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(54) Titre : DERIVES DE COUMARINE ET METHODES D'UTILISATION DANS LE TRAITEMENT DE MALADIES
 HYPERPROLIFERATIVES

(54) Title: COUMARIN DERIVATIVES AND METHODS OF USE IN TREATING HYPERPROLIFERATIVE DISEASES

(57) **Abrégé/Abstract:**

Coumarin derivative compounds and methods for the treatment of hyperproliferative diseases, such as cancer, polycystic kidney disease, and fibrosis of different tissues (e.g., idiopathic pulmonary fibrosis), are provided. The methods include administering to a subject a compound as described herein. Also provided are methods for inhibiting the interaction between two or more heat shock protein chaperones in a cell.

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(54) Title: COUMARIN DERIVATIVES AND METHODS OF USE IN TREATING HYPERPROLIFERATIVE DISEASES

(57) Abstract: Coumarin derivative compounds and methods for the treatment of hyperproliferative diseases, such as cancer, polycystic kidney disease, and fibrosis of different tissues (e.g., idiopathic pulmonary fibrosis), are provided. The methods include administering to a subject a compound as described herein. Also provided are methods for inhibiting the interaction between two or more heat shock protein chaperones in a cell.



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Coumarin Derivatives and Methods of Use in Treating Hyperproliferative Diseases

5

BACKGROUND

A variety of diseases involve the hyperproliferation of cells. Cancer, for example, is a commonly known hyperproliferative disease. Cancer is a large, heterogeneous class of diseases in which a group of cells display uncontrolled growth, resulting in an invasion that intrudes upon and destroys adjacent tissues. The cells often metastasize, wherein the tumor cells spread to other locations in the body via the lymphatic system or through the bloodstream. Cancer can be caused by environmental factors or genetic factors (or a combination of both). Common environmental factors leading to cancer include tobacco use, poor diet and obesity, infection, radiation, lack of physical activity, and environmental pollutants. These environmental factors may cause or enhance abnormalities in the genetic material of cells. Cell reproduction is an extremely complex process that is normally tightly regulated by several classes of genes, including oncogenes and tumor suppressor genes. Abnormalities/mutations in these regulatory genes can lead to the development of cancer. A small percentage of cancers, approximately five to ten percent, are entirely hereditary. In 2007, cancer caused about 13% of all human deaths worldwide (7.9 million). Rates are rising as more people live to an old age and as mass lifestyle changes occur in the developing world.

Other forms of hyperproliferative diseases also exist, such as, but not limited to, polycystic kidney disease (PKD) and related cystic kidney diseases. Polycystic kidney disease (PKD or PCKD) is a cystic genetic disorder of the kidneys. There are two types of PKD: autosomal dominant polycystic kidney disease (ADPKD) and the less-common autosomal recessive polycystic kidney disease (ARPKD). Both forms cause hyperproliferation of kidney epithelial cells but neither form is a cancer. It occurs in humans and some other animals. PKD is characterized by the presence of multiple cysts (hence, "polycystic") typically in both kidneys; however, 17% of cases initially present with observable disease in one kidney, with most cases progressing to bilateral disease in adulthood. The cysts are numerous and are fluid-filled, resulting in massive enlargement of the kidneys. The disease can also damage the liver, the pancreas, and, in some rare cases, the vasculature of the heart and the brain. PKD is the most

common life-threatening genetic disease and the leading genetic cause of dialysis and transplantation, affecting an estimated 12.5 million people worldwide. In half of the people with PKD, there is no family history of the disease. However, in the dominant form of the disease, it affects multiple family members with variable times of emergence and with some variance in severity.

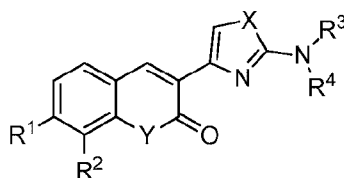
Other hyperproliferative diseases include fibrosis of different tissues. Fibrosis is the formation of excess fibrous connective tissue in an organ or tissue. Fibrosis can lead to degeneration of the tissue or organ and/or loss of function if it becomes widespread and aggressive. Fibrosis plays a role in a number of diseases states in mammals, including, but not limited to, pulmonary fibrosis, idiopathic pulmonary fibrosis, cirrhosis, endomyocardial fibrosis, vascular or spinal stenosis, mediastinal fibrosis, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis, nephrogenic systemic fibrosis, Crohn's Disease, keloid or old myocardial infarction, scleroderma/systemic sclerosis, arthrofibrosis, and adhesive capsulitis.

Such hyperproliferative diseases have been known for decades; however, effective treatments remain elusive.

SUMMARY

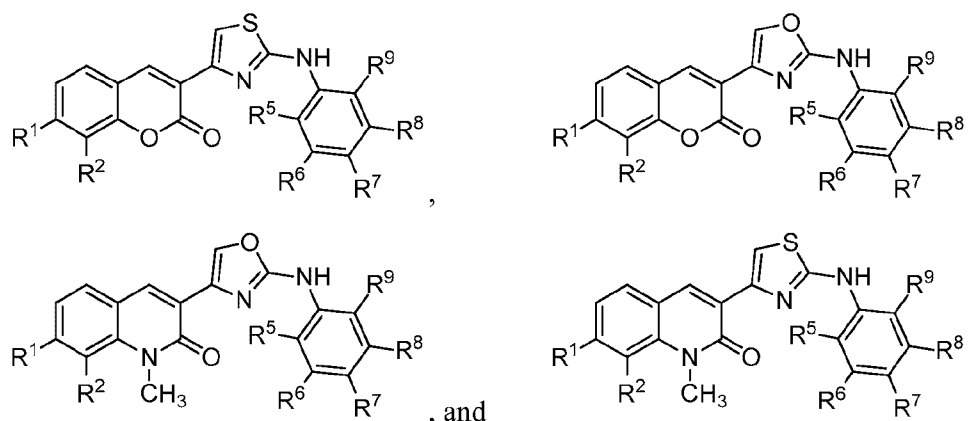
Coumarin derivative compounds and methods for the treatment of hyperproliferative diseases, such as cancer, polycystic kidney disease, and fibrosis of different tissues (e.g., idiopathic pulmonary fibrosis), are provided. The methods include administering to a subject a compound as described herein.

A class of CFTR correctors includes compounds of the following formula:



