = 8.8, 3.8 Hz), 132.46, 131.31, 128.98, 127.55, 118.99, 118.30 (dd, J = 16.4, 3.8 Hz), 113.23 (dd, J = 21.4, 3.8 Hz), 105.57 (t, J = 25.2 Hz), 41.29, 31.37, 21.03, 18.35, 14.95.



JN324

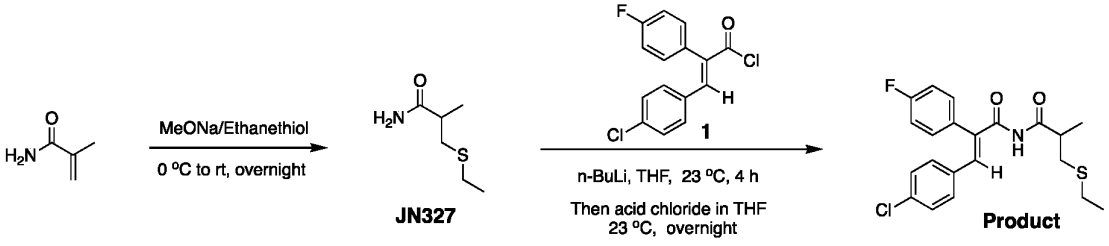
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.87 (s, 1H), 7.32 – 7.27 (m, 2H), 7.26 – 7.19 (m, 3H), 7.19 – 7.07 (m, 2H), 7.01 – 6.84 (m, 2H), 5.66 (s, 1H), 5.51 (s, 1H), 3.51 – 3.45 (m, 1H), 1.98 – 1.83 (m, 1H), 1.67 – 1.53 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.16, 164.28, 163.36 (d, J = 252 Hz), 140.41, 139.60 (q, J = 1.3 Hz), 136.00, 133.02, 132.53, 132.00, 131.89 (d, J = 7.6 Hz), 130.57 (d, J = 3.8 Hz), 128.99, 126.44 (q, J = 281 Hz), 123.56, 117.76 (d, J = 22.7 Hz), 44.62 (q, J = 26.5 Hz), 21.67 (q, J = 2.5 Hz), 11.19.



JN325

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.91 (s, 1H), 7.25 – 7.17 (m, 3H), 7.10 – 6.92 (m, 4H), 5.74 (s, 1H), 5.72 (s, 1H), 3.48 – 3.37 (m, 1H), 1.98 – 1.81 (m, 1H), 1.72 – 1.59 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H).

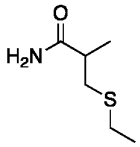
Preparation of imides **JN327** to **JN329**



Ethanethiol (15 ml) and sodium methoxide (NaOMe,1.0 eq) were added to a 50-mL round-bottomed flask, and the solution was cooled to 0 °C. Methacrylamide (1.0 eq) was added dropwise over a period of approximately 10 min, during which time the temperature of

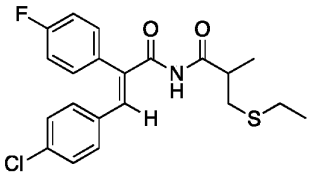
the reaction was not allowed to exceed 10 °C. The reaction was allowed to come to 22 °C with stirring overnight. The crude residue was purified by column chromatography to yield the desired product **JN327** as a white solid.

In a flask cooled in a Dry Ice-acetone bath, *n*-BuLi (2.50 M solution in hexanes, 0.95 eq) was added to a suspension of the amide **JN327** (0.95 eq) in THF (75 mL), and stirring was continued for a further 4 h at 22 °C. Then the acid chloride 1 (1.0 eq) was slowly added to the flask as a solution in THF (50 mL). The resultant mixture was stirred overnight at 22 °C, and then the mixture was partitioned between ethyl acetate (150 mL) and saturated NH_4Cl (150 mL). The organic layer was separated and washed sequentially with saturated $NaHCO_3$ (150 mL) and brine (150 mL). It was then dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel using a mobile phase gradient of 0-20% ethyl acetate/hexanes, followed by a gradient of 15-20% ethyl acetate/hexanes containing 2% triethylamine additive. The isolated pale-yellow solid was then further purified by recrystallization in dichloromethane/hexanes to yield the desired product as a white solid.



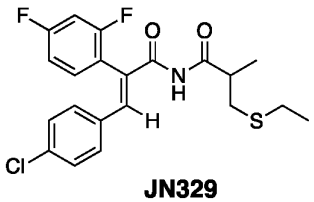
JN327

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (s, 1H), 5.89 (s, 1H), 2.81 (dd, *J* = 13.0, 7.8 Hz, 1HH), 2.62 – 2.51 (m, 3H), 2.51 – 2.42 (m, 1H), 1.28 – 1.18 (m, 6H).



JN328

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.82 (s, 1H), 7.25 – 7.18 (m, 4H), 7.18 – 7.13 (m, 2H), 6.97 – 6.86 (m, 2H), 3.79 – 3.61 (m, 1H), 2.90 (dd, *J* = 13.2, 7.8 Hz, 1H), 2.65 – 2.49 (m, 3H), 1.32 – 1.17 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.22, 164.57, 163.27 (d, *J* = 252.5 Hz), 140.15, 135.79, 133.18, 132.45, 131.86, 131.82 (d, *J* = 9.1 Hz), 130.00 (d, *J* = 3.0 Hz), 128.82, 117.56 (d, *J* = 22.2 Hz), 40.83, 34.74, 26.59, 16.93, 14.77.



JN329

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.86 (s, 1H), 7.22 – 7.10 (m, 3H), 7.06 – 6.91 (m, 4H), 3.77 – 3.65 (m, 1H), 2.91 (dd, *J* = 13.3, 7.7 Hz, 1H), 2.64 – 2.47 (m, 3H), 1.34 – 1.20 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.35, 164.11, 163.97 (dd, *J* = 252.5, 12.1 Hz), 160.39 (dd, *J* = 252.5, 12.1 Hz), 141.92, 136.10, 132.78 (dd, *J* = 9.1, 4.0 Hz), 132.29, 131.27, 128.98, 127.40, 117.77 (dd, *J* = 16.2, 4.0 Hz), 113.31 (dd, *J* = 21.2, 4.0 Hz), 105.75 (t, *J* = 25.3 Hz), 40.79, 34.70, 26.54, 16.87, 14.74.

Example 2: Biological Assays Conducted on Exemplary Compounds

The growth inhibitory effect of the JN compounds was assessed through the MTT assay, which assesses the total number of viable cells *in vitro*. These experiments were performed in AR-expressing (AR-positive) prostate cancer cell lines to assess on target effects and AR-null (AR-negative) prostate cancer cell lines to assess off target effects (i.e. specificity).

Materials and Methods for Cell Viability and Reporter Gene Assays

Cell lines: All cell lines were purchased from ATCC and grown RPMI + 10% serum

Cell Viability Assay: Cells were seeded in 96 well plates at 1.5 x 104cells per well in 100µl of culture medium. Cell viability was assessed by the MTT (3,[4,5-dimethylthiazol-2-yl-]diphenyltatrazolium bromide) assay. Twenty-five µl of MTT (5 mg/ml) was added to each well for 3 h at 37°C. Subsequently, 100µl of 10% sodium dodecyl sulfate/0.01 NHCl was added overnight at 37°C. Absorbance was measured at 570 nm on a microplate reader. All experiments were performed in quadruplicate. The cell line tested in each sub-figure is indicated at the top of each graph. DMSO served as the vehicle and was maintained at 0.1% in all experiments.

Transient transfections and reporter gene assays: Cells were plated at 10^5 cells/well in 24-well plates the day prior to transfection. Reporter constructs, which express Firefly luciferase, were co-transfected with the pRL-SV40 plasmid (Promega, Madison, WI; 1 ng/well), the latter which expresses Renilla luciferase, to normalize for transfection efficiency. The plasmids were transfected with Lipofectamine 2000(Invitrogen, Carlsbad, CA) according to the

manufacturer's instructions. Protein was extracted 48 hours after transfection, and firefly and Renilla luciferase were measured on a TD20/20 tube luminometer using a Dual Luciferase Assay kit (Promega) according to the manufacturer's instructions.

AR-expressing (AR-pos):

LNCaP AR: overexpression of full length AR

22Rv1: full length AR and ARV7

VCaP: full length AR and ARV7

CWR22: full length AR and ARV7

T47D: breast cancer cell line that expresses the androgen receptor (and estrogen/progesterone receptors) and is dependent on the androgen receptor for growth/survival.AR-negative:

PC3

DU145

HCT8: colon cancer cell line that does not express the androgen receptor and is not dependent on the androgen receptor for growth/survival.

Only those compounds that exhibit strong inhibition of AR-expressing (AR-positive) prostate cancer cell lines and minimal inhibition of AR-null (AR-negative) prostate cancer cell lines were subjected to biochemical assays to assess inhibitory effects on AR transcriptional activity.

The biochemical assays include reporter assays to determine the activity and specificity of these JN compounds to inhibit the transcriptional activity of the androgen receptor (AR). The reporter assays were conducted in various cell lines that either endogenously or exogenously express the full-length AR and ARV7, a constitutively active splice variant that is resistant to all clinically available AR targeting compounds. The reporter assays were performed in replicates and across a wide range of concentrations (generally 0 – 10 mM). The results are shown in micromolar (μM).

The reporter systems utilized include:

MMTV-luciferase: AR-dependent

ARE-luciferase: AR-dependent

GRE-luciferase: glucocorticoid receptor (GR)-dependent

CRE-luciferase: CREB-dependent

AR-TAD-luciferase: dependent on AR transactivation domain

CREB-TAD-luciferase: dependent on CREB transactivation domain

JUN-TAD-luciferase: dependent on c-Jun transactivation domain

The data for the reporter assays and MTT assays are summarized in the table below.

Table MTT Assay IC_{50} values (μM)

Inhibitor	LNCaP-AR	22RV1	DU145	PC3	HCT8	T47D	vCAP
JN103	++	++	>10	>10	>10	+	+
JN169	>10	>10	>10	>10			
JN170	>10	>10	>10	>10			
JN171	>10	++	>10	+			
JN172	+	+	>10	+			
JN174		>10		>10			
JN175		+		>10			
JN176		>10		>10			
JN177	>10	>10		>10			
JN178		>10		>10			
JN179		>10		>10			
JN180		+		+			
JN181	+	>10	>10	>10		>10	
JN182	++	>10	>10	>10	>10		+
JN183	++	+	>10	++	>10		+
JN184	++	+	>10	>10	>10		+
JN185	++	+	+	>10	>10	++	+
JN186	++	+	>10	>10			
JN192	>10	>10	>10				
JN209	>10	>10	>10	>10			
JN219	>10	>10	>10	>10			
JN254	+	++	+	++			
JN279	+	>10		>10			
JN280	+	+		>10			
JN283	++	+	>10	>10			
JN284	+	>10	>10	>10			
JN286	+	>10		>10			
JN296	++	+	>10	+			
JN297	++	+	>10	>10			
JN298	>10	>10	+				
JN300	+	+	>10				
JN301	+	+	>10	>10			
JN302	++	+	+	++			

Inhibitor	LNCaP-AR	22RV1	DU145	PC3	HCT8	T47D	vCAP
JN303	++	+	+++	++			
JN305	++	>10	>10	>10			
JN306	+	+	+	+			
JN307	>10	+		>10			
JN308	+	++	>10	>10			
JN309	+	>10	>10	>10			
JN310	>10	>10	>10	>10			
JN311	+	+	>10	>10			
JN312	++	++	>10	+			
JN313	+	+	>10	>10			
JN314	+	+	>10	+			

+ = 5-10 μM; ++ = 2-5 μM; +++ = <2 μM

Table Reporter Assay IC_{50} values (μM):

Compound	Reporter	LNCaP-AR	22RV1	DU145	PC3
JN103	MMTV-LUC	++			
	ARE-LUC		++		
	C-JUN TAD-LUC			>10	
	CREB TAD-LUC			>10	
	AR TAD-LUC				>10
JN169	MMTV-LUC	>10			
	MMTV-LUC		+		
	MMTV-LUC				>10
JN170	MMTV-LUC	>10			
	MMTV-LUC		>10		
	MMTV-LUC				>10
JN171	MMTV-LUC	+			
	MMTV-LUC		+		
	MMTV-LUC				+
JN172	MMTV-LUC	+			
	MMTV-LUC		++		

	MMTV-LUC				+
JN173	MMTV-LUC	++			
	MMTV-LUC		++		
	MMTV-LUC				+
JN181	MMTV-LUC	+			
	MMTV-LUC		+		
	AR TAD-LUC				>10
JN182	MMTV-LUC	+			
	MMTV-LUC		++		
	GRE-LUC				>10
JN183	MMTV-LUC	++			
	MMTV-LUC		++		
	GRE-LUC				+
JN184	MMTV-LUC	+			
	MMTV-LUC		++		
	C-JUN TAD-LUC				>10
	CREB TAD-LUC				>10
	GRE-LUC				+
JN185	MMTV-LUC	++			
	MMTV-LUC		++		
	C-JUN TAD-LUC				>10
	CREB TAD-LUC				
	AR TAD		++		>10
	GRE-LUC				>10
JN186	MMTV-LUC	+			
	ARE-LUC		+		
	GRE-LUC				>10

JN279	MMTV-LUC		+		
	GRE-LUC				+
JN297	MMTV-LUC		+		
JN301	MMTV-LUC		+		
JN308	MMTV-LUC		+		
JN312	MMTV-LUC		++		

+ = 5-10 μM; ++ = 2-5 μM

INCORPORATION BY REFERENCE

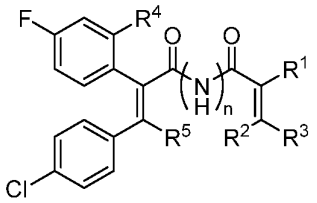
All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein,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

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the compounds and methods of use thereof described herein. Such equivalents are considered to be within the scope of this invention and are covered by the following claims. Those skilled in the art will also recognize that all combinations of embodiments described herein are within the scope of the invention.

We claim:

1. A compound having the structure of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, alkyl, aryl, alkynyl, cycloalkyl, or heterocycloalkyl;

R^2 is H, alkyl, or aryl;

or R^1 and R^3 combine to form cycloalkenyl; and

R^3 is H, alkyl, or aryl;

R^4 is H or fluoro;

R^5 is H or alkyl;

n is 1 or 2;

provided that when n is 1:

at least one of R^1, R^2, R^3, R^4, and R^5 is not H,

if each of R^2, R^3, and R^5 is H, and R^4 is F, then R^1 is not benzyl,

if each of R^2, R^3, and R^5 is H, then R^1 is not methyl, and

if each of R^1, R^2, and R^5 are H and R^4 is F, then R^3 is not phenyl or trifluoromethyl.

2. The compound of claim 1, wherein R^1 is alkyl, such as C_1-C_6 alkyl.

3. The compound of claim 1 or 2, wherein R^1 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, or neopentyl, each of which is optionally substituted.

4. The compound of claim 1, wherein R^1 is cycloalkyl, such as C_3-C_6 cycloalkyl.

5. The compound of claim 1 or 4, wherein R^1 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is optionally substituted.

6. The compound of claim 1, wherein R^1 is heterocycloalkyl, such as 3-to 7-membered heterocycloalkyl.

7. The compound of claim 6, wherein R^1 is tetrahydropyran, which is optionally substituted.

8. The compound of claim 1, wherein R^1 is alkynyl, such as C_2-C_6 alkynyl.

9. The compound of claim 8, wherein R^1 is optionally substituted propargyl.

10. The compound of any preceding claim, wherein each of R^2 and R^3 is H.

11. The compound of any one of claims 1-9, wherein one of R^2 and R^3 is alkyl, such as C_1-C_6 alkyl.

12. The compound of claim 1, wherein R^1 and R^3 combine to form cycloalkenyl, such as C_3-C_7 cycloalkenyl.

13. The compound of claim 12, wherein the cycloalkenyl is optionally substituted cyclohexenyl.

14. The compound of any one of claims 1-9 or 11-13, wherein R^2 is H.

15. The compound of any one of claims 1-9 or 11-13, wherein R^2 is alkyl, such as C_1-C_6 alkyl.

16. The compound of any one of claims 1-9 or 11-14, wherein R^3 is alkyl, such as C_1-C_6 alkyl.

17. The compound of any one of claims 1-9 or 11-14, wherein R^3 is H.

18. The compound of any one of claims 1-9 or 11-14, wherein R^3 is aryl, such as optionally substituted phenyl.

19. The compound of any preceding claim, wherein R^4 is H.

20. The compound of any one of claims 1-18, wherein R^4 is fluoro.

21. The compound of claim 1, wherein each of R^2, R^3, and R^5 are H and R^1 is alkyl, such as C_1-C_6 alkyl, or cycloalkyl, such as C_3-C_6 cycloalkyl.

22. The compound of claim 21, wherein R^4 is H.

23. The compound of claim 21, wherein R^4 is fluoro.

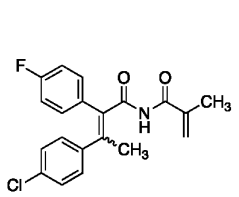
24. The compound of any preceding claim, wherein R^5 is H.

25. The compound of any one of claims 1-23, wherein R^5 is alkyl, such as C_1-C_6 alkyl.

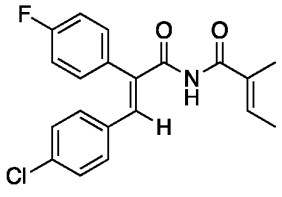
26. The compound of any preceding claim, wherein n is 1.

27. The compound of any one of claims 1-25, wherein n is 2.

28. The compound of claim 1, selected from:



JN172 ,



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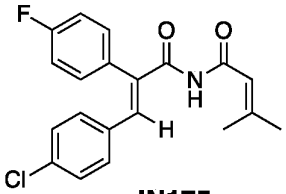

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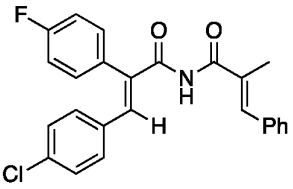

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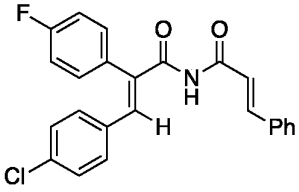

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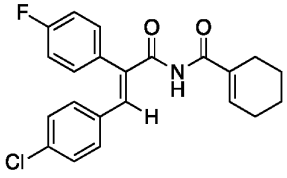

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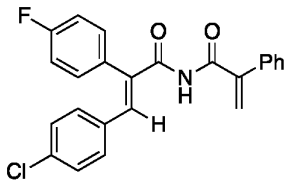
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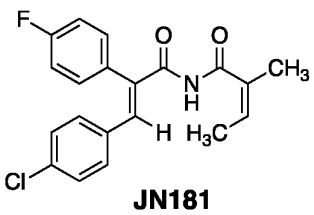
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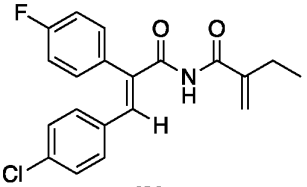
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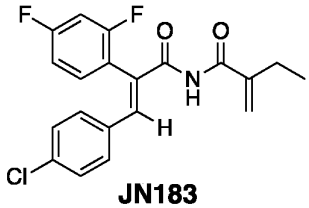
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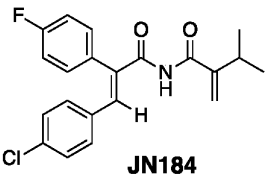
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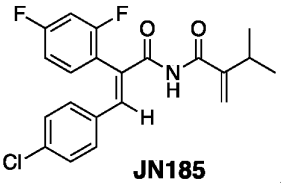
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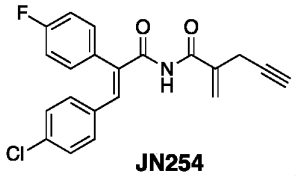
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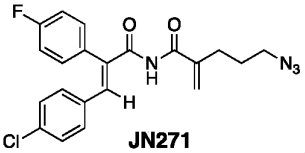
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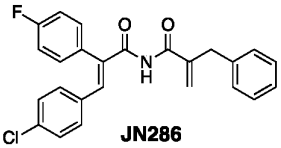
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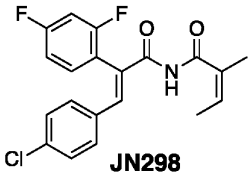
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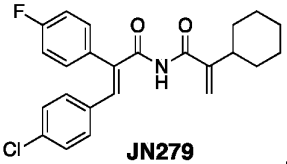
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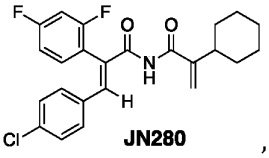
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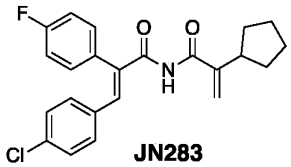
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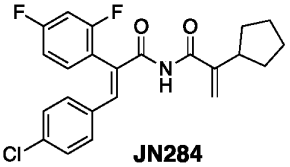
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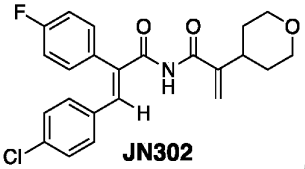
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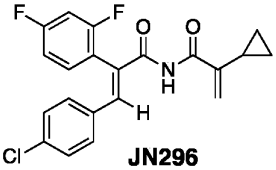
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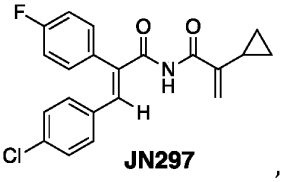
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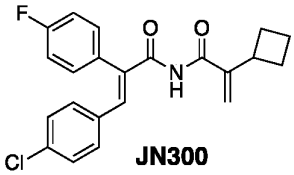
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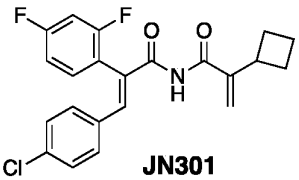
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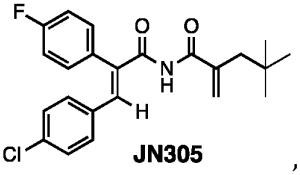
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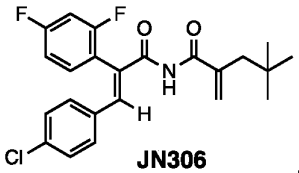
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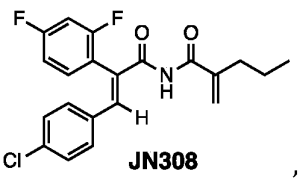
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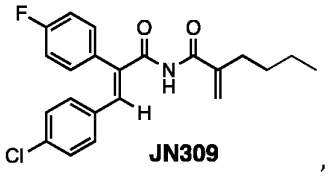
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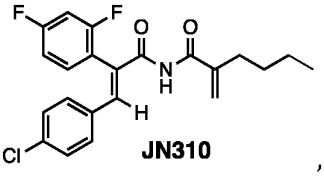
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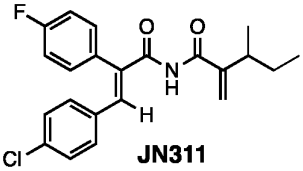
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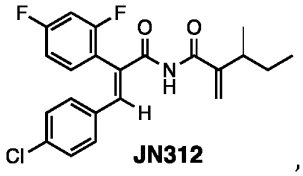
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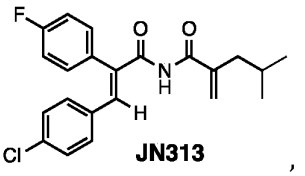
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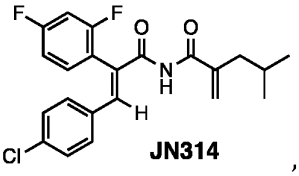
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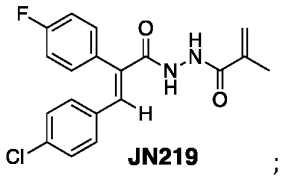
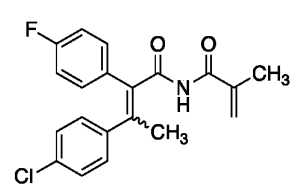

JN219 ;

or a pharmaceutically acceptable salt thereof.

29. The compound of claim 1, selected from: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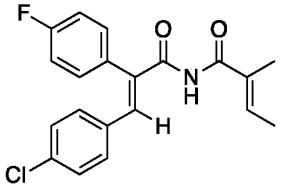
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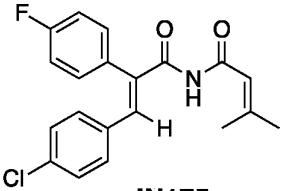
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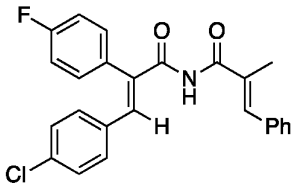
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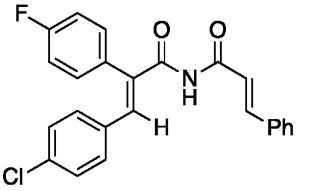
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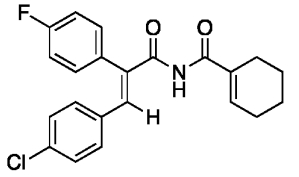
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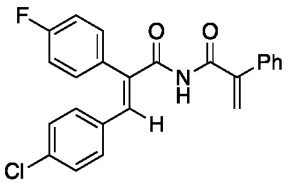
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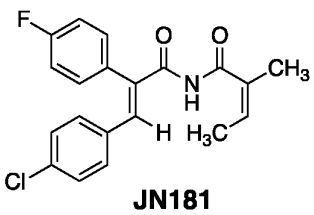
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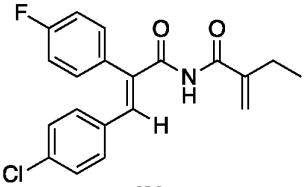
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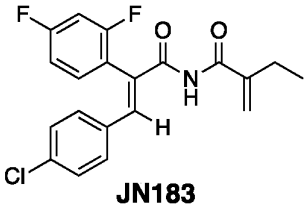
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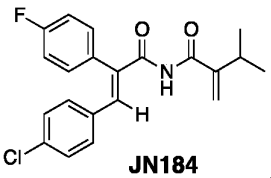
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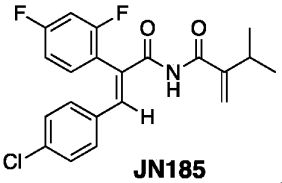
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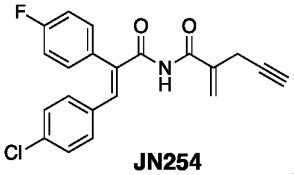
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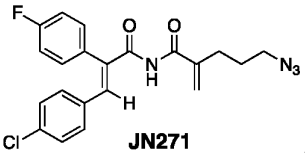
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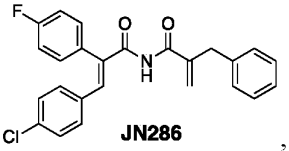
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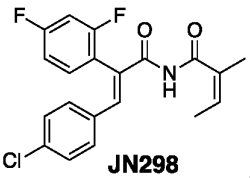
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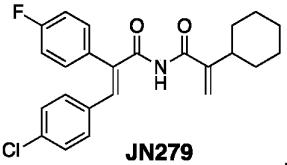
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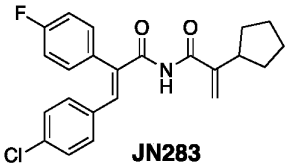
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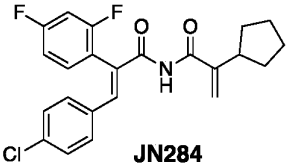
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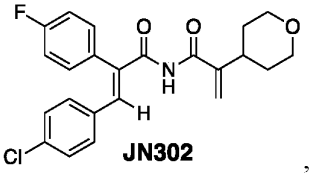
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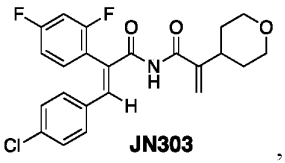
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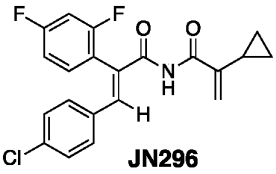
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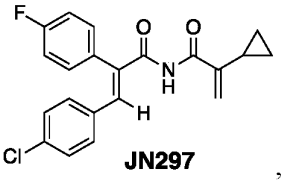
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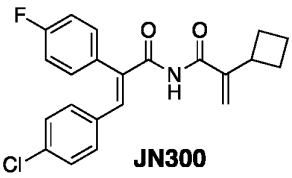
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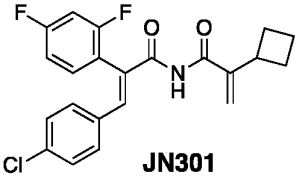
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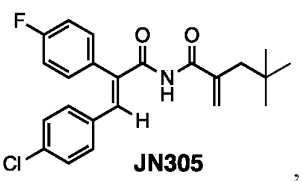
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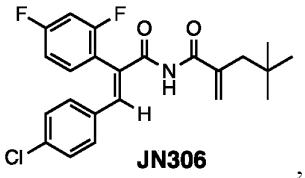
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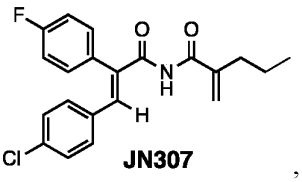
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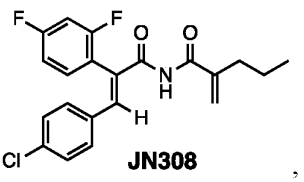
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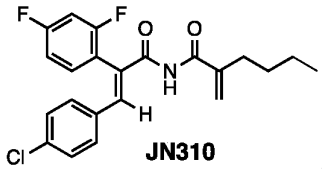
JN309,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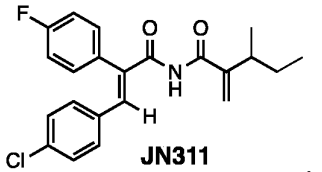
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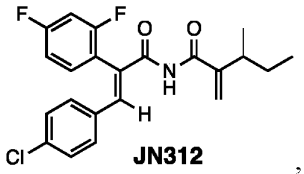
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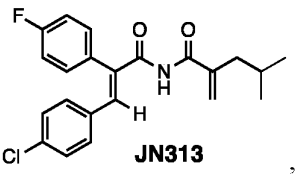
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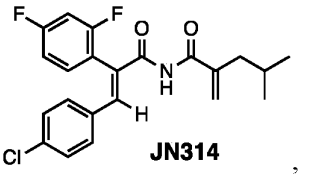
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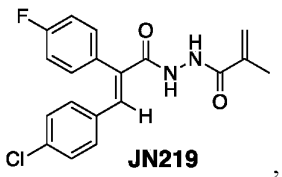
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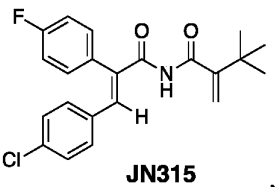
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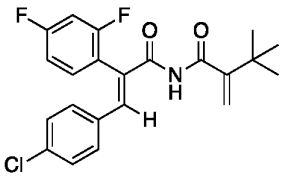
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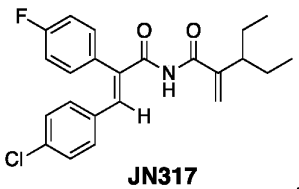
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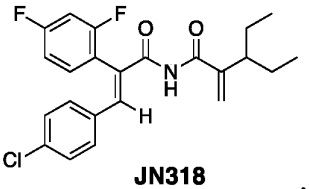
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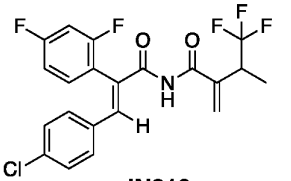
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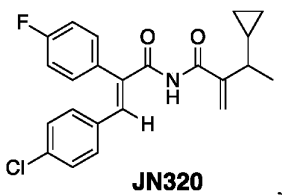
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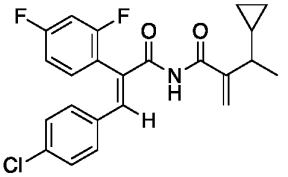
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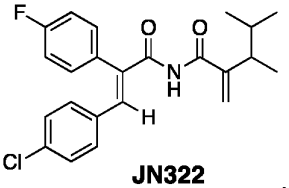
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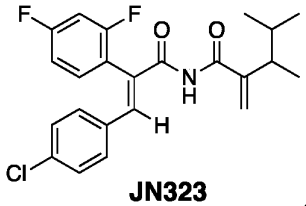
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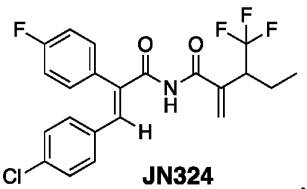
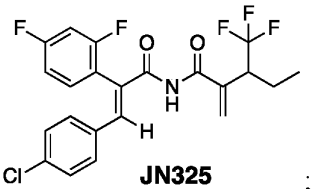
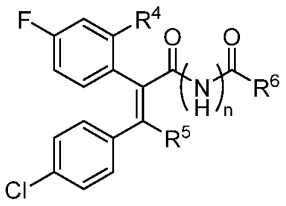

JN324, and


JN325; or a pharmaceutically acceptable salt thereof.

30. A compound having the structure of formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein:

R^4 is H or fluoro;

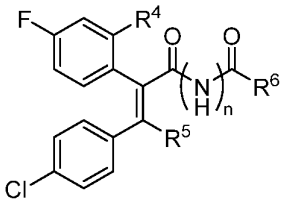
R^5 is H or alkyl;

R^6 is haloalkyl, cycloalkyl, or heterocycloalkyl; and

n is 1 or 2,

provided that if R^4 is fluoro, R^5 is H, and n is 1, then R^6 is not cyclopropyl.

31. A compound having the structure of formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein:

R^4 is H or fluoro;

R^5 is H or alkyl;

R^6 is thioalkyl, haloalkyl, cycloalkyl, or heterocycloalkyl; and

n is 1 or 2,

provided that if R^4 is fluoro, R^5 is H, and n is 1, then R^6 is not cyclopropyl.

32. The compound of claim 30 or 31, wherein R^6 is thioalkyl, such as C_1-C_4 thioalkyl.

33. The compound of claim 30 or 31, wherein R^6 is haloalkyl, such as C_1-C_3 haloalkyl.

34. The compound of claim 30 or 31, wherein R^6 is cycloalkyl, such as C_3-C_6 cycloalkyl.

35. The compound of claim 30 or 31, wherein R^6 is optionally substituted cyclopropyl.

36. The compound of claim 30 or 31, wherein R^6 is heterocycloalkyl, such as C_3-C_6 heterocycloalkyl.

37. The compound of claim 30 or 31, wherein R^6 is oxirane optionally substituted by alkyl, such as methyl.

38. The compound of any one of claims 30-37, wherein n is 1.

39. The compound of any one of claims 30-37, wherein n is 2.

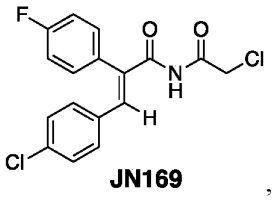
40. The compound of any one of claims 30-39, wherein R^2 is H.

41. The compound of any one of claims 30-39, wherein R^2 is fluoro.

42. The compound of any one of claims 30-41, wherein R^5 is H.

43. The compound of any one of claims 30-41, wherein R^5 is alkyl, such as C_1-C_6 alkyl.

44. The compound of claim 30, selected from: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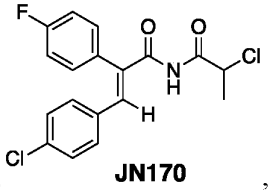
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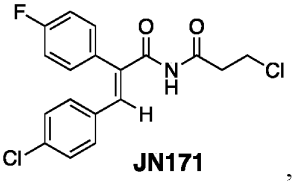
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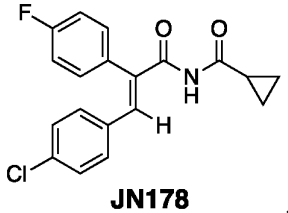
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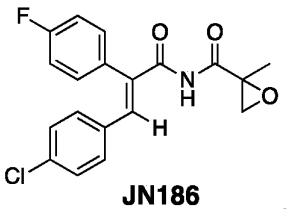
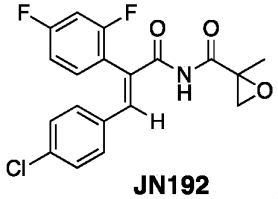
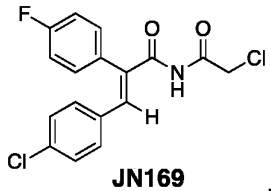

JN186 , and

JN192 ; or a pharmaceutically acceptable salt thereof.

45. The compound of claim 31, selected from: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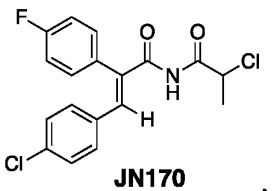
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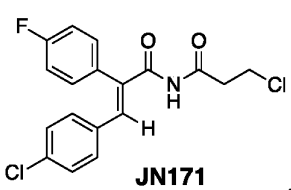
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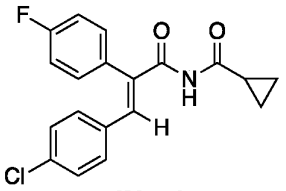
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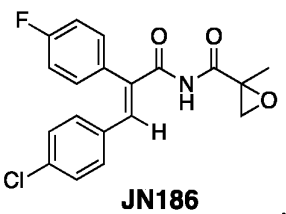
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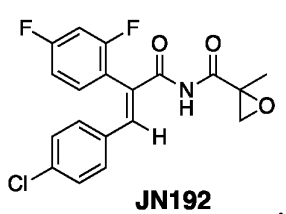
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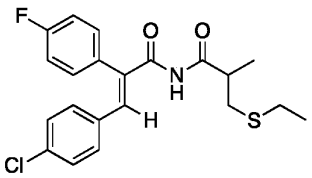
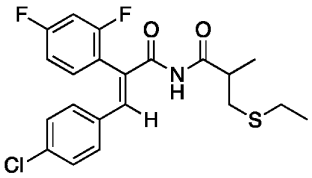

JN328 , and

JN329 ; or a pharmaceutically acceptable salt thereof.

46. A pharmaceutical composition comprising the compound of any one of claims 1-45 and a pharmaceutically acceptable excipient.

47. Use of a compound or composition of any one of claims 1-46 for inhibiting an androgen receptor.

48. Use of a compound or composition of any one of claims 1-46 for inducing degradation of an androgen receptor in a cell expressing an androgen receptor.

49. Use of a compound or composition of any one of claims 1-46 for treating a mammal suffering from cancer.

50. The use of claim 49, wherein the cancer is prostate cancer.

51. The use of claim 49, wherein the cancer is castration-resistant prostate cancer.

52. The use of any one of claims 49-51, wherein the cancer is metastatic.

53. The use of any one of claims 49-51, wherein the cancer is non-metastatic.

54. The use of any one of claims 49-53, wherein the cancer is resistant to antiandrogen therapy.

55. The use of claim 54, wherein the cancer is resistant to treatment with enzalutamide, bicalutamide, abiraterone, flutamide, or nilutamide.

56. The use of claim 54, wherein the cancer is resistant to treatment with abiraterone acetate.

57. The use of claim 54, wherein the cancer is resistant to conjoint treatment with abiraterone acetate and prednisone.

58. A method of inhibiting an androgen receptor, comprising contacting the androgen receptor with a compound or composition of any one of claims 1-46.

59. A method of inducing degradation of an androgen receptor, comprising contacting the androgen receptor with a compound or composition of any one of claims 1-46.

60. A method of treating a mammal suffering from cancer, comprising administering a compound or composition of any one of claims 1-46.

61. The method of claim 60, wherein the cancer is prostate cancer.

62. The method of claim 61, wherein the cancer is castration-resistant prostate cancer.

63. The method of any one of claims 60-62, wherein the cancer is metastatic.

64. The method of any one of claims 60-62, wherein the cancer is non-metastatic.

65. The method of any one of claims 60-64, wherein the cancer is resistant to antiandrogen therapy.

66. The method of claim 65, wherein the cancer is resistant to treatment with enzalutamide, bicalutamide, abiraterone, flutamide, or nilutamide.

67. The use of claim 65, wherein the cancer is resistant to treatment with abiraterone acetate.

68. The use of claim 65, wherein the cancer is resistant to conjoint treatment with abiraterone acetate and prednisone.

FIG. 1

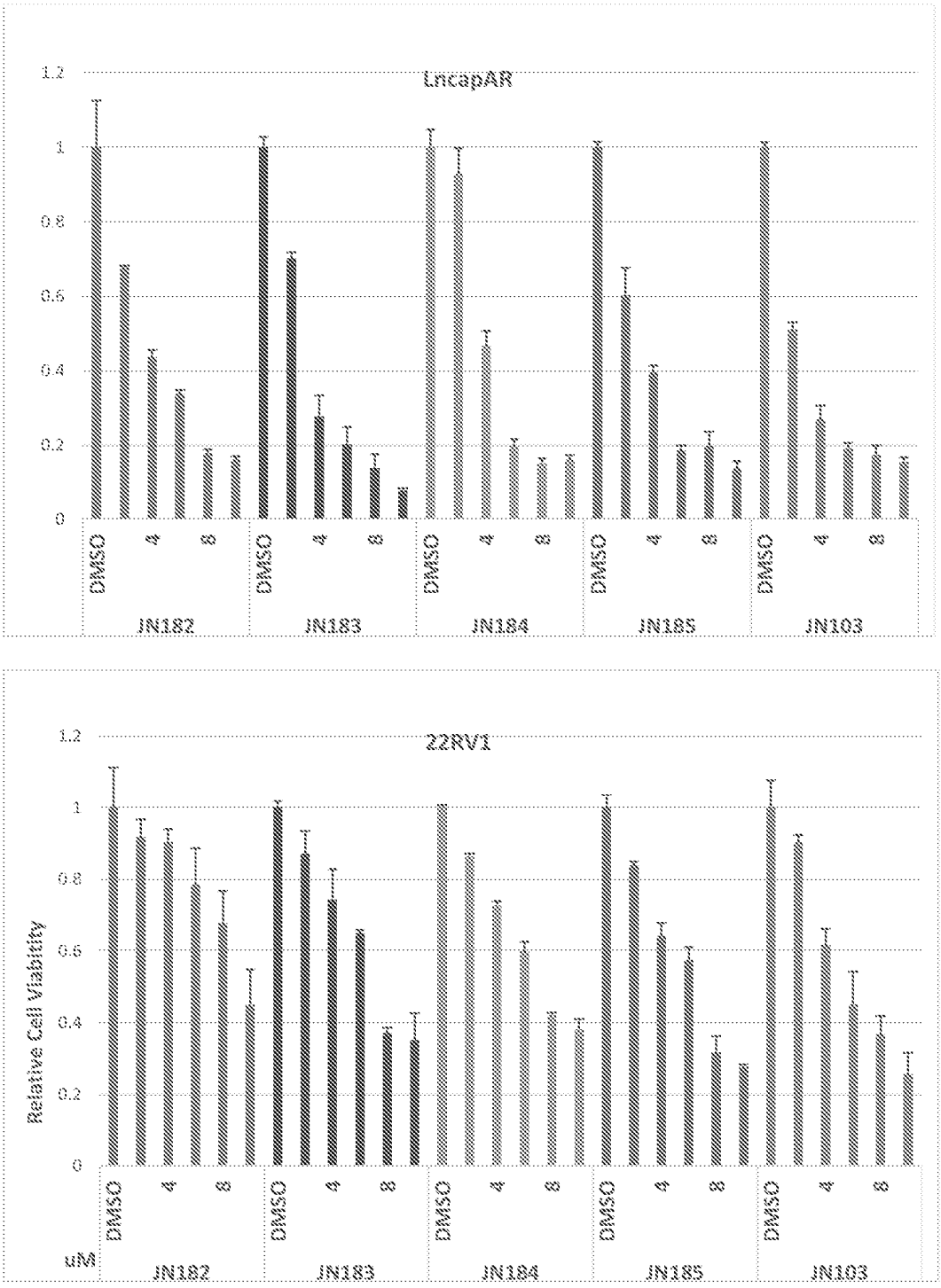

LncapAR
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
JN182
JN183
JN184
JN185
JN103
22RV1
Relative Cell Viability
uM

FIG. 2

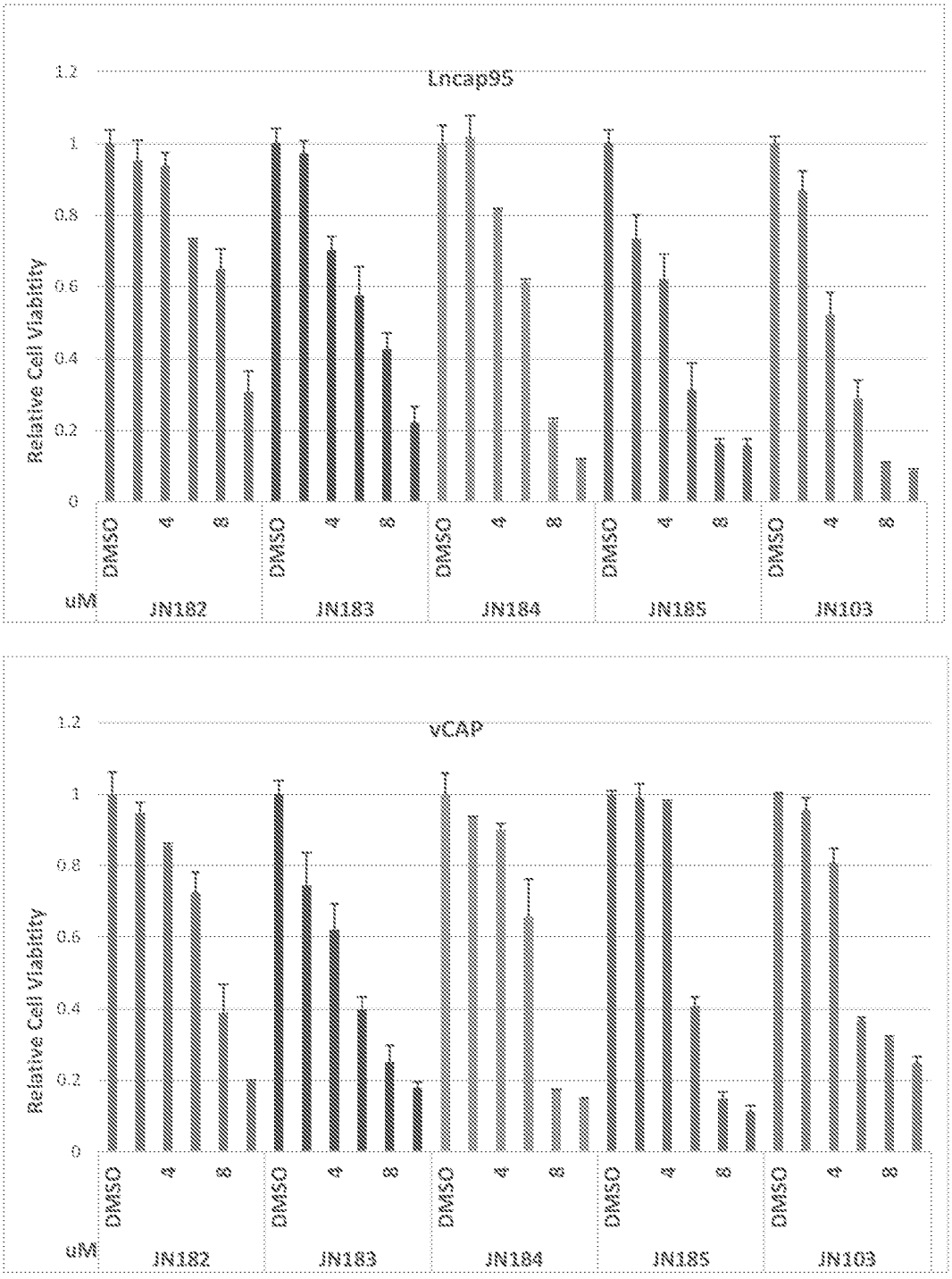
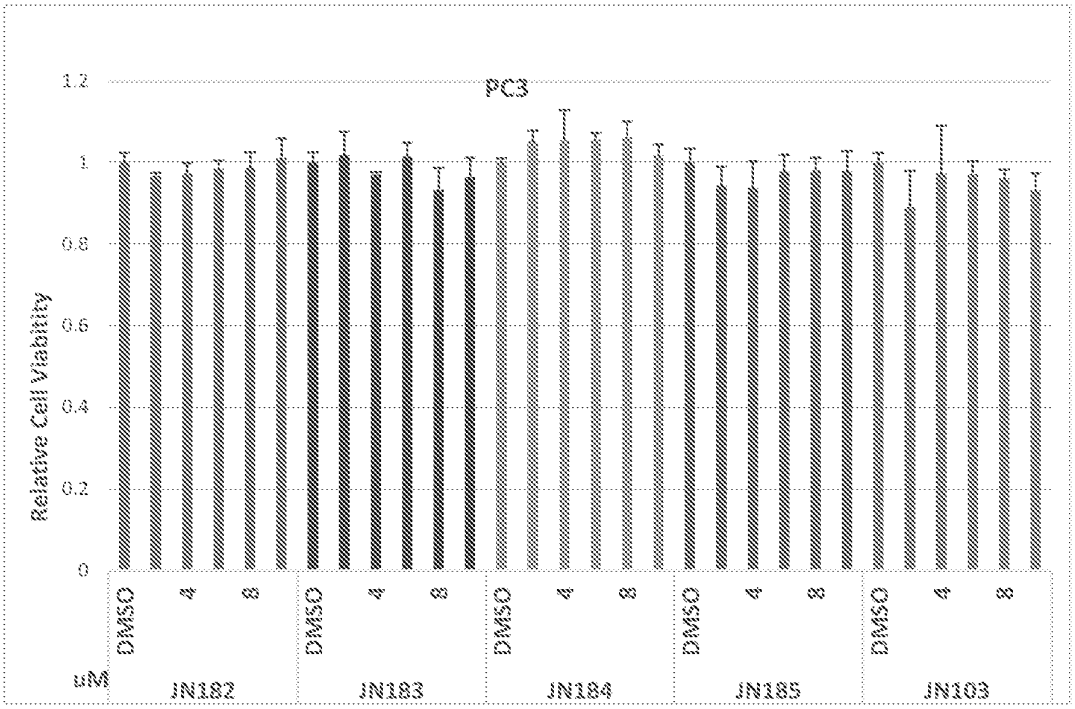
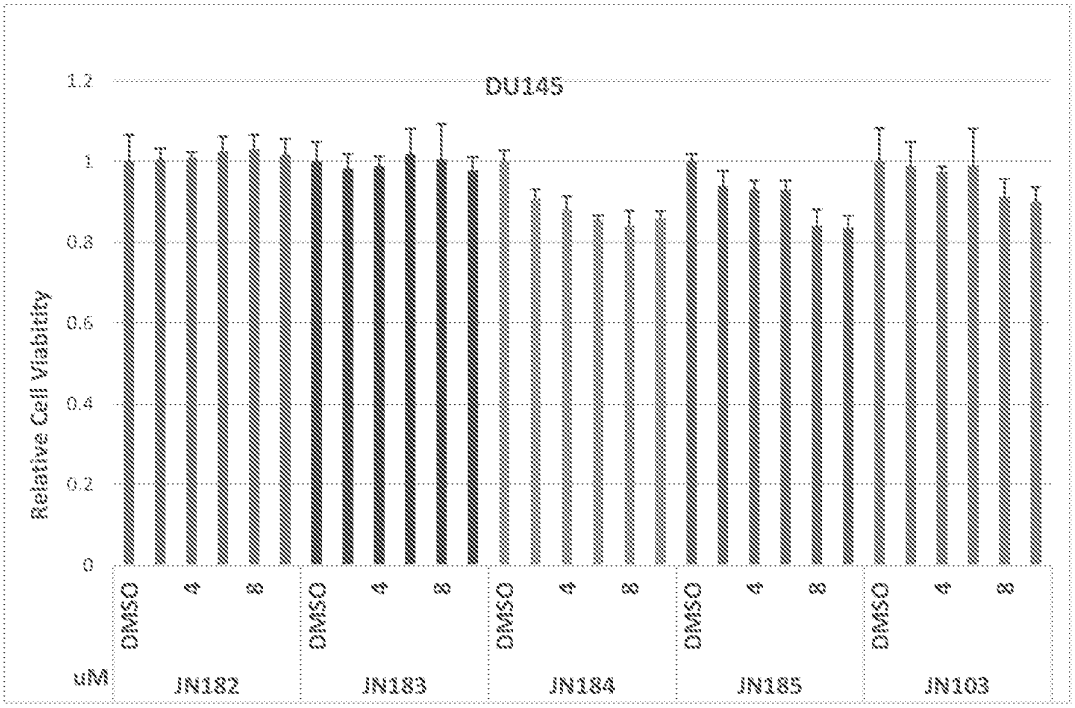

Lncap95
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
uM
JN182
JN183
JN184
JN185
JN103
vCAP
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
uM
JN182
JN183
JN184
JN185
JN103

FIG. 3


PC3
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
uM
JN182
JN183
JN184
JN185
JN103


DU145
Relative Cell Viability
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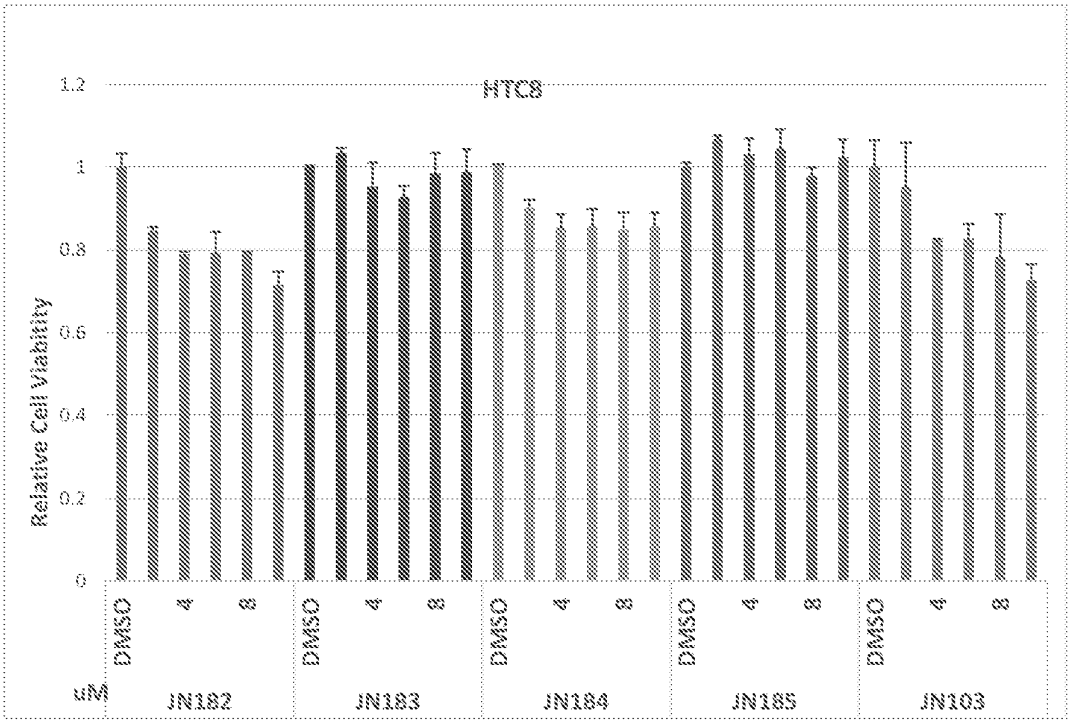
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
uM
JN182
JN183
JN184
JN185
JN103

FIG. 4


HTC8
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
uM
JN182
JN183
JN184
JN185
JN103

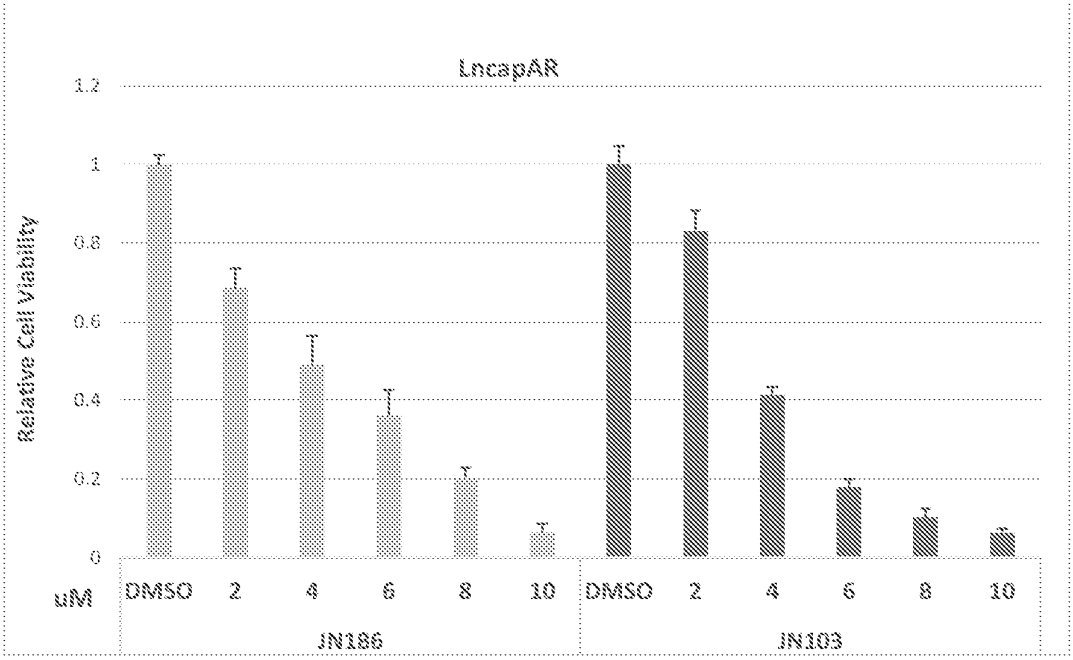
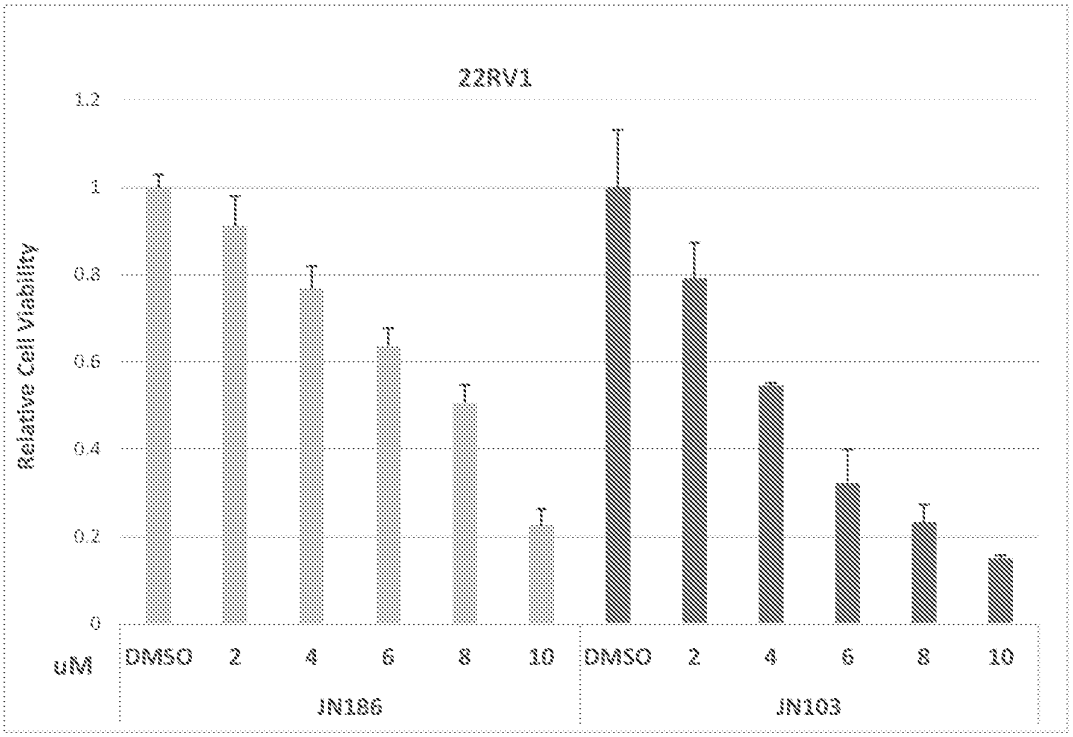

LncapAR
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
uM
JN186
JN103

FIG. 5


22RV1
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO 2 4 6 8 10 DMSO 2 4 6 8 10
JN186
JN103

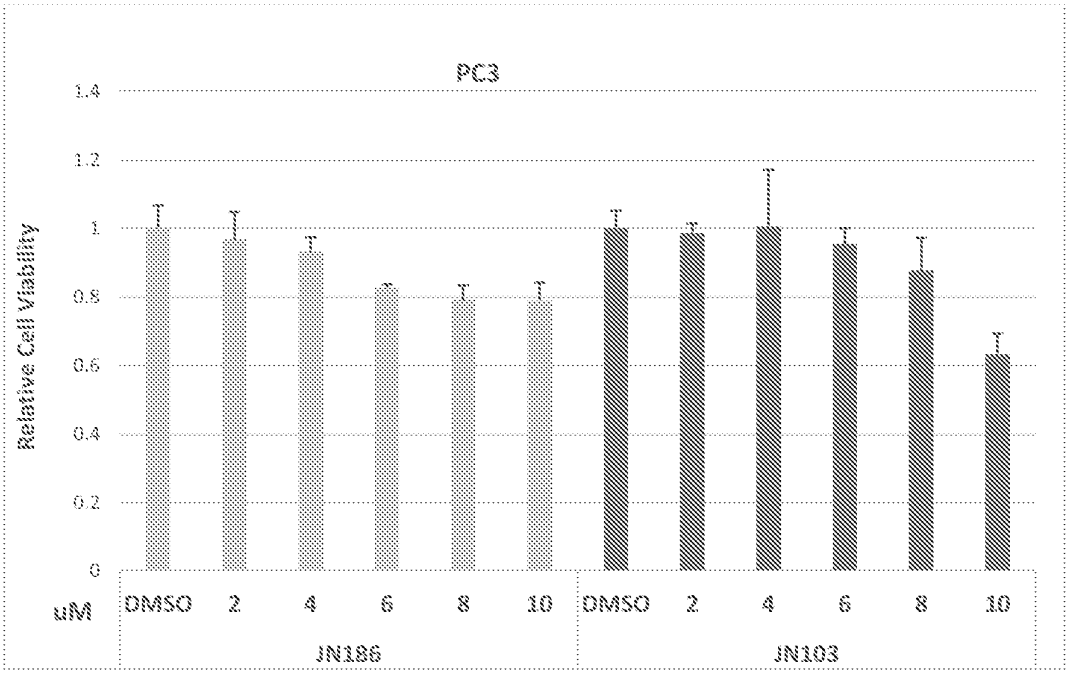

PC3
Relative Cell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO 2 4 6 8 10 DMSO 2 4 6 8 10
JN186
JN103

FIG. 6

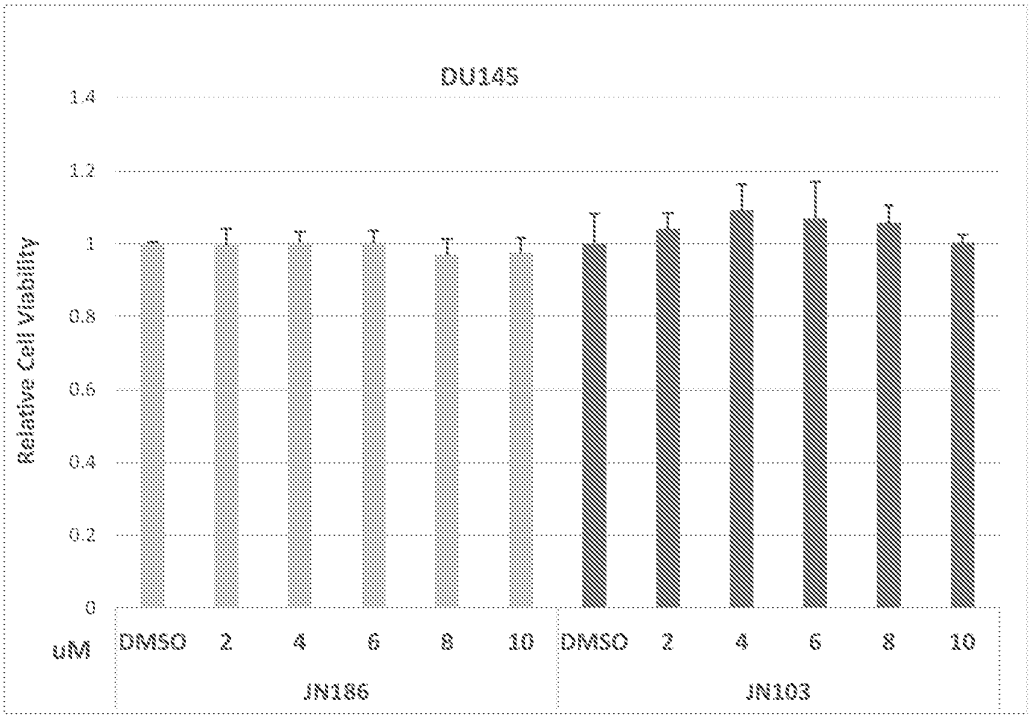

DU145
Relative Cell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
DMSO
2
4
6
8
10
JN186
JN103

FIG. 7

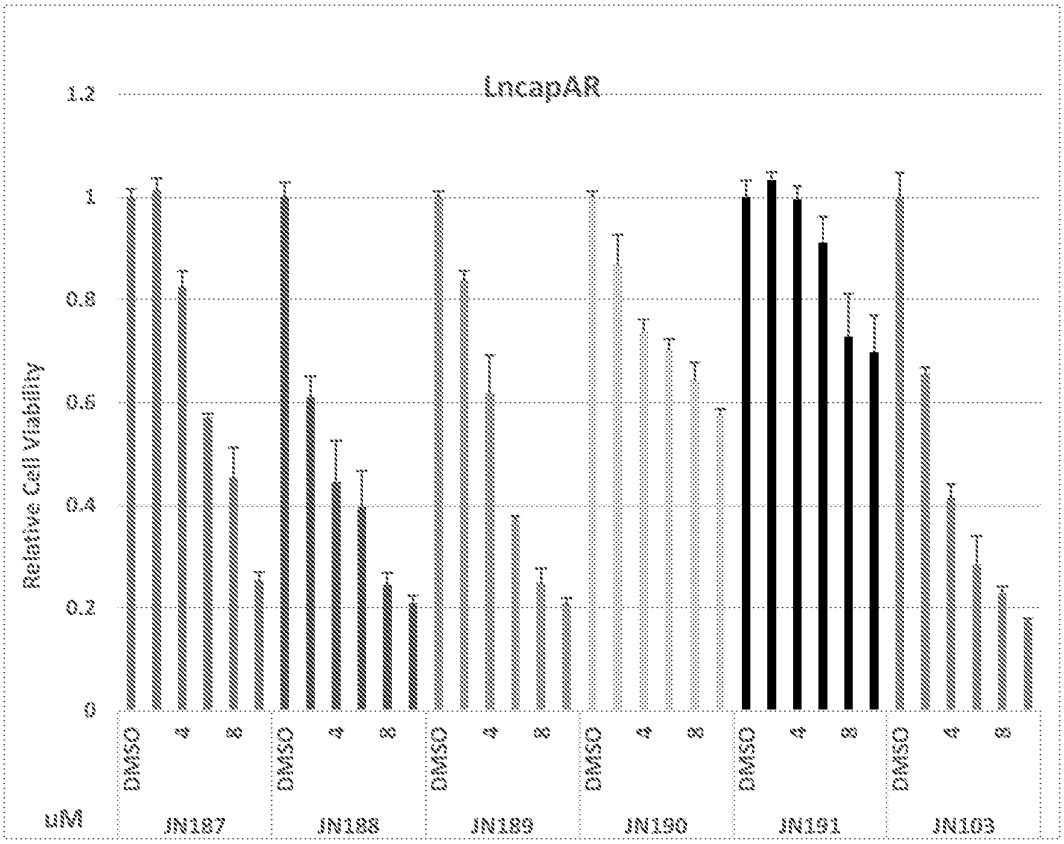

LncapAR
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
uM
JN187
JN188
JN189
JN190
JN191
JN103

FIG. 8

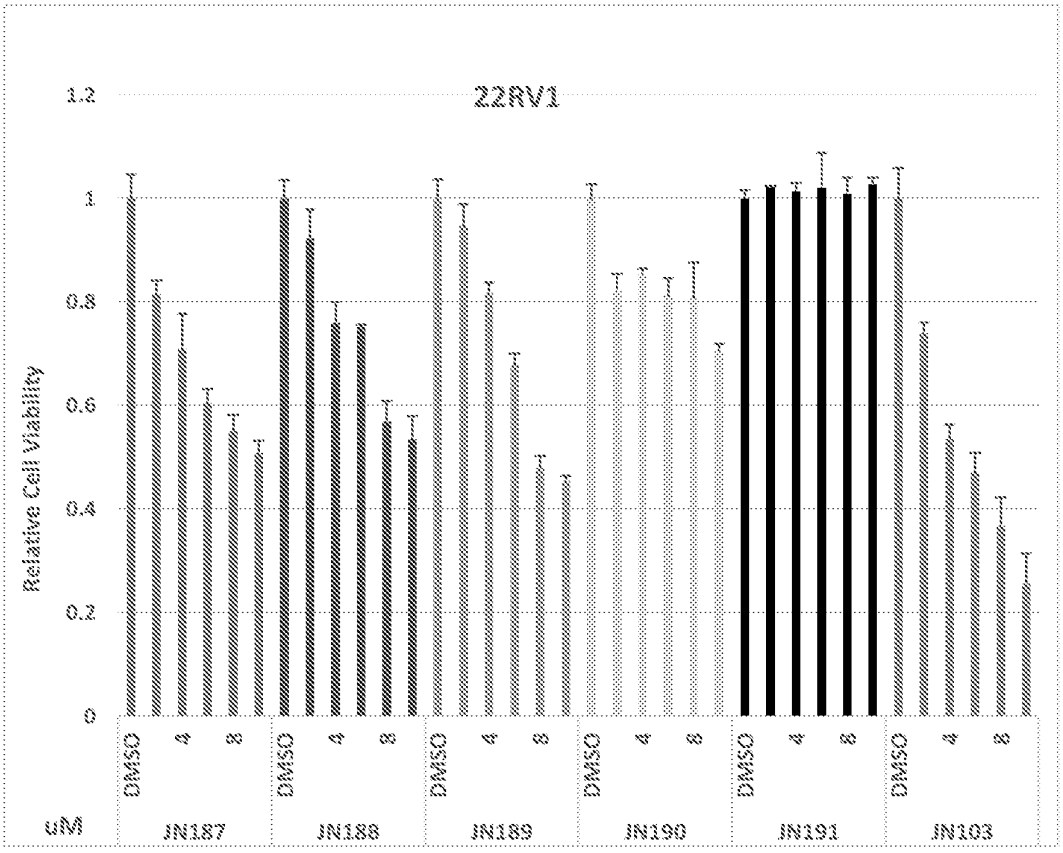

22RV1
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
uM
JN187
JN188
JN189
JN190
JN191
JN103

FIG. 9

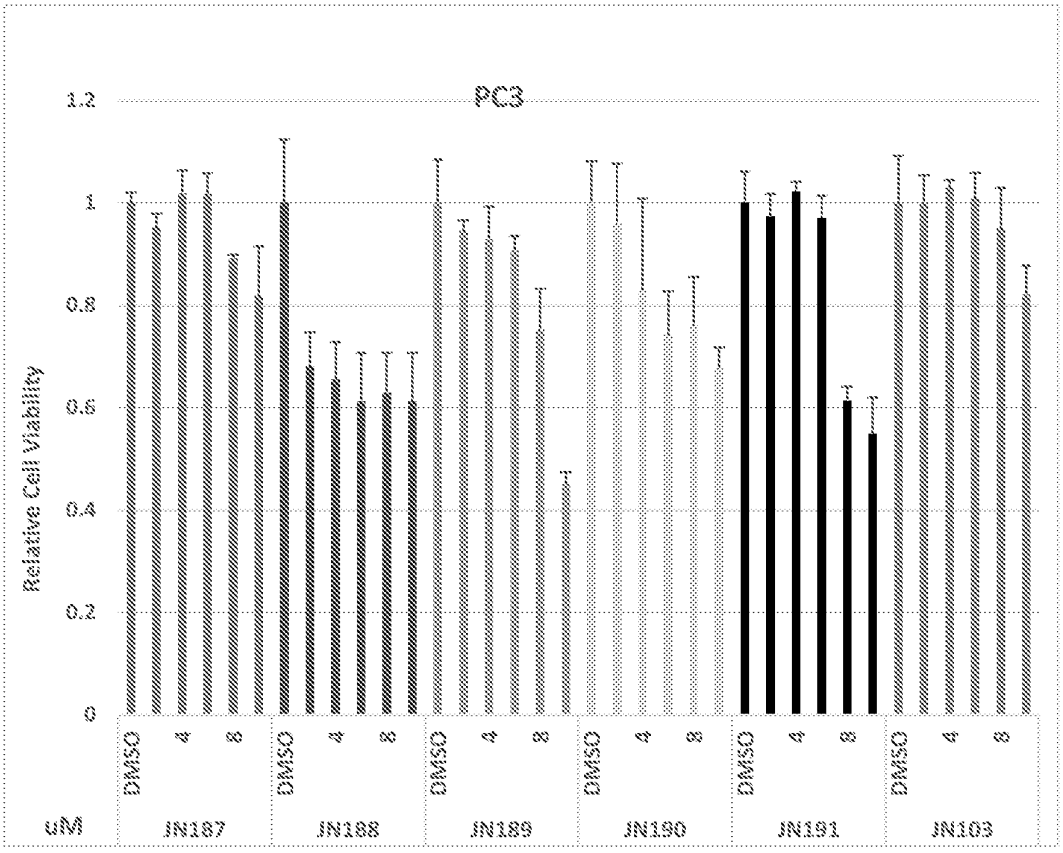

PC3
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
uM
JN187
JN188
JN189
JN190
JN191
JN103

FIG. 10

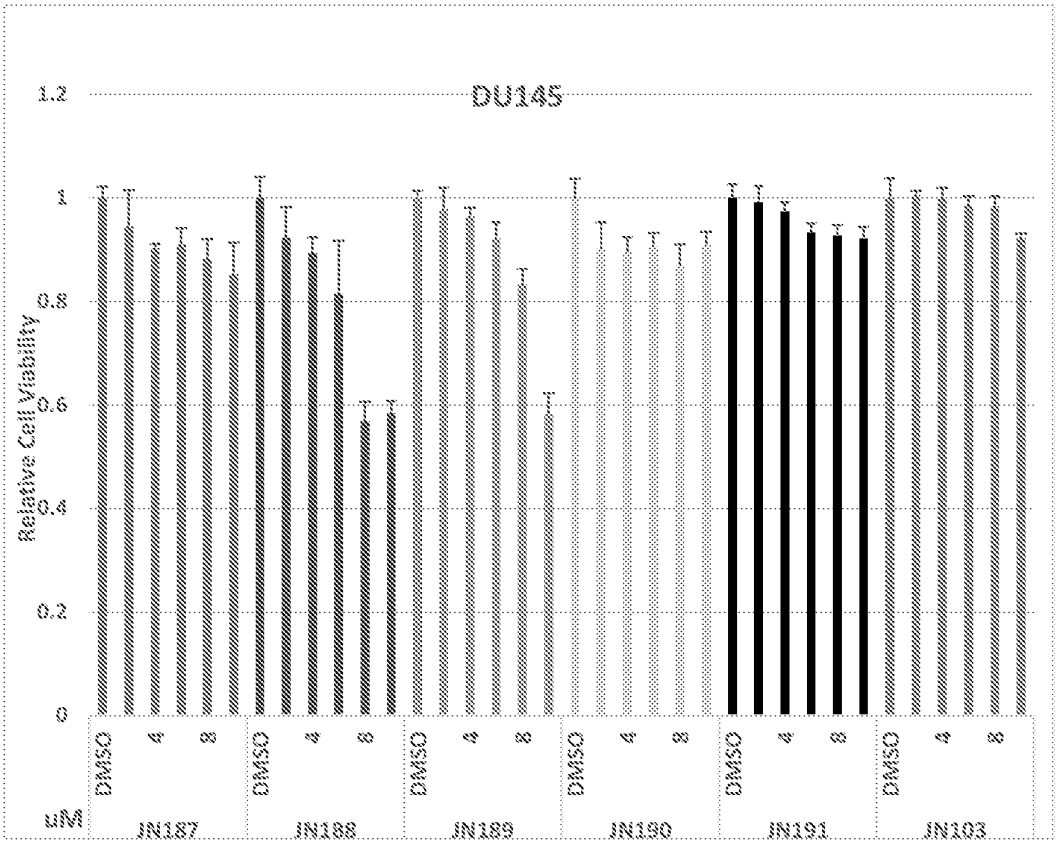

DU145
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
uM
JN187
JN188
JN189
JN190
JN191
JN103

FIG. 11

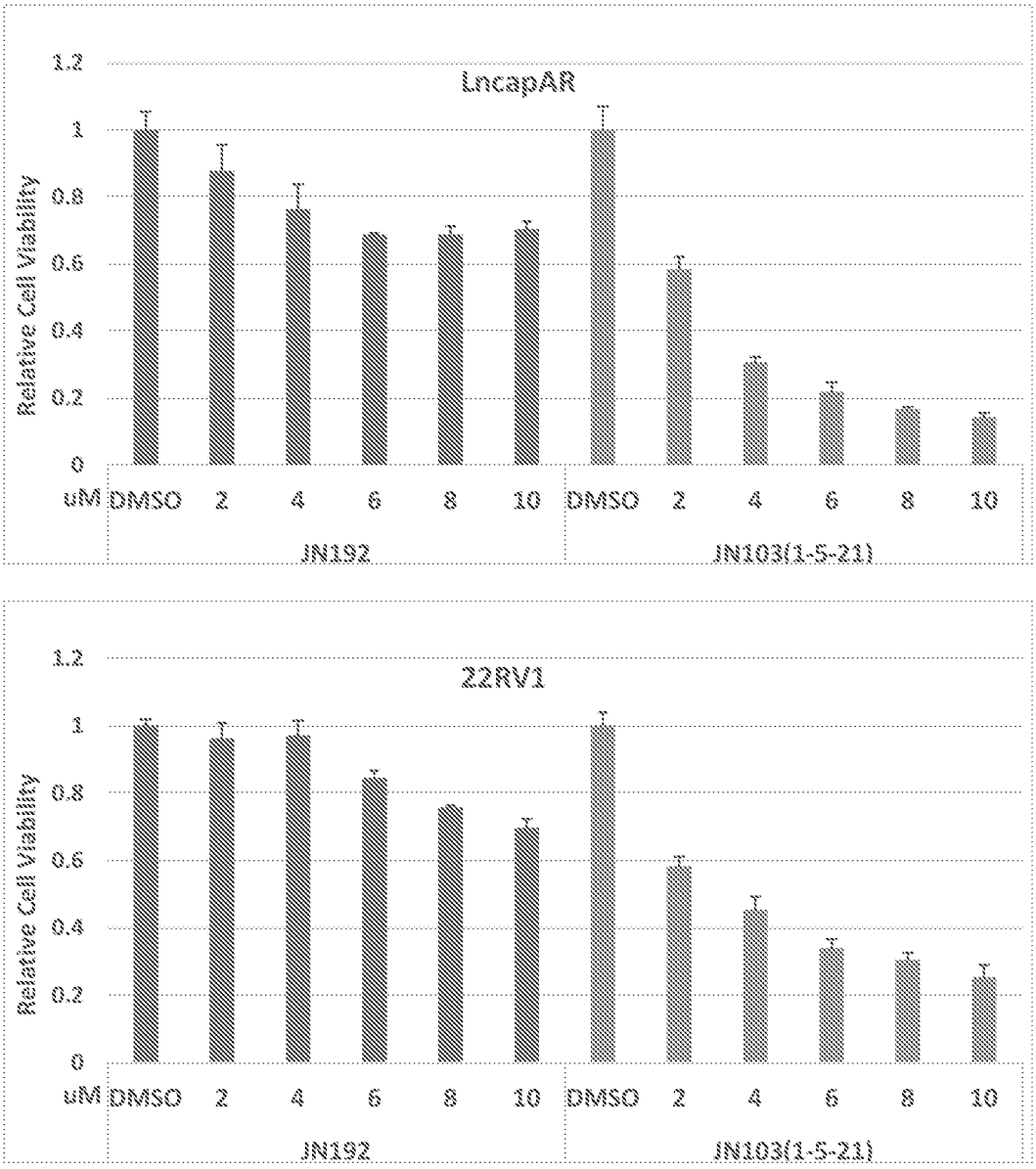
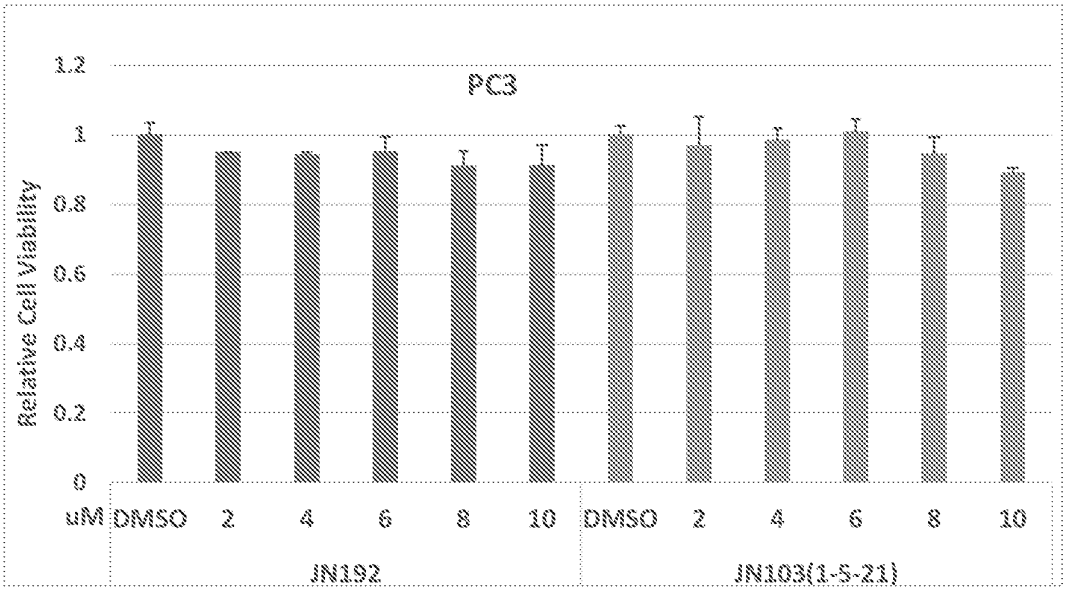

LncapAR
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO 2 4 6 8 10 DMSO 2 4 6 8 10
JN192
JN103(1-5-21)
22RV1
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO 2 4 6 8 10 DMSO 2 4 6 8 10
JN192
JN103(1-5-21)

FIG. 12


PC3
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
DMSO
2
4
6
8
10
JN192
JN103(1-5-21)

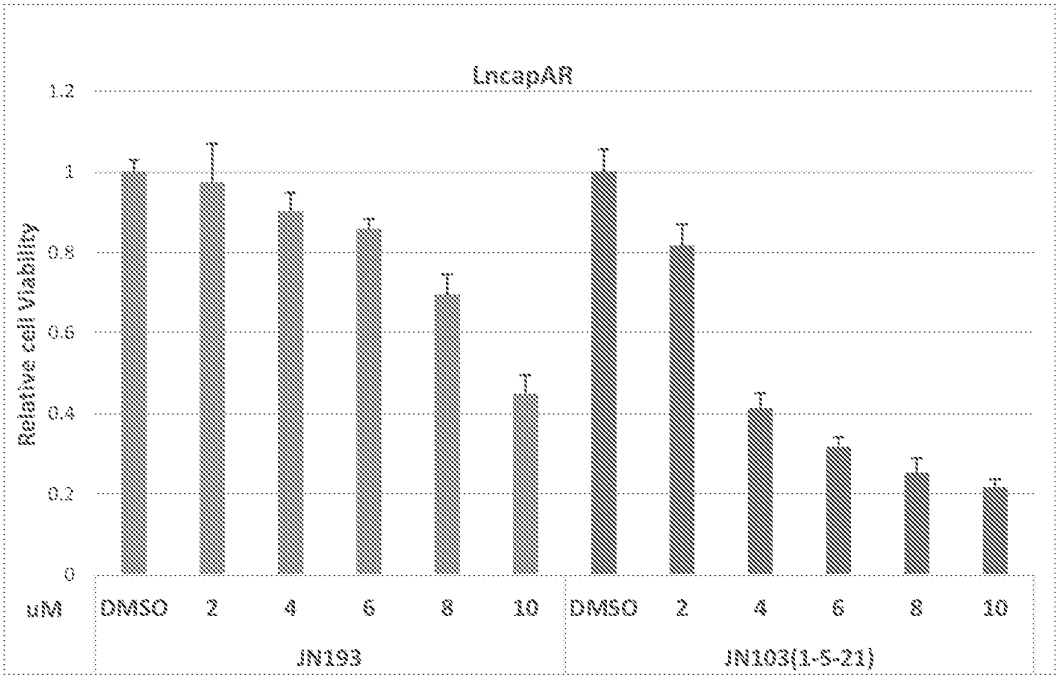
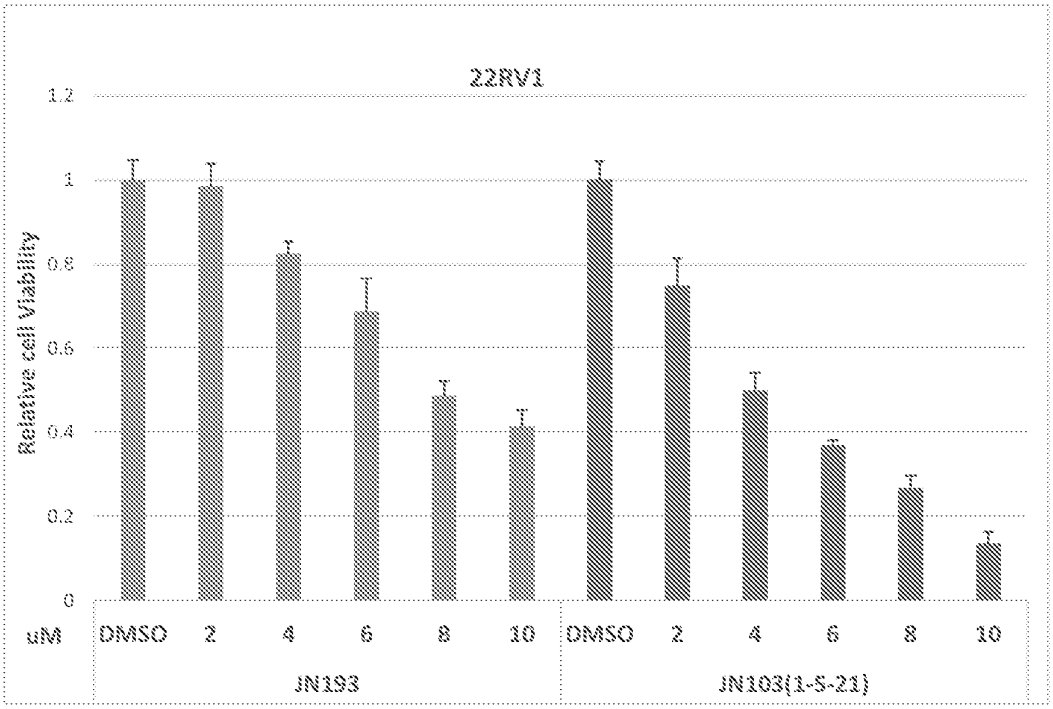

LncapAR
Relative cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
DMSO
2
4
6
8
10
JN193
JN103(1-5-21)

FIG. 13


22RV1
Relative cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
DMSO
2
4
6
8
10
JN193
JN103(1-5-21)

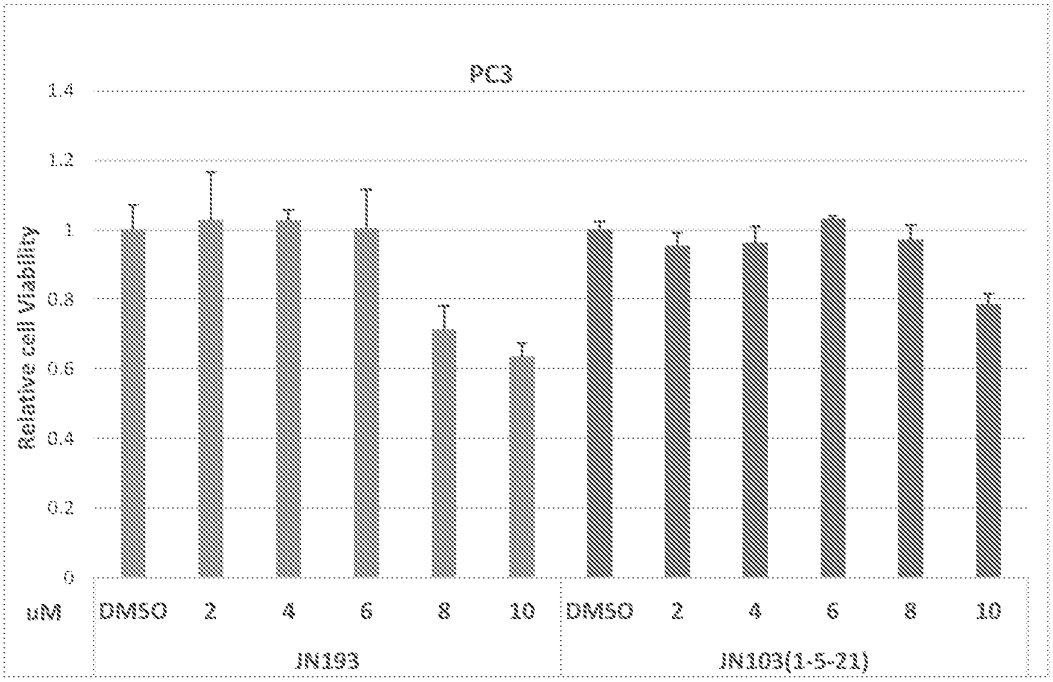

PC3
Relative cell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
DMSO
2
4
6
8
10
JN193
JN103(1-5-21)

FIG. 14

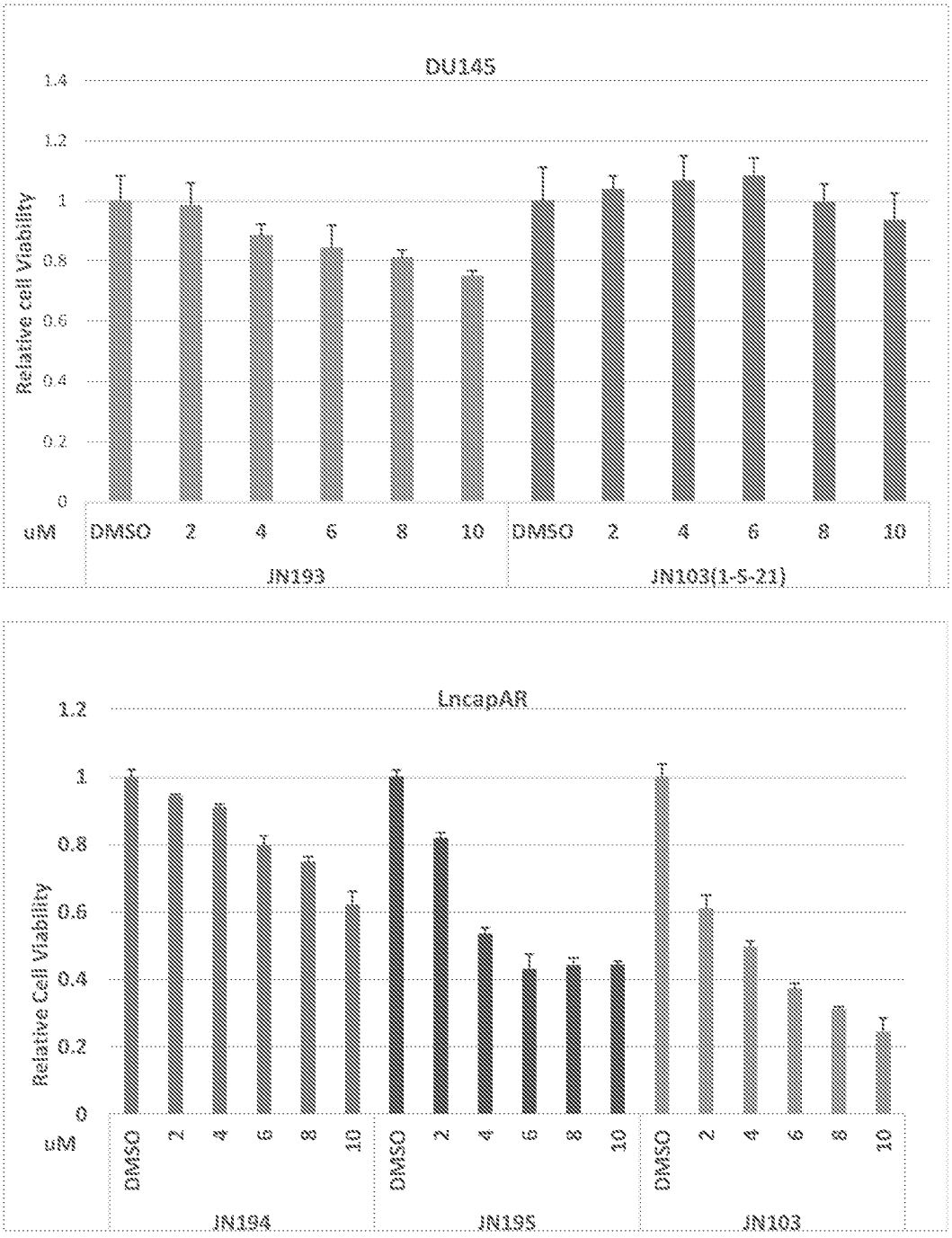

DU145
Relative cell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO 2 4 6 8 10 DMSO 2 4 6 8 10
JN193
JN103(1-5-21)
LncapAR
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO 2 4 6 8 10 DMSO 2 4 6 8 10 DMSO 2 4 6 8 10
JN194
JN195
JN103

FIG. 15

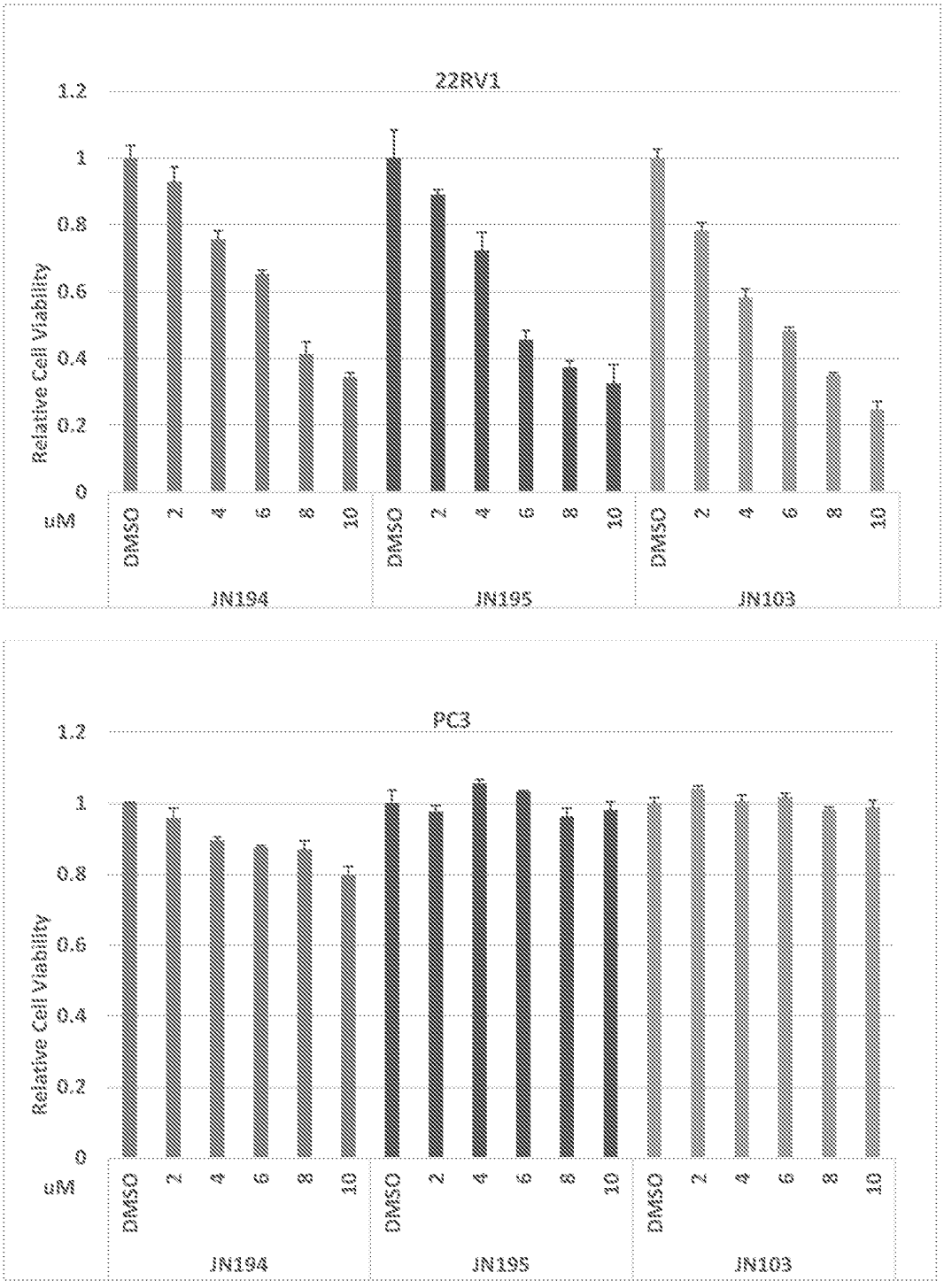

22RV1
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN194
JN195
JN103
PC3
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN194
JN195
JN103

FIG. 16

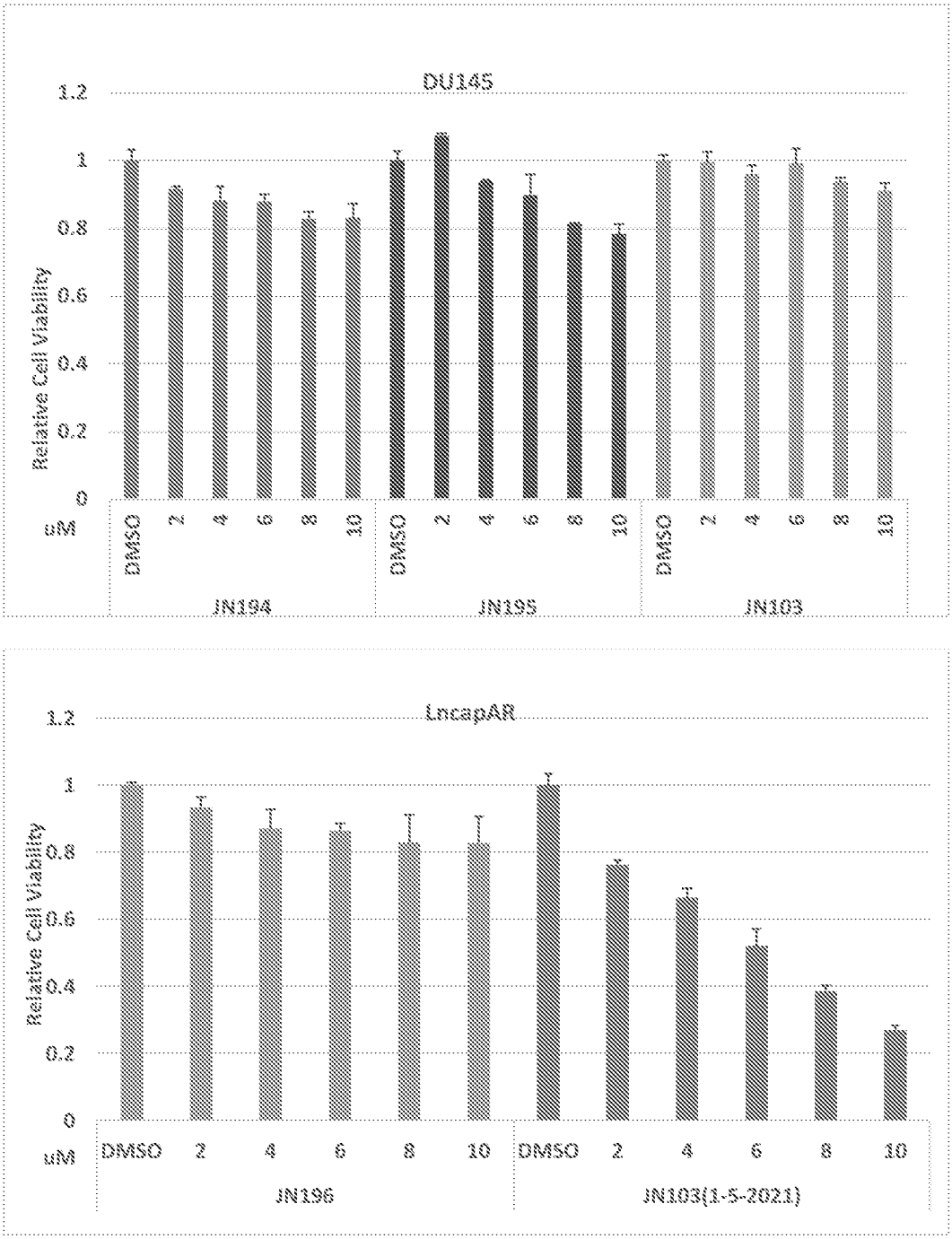
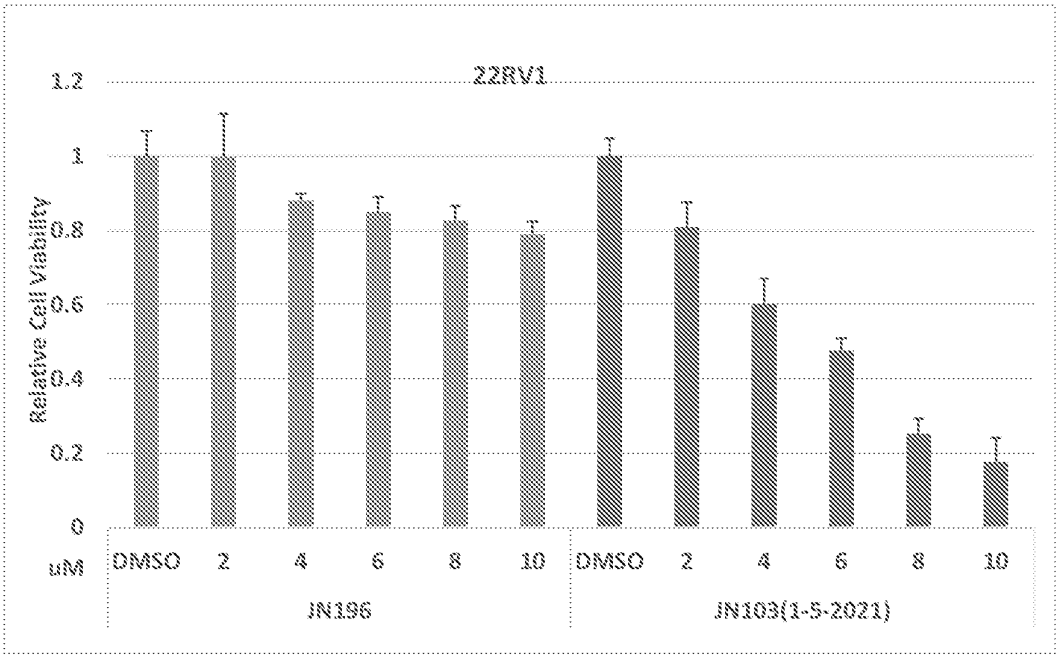

DU145
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN194
JN195
JN103
LncapAR
JN196
JN103(1-5-2021)

FIG. 17


22RV1
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO 2 4 6 8 10
JN196
DMSO 2 4 6 8 10
JN103(1-5-2021)

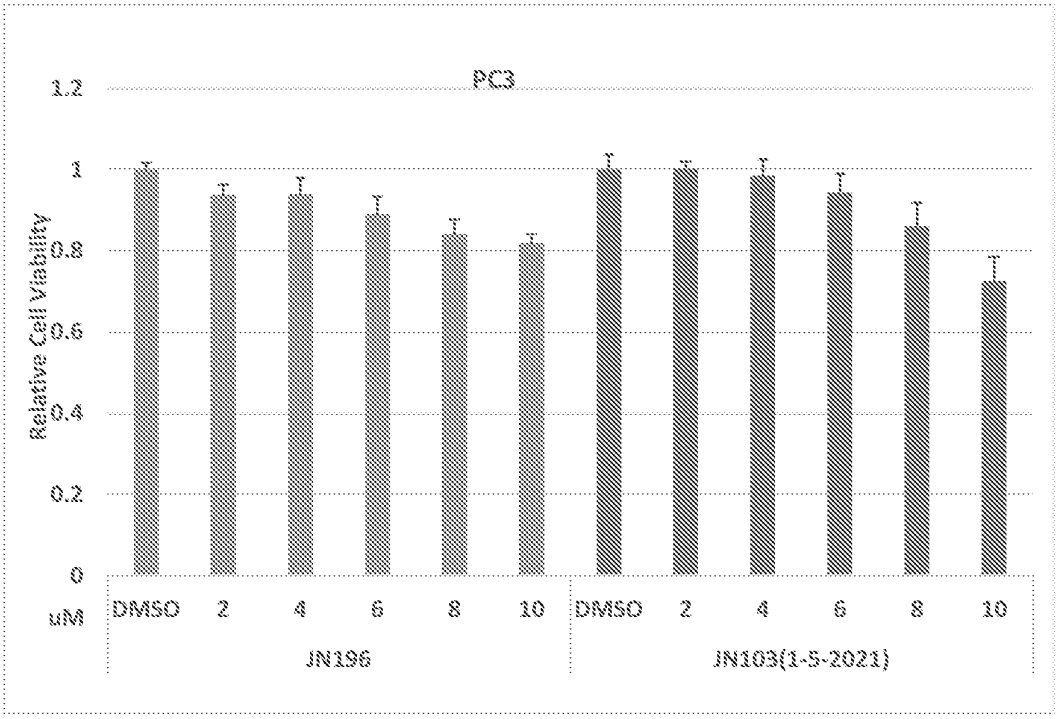
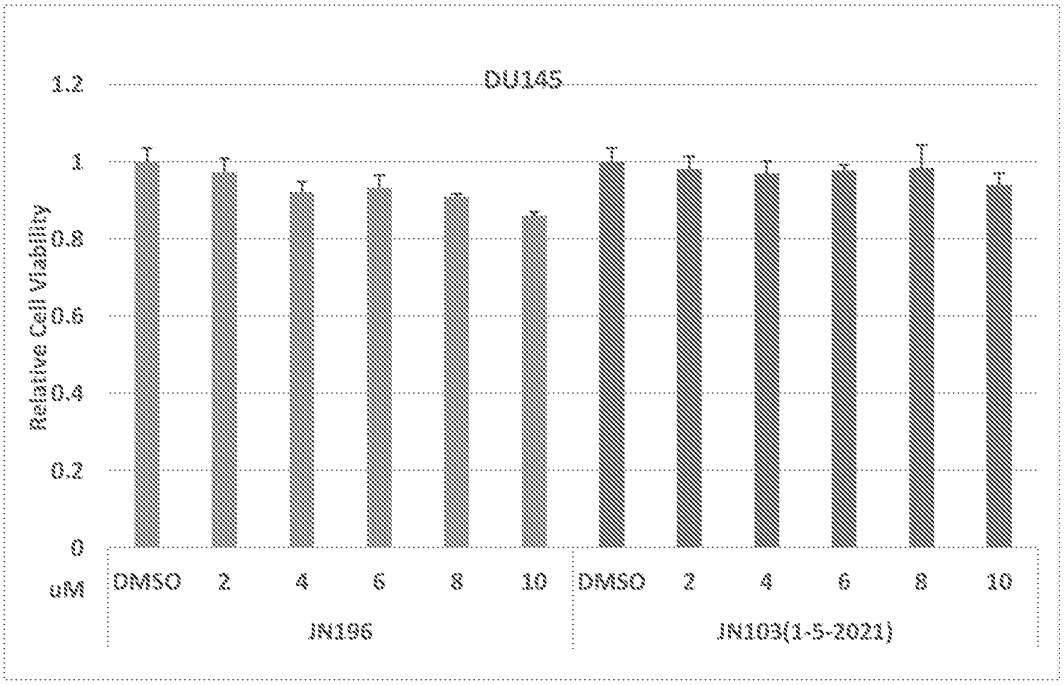

PC3
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO 2 4 6 8 10
JN196
DMSO 2 4 6 8 10
JN103(1-5-2021)

FIG. 18


DU145
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO 2 4 6 8 10 DMSO 2 4 6 8 10
JN196
JN103(1-5-2021)

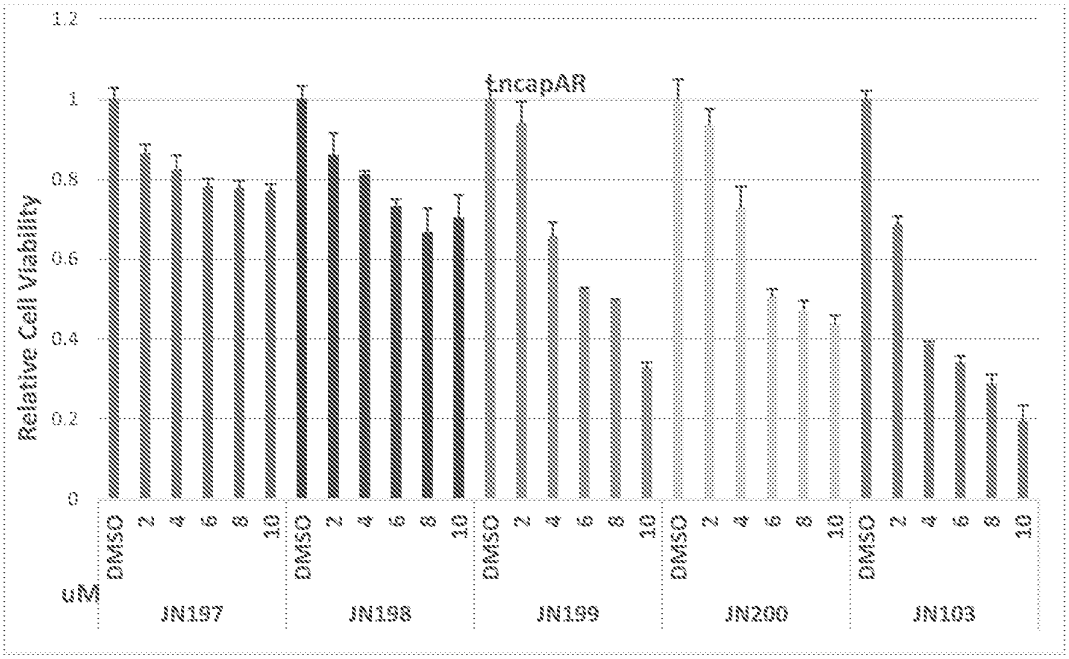
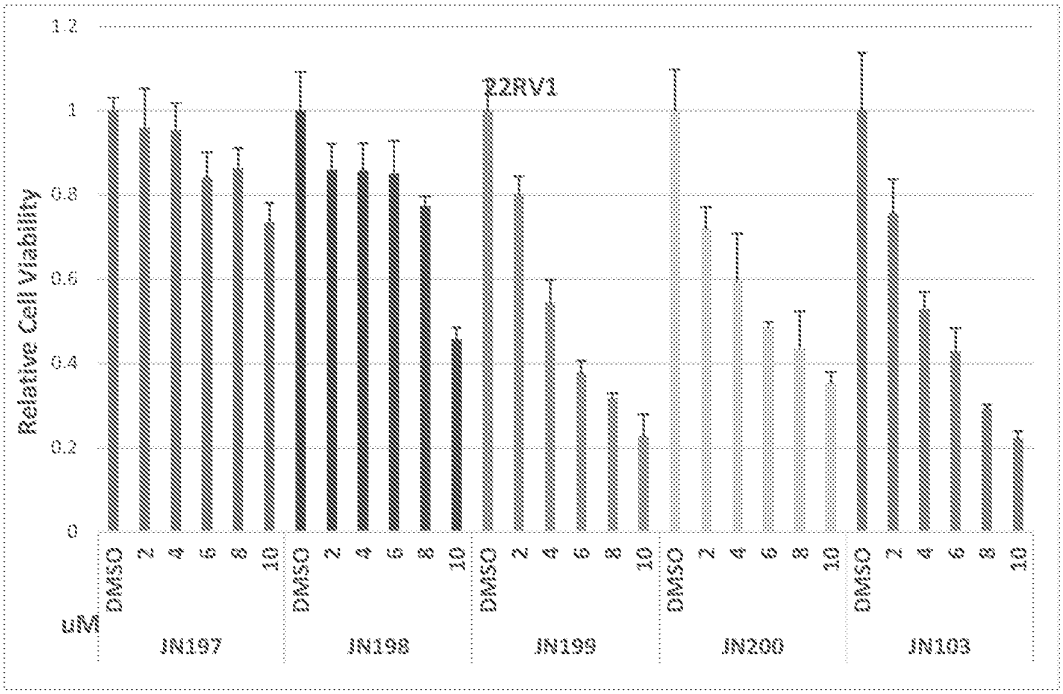

LncapAR
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO 2 4 6 8 10 DMSO 2 4 6 8 10 DMSO 2 4 6 8 10 DMSO 2 4 6 8 10 DMSO 2 4 6 8 10
JN197
JN198
JN199
JN200
JN103

FIG. 19


22RV1
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
uM
JN197
JN198
JN199
JN200
JN103

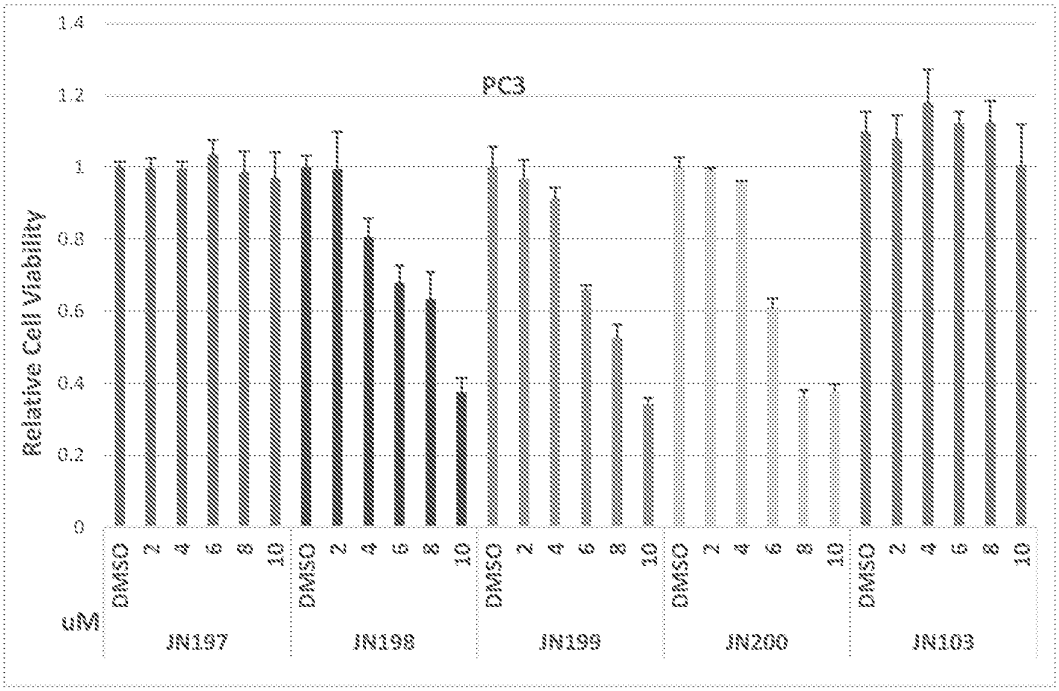
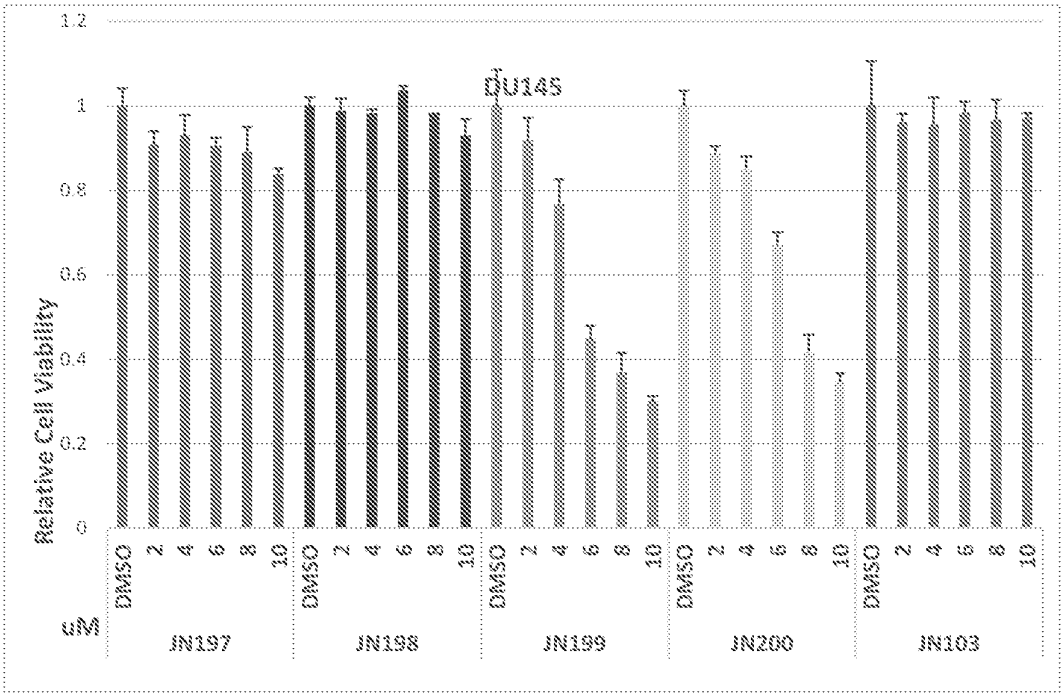

PC3
Relative Cell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
uM
JN197
JN198
JN199
JN200
JN103

FIG. 20


DU145
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
uM
JN197
JN198
JN199
JN200
JN103

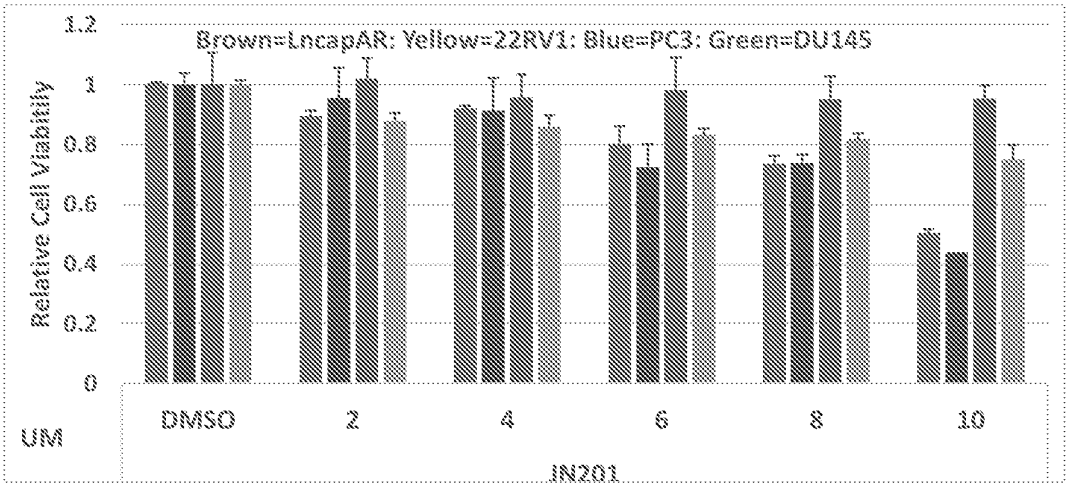
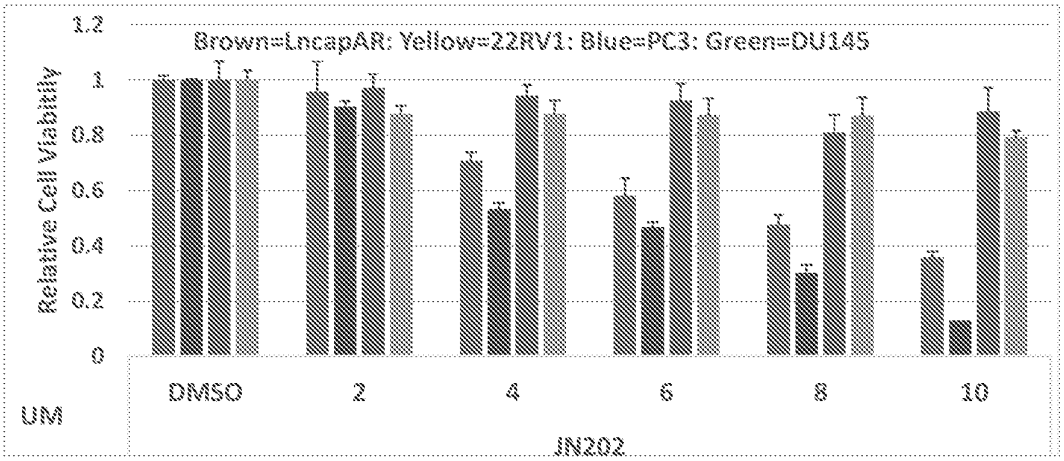
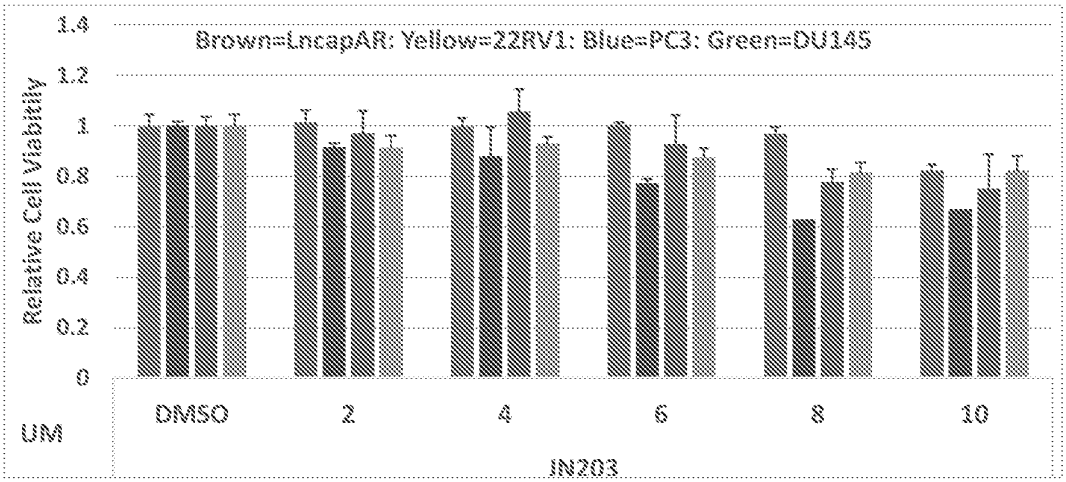

Brown=LncapAR: Yellow=22RV1: Blue=PC3: Green=DU145
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
UM
JN201

FIG. 21


Brown=LncapAR: Yellow=22RV1: Blue=PC3: Green=DU145
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
UM
JN202


Brown=LncapAR: Yellow=22RV1: Blue=PC3: Green=DU145
Relative Cell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
UM
JN203

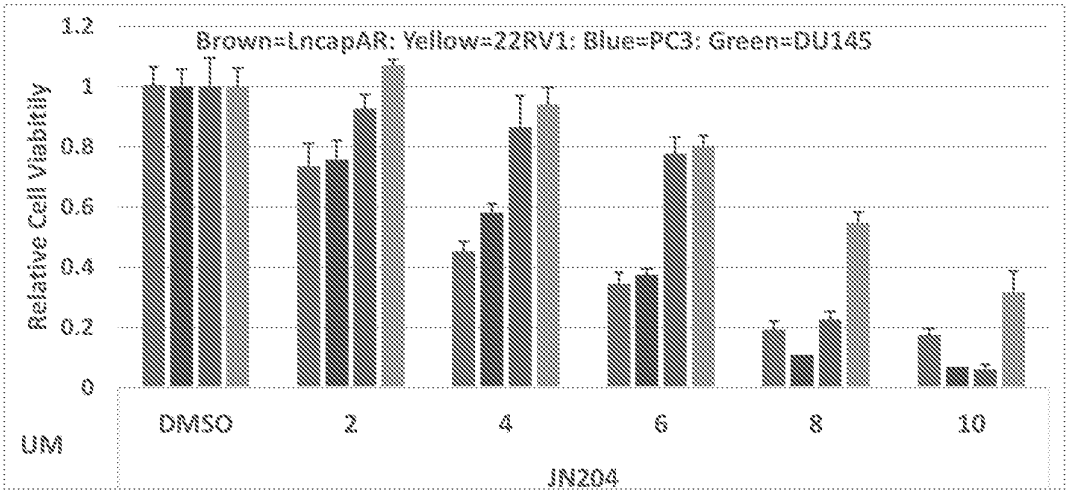

Brown=LncapAR: Yellow=22RV1: Blue=PC3: Green=DU145
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
UM
JN204

FIG. 22

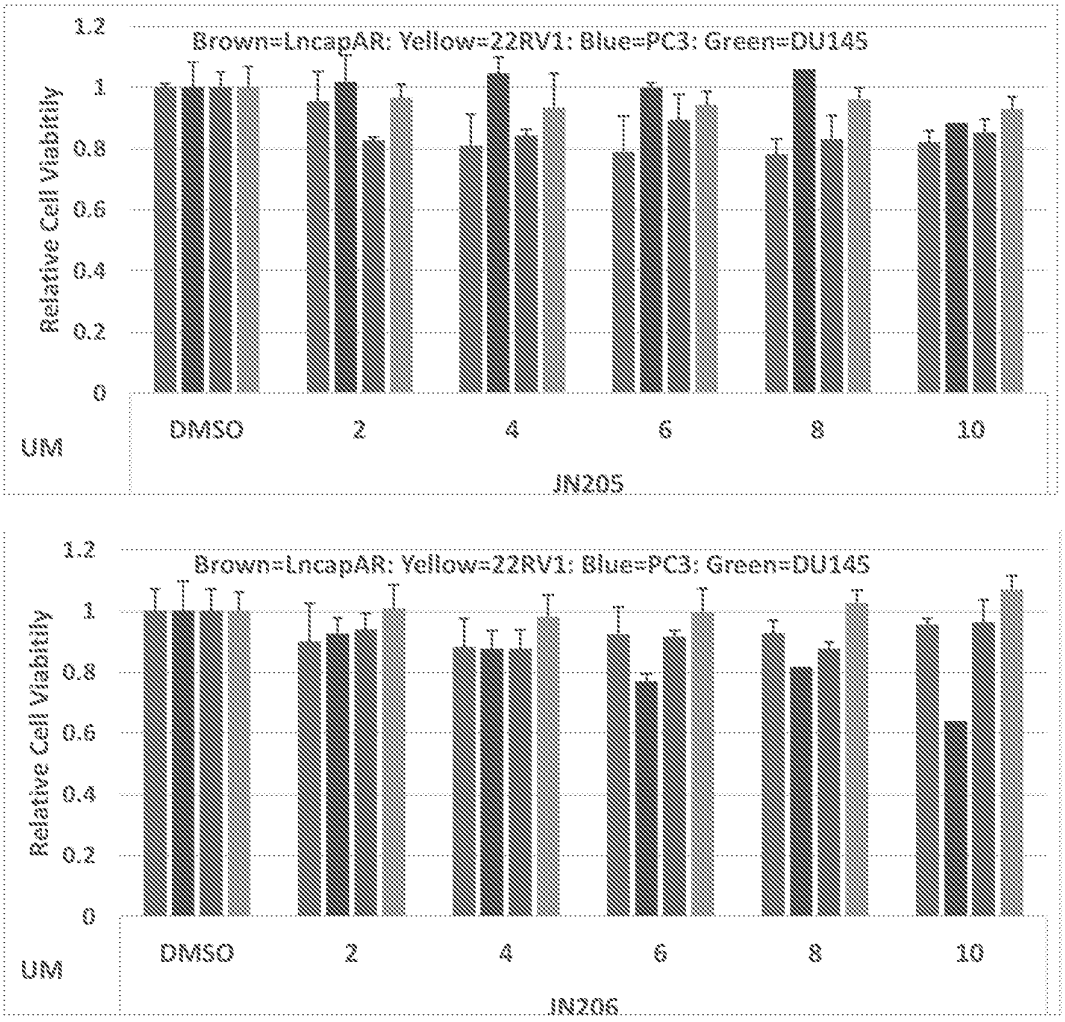

Brown=LncapAR: Yellow=22RV1: Blue=PC3: Green=DU145
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
UM
JN205
Brown=LncapAR: Yellow=22RV1: Blue=PC3: Green=DU145
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
UM
JN206

FIG. 23

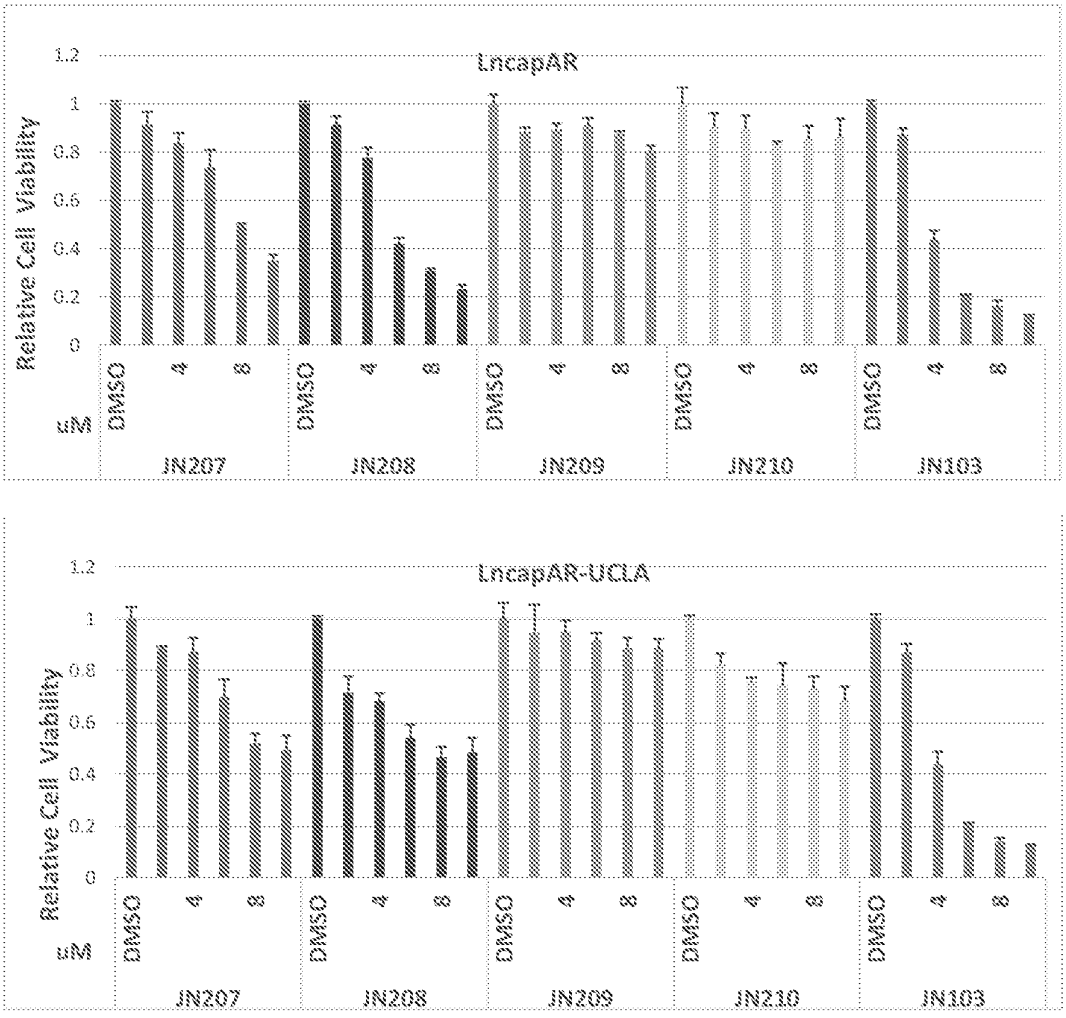

LncapAR
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
uM
JN207
JN208
JN209
JN210
JN103
LncapAR-UCLA
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
uM
JN207
JN208
JN209
JN210
JN103

FIG. 24

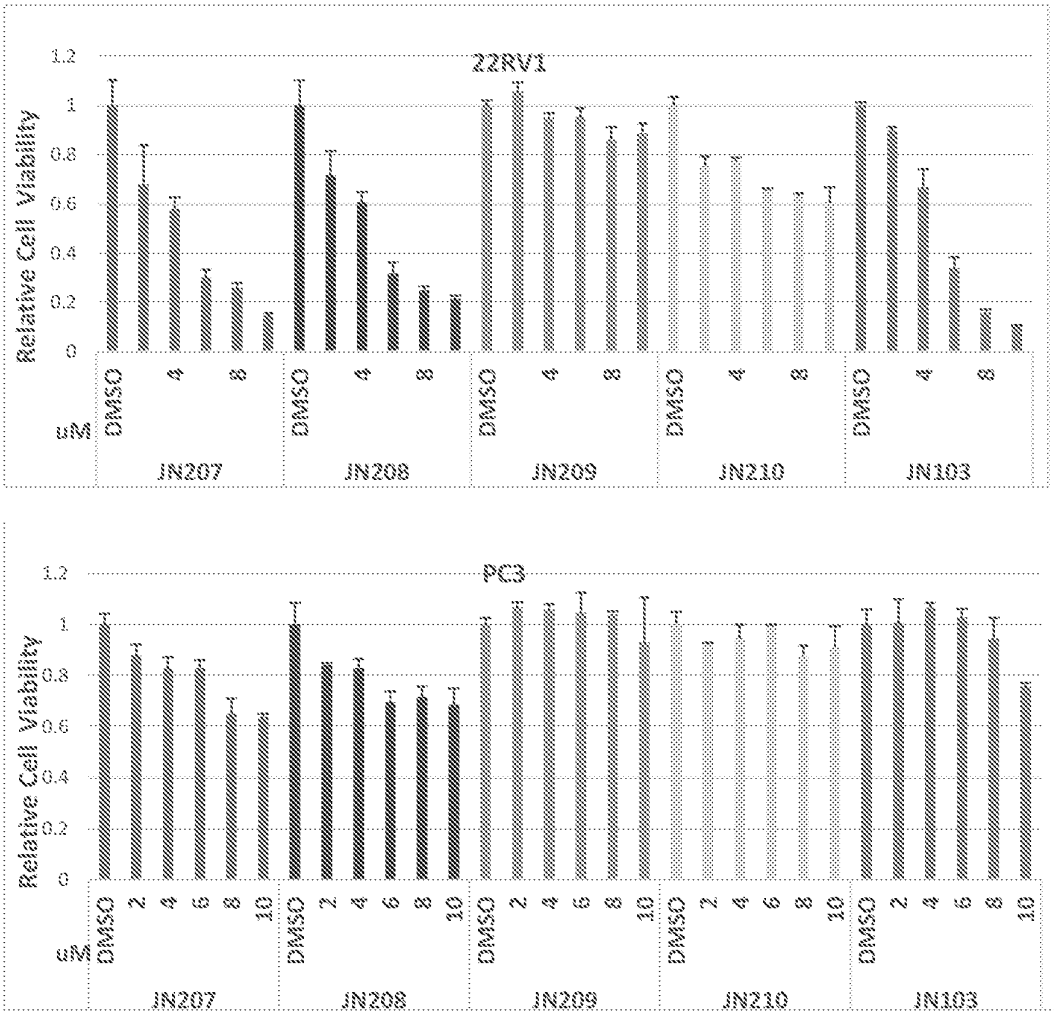
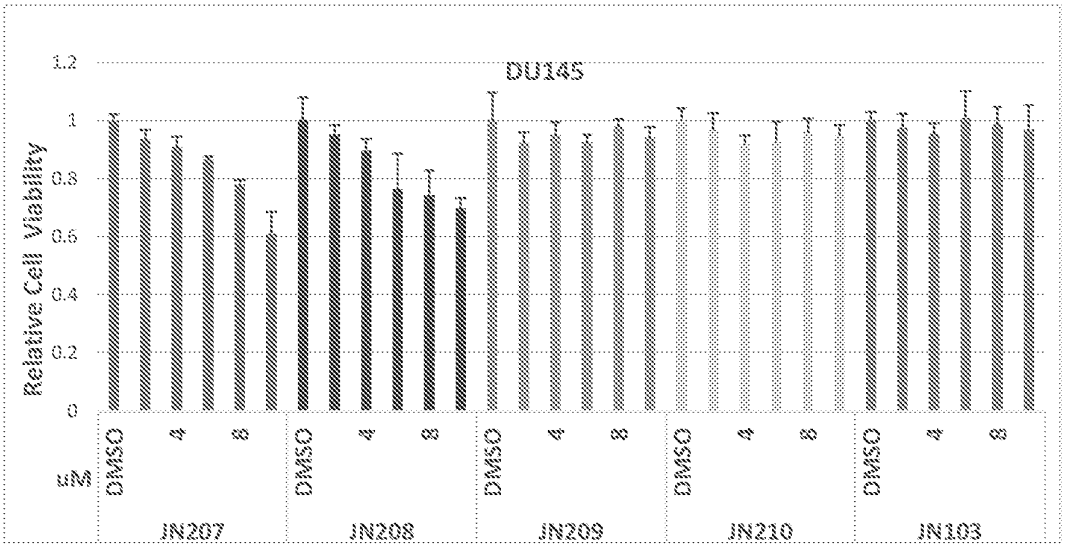

22RV1
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
uM
JN207
JN208
JN209
JN210
JN103
PC3
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
uM
JN207
JN208
JN209
JN210
JN103

FIG. 25


DU145
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
4
8
JN207
JN208
JN209
JN210
JN103

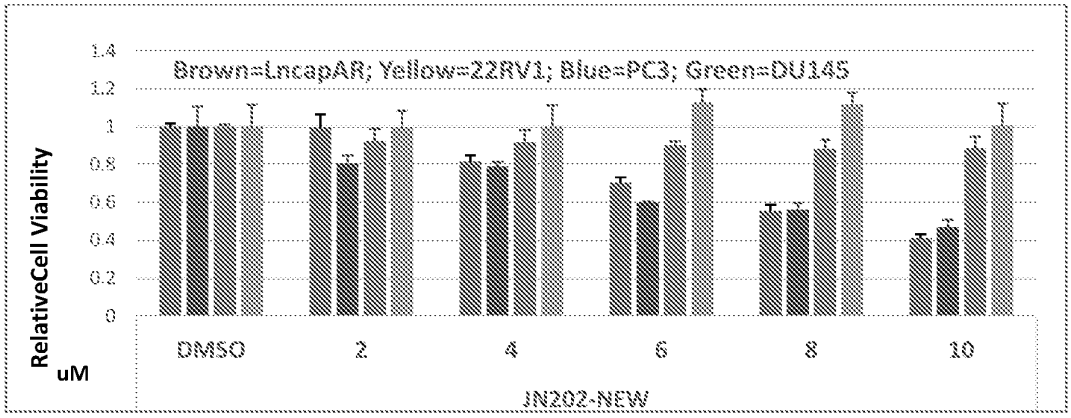
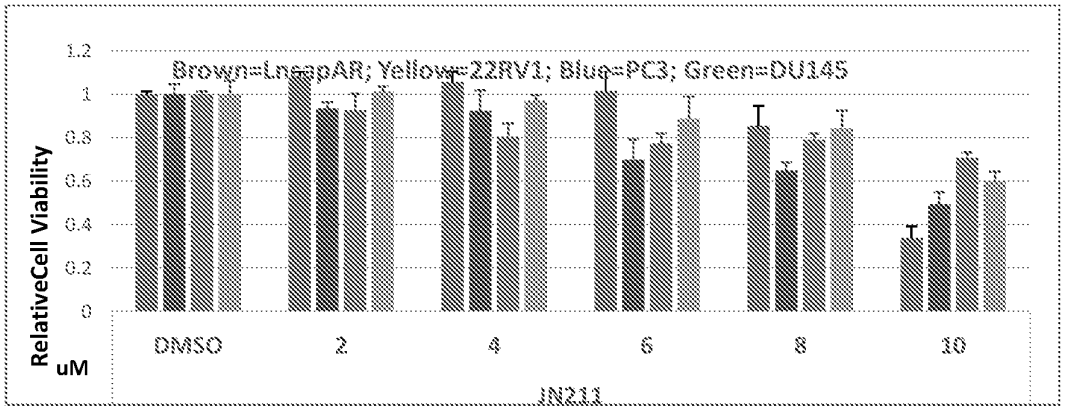

Brown=LncapAR; Yellow=22RV1; Blue=PC3; Green=DU145
RelativeCell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN202-NEW

FIG. 26


Brown=LncapAR; Yellow=22RV1; Blue=PC3; Green=DU145
RelativeCell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
uM
JN211

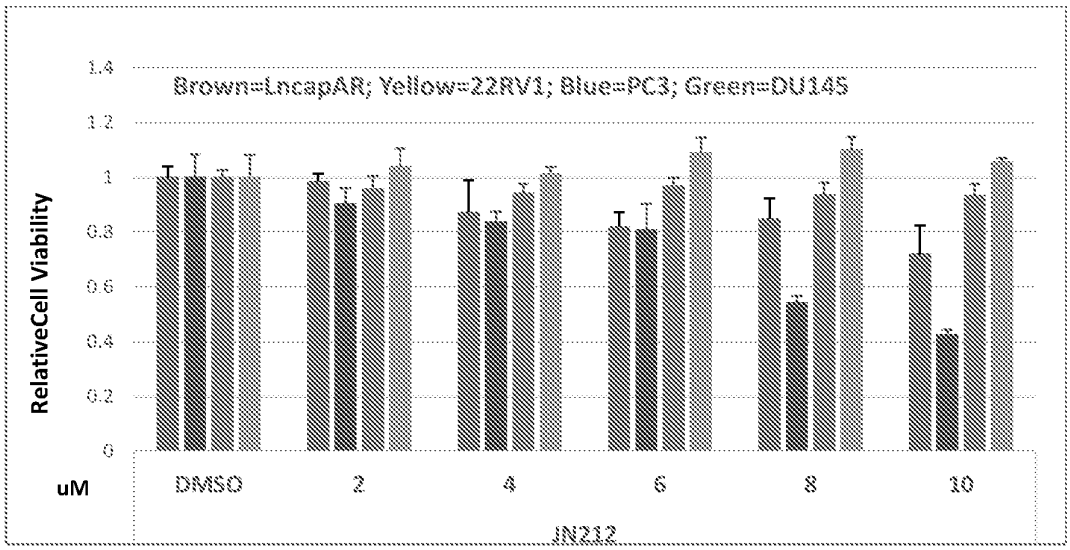
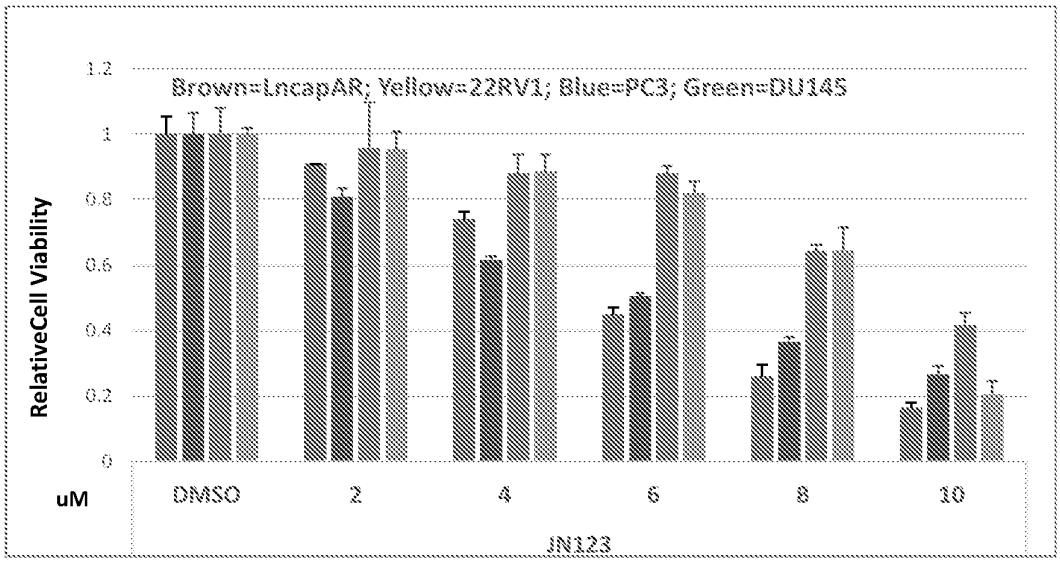

Brown=LncapAR; Yellow=22RV1; Blue=PC3; Green=DU145
RelativeCell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
uM
JN212

FIG. 27


Brown=LncapAR; Yellow=22RV1; Blue=PC3; Green=DU145
RelativeCell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN123

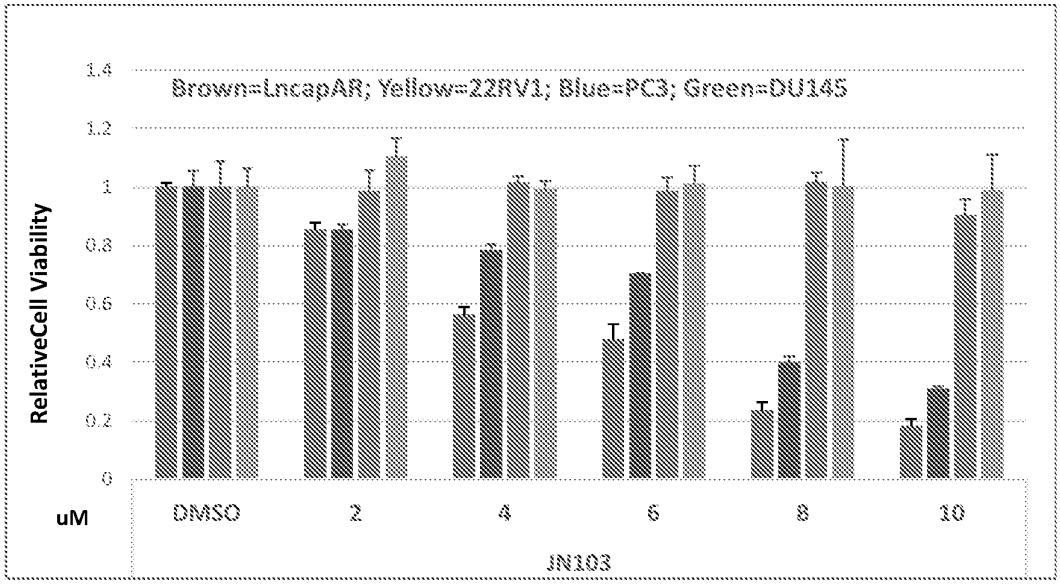

Brown=LncapAR; Yellow=22RV1; Blue=PC3; Green=DU145
RelativeCell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN103

FIG. 28

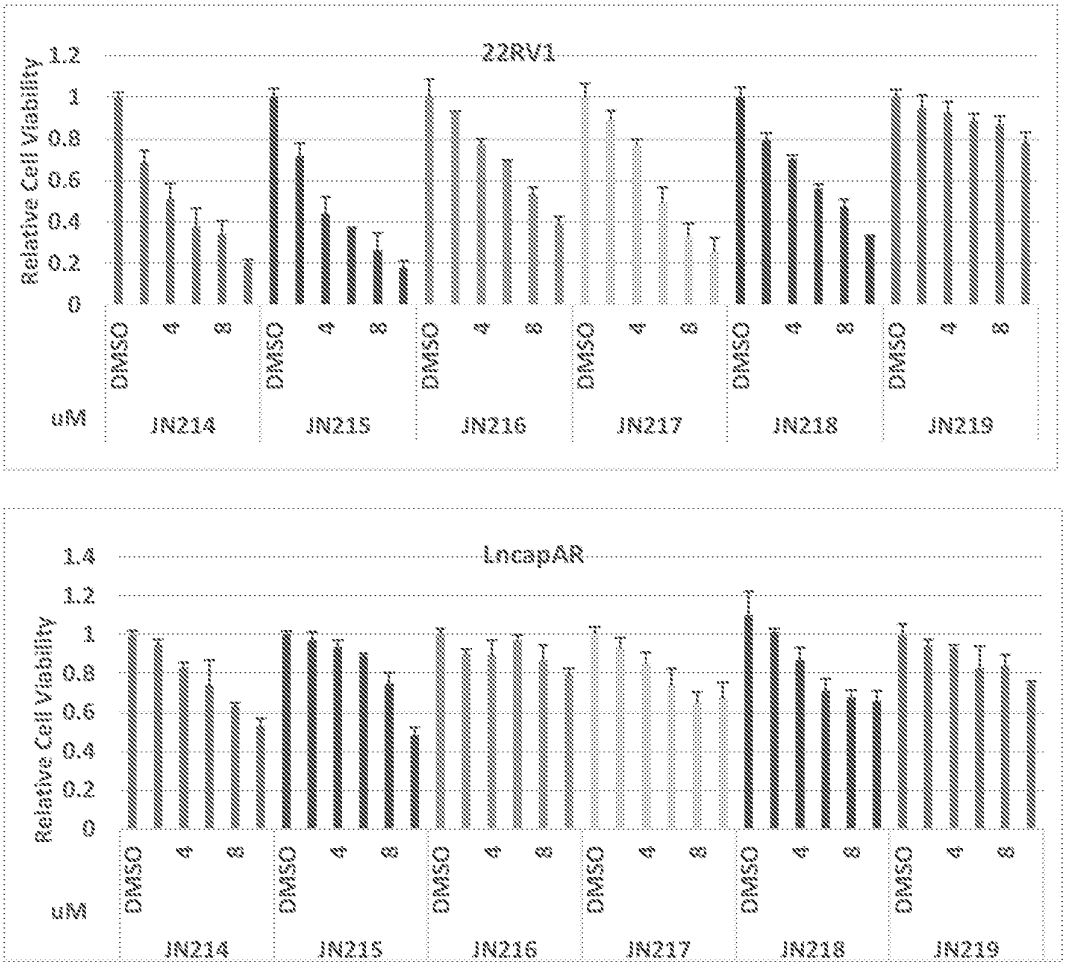

22RV1
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
uM
JN214
JN215
JN216
JN217
JN218
JN219
LncapAR
1.4
1.2
1
0.8
0.6
0.4
0.2
0

FIG. 29

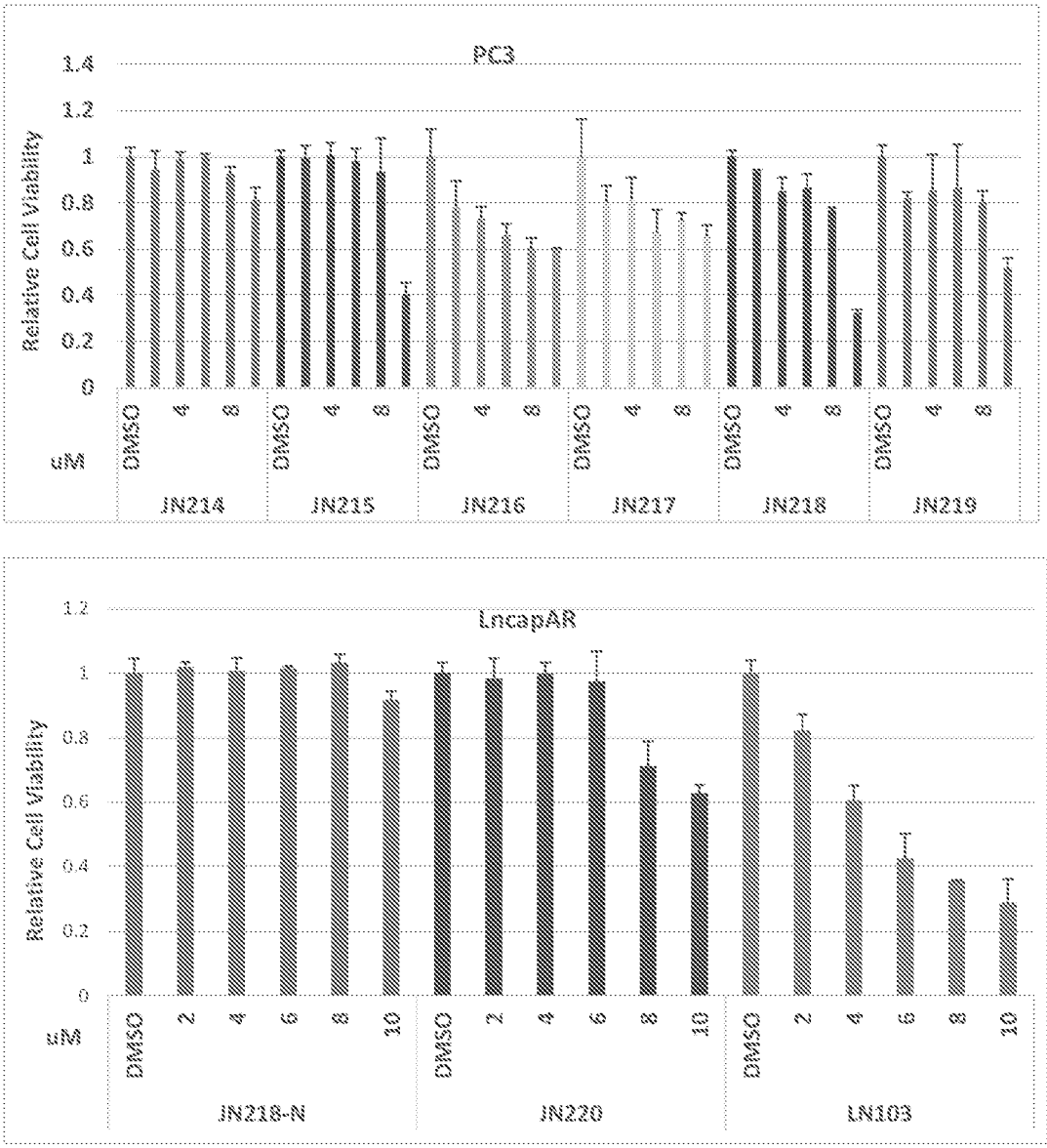
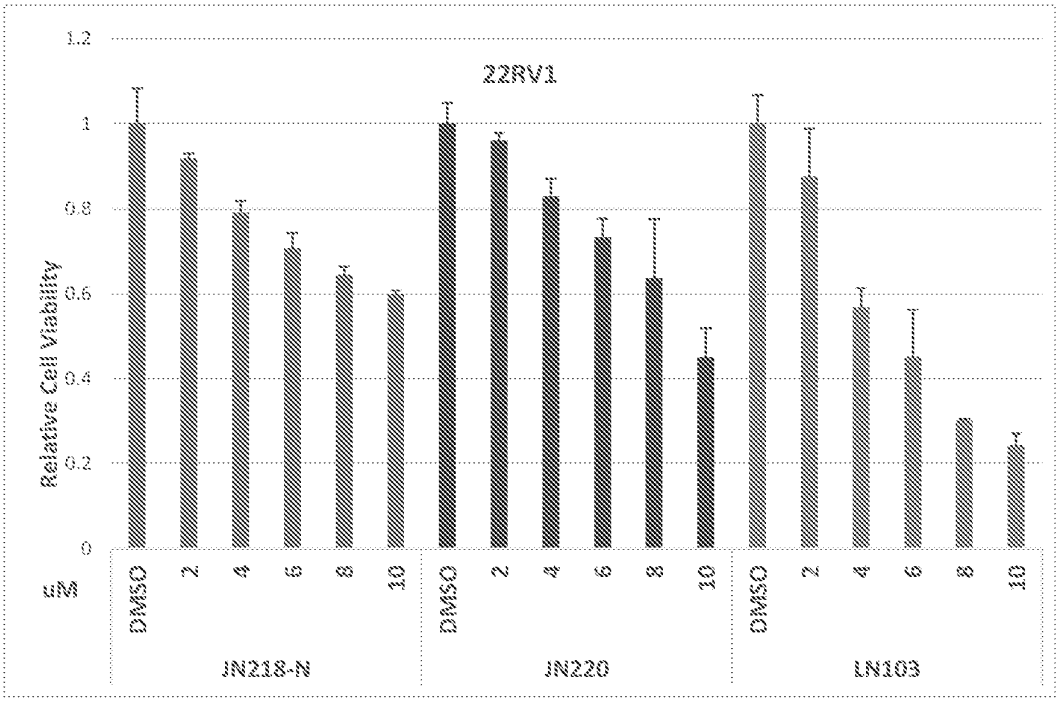

PC3
Relative Cell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
4
8
JN214
JN215
JN216
JN217
JN218
JN219
LncapAR
2
6
10
JN218-N
JN220
LN103

FIG. 30


22RV1
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN218-N
JN220
LN103

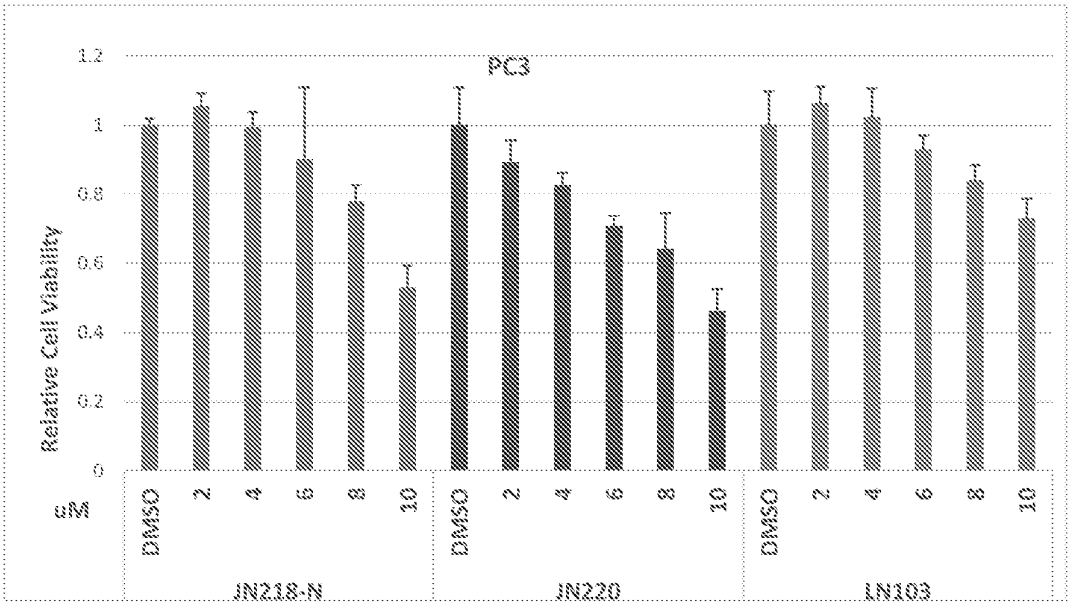

PC3
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN218-N
JN220
LN103

FIG. 31

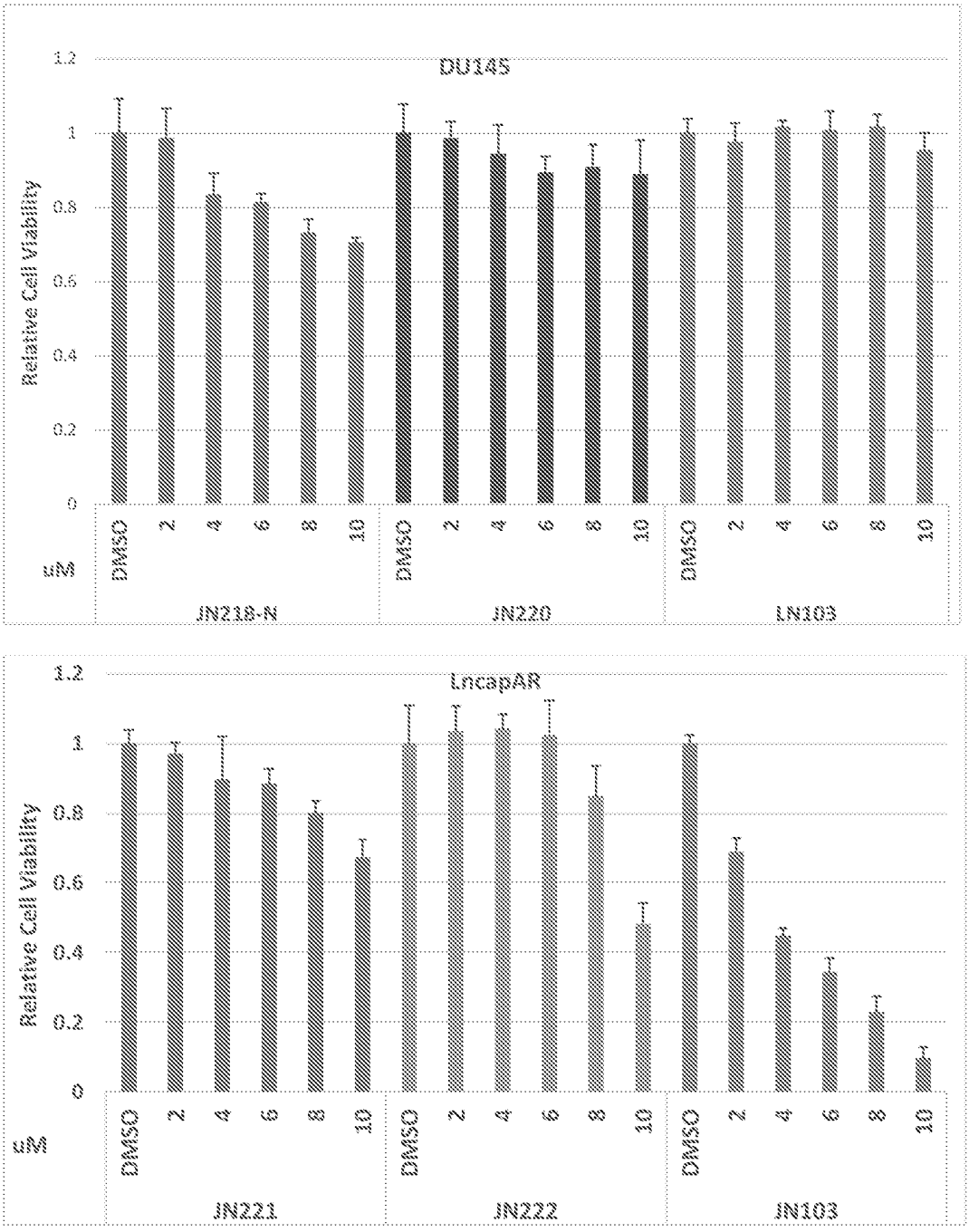

DU145
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN218-N
JN220
LN103
LncapAR
JN221
JN222
JN103

FIG. 32

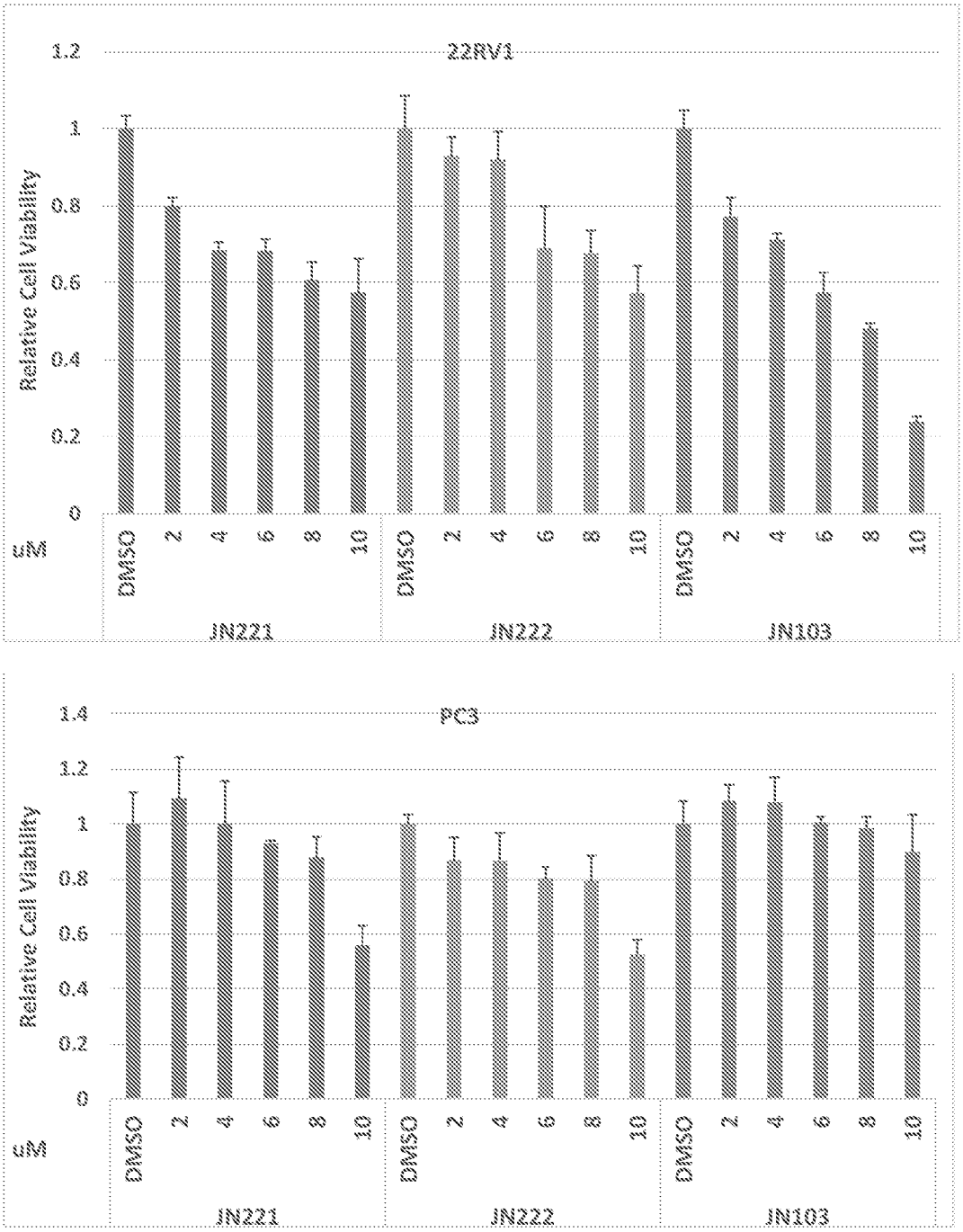
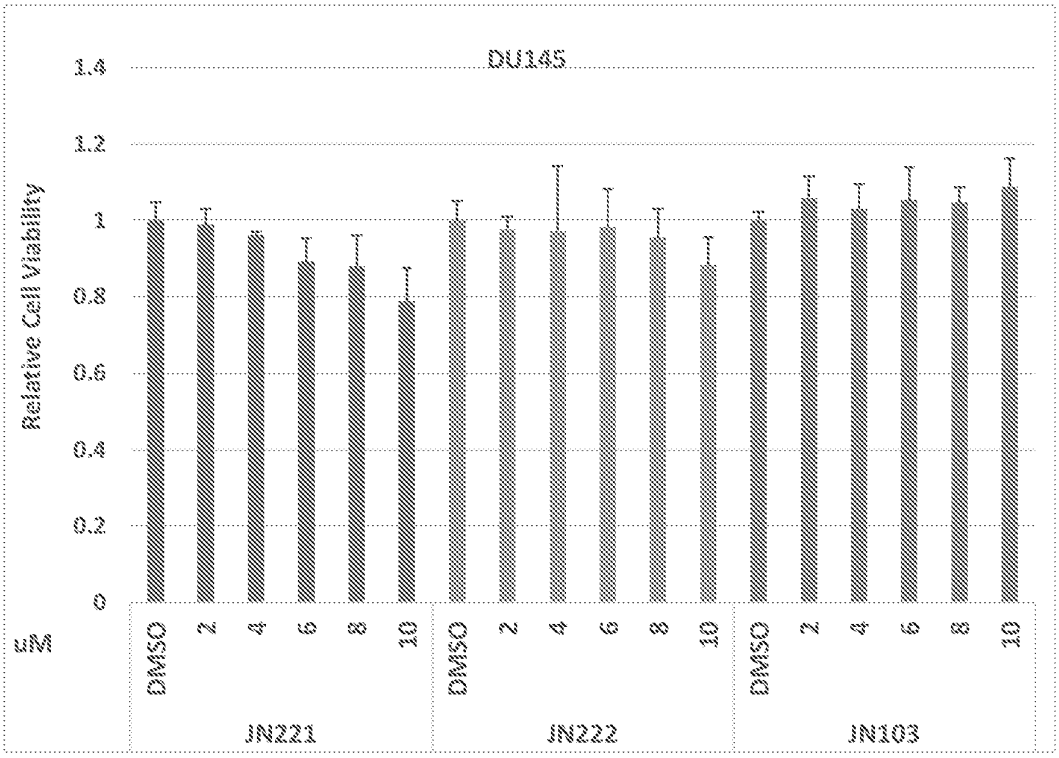

22RV1
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN221
JN222
JN103
PC3
1.4
1.2
1
0.8
0.6
0.4
0.2
0

FIG. 33


DU145
Relative Cell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN221
JN222
JN103

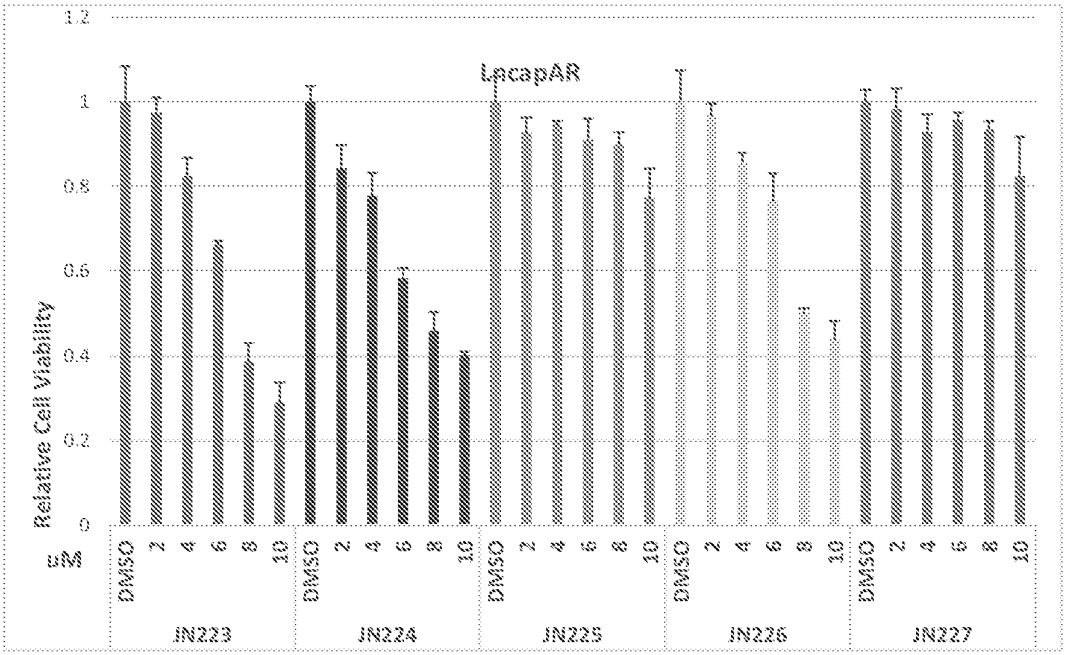

LncapAR
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN223
JN224
JN225
JN226
JN227

FIG. 34

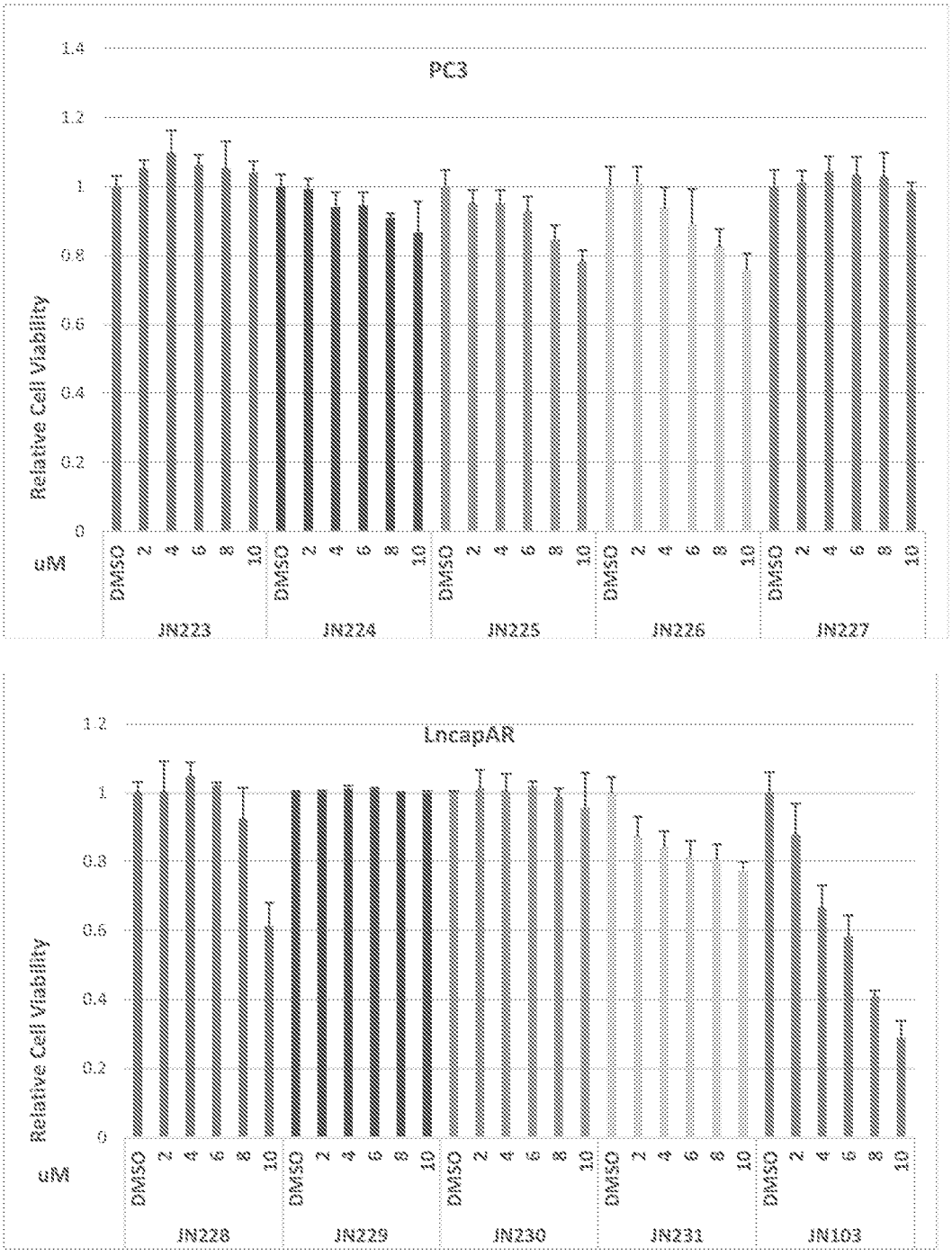
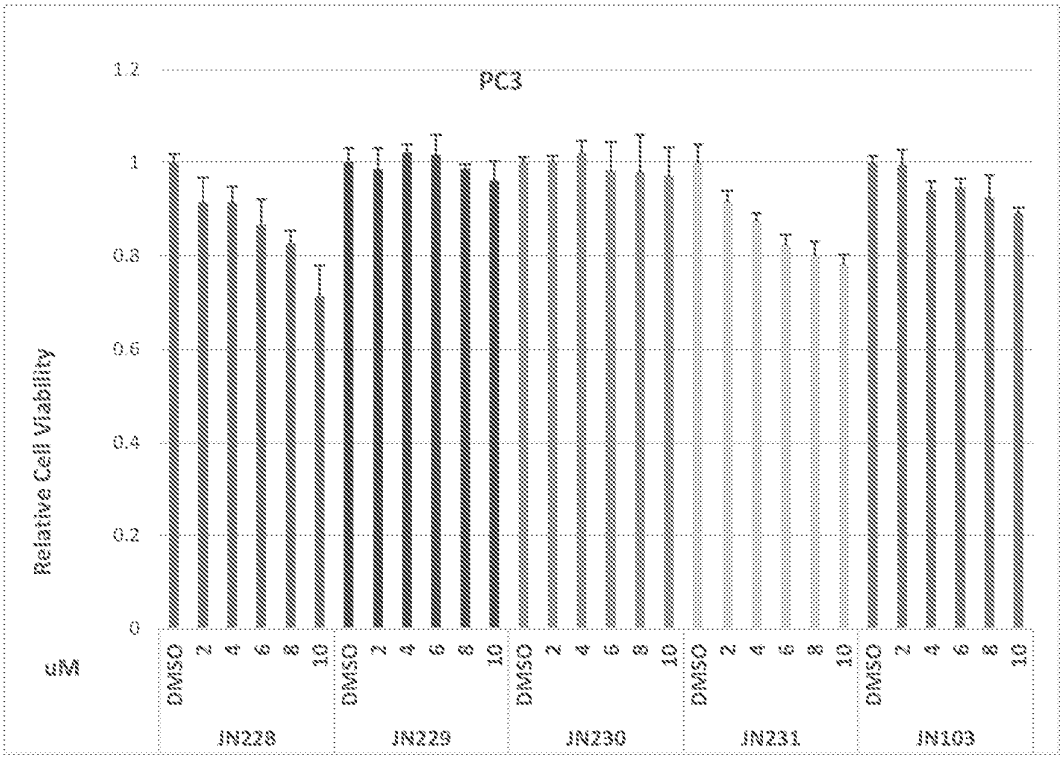

PC3
Relative Cell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN223
JN224
JN225
JN226
JN227
LncapAR
JN228
JN229
JN230
JN231
JN103

FIG. 35


PC3
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN228
JN229
JN230
JN231
JN103

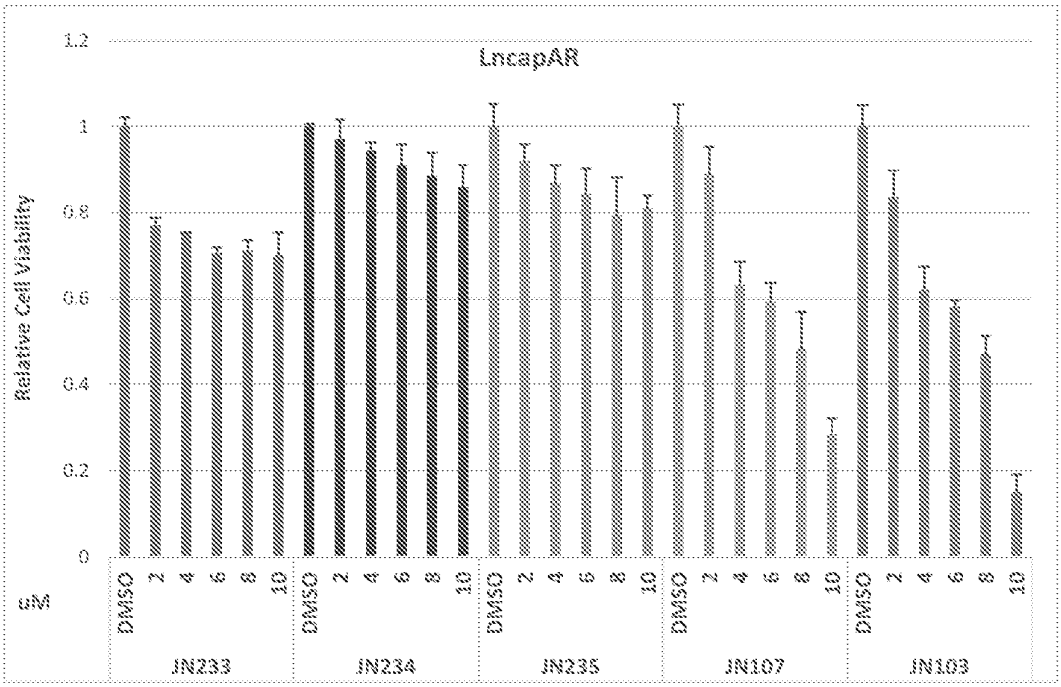

LncapAR
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN233
JN234
JN235
JN107
JN103

FIG. 36

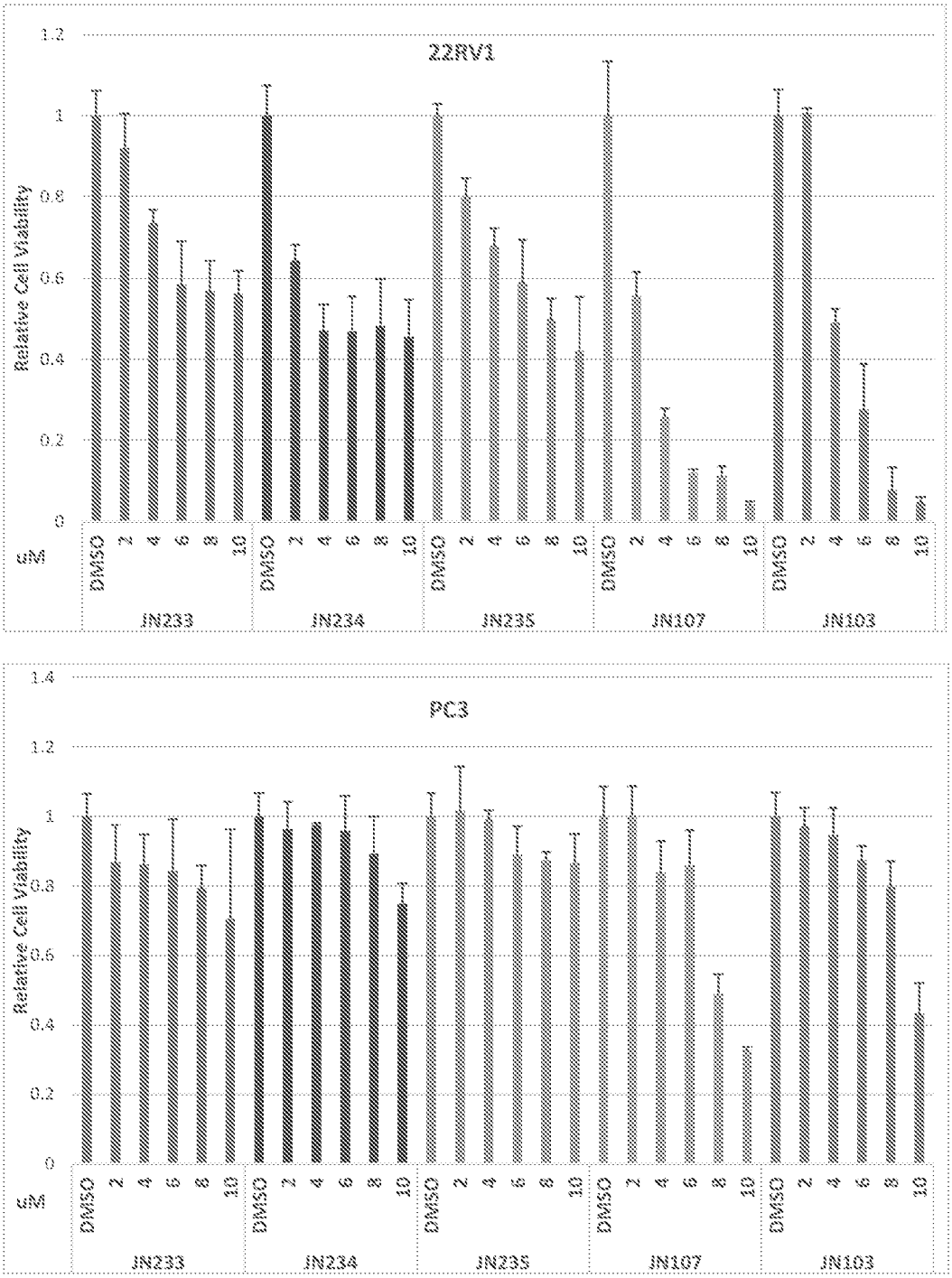

22RV1
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN233
JN234
JN235
JN107
JN103
PC3
Relative Cell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN233
JN234
JN235
JN107
JN103

FIG. 37

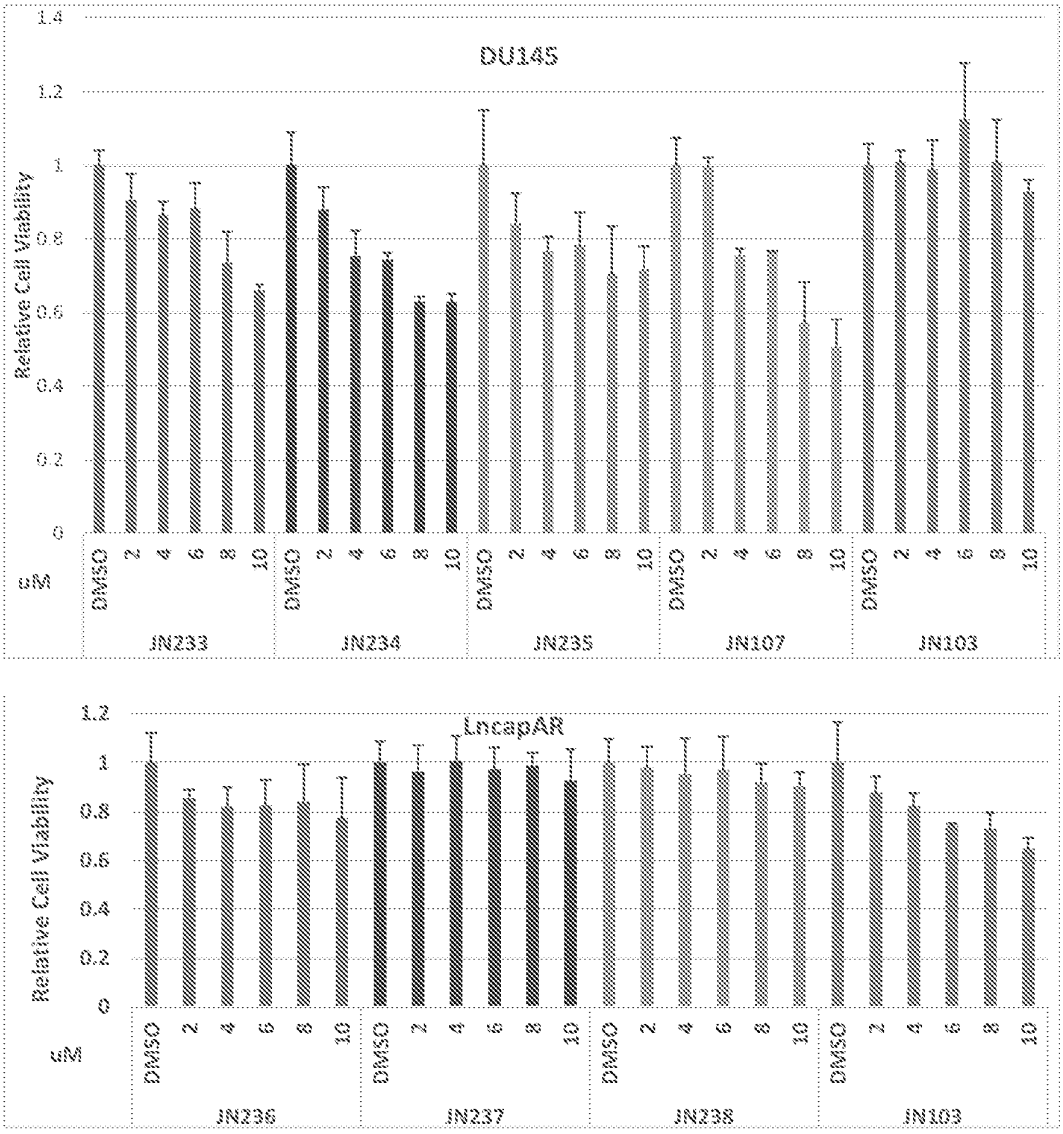

DU145
Relative Cell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN233
JN234
JN235
JN107
JN103
LncapAR
JN236
JN237
JN238
JN103

FIG. 38

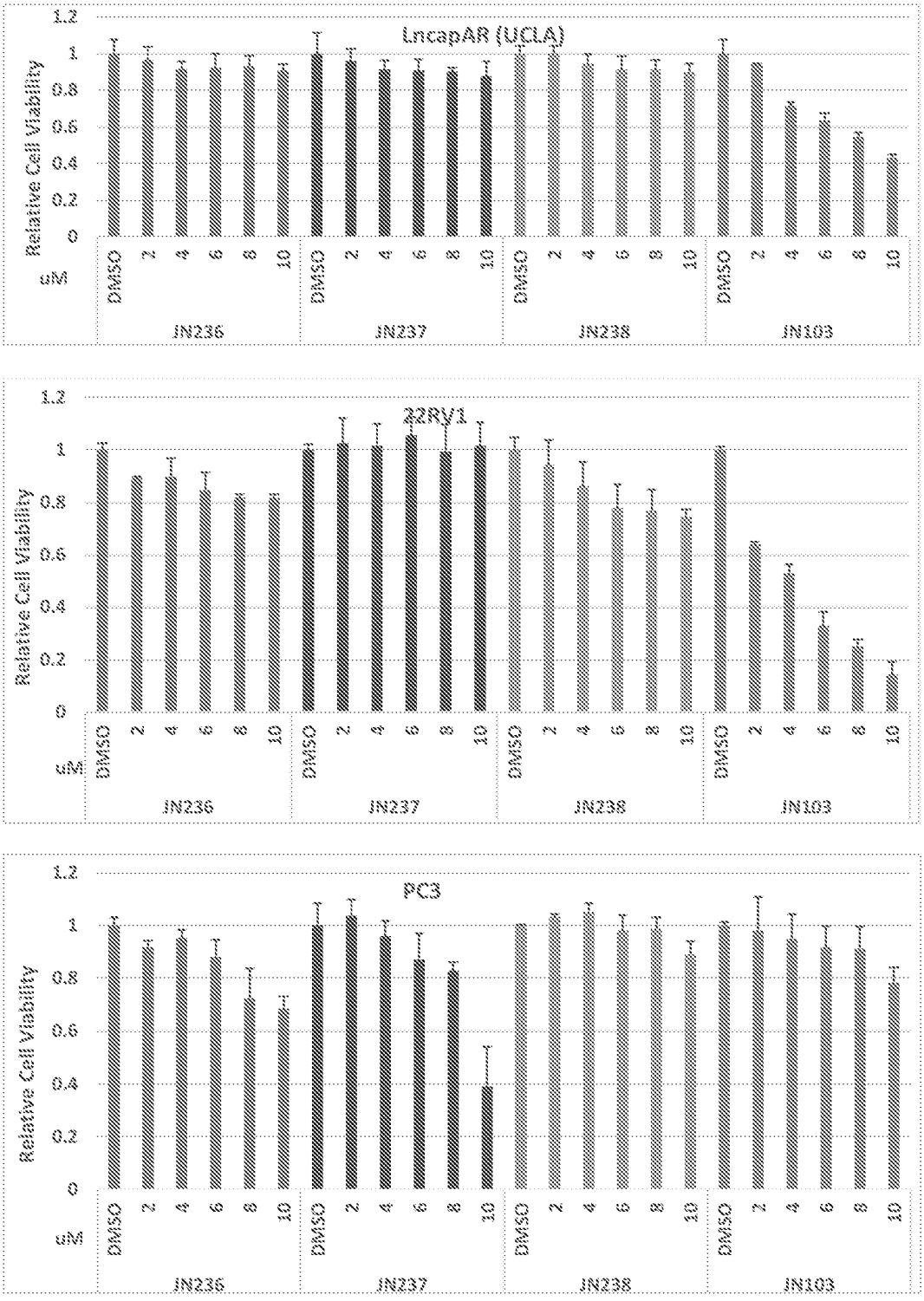

LncapAR (UCLA)
22RV1
PC3
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN236
JN237
JN238
JN103

FIG. 39

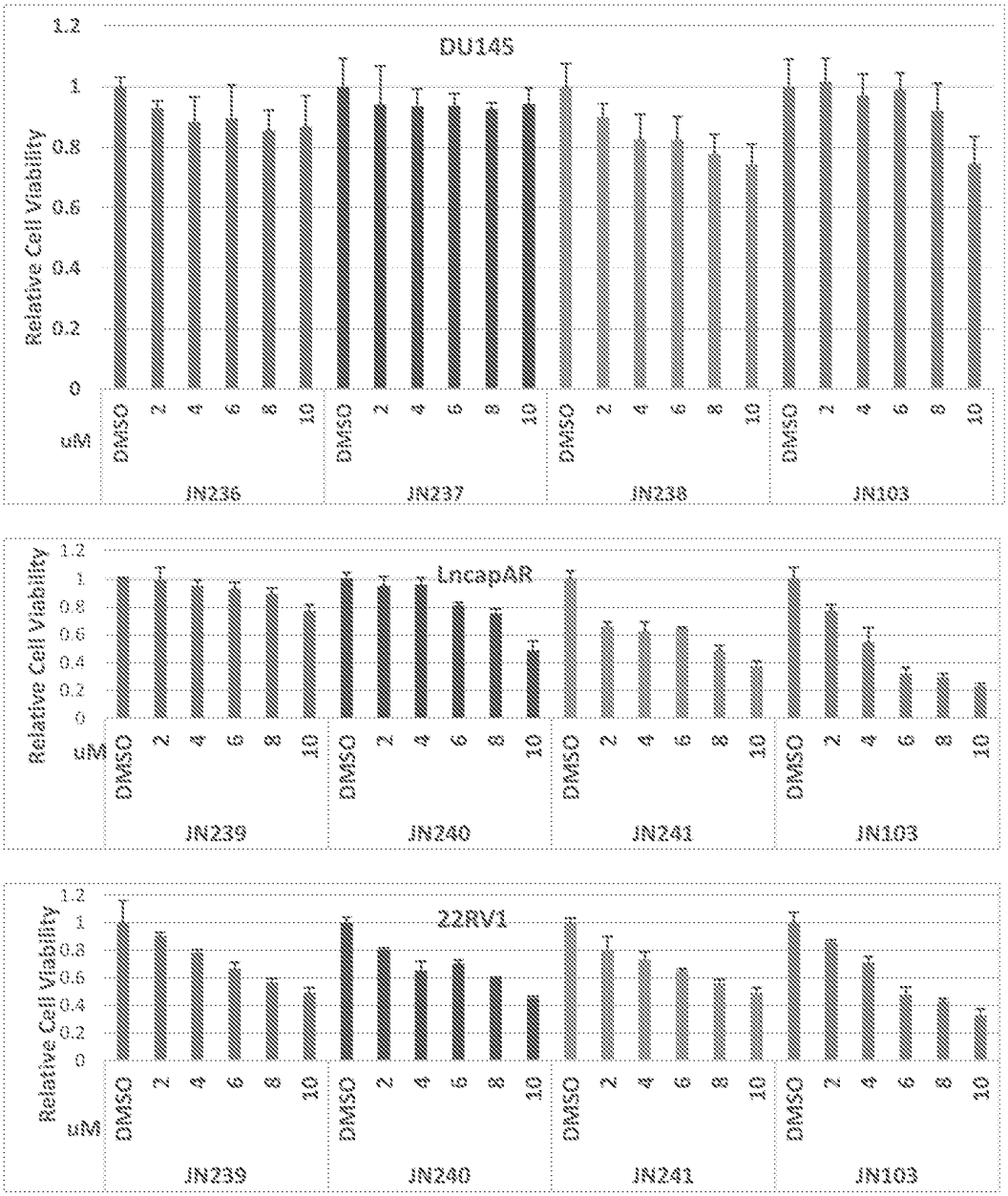

DU145
LncapAR
22RV1
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN236
JN237
JN238
JN103
JN239
JN240
JN241

FIG. 40

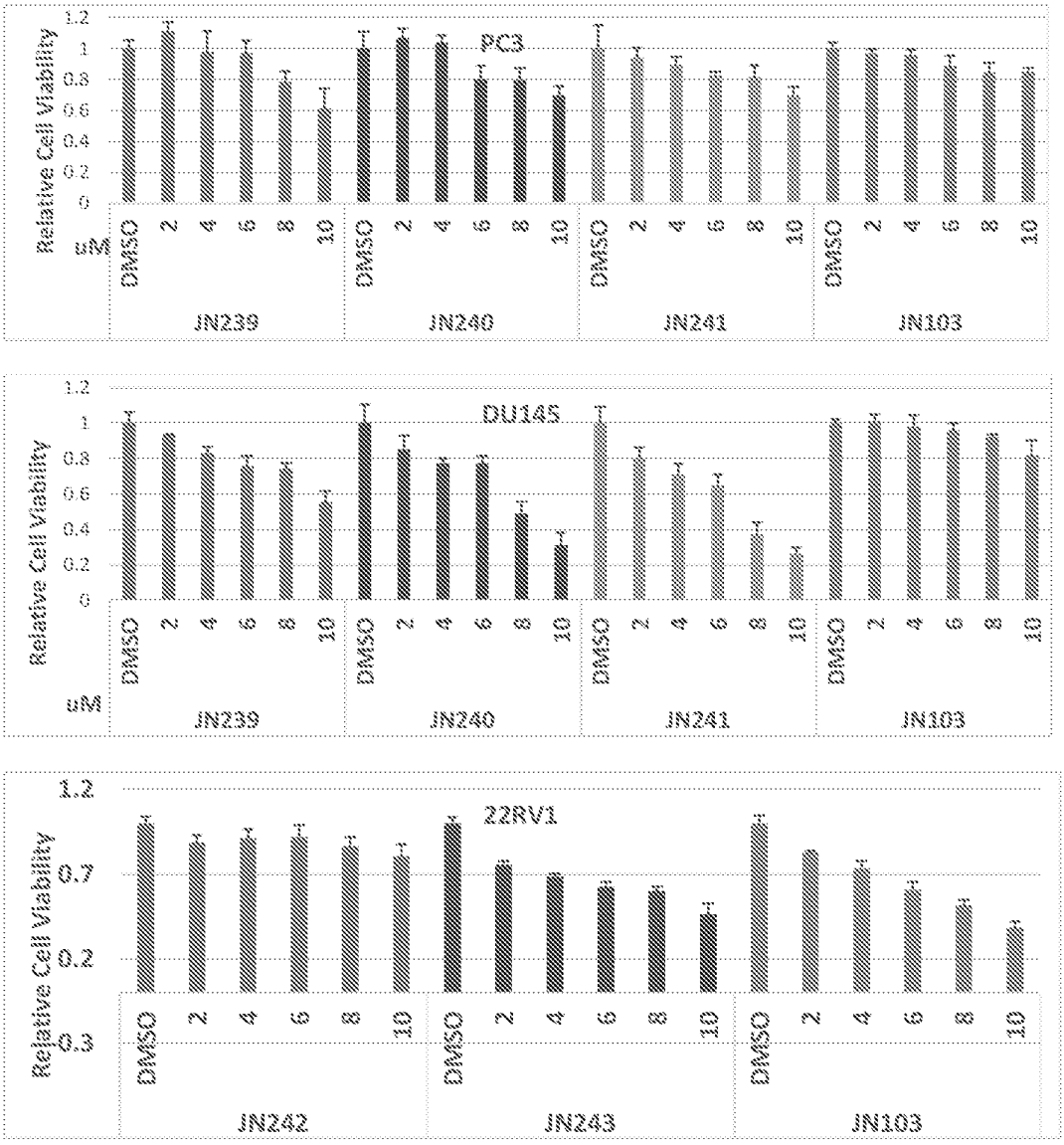

PC3
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN239
JN240
JN241
JN103
DU145
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN239
JN240
JN241
JN103
22RV1
Relative Cell Viability
1.2
0.7
0.2
0.3
DMSO
2
4
6
8
10
JN242
JN243
JN103

FIG. 41

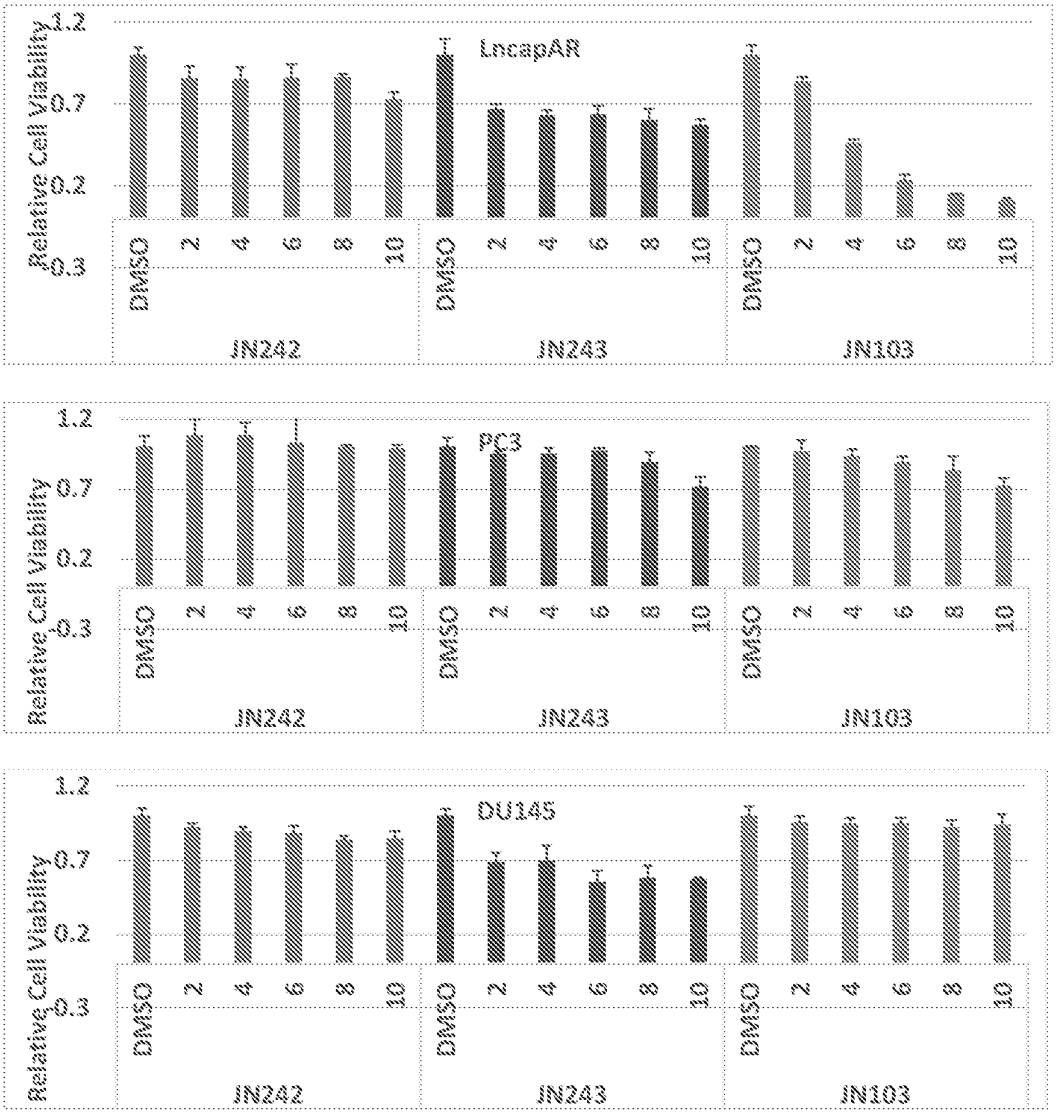

LncapAR
PC3
DU145
Relative Cell Viability
1.2
0.7
0.2
-0.3
DMSO
2
4
6
8
10
JN242
JN243
JN103

FIG. 42

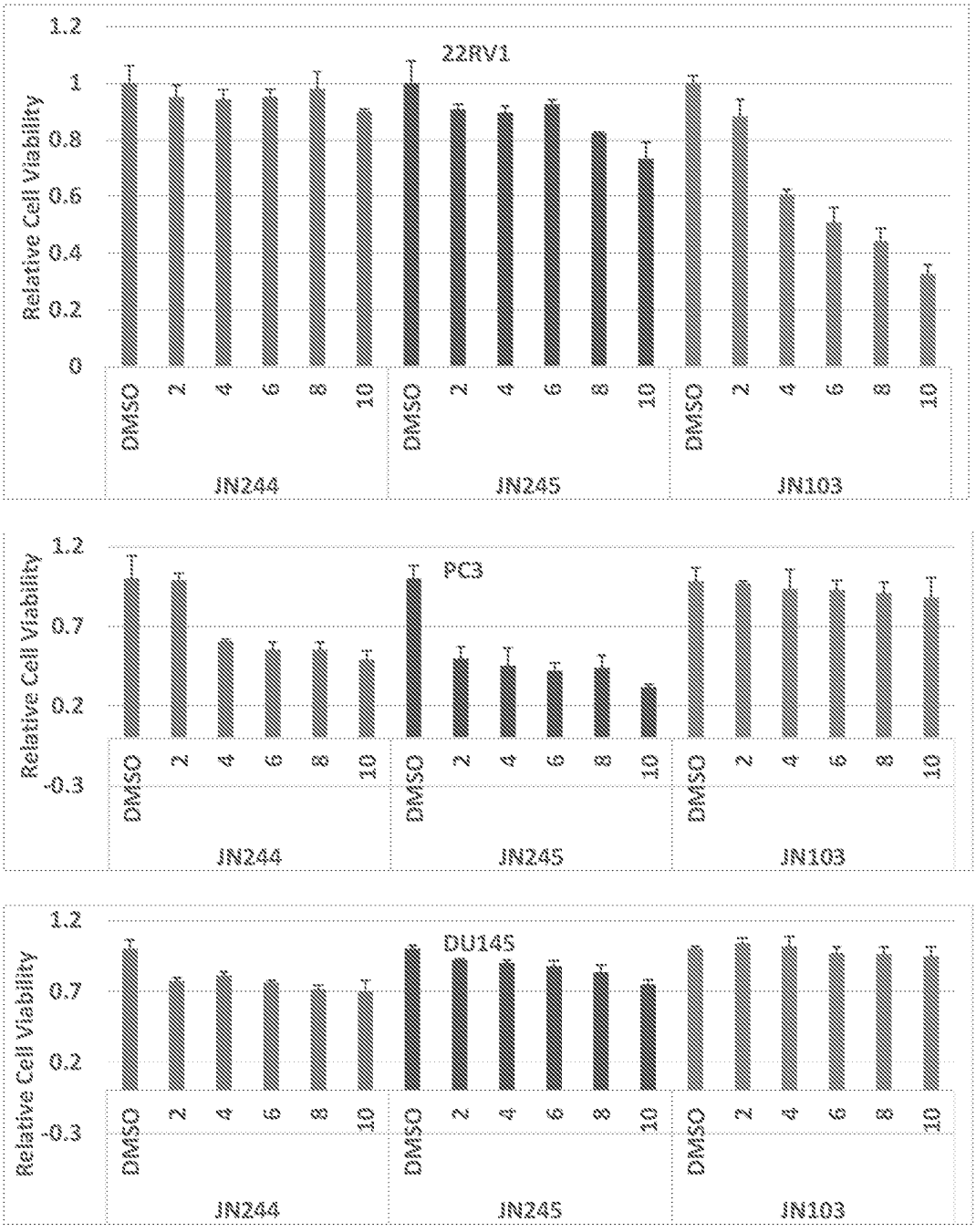
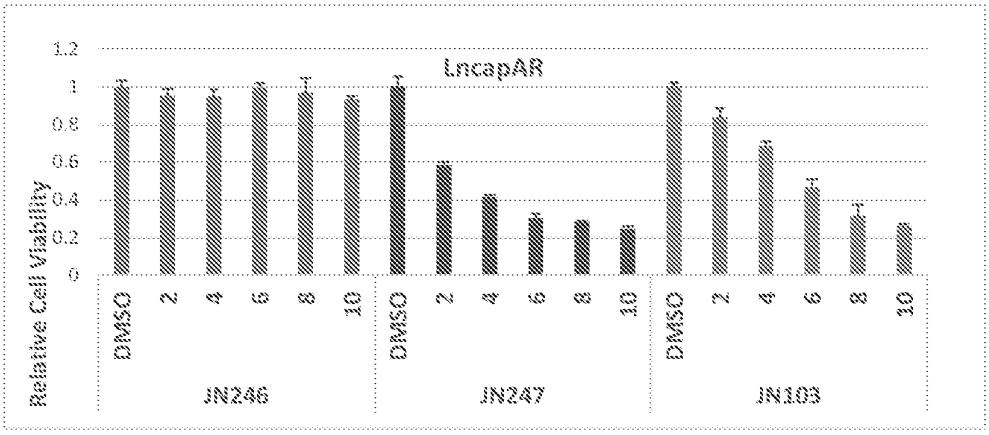
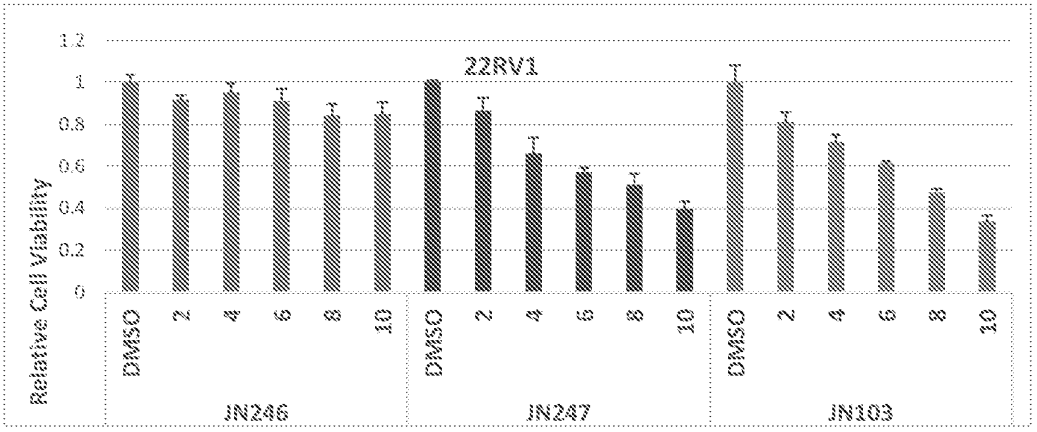

22RV1
PC3
DU145
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
0.7
-0.3
DMSO
2
4
6
8
10
JN244
JN245
JN103

FIG. 43


LncapAR
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
JN246
JN247
JN103


22RV1
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
JN246
JN247
JN103

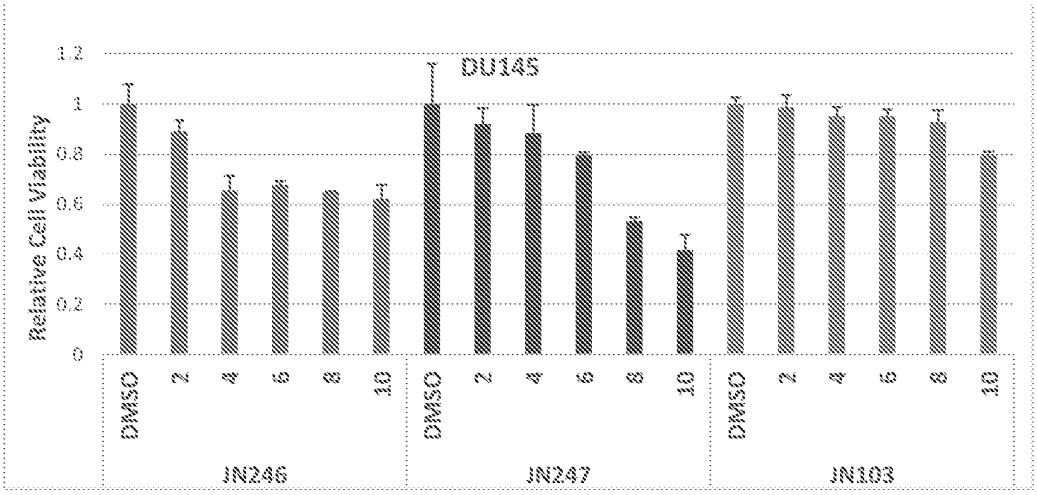

DU145
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
JN246
JN247
JN103

FIG. 44

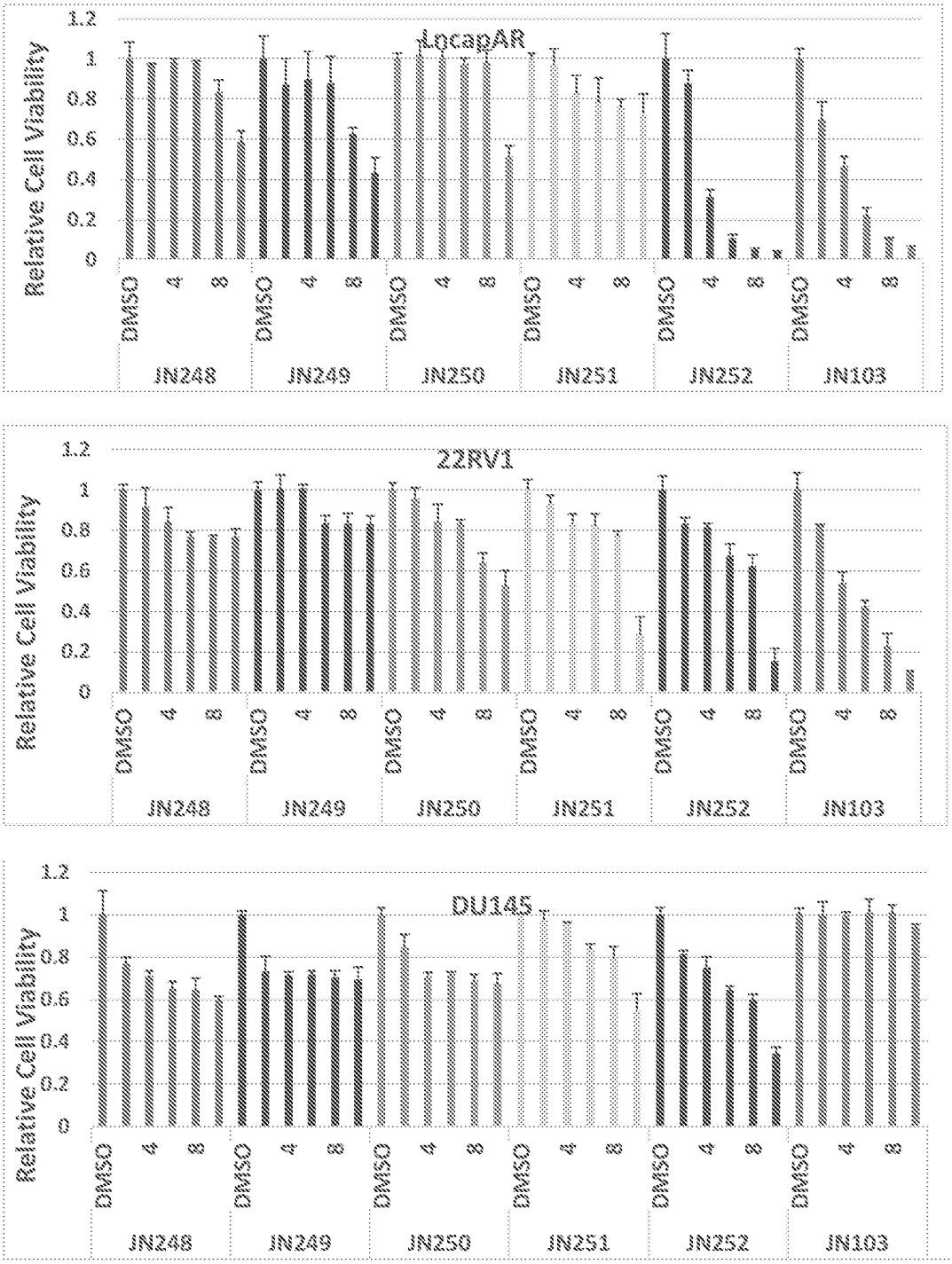

LocapAR
22RV1
DU145
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
JN248
JN249
JN250
JN251
JN252
JN103

FIG. 45

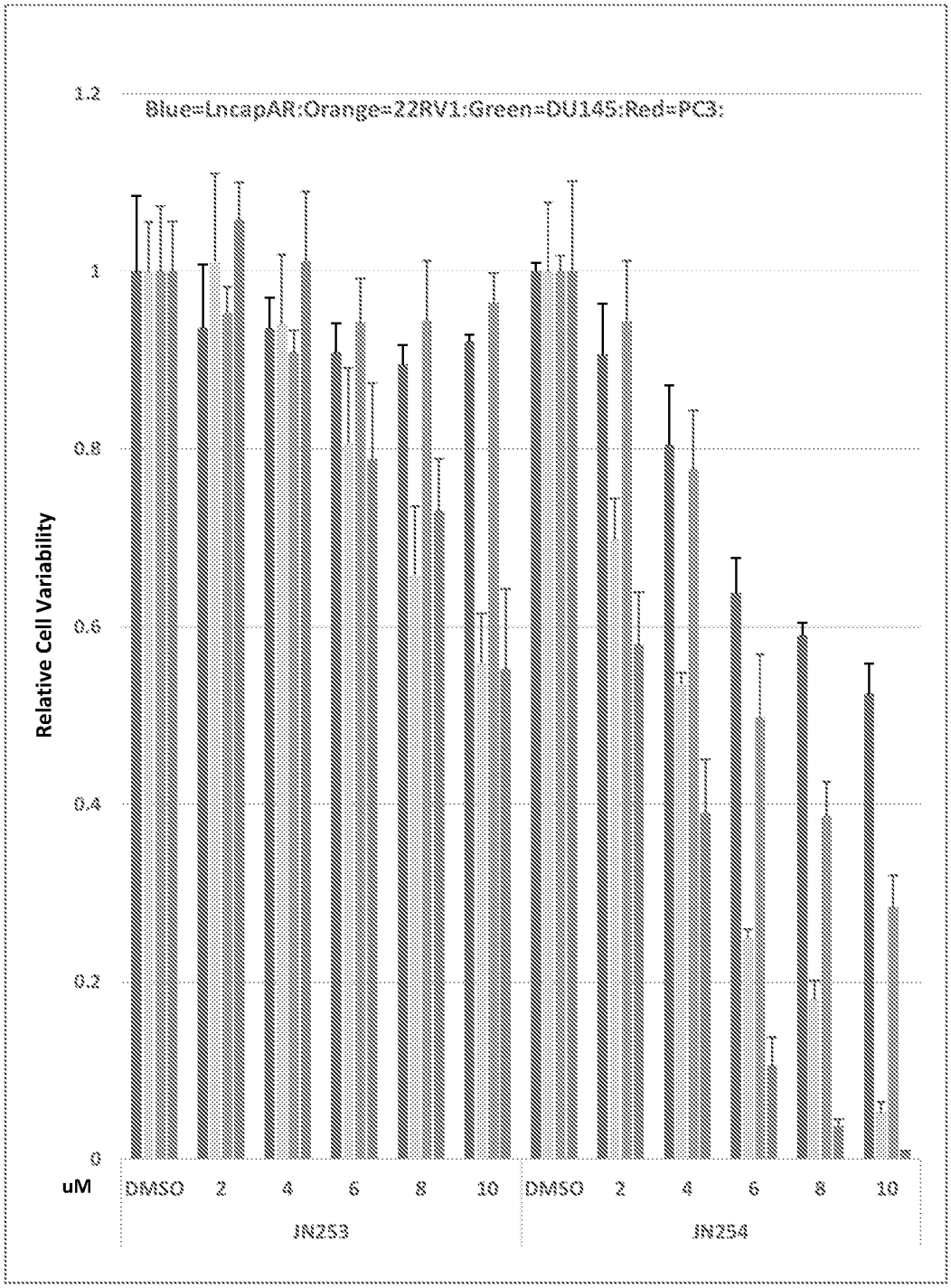
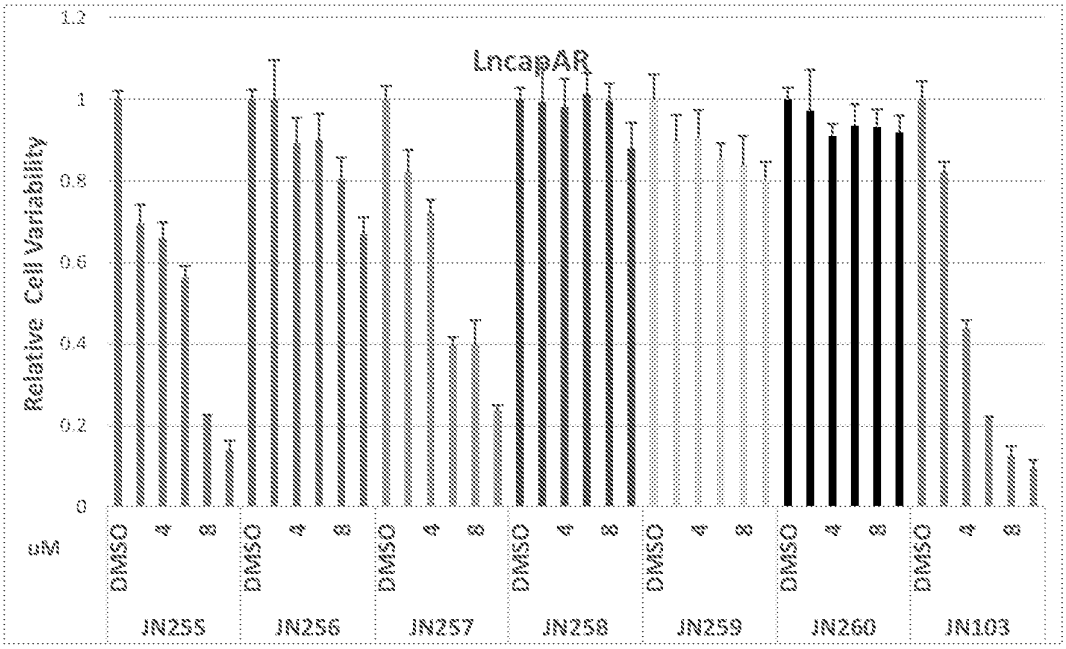

Blue=LncapAR:Orange=22RV1:Green=DU145:Red=PC3:
Relative Cell Variability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
DMSO
2
4
6
8
10
JN253
JN254

FIG. 46


LncapAR
Relative Cell Variability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
4
8
JN255
JN256
JN257
JN258
JN259
JN260
JN103

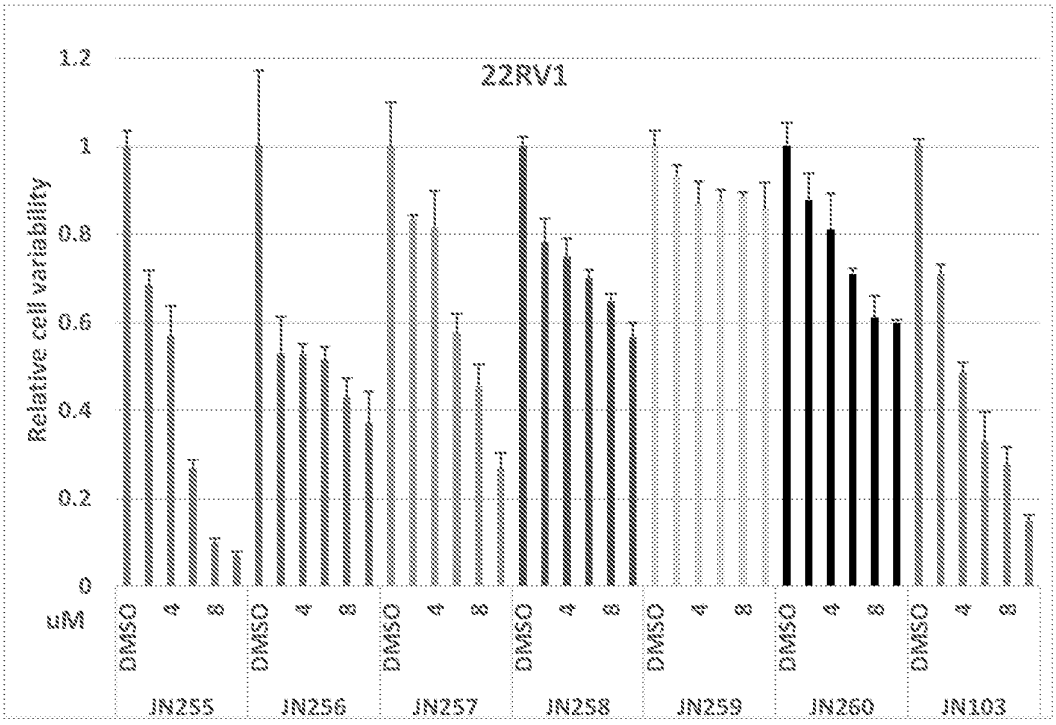

22RV1
Relative cell variability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
4
8
JN255
JN256
JN257
JN258
JN259
JN260
JN103

FIG. 47

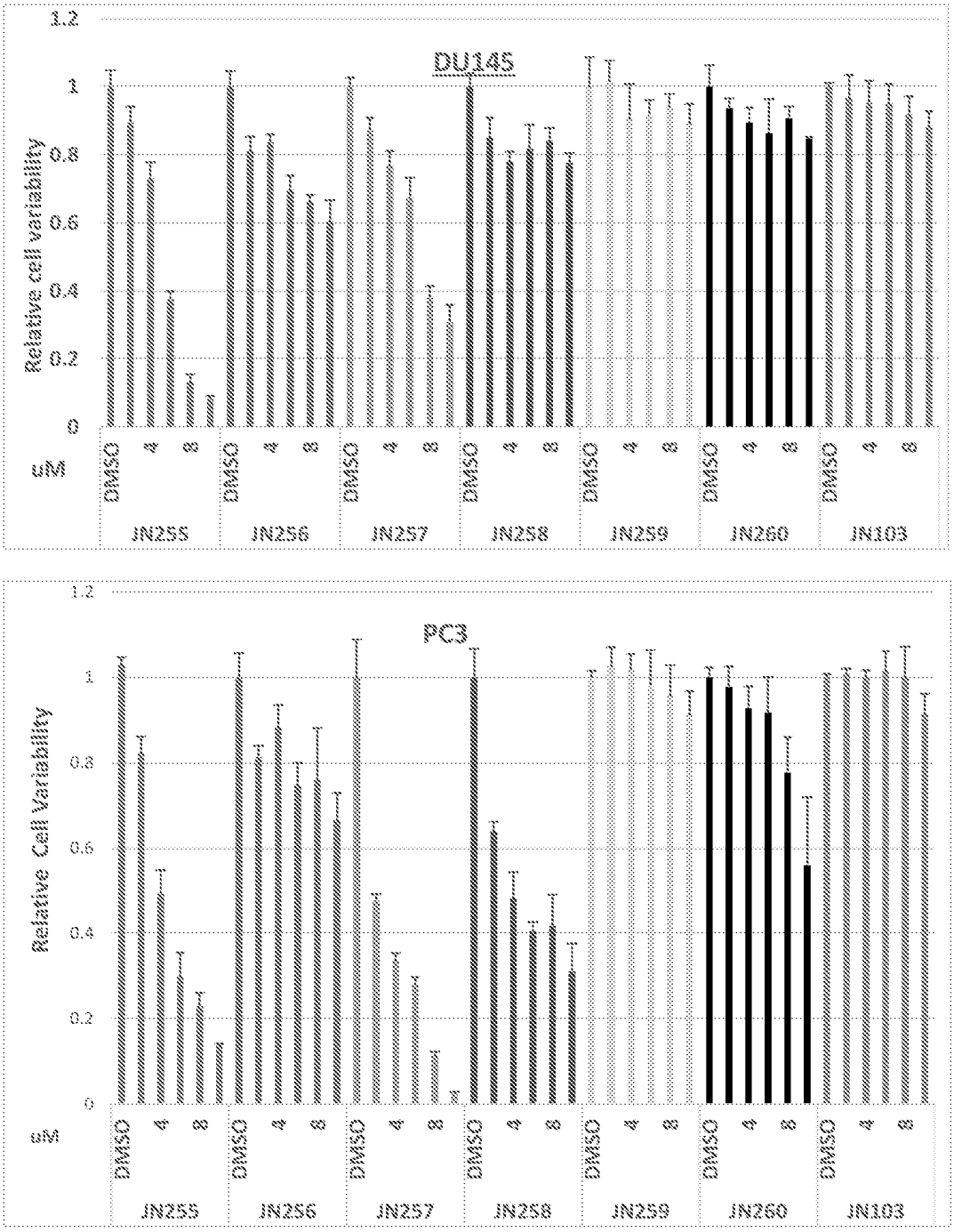
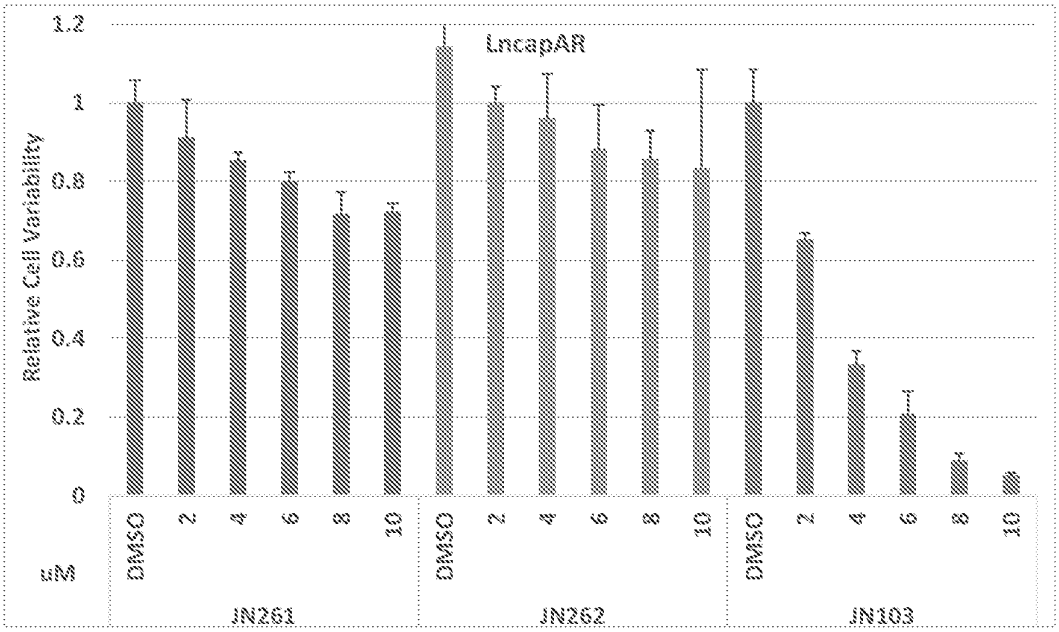

DU145
Relative cell variability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
4
8
JN255
JN256
JN257
JN258
JN259
JN260
JN103
PC3
Relative Cell Variability

FIG. 48


LncapAR
Relative Cell Variability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
uM
JN261
JN262
JN103

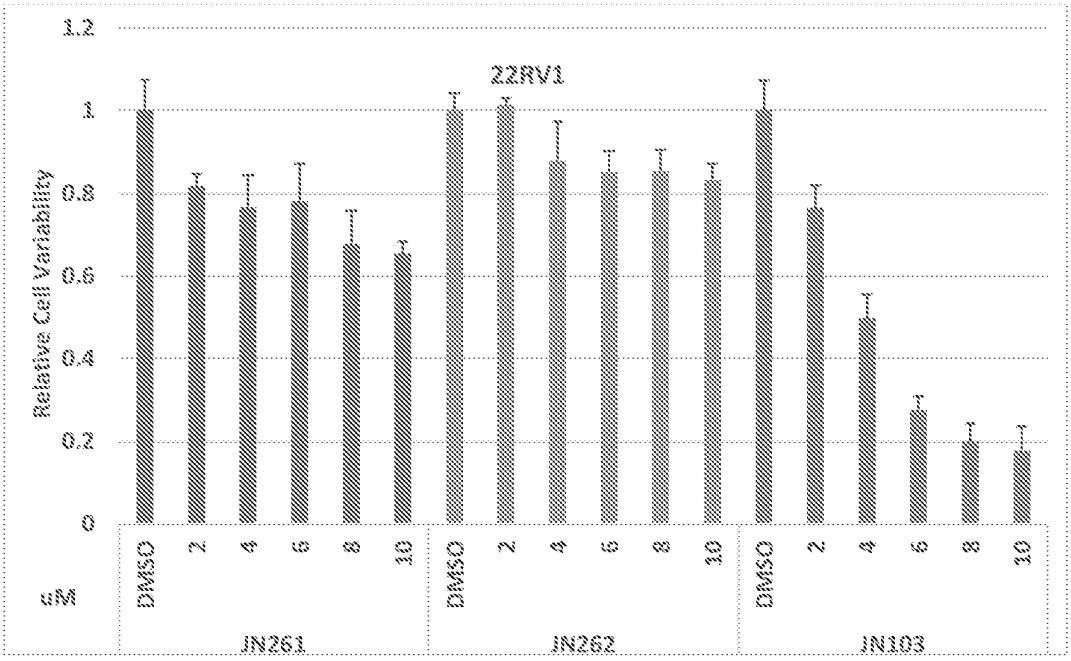

22RV1
Relative Cell Variability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
uM
JN261
JN262
JN103

FIG. 49

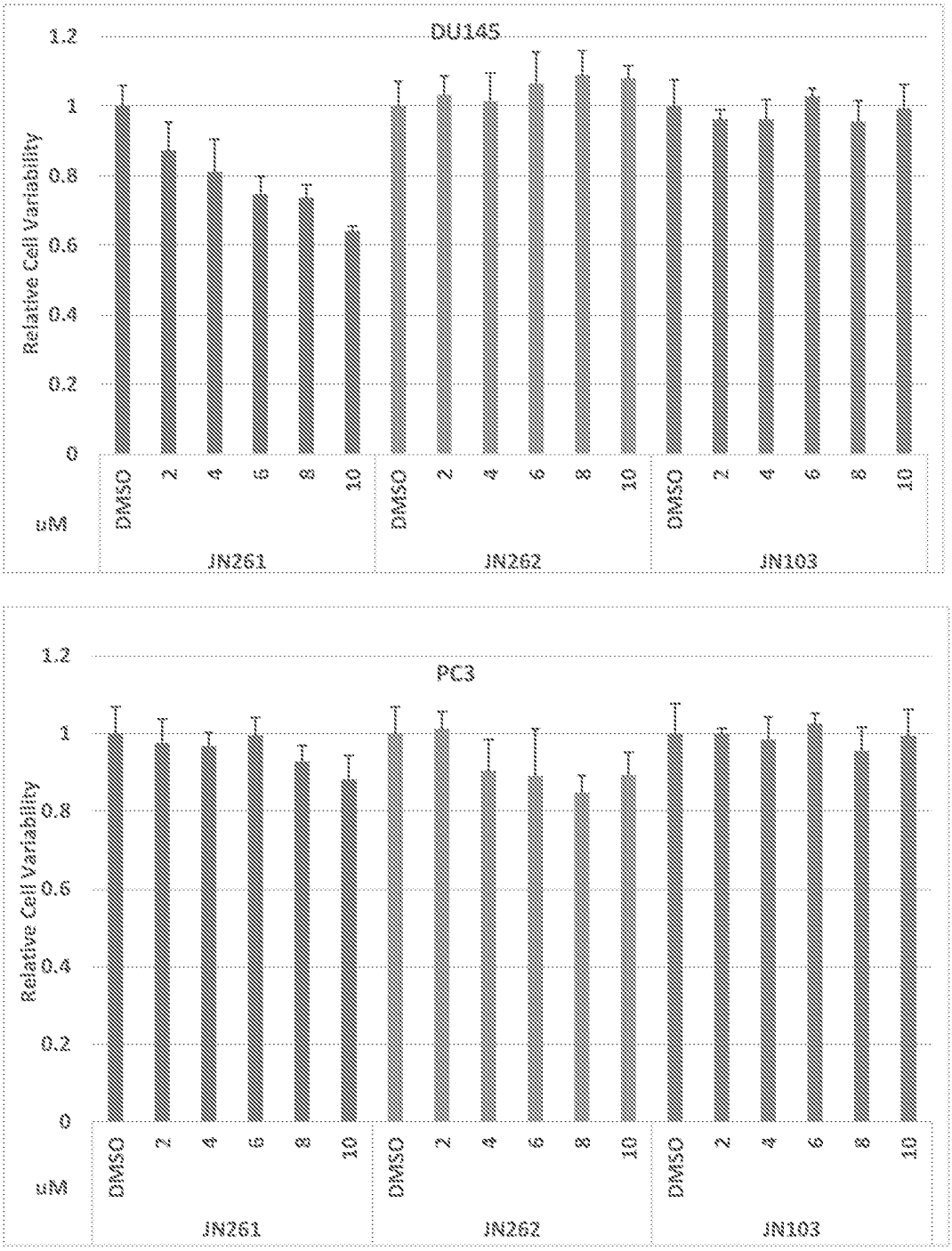

DU145
Relative Cell Variability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN261
JN262
JN103
PC3
Relative Cell Variability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN261
JN262
JN103

FIG. 50

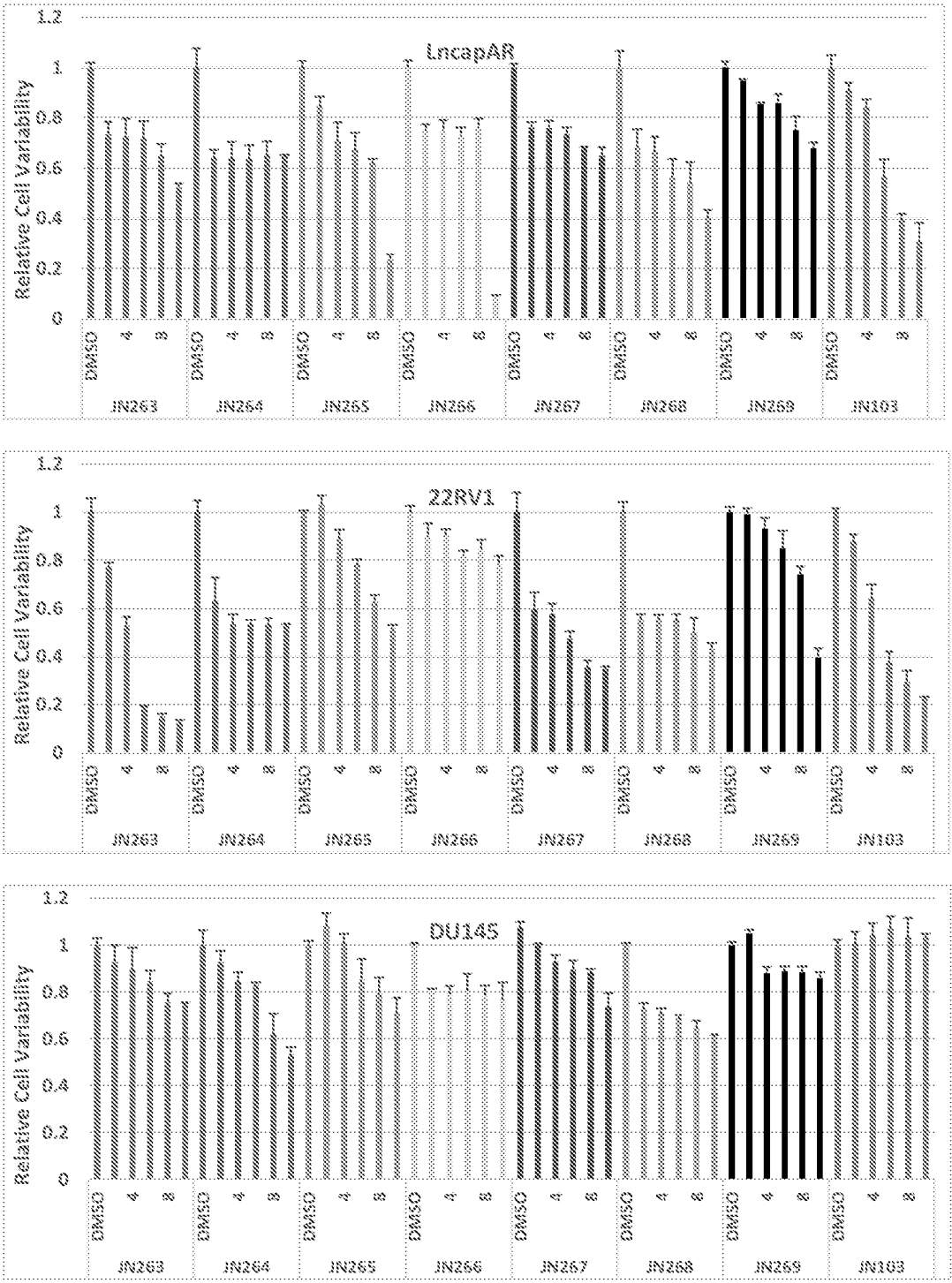

LncapAR
22RV1
DU145
Relative Cell Variability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
JN263
JN264
JN265
JN266
JN267
JN268
JN269
JN103

FIG. 51

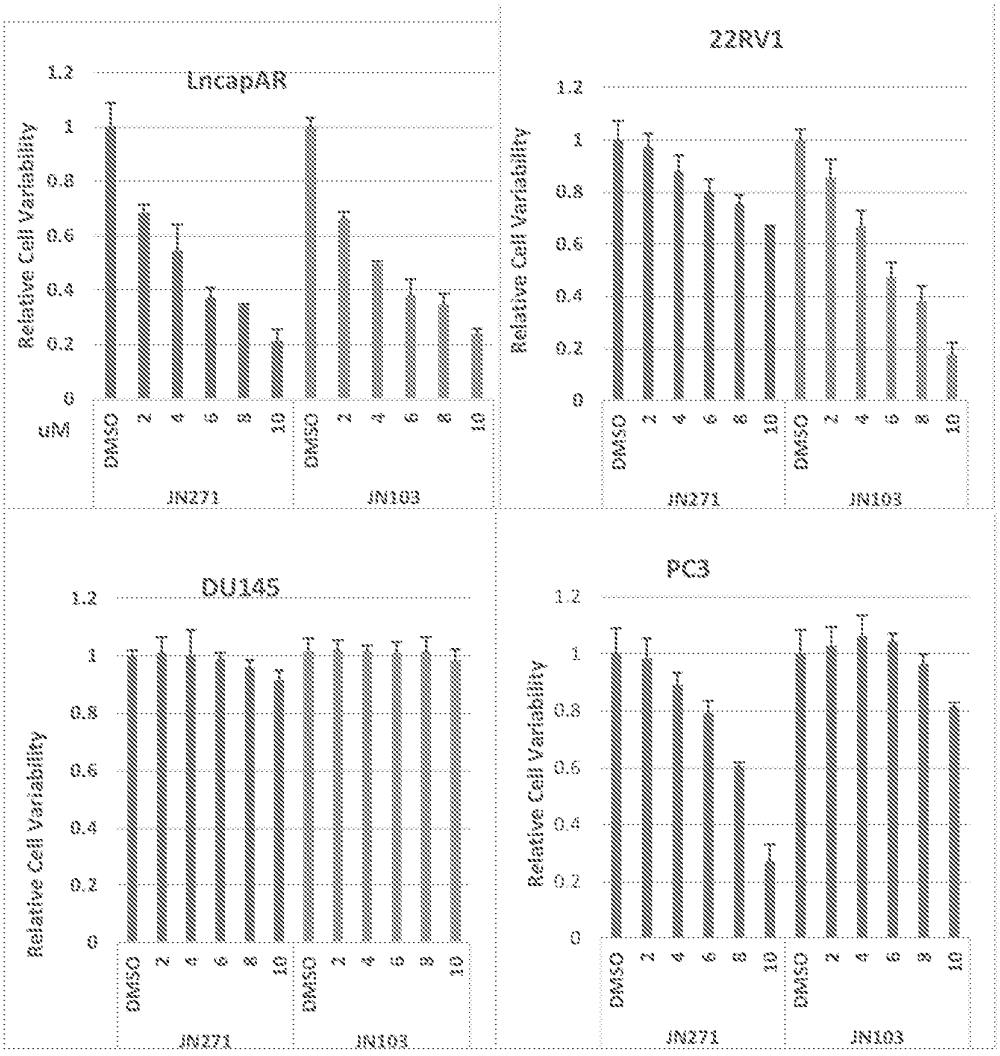

LncapAR
22RV1
DU145
PC3
Relative Cell Variability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN271
JN103

FIG. 52

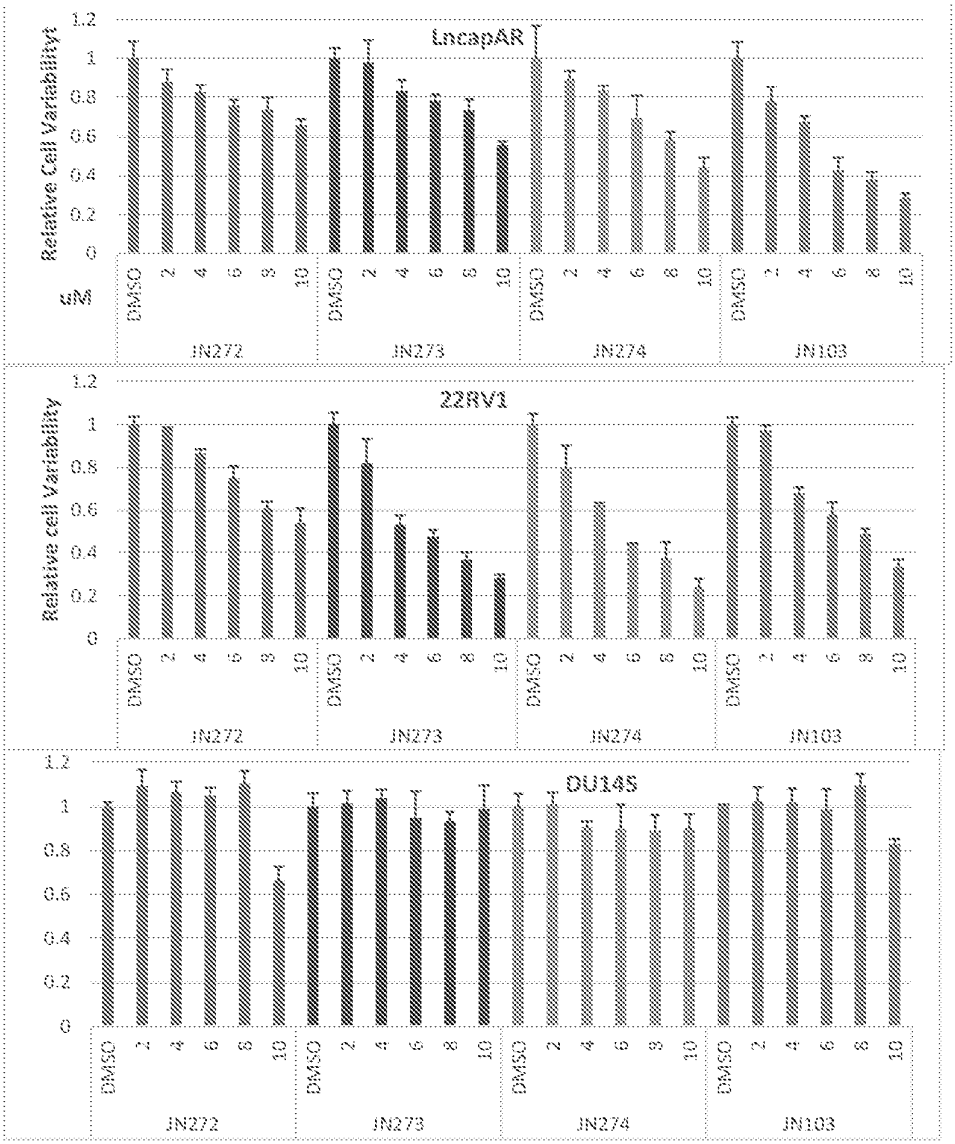

LncapAR
22RV1
DU145
Relative Cell Variability
uM
DMSO
2
4
6
8
10
JN272
JN273
JN274
JN103

FIG. 53

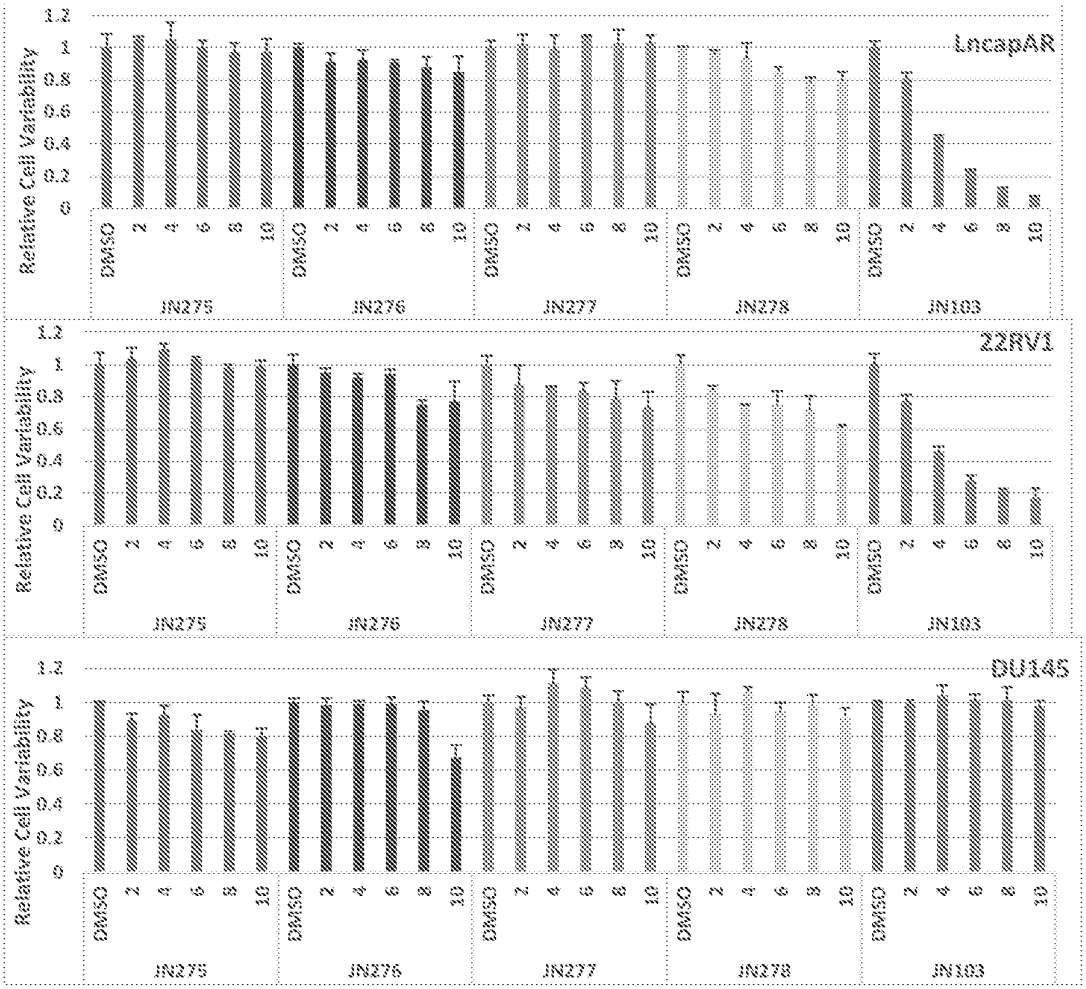

LncapAR
22RV1
DU145
Relative Cell Variability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
JN275
JN276
JN277
JN278
JN103

FIG. 54

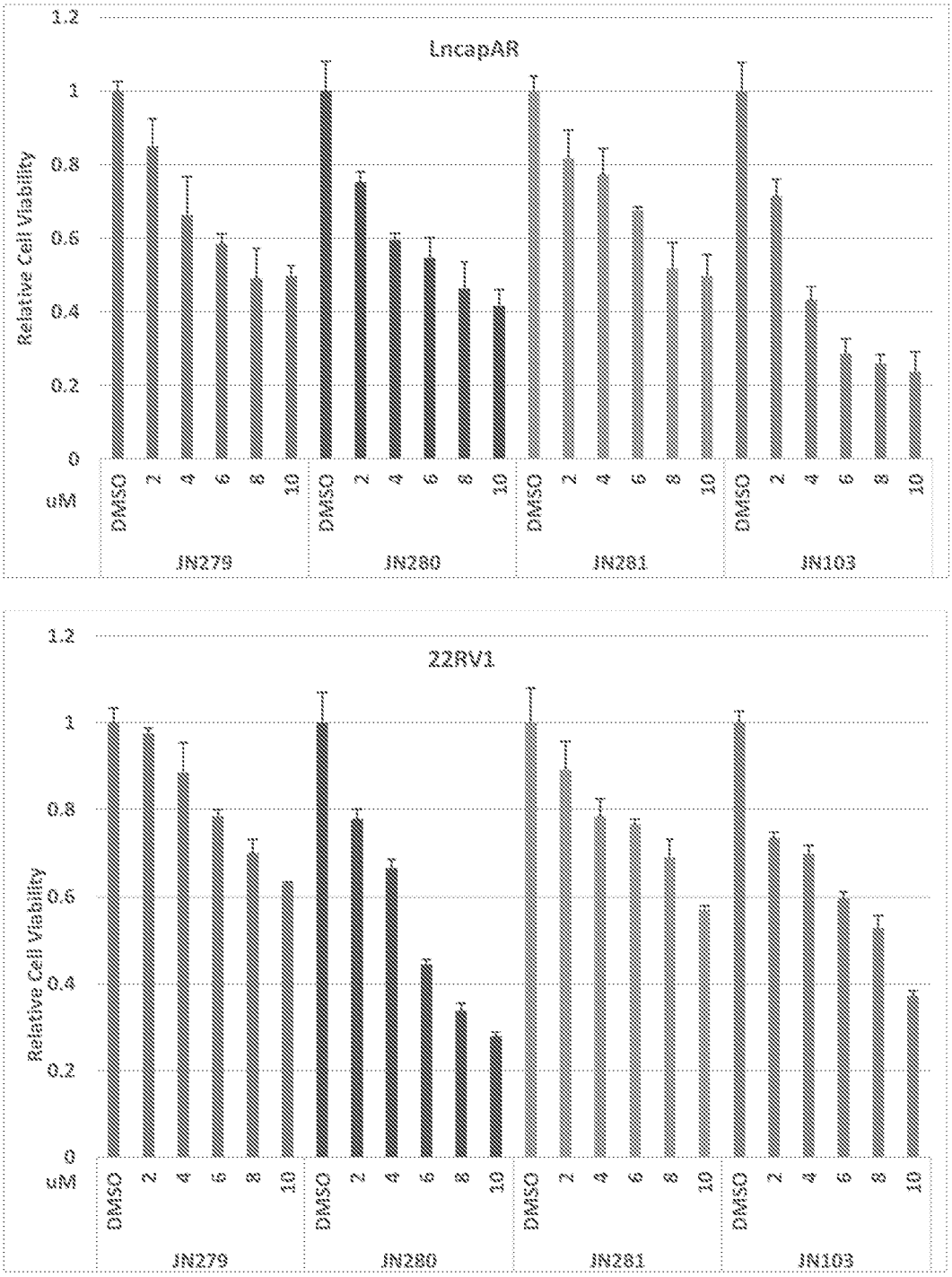
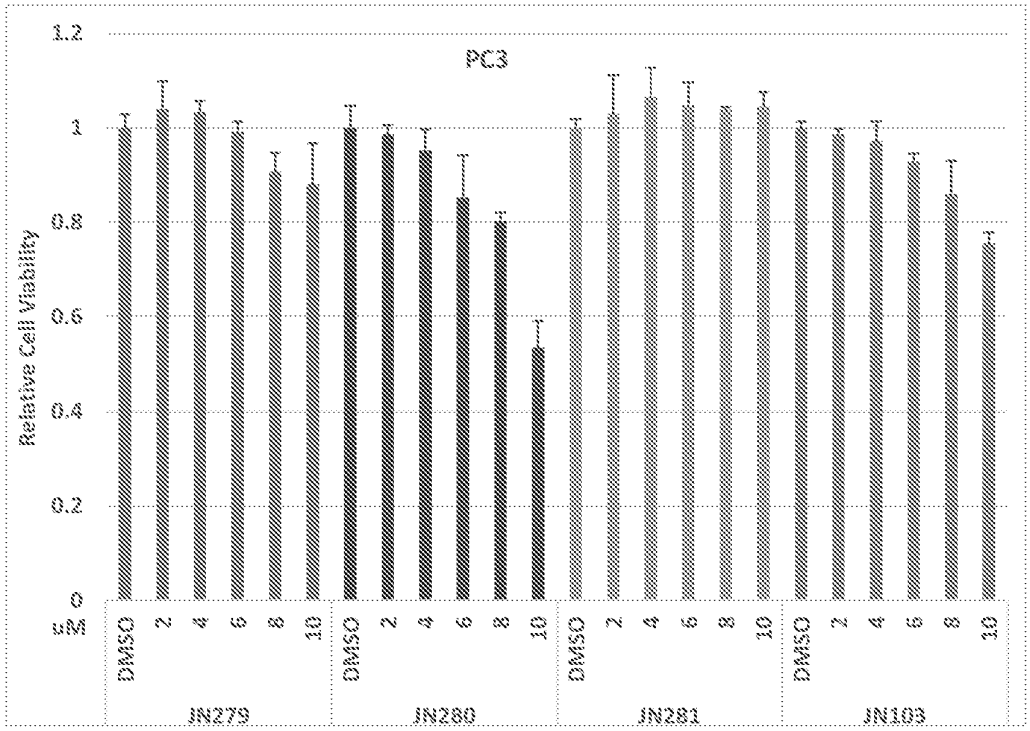

LncapAR
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN279
JN280
JN281
JN103
22RV1
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN279
JN280
JN281
JN103

FIG. 55


PC3
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN279
JN280
JN281
JN103

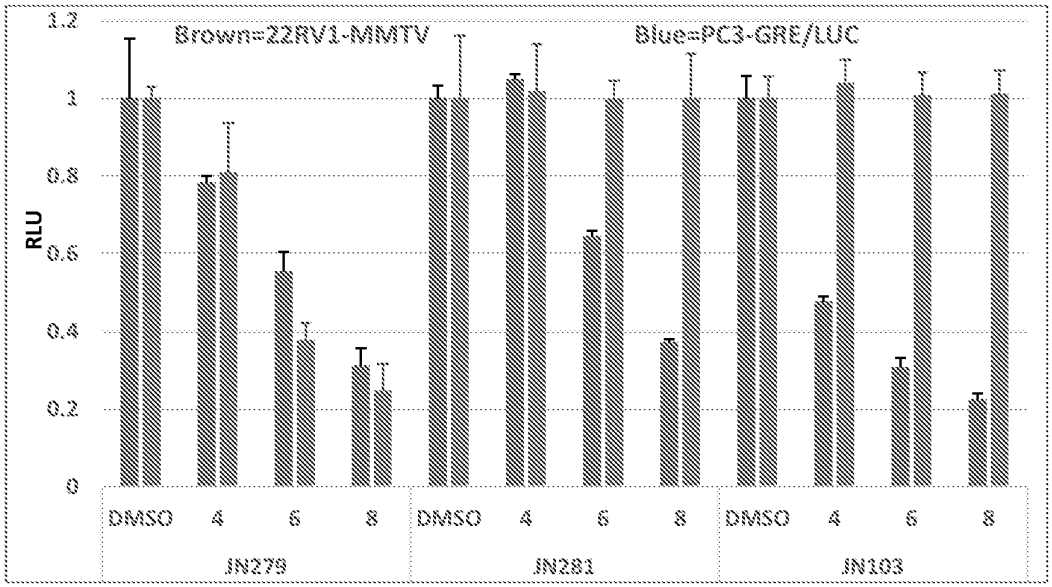

Brown=22RV1-MMTV
Blue=PC3-GRE/LUC
RLU
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
6
8
JN279
JN281
JN103

FIG. 56

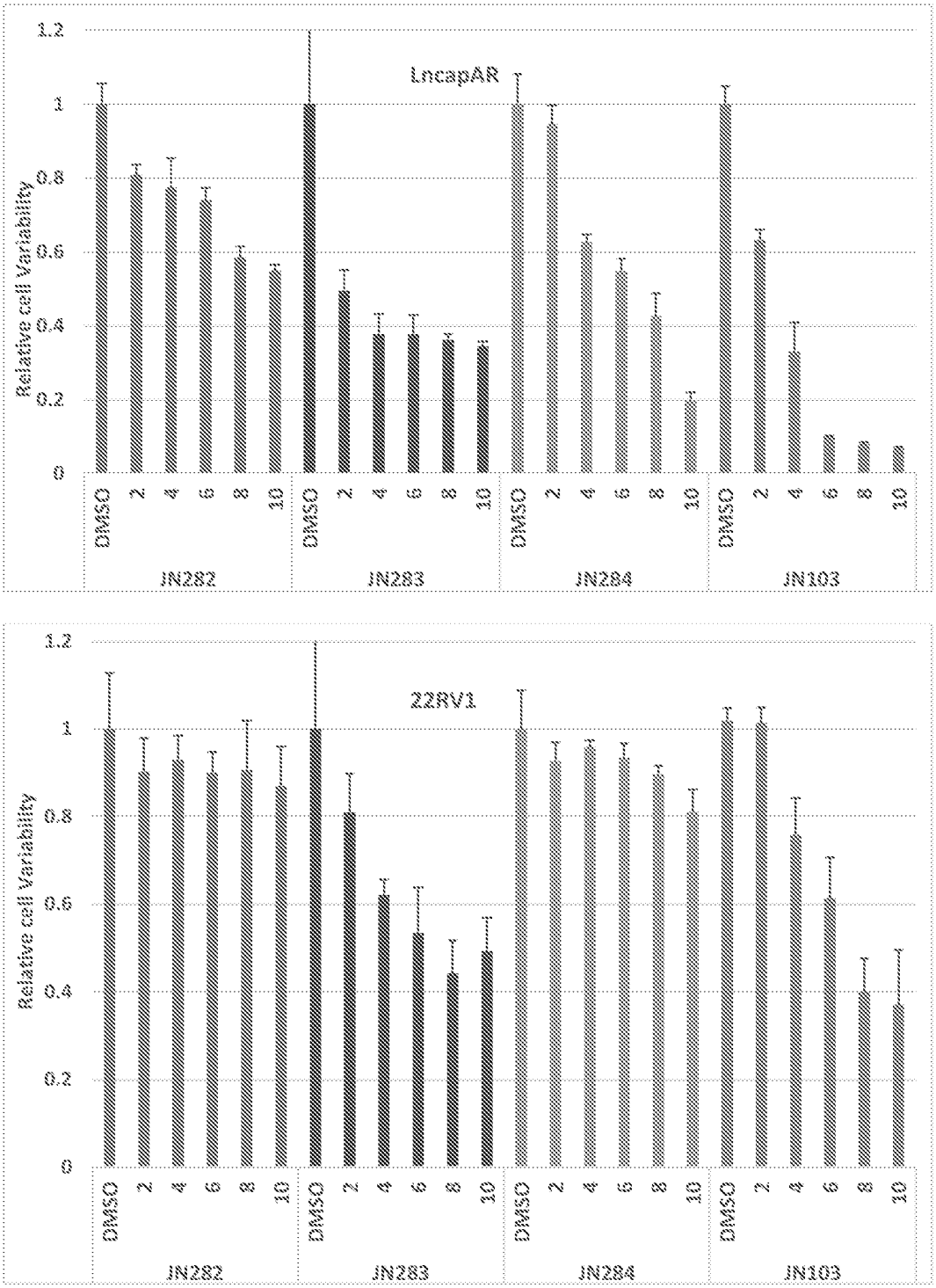

LncapAR
Relative cell Variability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
JN282
JN283
JN284
JN103
22RV1
Relative cell Variability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
JN282
JN283
JN284
JN103

FIG. 57

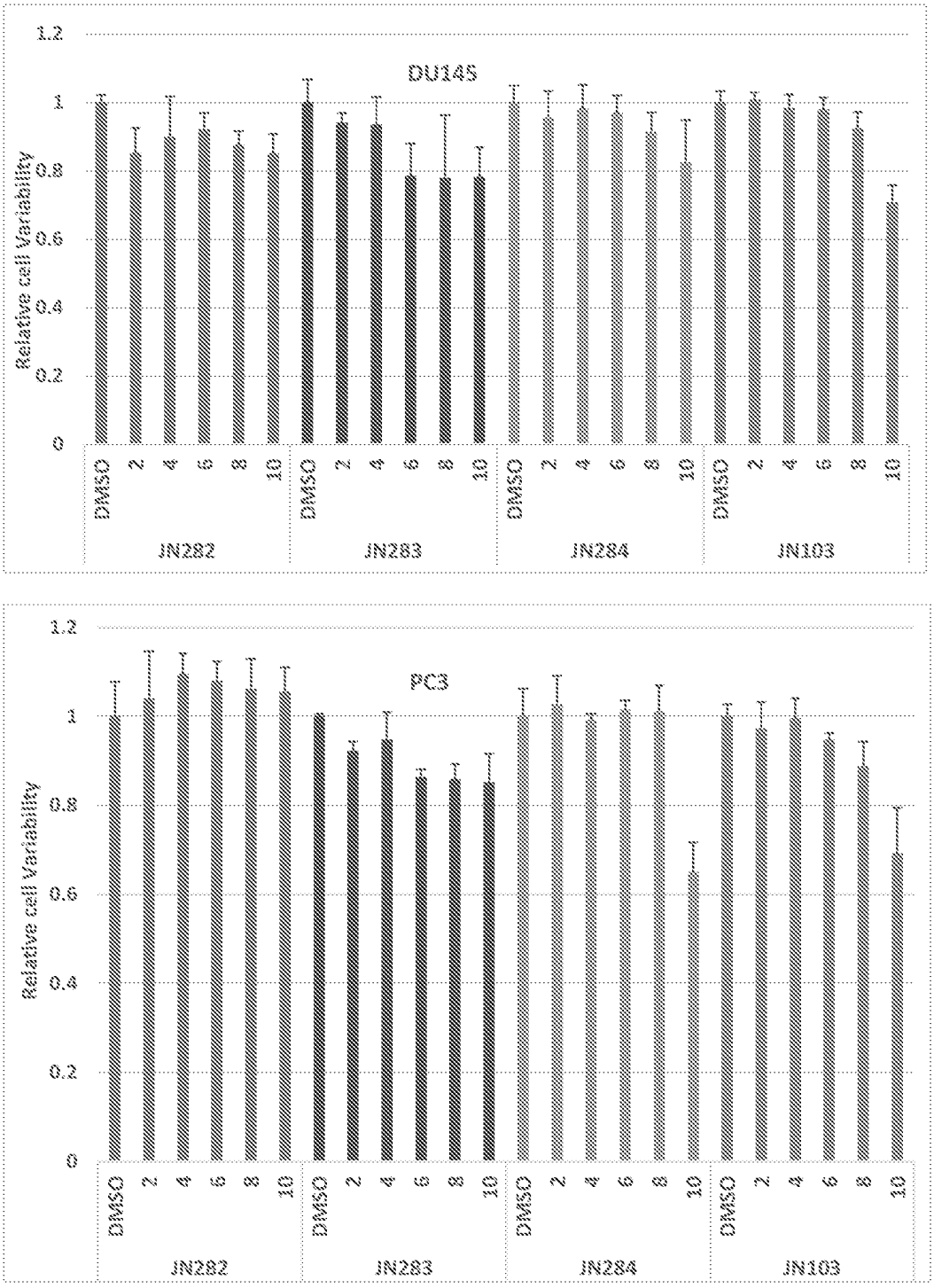

DU145
Relative cell Variability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
JN282
JN283
JN284
JN103
PC3
Relative cell Variability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
JN282
JN283
JN284
JN103

FIG. 58

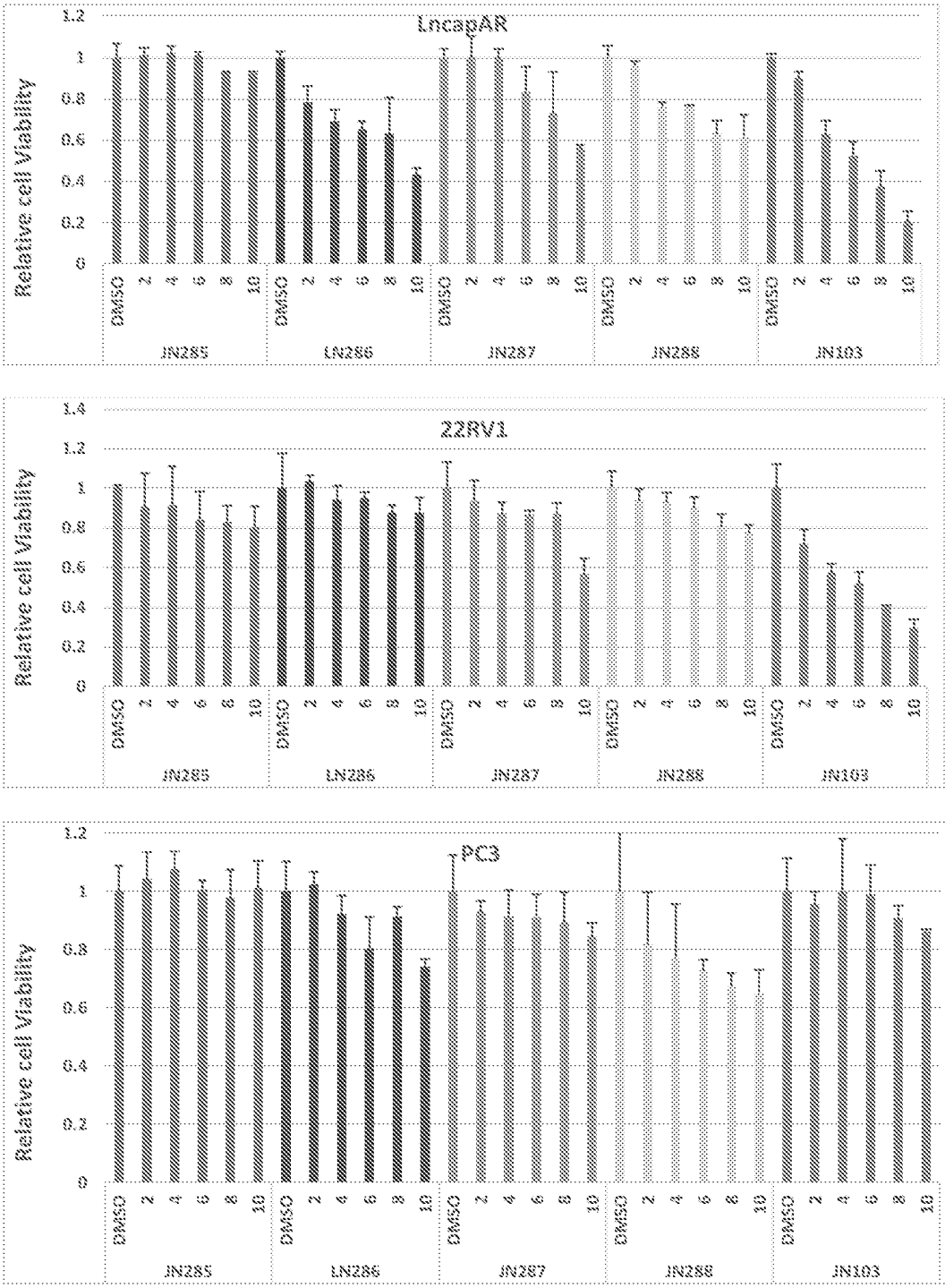
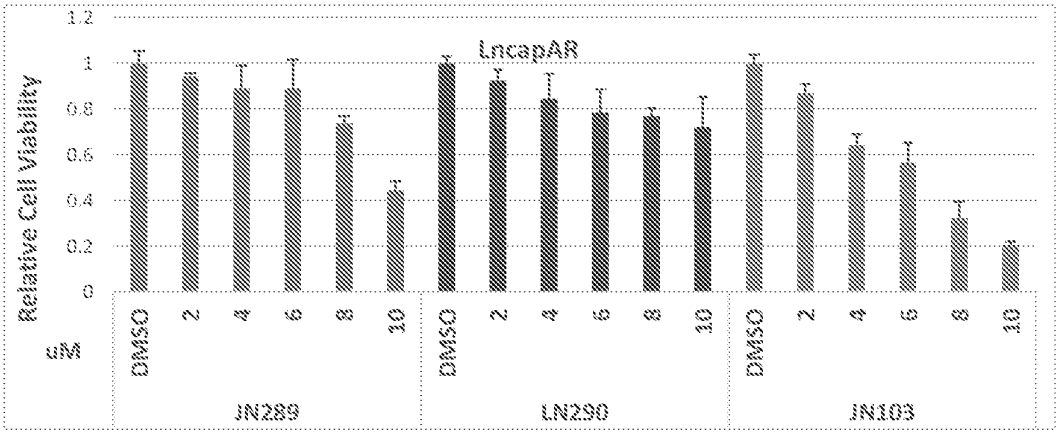
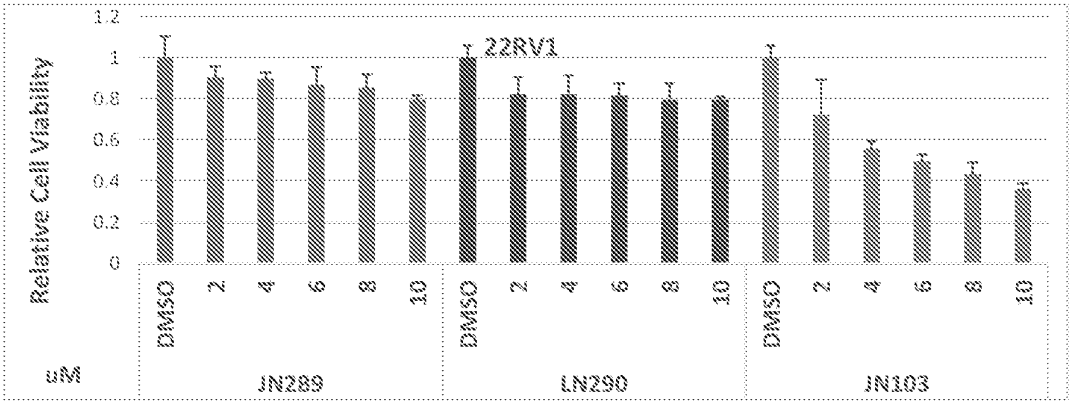

LncapAR
22RV1
PC3
Relative cell Viability
0
0.2
0.4
0.6
0.8
1
1.2
1.4
DMSO
2
4
6
8
10
JN285
LN286
JN287
JN288
JN103

FIG. 59


LncapAR
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
uM
JN289
LN290
JN103


22RV1
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
uM
JN289
LN290
JN103

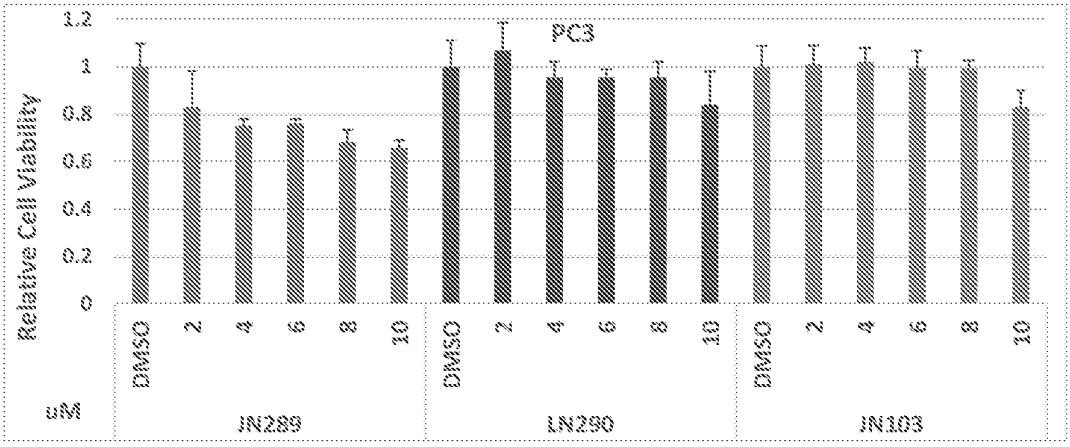

PC3
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
uM
JN289
LN290
JN103

FIG. 60

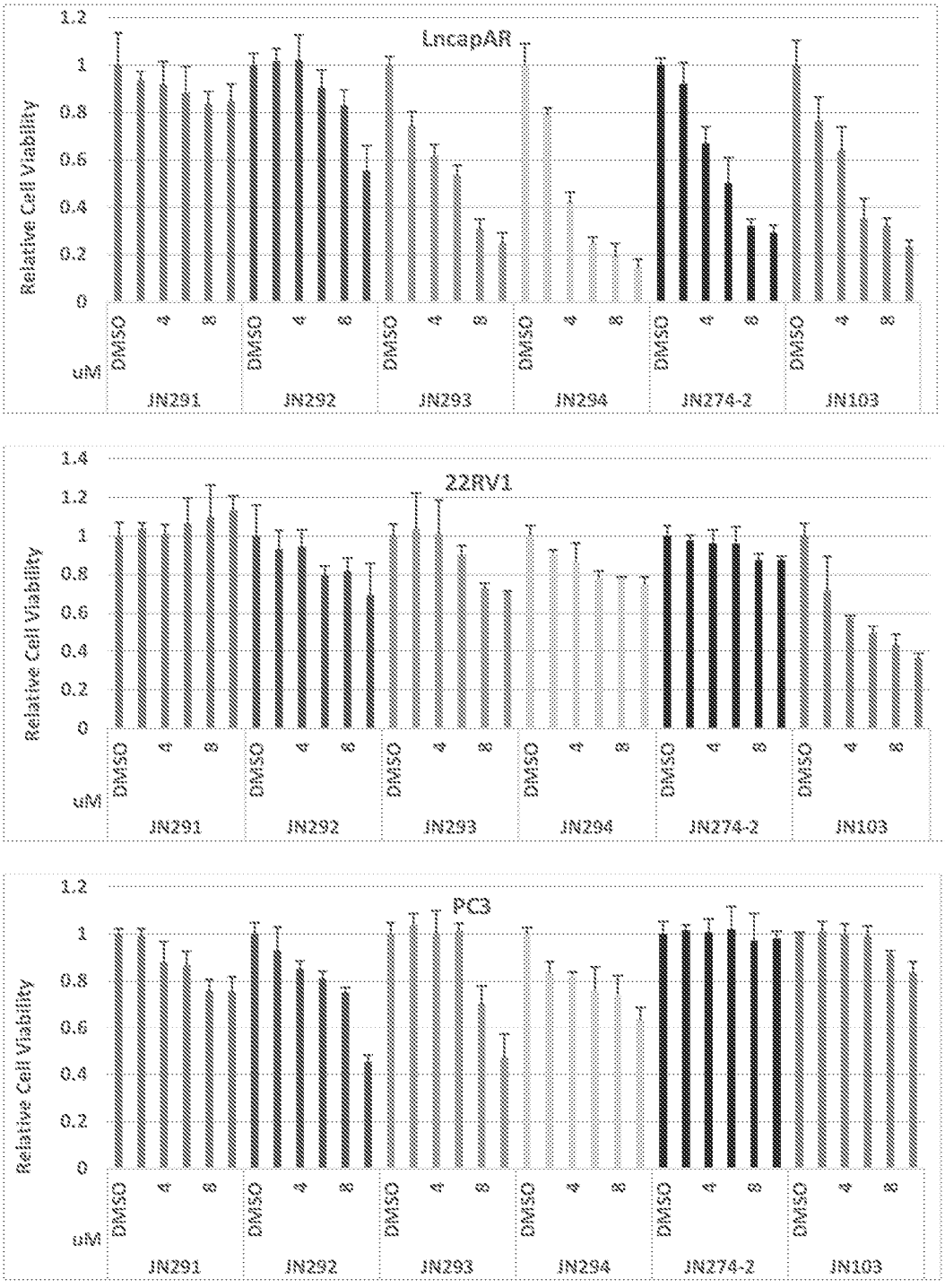

LncapAR
22RV1
PC3
Relative Cell Viability
DMSO
4
8
uM
JN291
JN292
JN293
JN294
JN274-2
JN103

FIG. 61

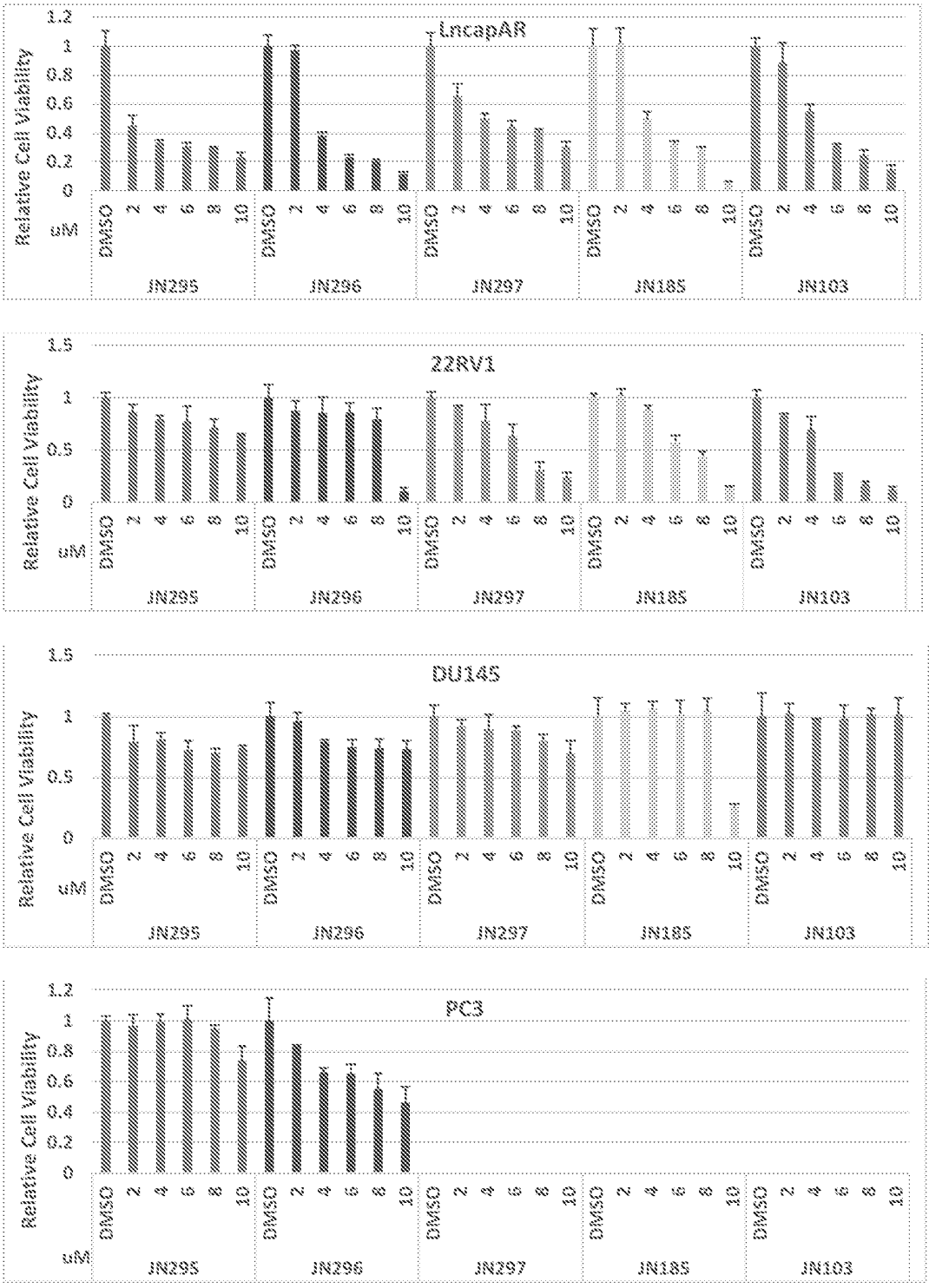

LncapAR
22RV1
DU145
PC3
Relative Cell Viability
uM
DMSO
2
4
6
8
10
JN295
JN296
JN297
JN185
JN103

FIG. 62

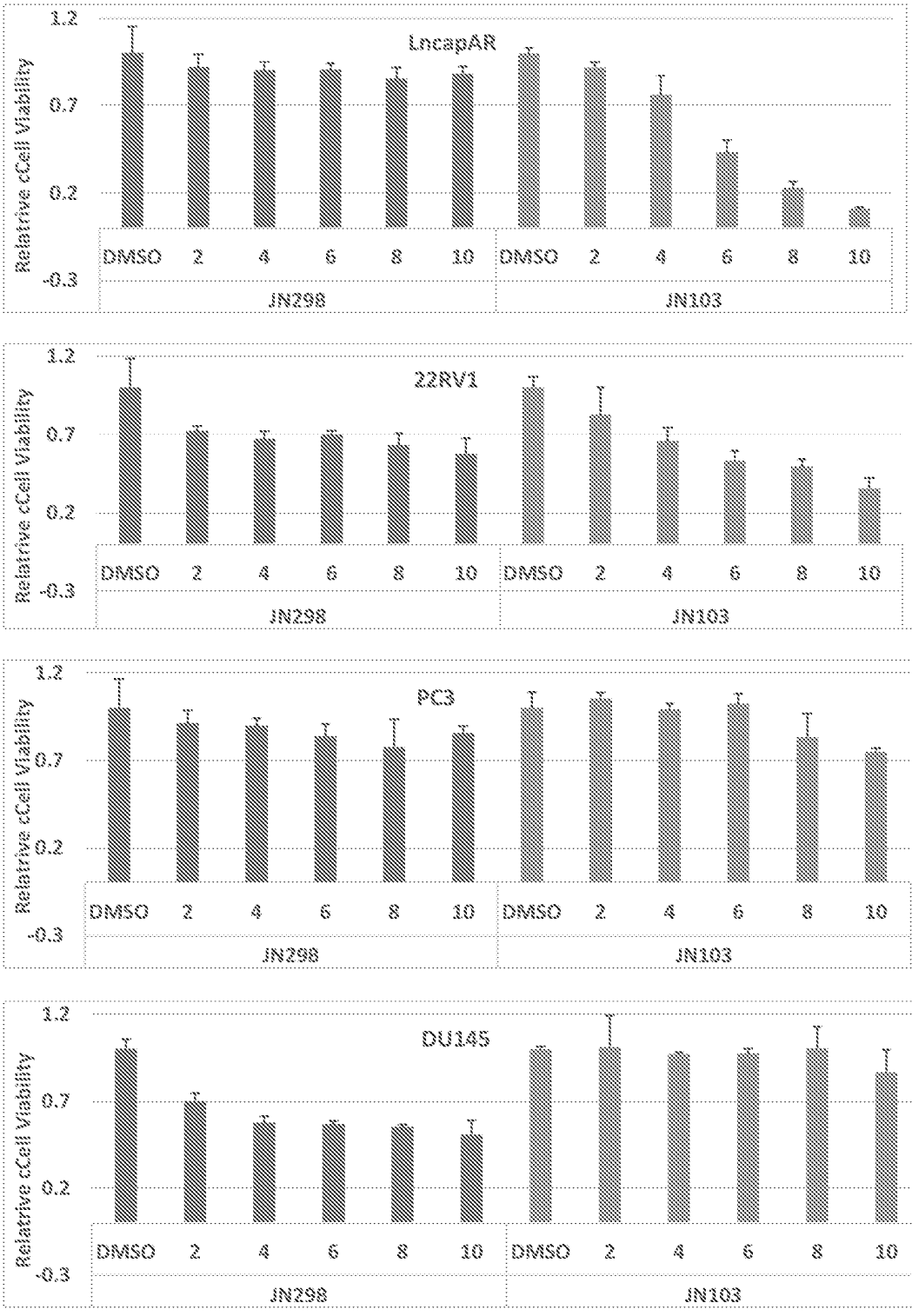

LncapAR
22RV1
PC3
DU145
Relatrive cCell Viability
1.2
0.7
0.2
-0.3
DMSO
2
4
6
8
10
JN298
JN103

FIG. 63

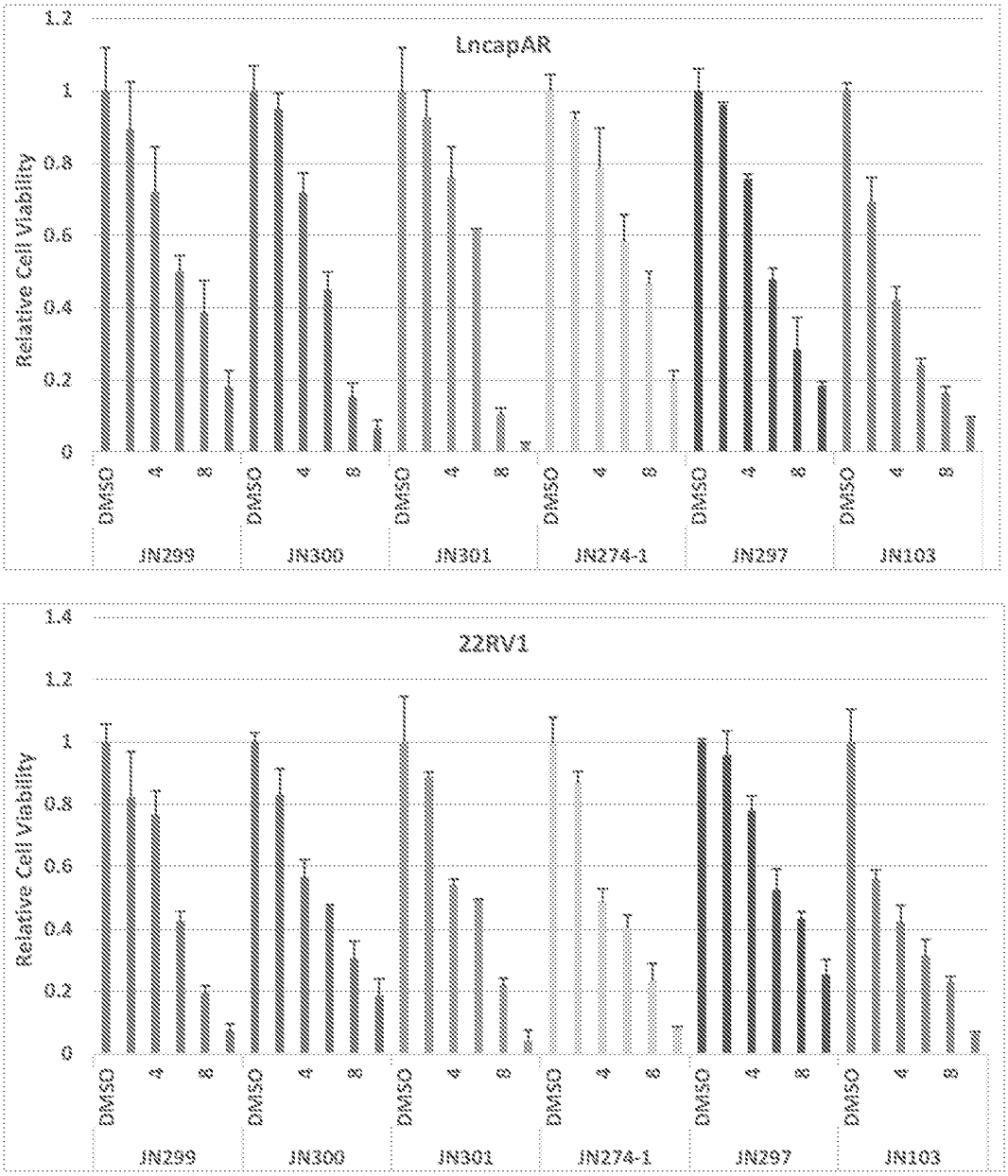

LncapAR
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
JN299
JN300
JN301
JN274-1
JN297
JN103
22RV1
Relative Cell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
JN299
JN300
JN301
JN274-1
JN297
JN103

FIG. 64

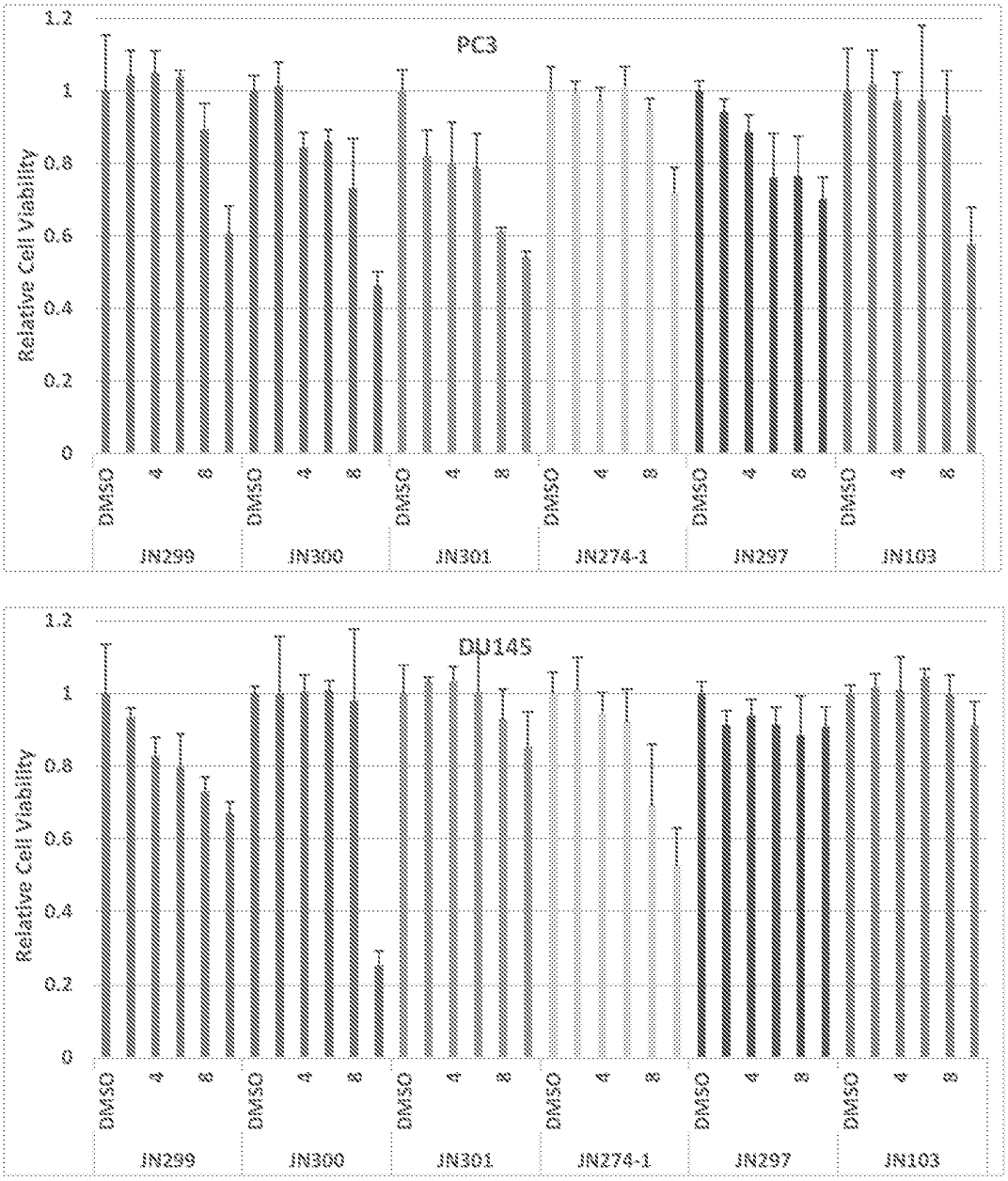

PC3
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
JN299
JN300
JN301
JN274-1
JN297
JN103
DU145
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
8
JN299
JN300
JN301
JN274-1
JN297
JN103

FIG. 65

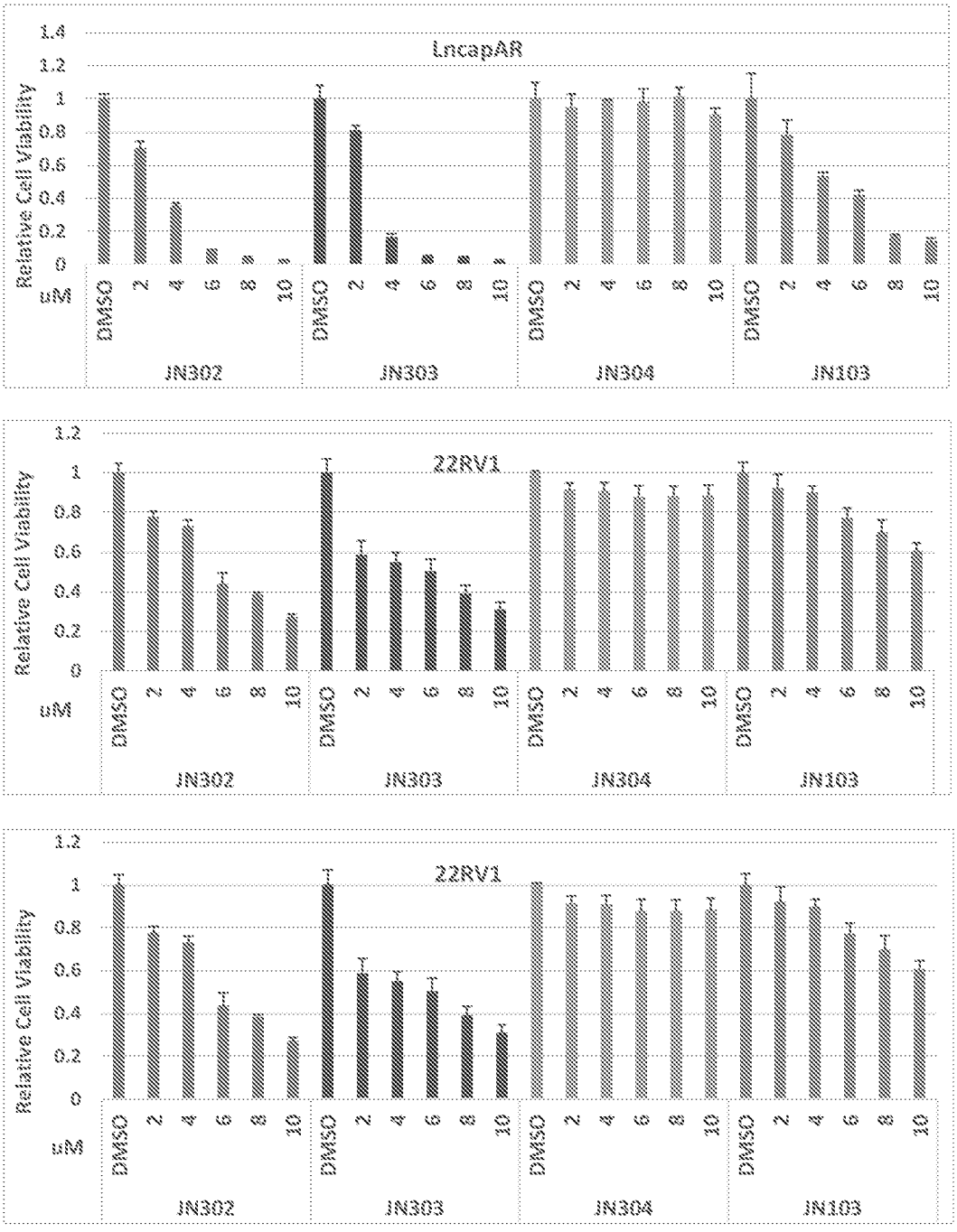

LncapAR
22RV1
22RV1
Relative Cell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN302
JN303
JN304
JN103

FIG. 66

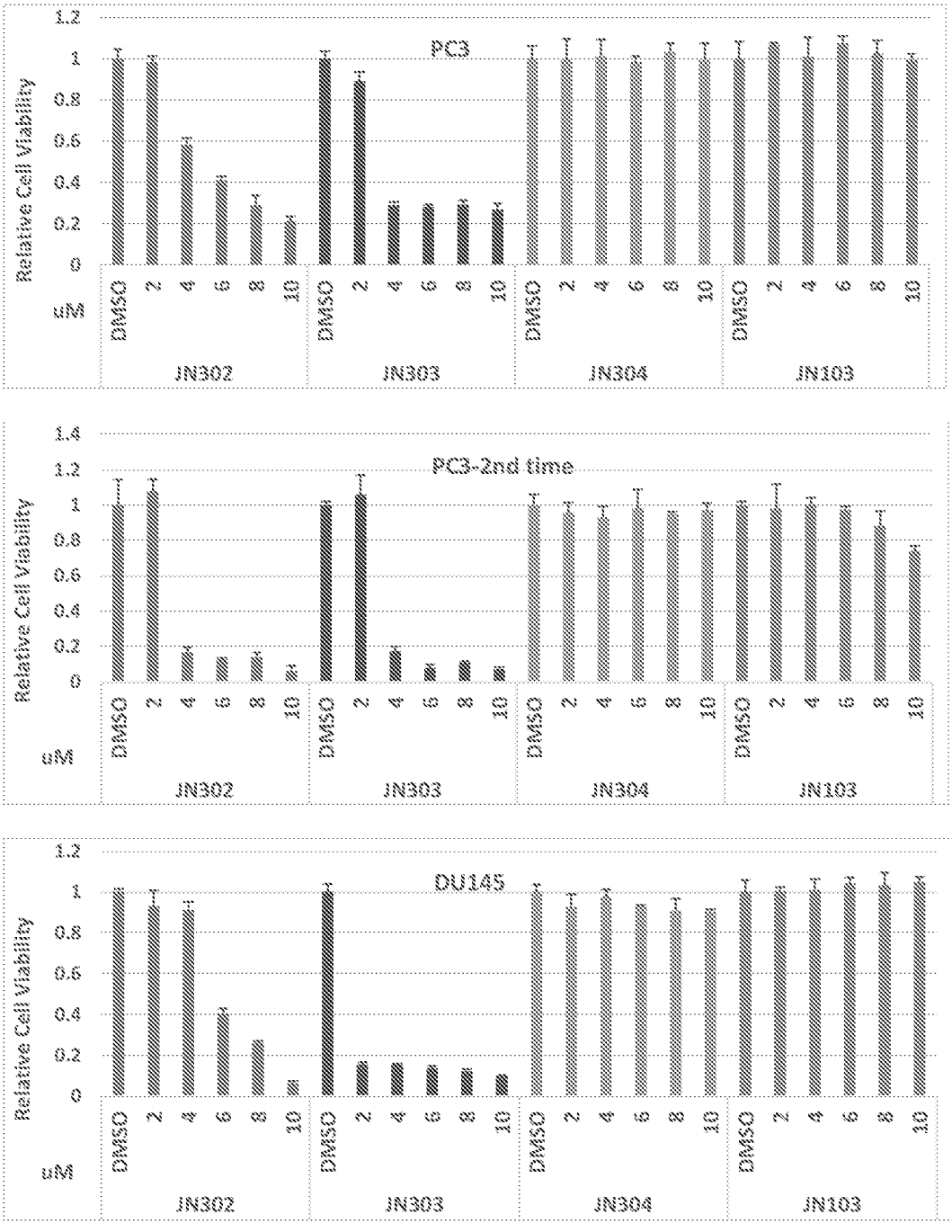

PC3
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
uM
JN302
JN303
JN304
JN103
PC3-2nd time
1.4
DU145

FIG. 67

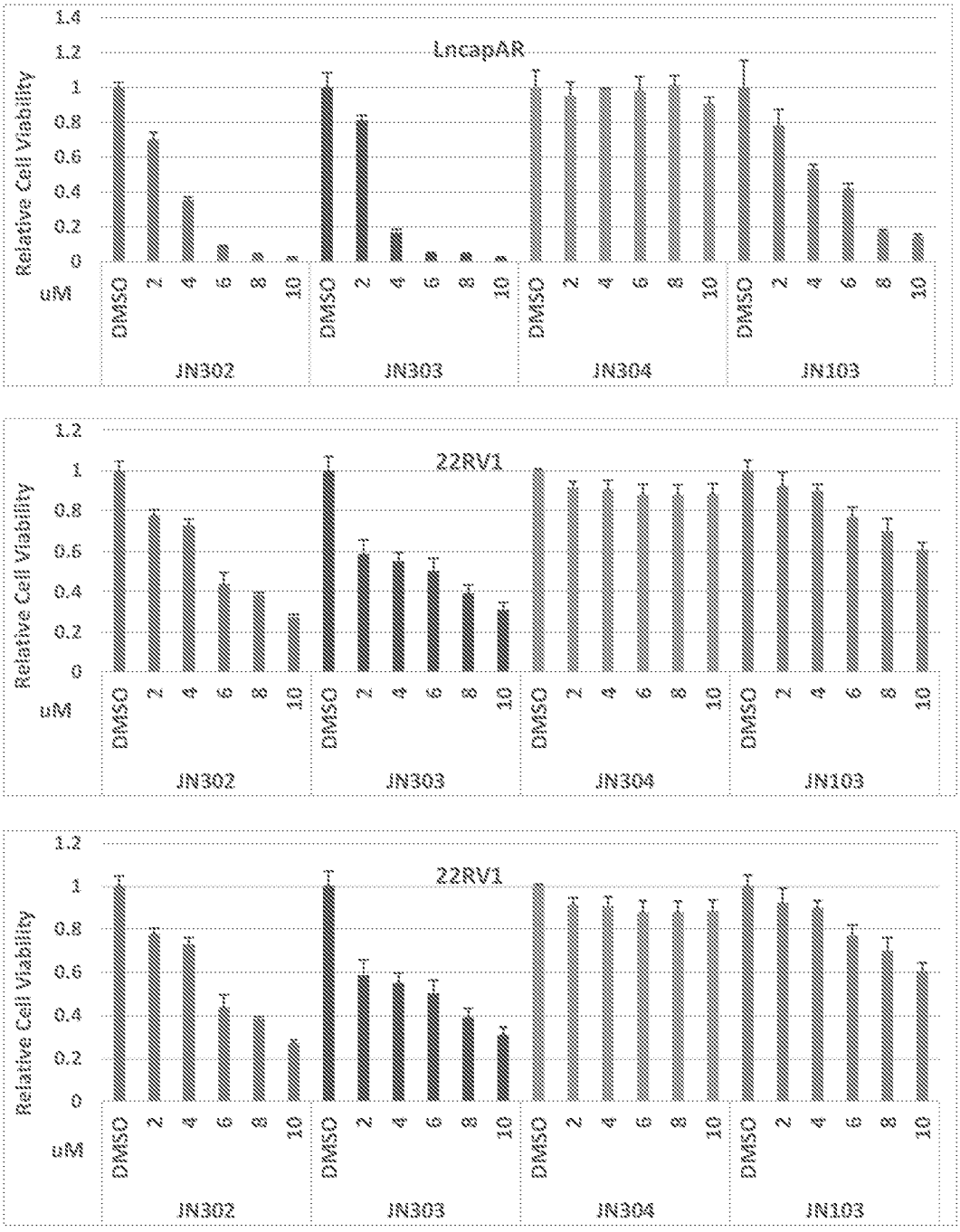

LncapAR
22RV1
22RV1
Relative Cell Viability
uM
DMSO
2
4
6
8
10
JN302
JN303
JN304
JN103

FIG. 68

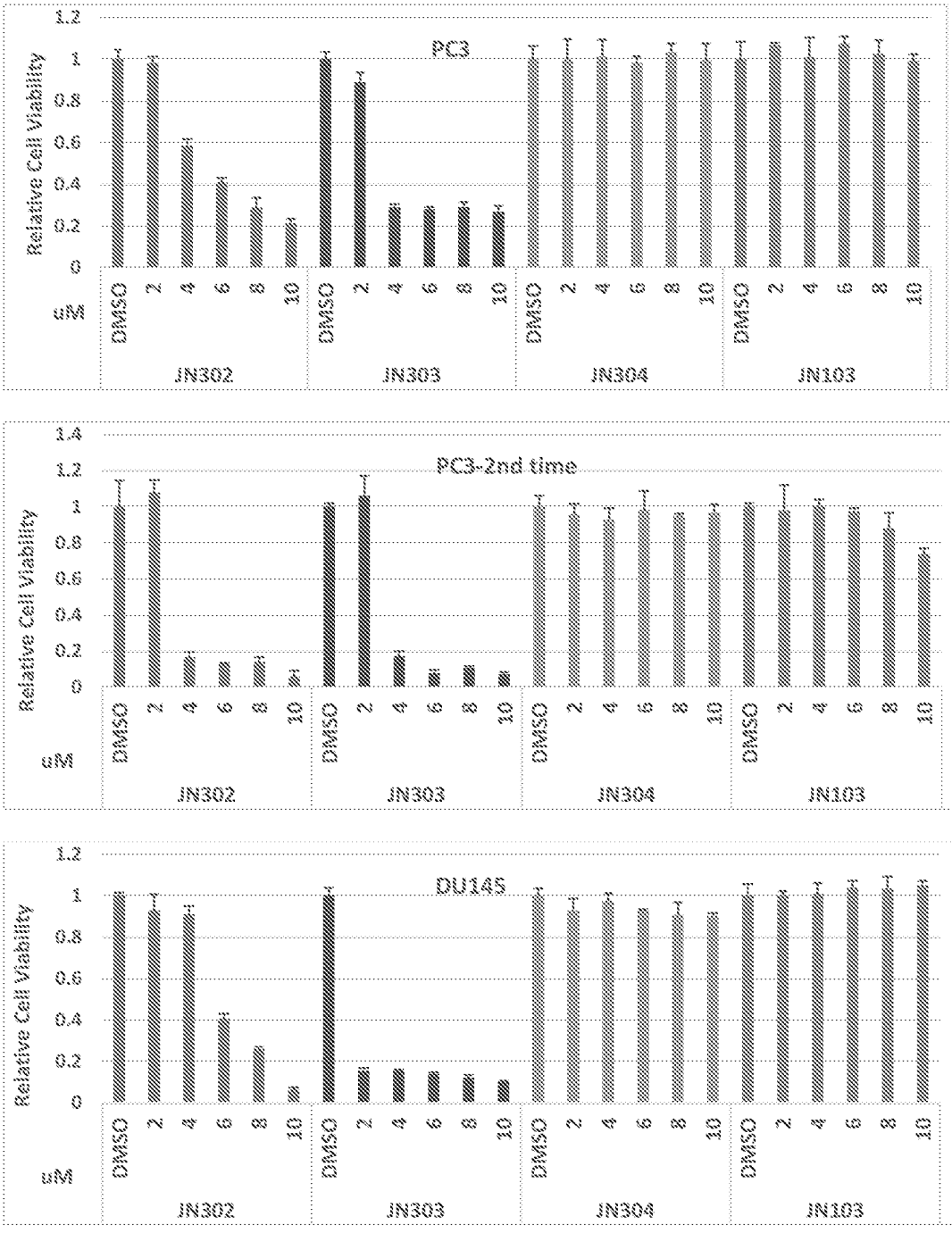

PC3
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN302
JN303
JN304
JN103
PC3-2nd time
1.4
DU145

FIG. 69

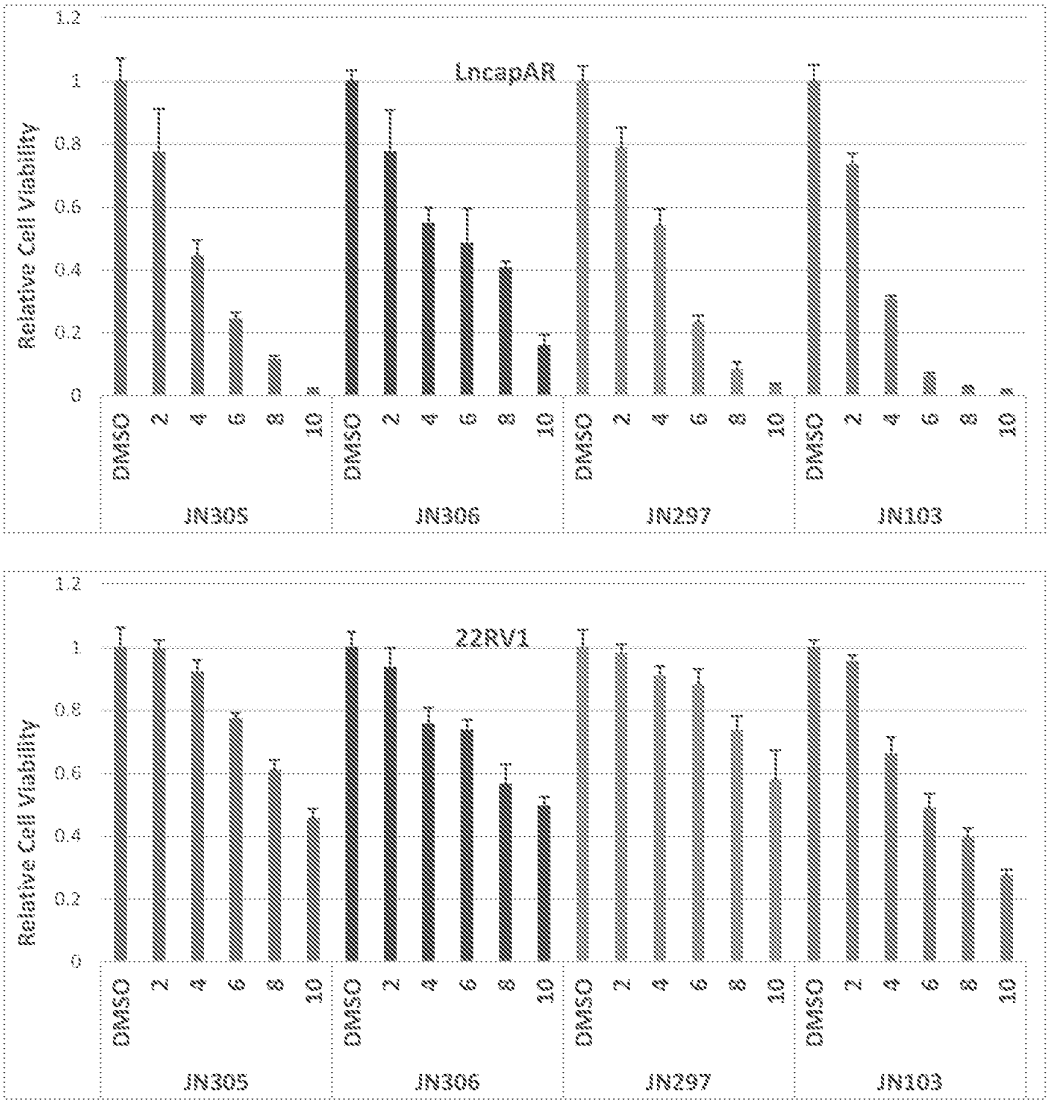

LncapAR
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
JN305
JN306
JN297
JN103
22RV1
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
JN305
JN306
JN297
JN103

FIG. 70

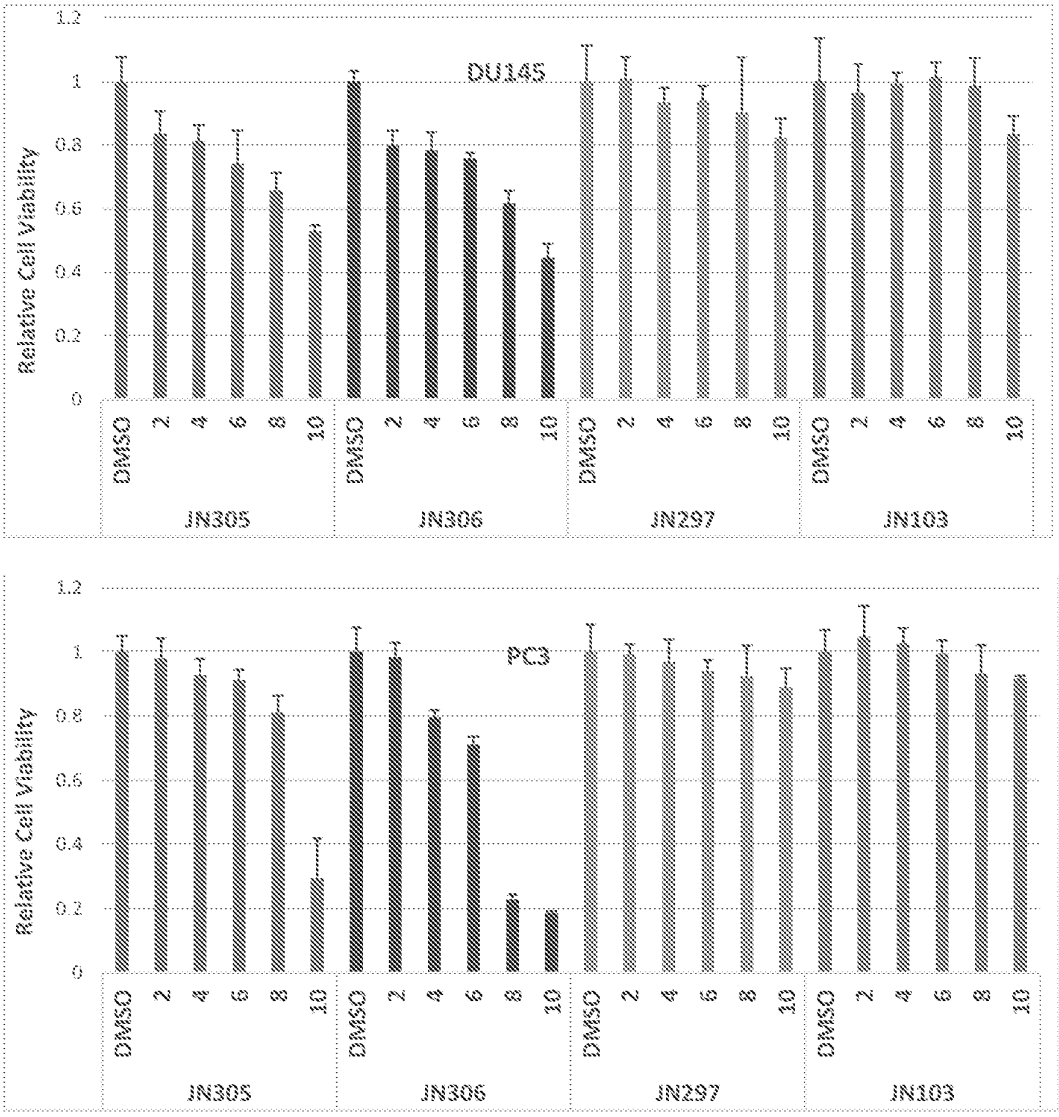

DU145
PC3
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
JN305
JN306
JN297
JN103

FIG. 71

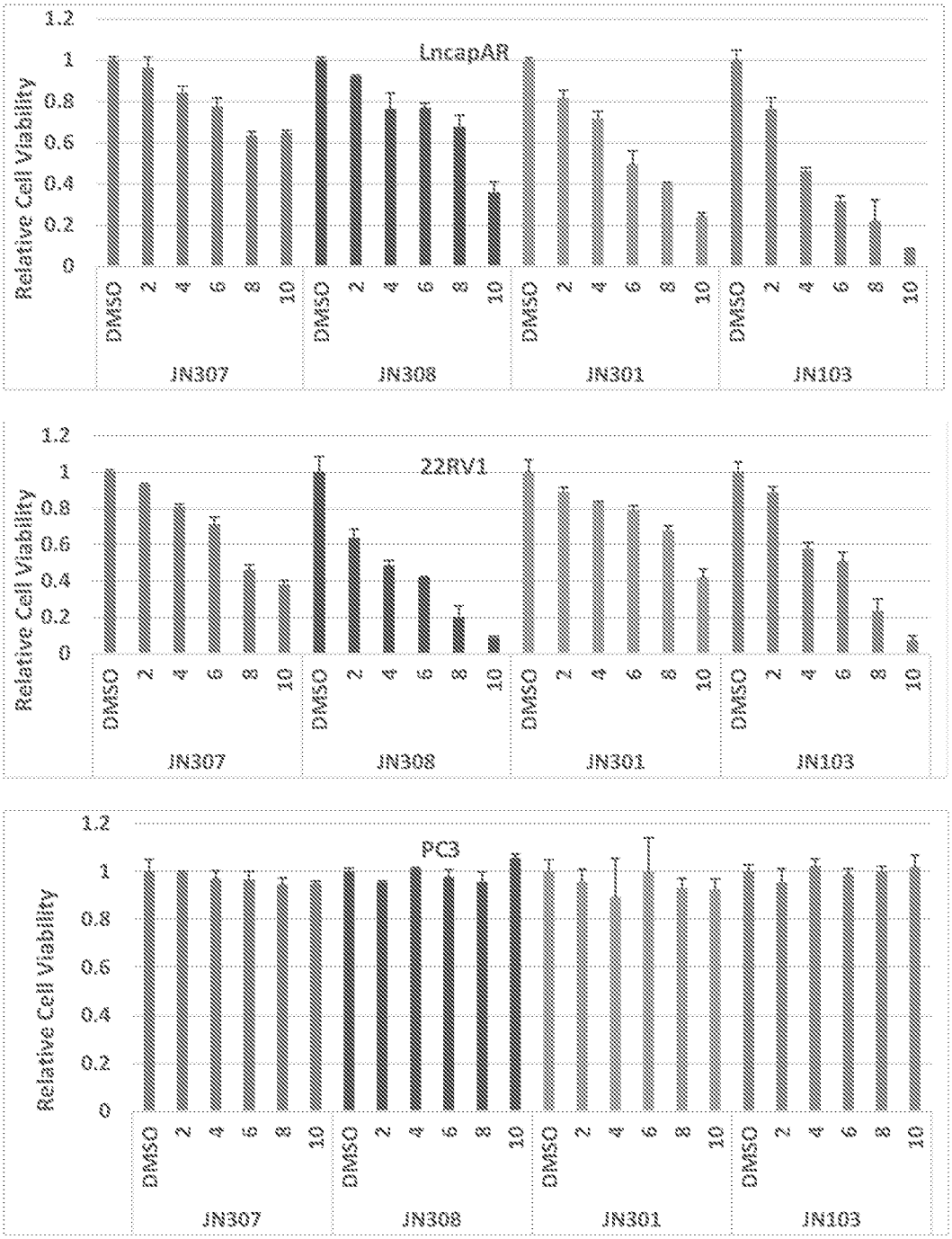
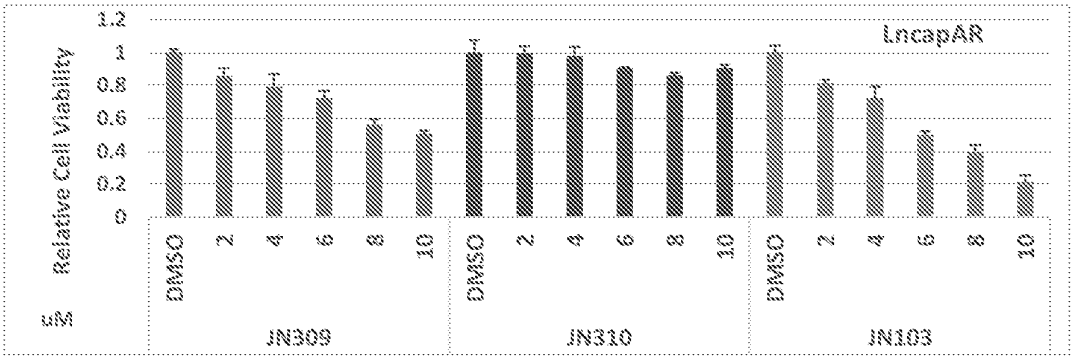
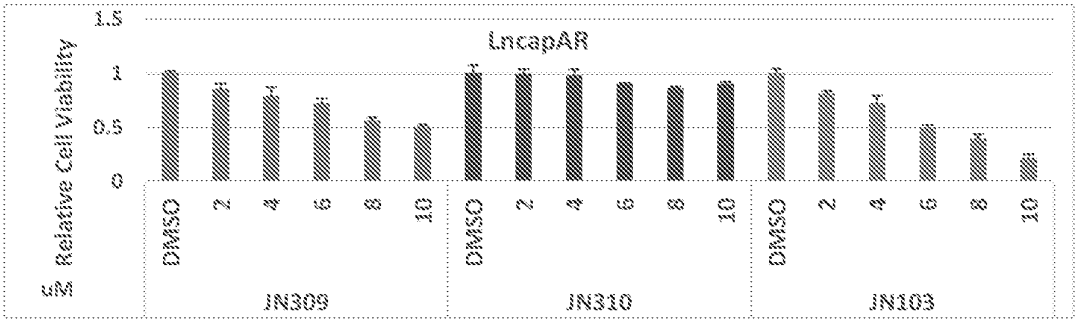
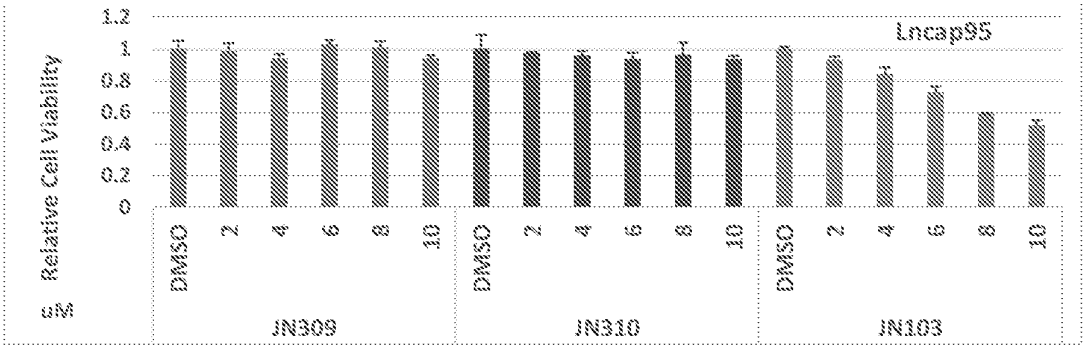

LncapAR
22RV1
PC3
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
JN307
JN308
JN301
JN103

FIG. 72


LncapAR
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
uM
JN309
JN310
JN103


LncapAR
Relative Cell Viability
1.5
1
0.5
0
DMSO
2
4
6
8
10
uM
JN309
JN310
JN103


Lncap95
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
2
4
6
8
10
uM
JN309
JN310
JN103

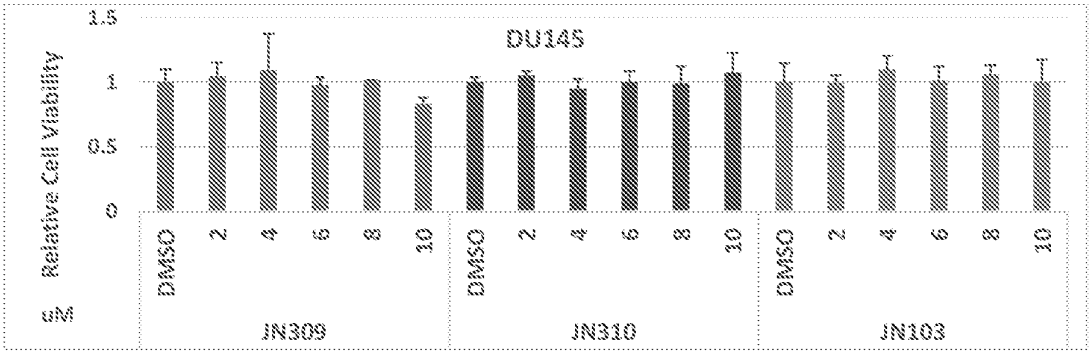

DU145
Relative Cell Viability
1.5
1
0.5
0
DMSO
2
4
6
8
10
uM
JN309
JN310
JN103

FIG. 73

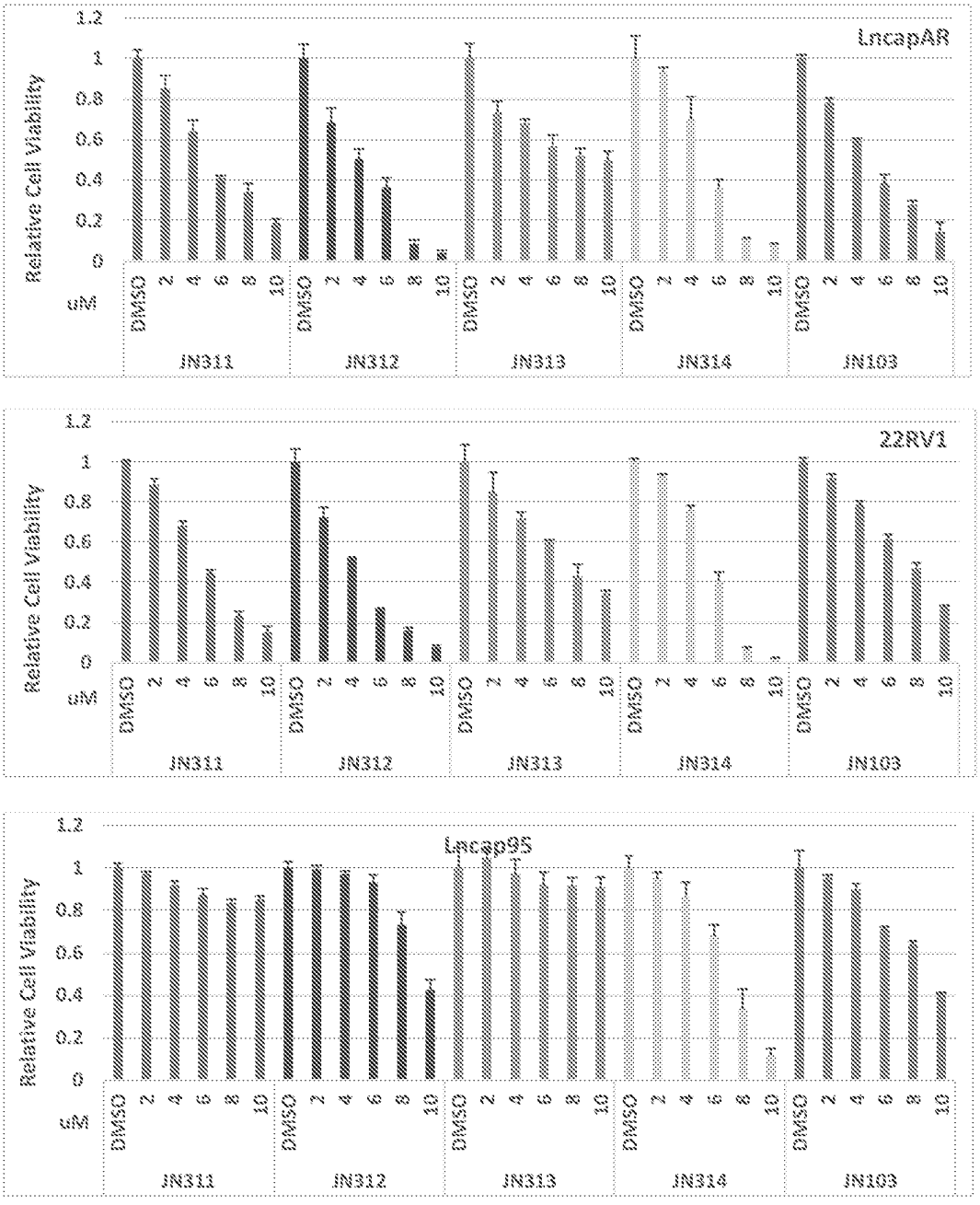

LncapAR
22RV1
Lncap95
Relative Cell Viability
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN311
JN312
JN313
JN314
JN103

FIG. 74

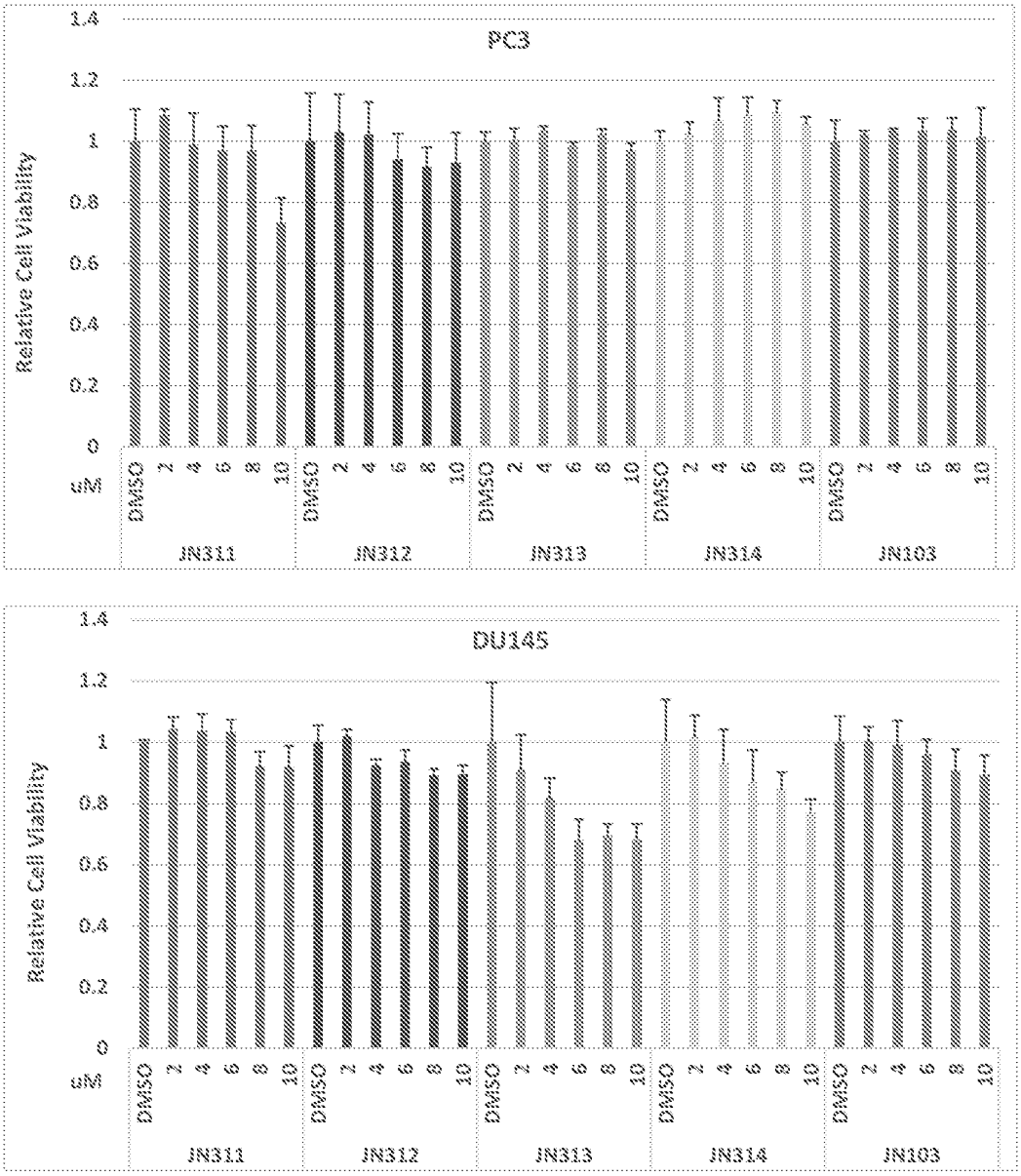

PC3
Relative Cell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN311
JN312
JN313
JN314
JN103
DU145
Relative Cell Viability
1.4
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
2
4
6
8
10
JN311
JN312
JN313
JN314
JN103

FIG. 75

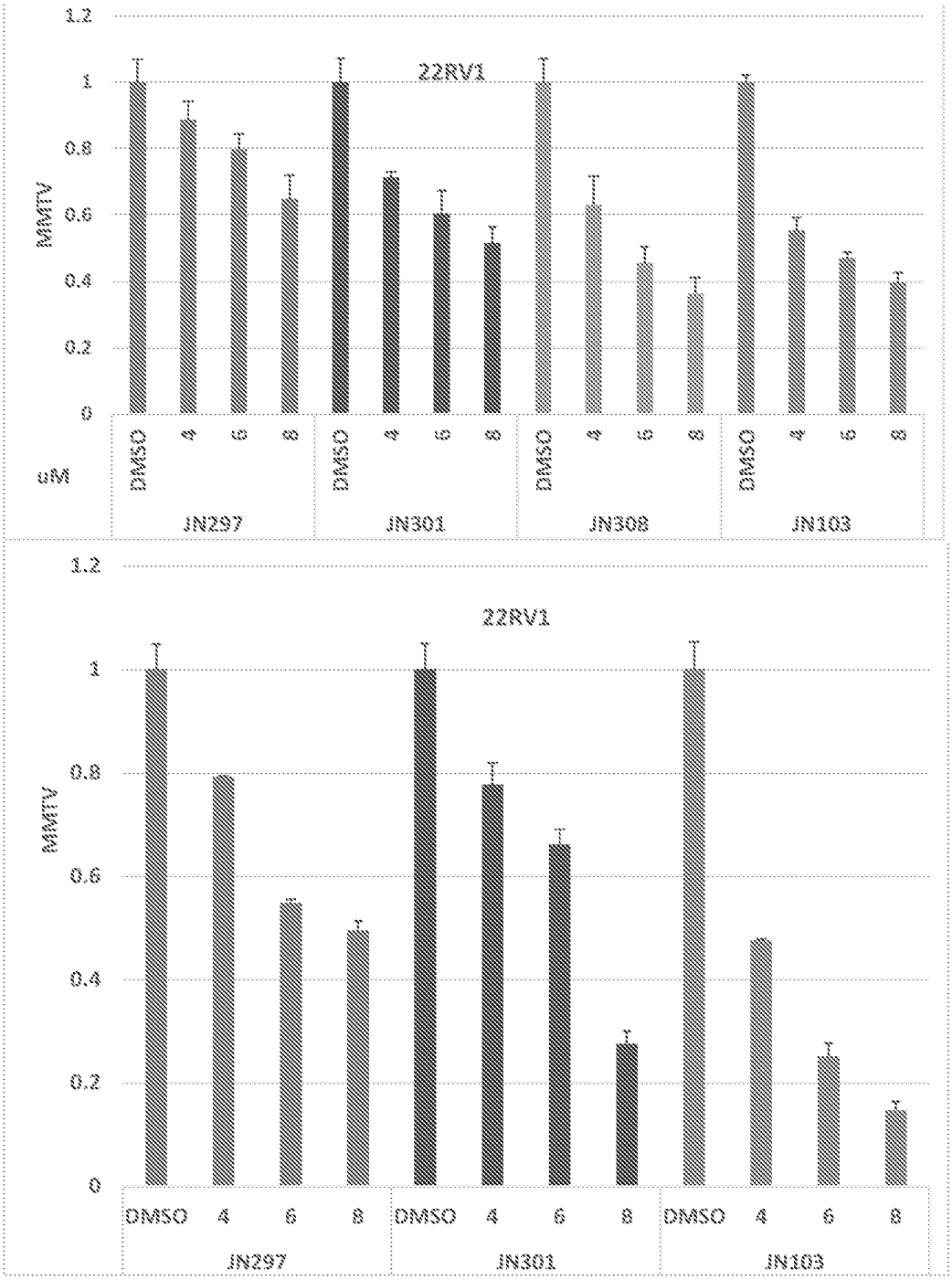

22RV1
MMTV
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
4
6
8
JN297
JN301
JN308
JN103
22RV1
MMTV
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
6
8
JN297
JN301
JN103

FIG. 76

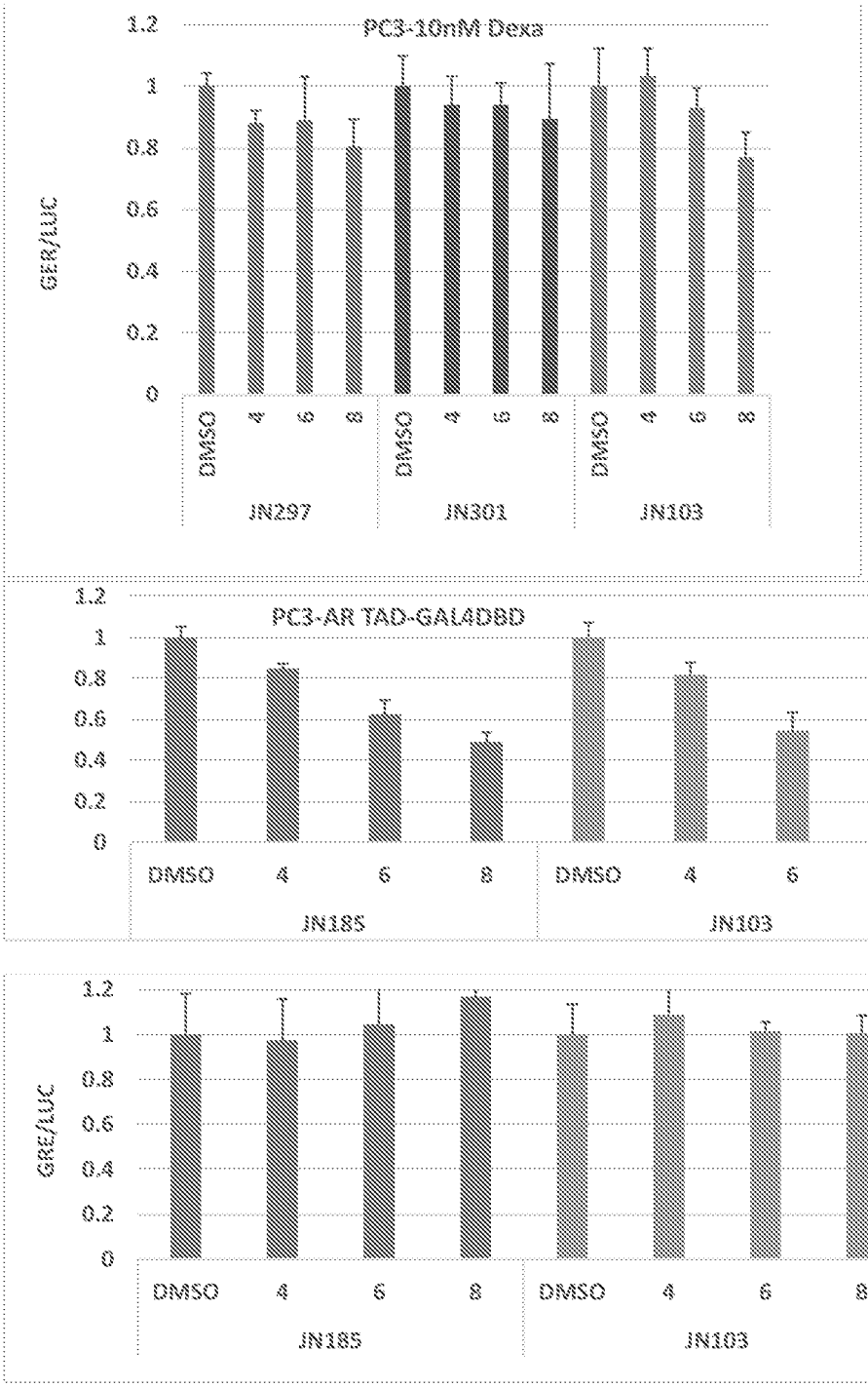

PC3-10nM Dexa
GRE/LUC
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
6
8
JN297
JN301
JN103
PC3-AR TAD-GAL4DBD
JN185
PC3

FIG. 77

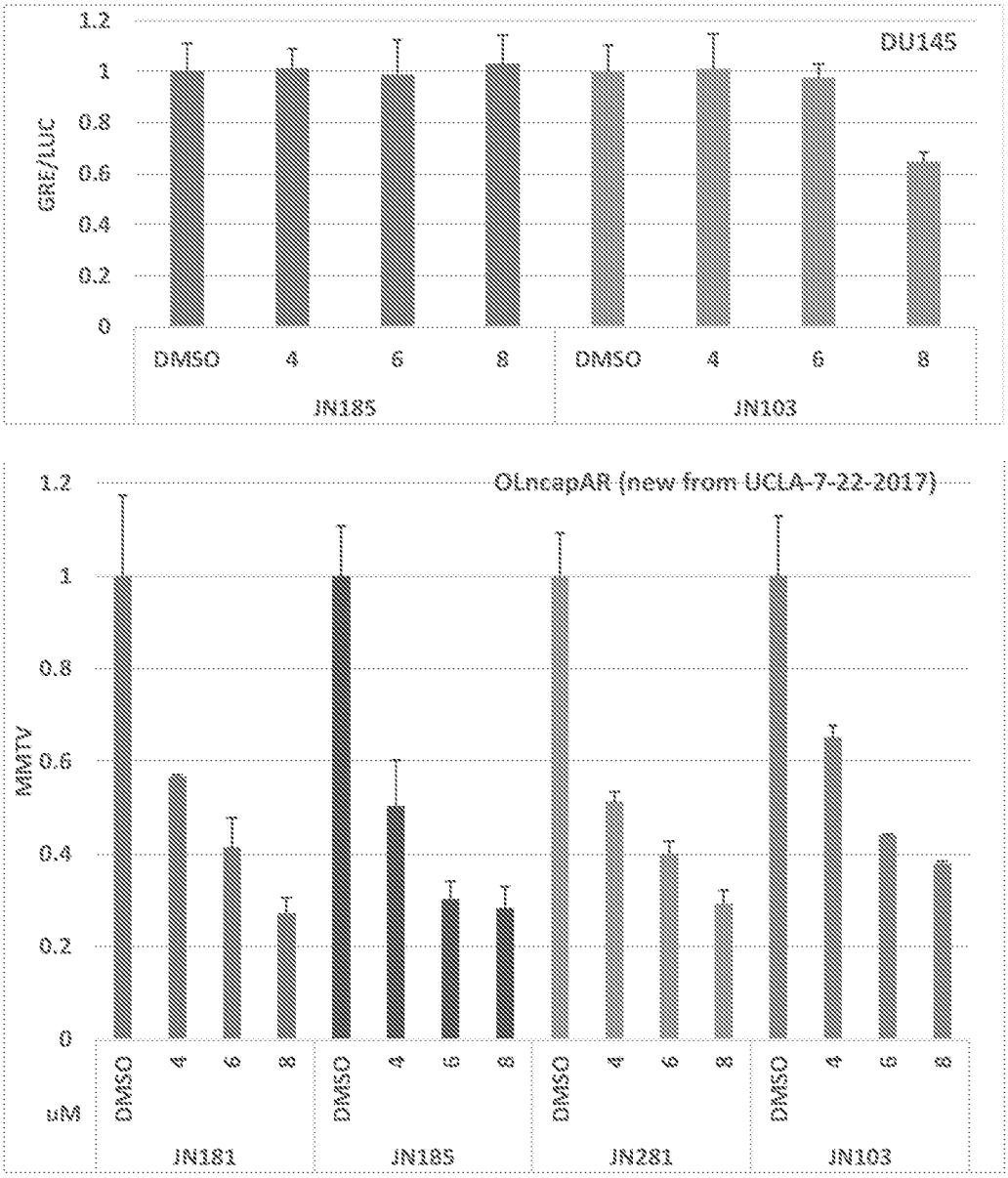
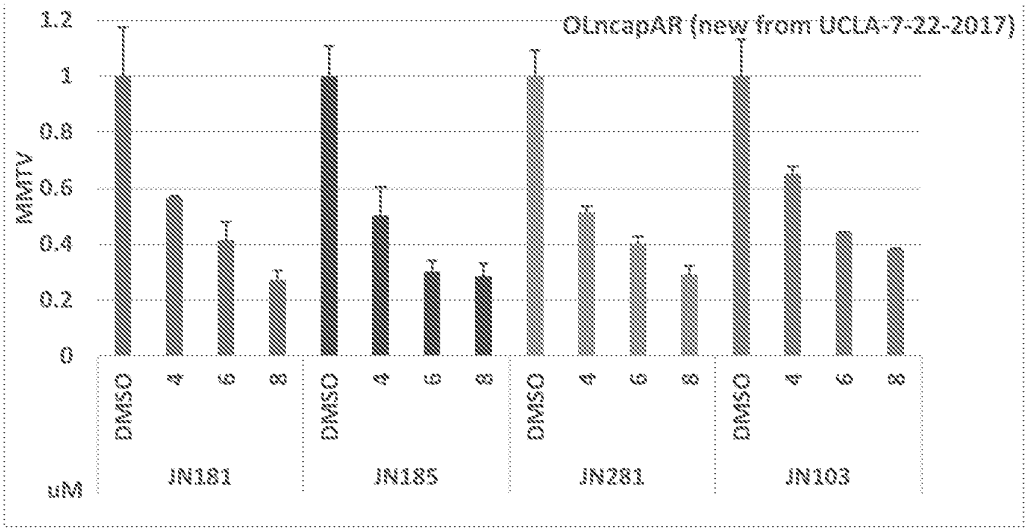
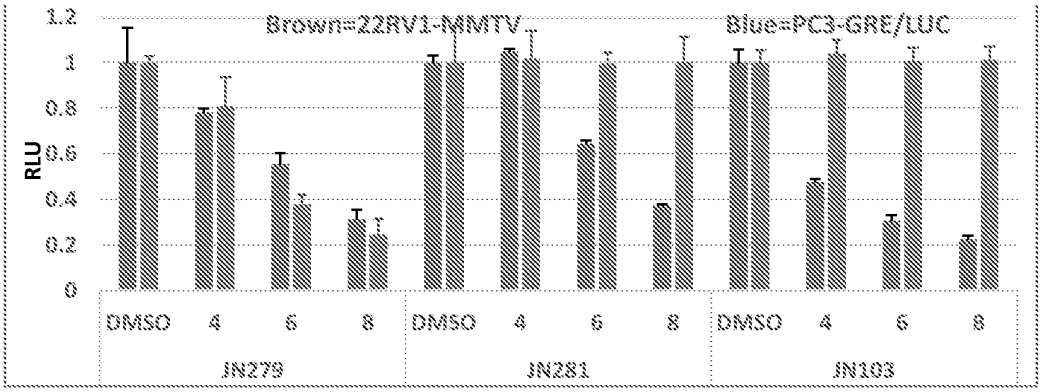

DU145
GRE/LUC
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
6
8
JN185
JN103
LNCaPAR (new from UCLA-7-22-2017)
MMTV
uM
JN181
JN281

FIG. 78


OLncapAR (new from UCLA-7-22-2017)
MMTV
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
6
8
uM
JN181
JN185
JN281
JN103


Brown=22RV1-MMTV
Blue=PC3-GRE/LUC
RLU
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
6
8
JN279
JN281
JN103

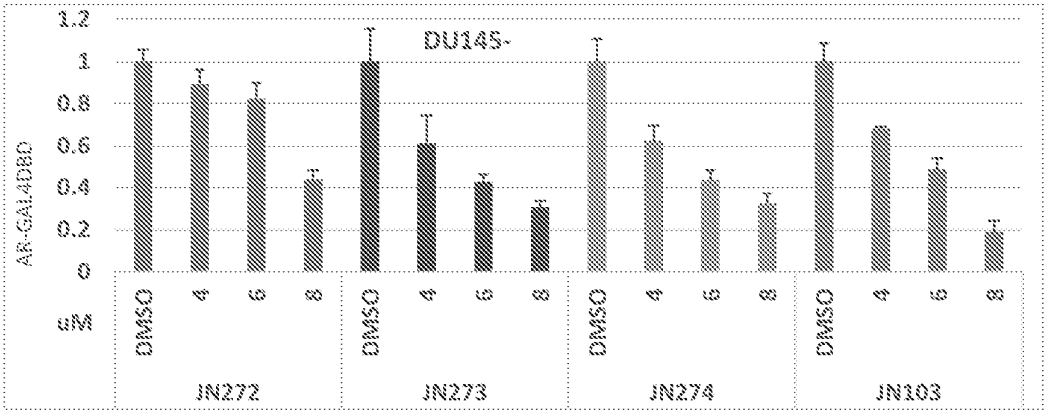

DU145-
AR-GAL4DBD
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
4
6
8
JN272
JN273
JN274
JN103

FIG. 79

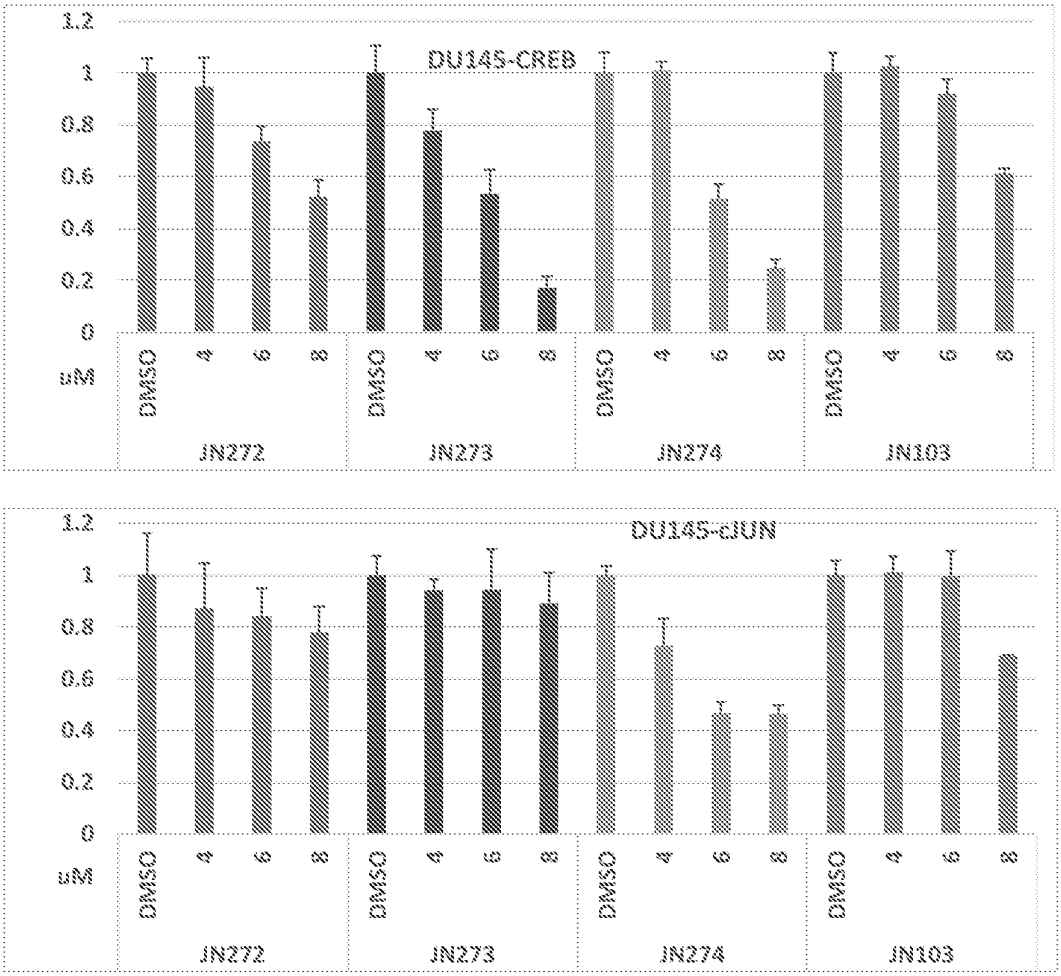

DU145-CREB
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
4
6
8
JN272
JN273
JN274
JN103
DU145-cJUN
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
4
6
8
JN272
JN273
JN274
JN103

FIG. 80

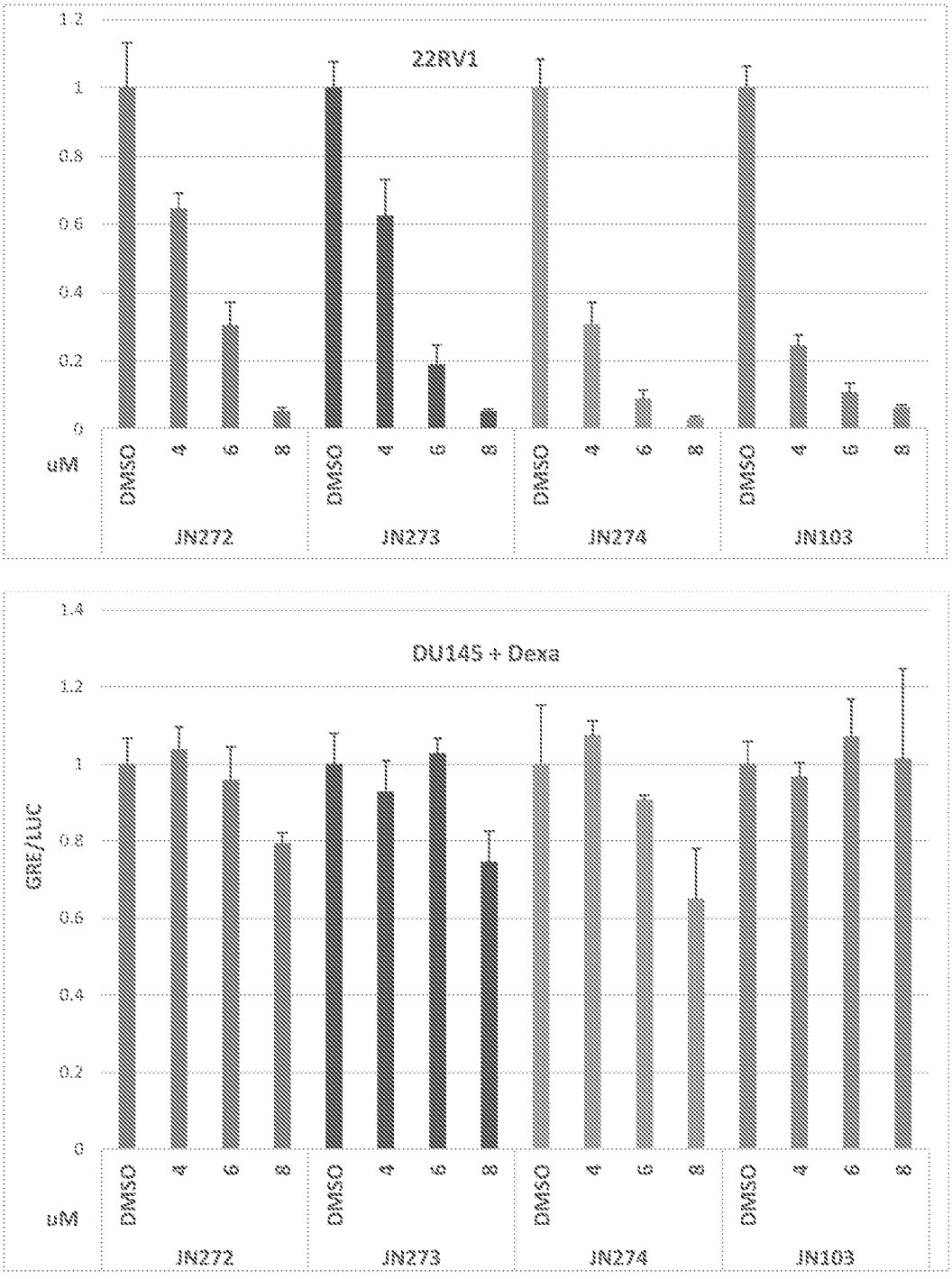
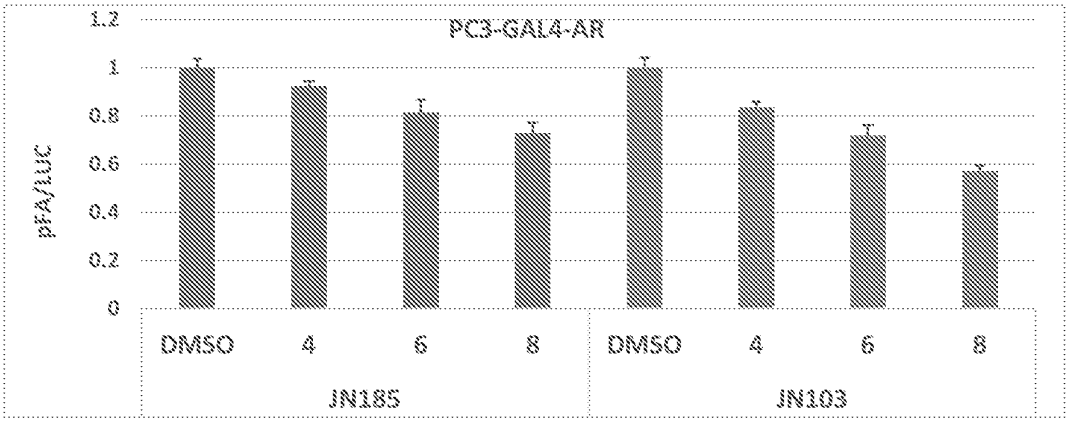
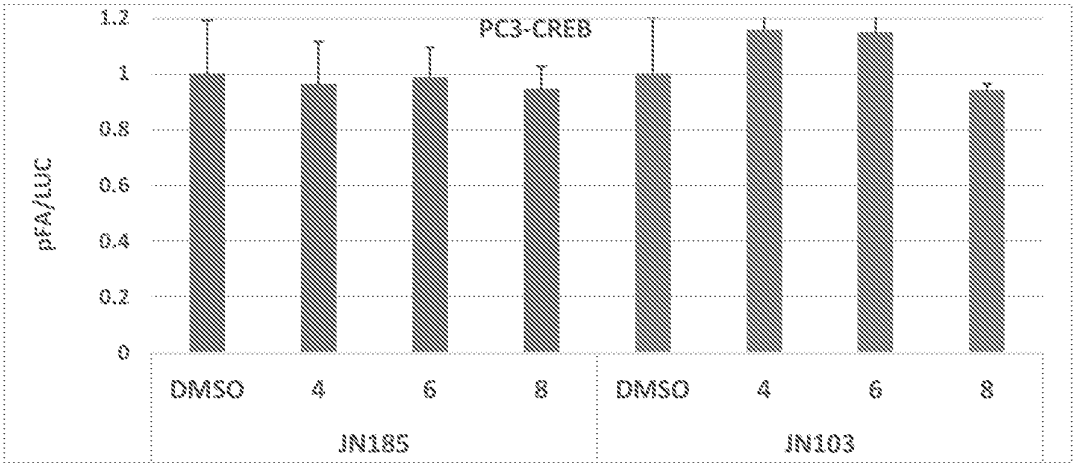

22RV1
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
4
6
8
JN272
JN273
JN274
JN103
DU145 + Dexa
GRE/LUC
1.4
1.2
1
0.8
0.6
0.4
0.2
0

FIG. 81


PC3-GAL4-AR
pFA/LUC
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
6
8
DMSO
4
6
8
JN185
JN103


PC3-CREB
pFA/LUC
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
6
8
DMSO
4
6
8
JN185
JN103

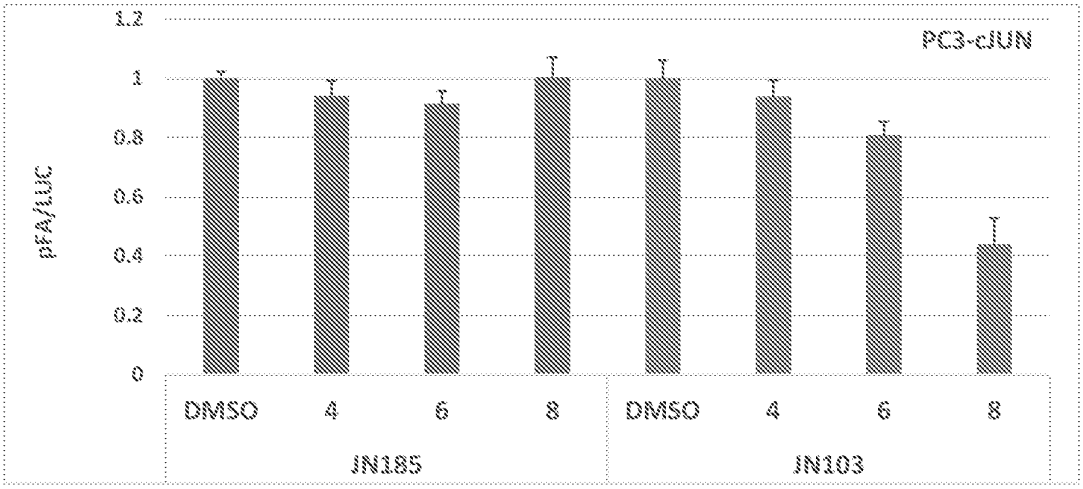
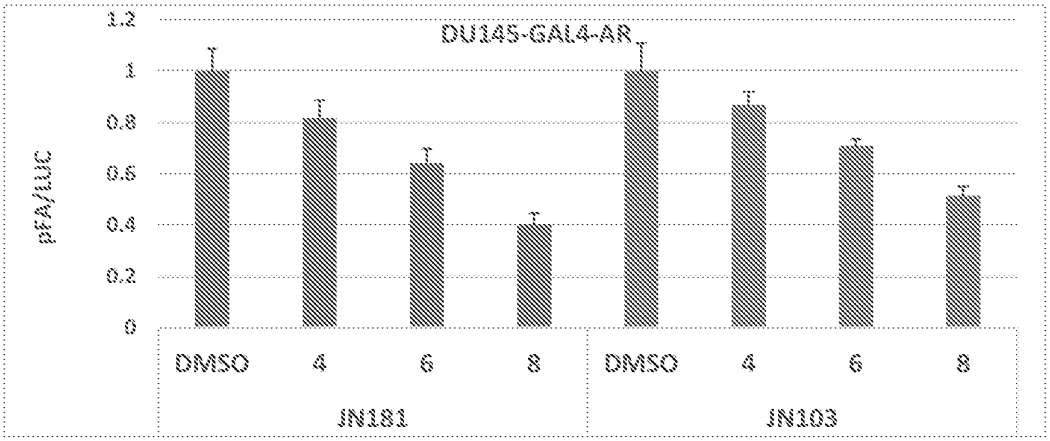
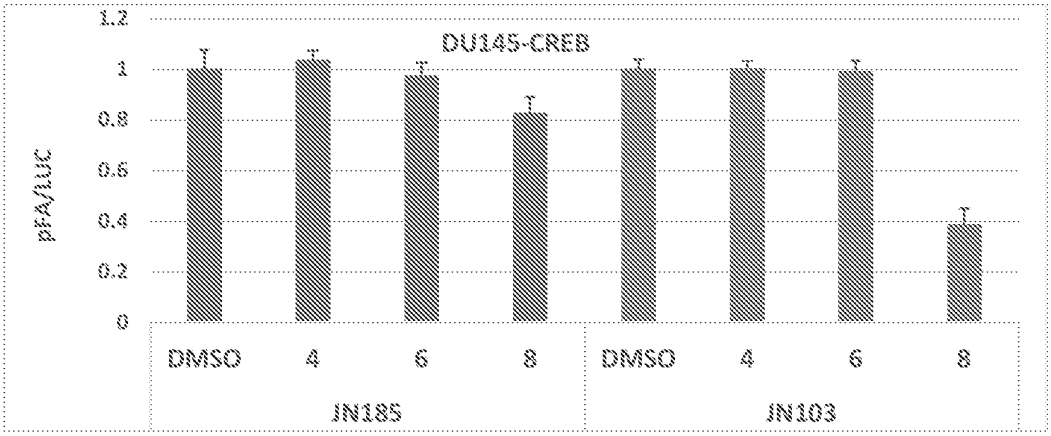

PC3-cJUN
pFA/LUC
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
6
8
DMSO
4
6
8
JN185
JN103

FIG. 82


DU145-GAL4-AR
pFA/LUC
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
6
8
DMSO
4
6
8
JN181
JN103


DU145-CREB
pFA/LUC
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
6
8
DMSO
4
6
8
JN185
JN103

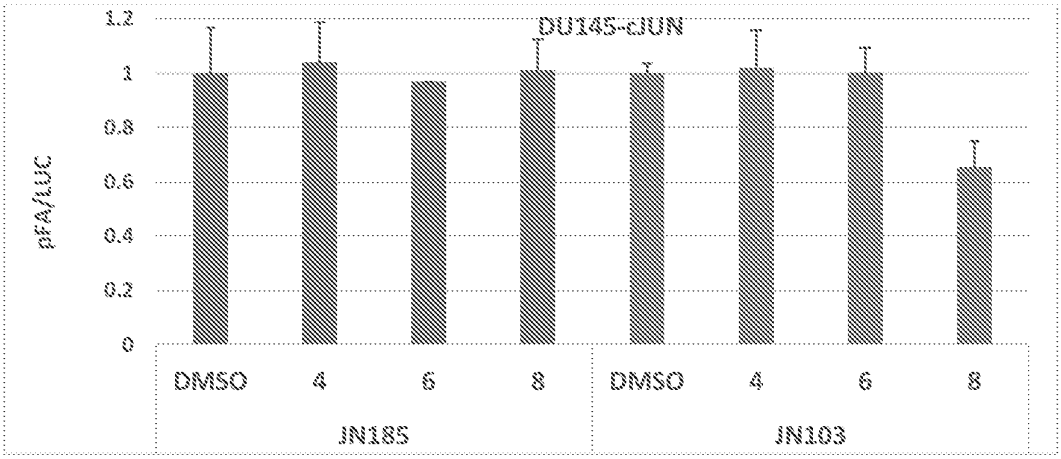
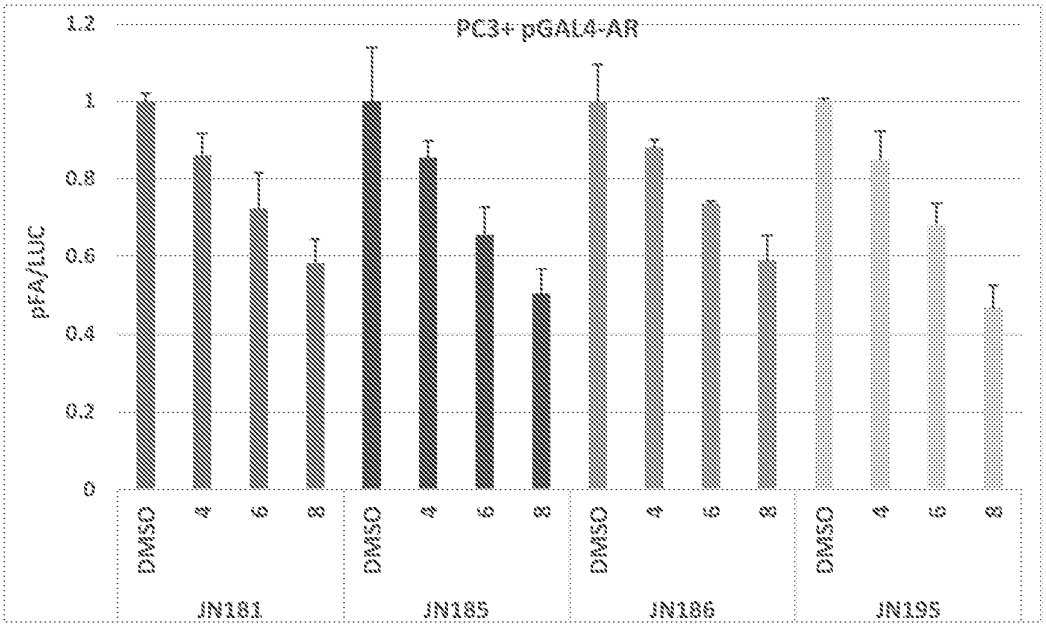

DU145-cJUN
pFA/LUC
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
6
8
DMSO
4
6
8
JN185
JN103

FIG. 83


PC3+ pGAL4-AR
pFA/LUC
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
6
8
JN181
JN185
JN186
JN195

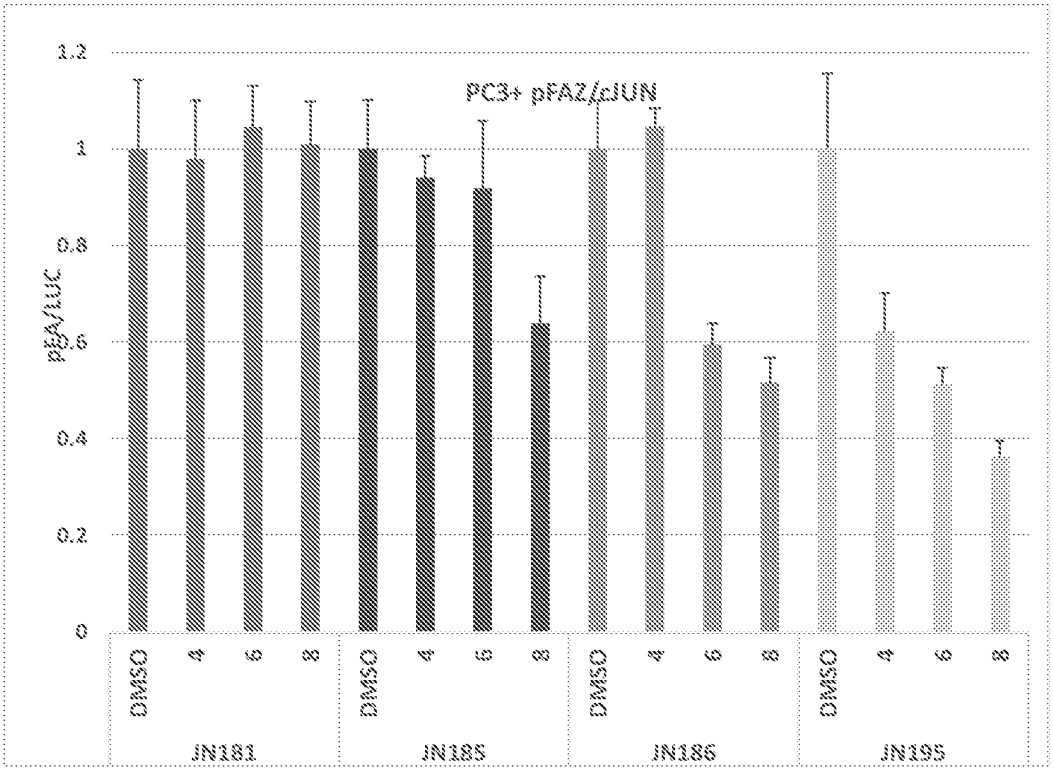
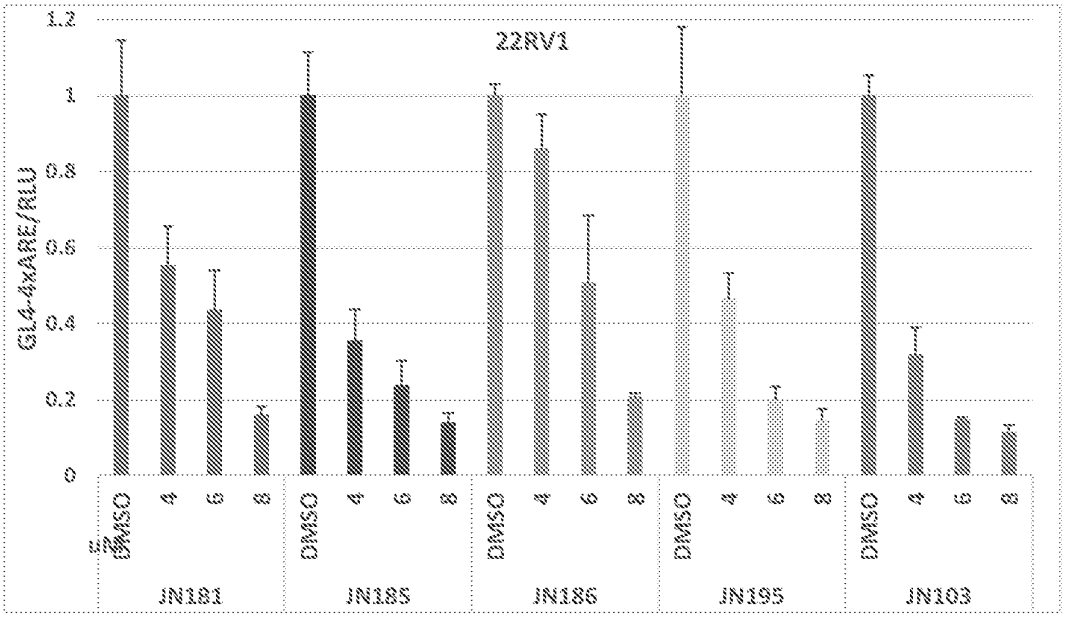

PC3+ pFAZ/cJUN
pFA/LUC
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
6
8
JN181
JN185
JN186
JN195

FIG. 84


22RV1
GL4-4xARE/RLU
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
4
6
8
JN181
JN185
JN186
JN195
JN103

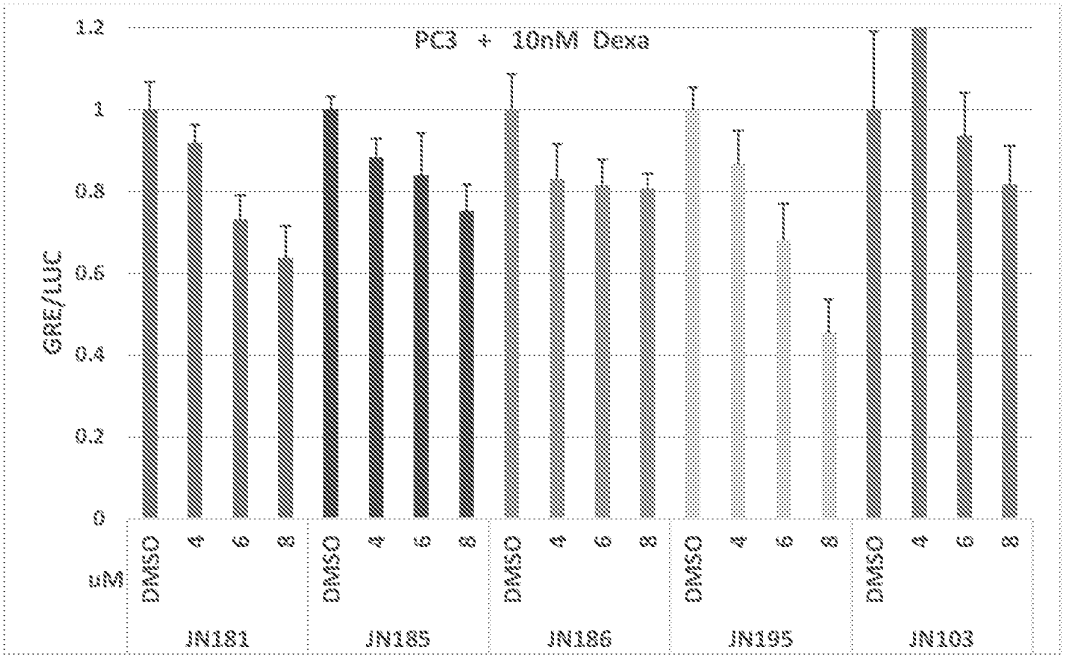

PC3 + 10nM Dexa
GRE/LUC
1.2
1
0.8
0.6
0.4
0.2
0
uM
DMSO
4
6
8
JN181
JN185
JN186
JN195
JN103

FIG. 85

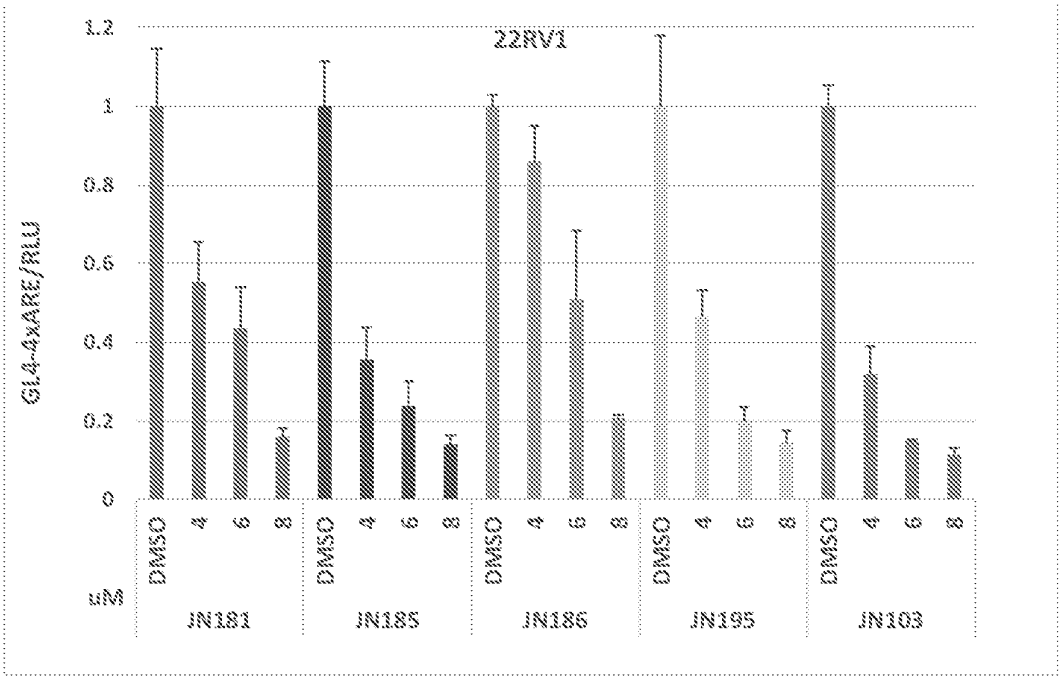
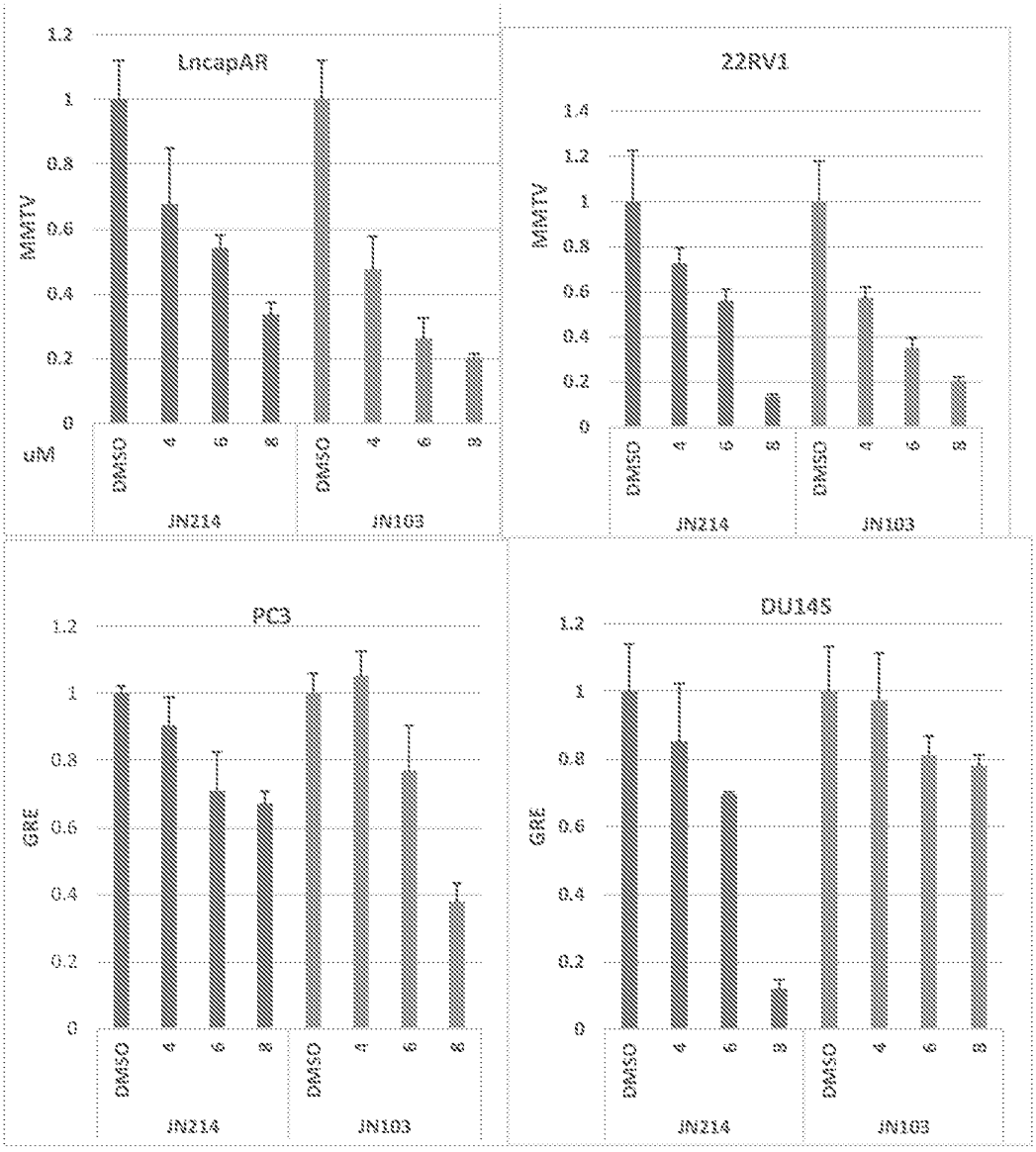

22RV1
GL4-4xARE/RLU
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
4
6
8
uM
JN181
JN185
JN186
JN195
JN103

FIG. 86



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/015756

A. CLASSIFICATION OF SUBJECT MATTER

C07C 233/91(2024.01)i; ***C07C 233/90***(2024.01)i; ***C07D 309/06***(2024.01)i; ***C07C 321/20***(2024.01)i; ***C07D 303/48***(2024.01)i; ***C07C 243/32***(2024.01)i; ***A61K 31/165***(2024.01)i; ***A61K 31/336***(2024.01)i; ***A61K 31/351***(2024.01)i; ***A61P 35/00***(2024.01)i; ***A61P 35/04***(2024.01)i

CPC:C07C 233/91; C07C 233/90; C07D 309/06; C07C 321/20; C07D 303/48; C07C 243/32; A61K 31/165; A61K 31/336; A61K 31/351; A61P 35/00; A61P 35/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C 233/91; C07C 233/90; C07D 309/06; C07C 321/20; C07D 303/48; C07C 243/32; A61K 31/165; A61K 31/336; A61K 31/351; A61P 35/00; A61P 35/04

CPC:C07C 233/91; C07C 233/90; C07D 309/06; C07C 321/20; C07D 303/48; C07C 243/32; A61K 31/165; A61K 31/336; A61K 31/351; A61P 35/00; A61P 35/04

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

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

Databases consulted: Google Patents, CAPLUS, REGISTRY, PubMed, Google Scholar, REAXYS Search terms used: ?androgen, ?cancer?, ?prolifer?, prostate cancer, resist?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2020/205470 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US])08 October 2020 (2020-10-08)	27,39
X	Claims (particularly formulae IV and VIIb) and examples (particularly compounds JN103, JN117, JN118, JN139, JN147, JN150, JN154 and JN155).	1-26,28-38,40-68
D,A	WO 2018/136792 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US])26 July 2018 (2018-07-26)	27,39
D,X	Claims and examples (particularly compounds JN103, JN117 and JN118).	1-26,28-38,40-68

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
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"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 June 2024	**13 June 2024**

Name and mailing address of the ISA/IL	Authorized officer
Israel Patent Office **Technology Park, Bldg.5, Malcha, Jerusalem, 9695101,** **Israel** **Israel**	**SOMECH Erez**
Telephone No. **972-73-3927252** Email: **pctoffice@justice.gov.il**	Telephone No.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Elshan, NGR Dayan, Matthew B. Rettig, and Michael E. Jung. "Synthesis of beta-amino diaryldienones using the Mannich reaction." Organic letters 21.11 (2019): 4039-4043. Published online: 13 May 2019. DOI: <10.1021/acs.orglett.9b01195>. Retrieved from URL: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10279484/>, Supporting Information retrieved from URL: <https://pubs.acs.org/doi/10.1021/acs.orglett.9b01195>. (2019/05/13) The active compounds E-6 and NSC-89160, and additional compounds in the supporting information, table S1 (particularly compound SI-4).	1-68
A	PubChem Compound Summary for CID 135254864; IUPAC Name: (E)-3-[3-chloro-5-[(E)-3-(2-methylprop-2-enoylamino)-3-oxo-2-phenylprop-1-enyl]phenyl]-N-[(E)-3-(4-chlorophenyl)-2-(2,4-difluorophenyl)prop-2-enoyl]-2-methylprop-2-enamide. National Center for Biotechnology Information. Create date: 15 December 2018. Retrieved from URL: <https://pubchem.ncbi.nlm.nih.gov/compound/135254864>. (2018/12/15) See: "5.1 Depositor-Supplied Patent Identifiers".	1-68

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2024/015756

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2020/205470 A1	08 October 2020	WO 2020205470 A1	08 October 2020
		AU 2020251993 A1	14 October 2021
		CA 3134470 A1	08 October 2020
		CN 114829330 A	29 July 2022
		EP 3947335 A1	09 February 2022
		IL 286708 A	01 December 2021
		JP 2022527916 A	07 June 2022
		KR 20210149763 A	09 December 2021
		SG 11202110271T A	28 October 2021
		US 2022177418 A1	09 June 2022
WO 2018/136792 A1	26 July 2018	WO 2018136792 A1	26 July 2018
		AU 2018210393 A1	25 July 2019
		AU 2022201524 A1	14 April 2022
		CA 3050255 A1	26 July 2018
		CN 110325508 A	11 October 2019
		CN 110325508 B	30 June 2023
		EP 3571183 A1	27 November 2019
		EP 3571183 A4	21 October 2020
		EP 3571183 B1	06 March 2024
		JP 2020505357 A	20 February 2020
		JP 2022115888 A	09 August 2022
		JP 7443414 B2	05 March 2024
		US 2019382335 A1	19 December 2019
		US 11261152 B2	01 March 2022
		US 2022380298 A1	01 December 2022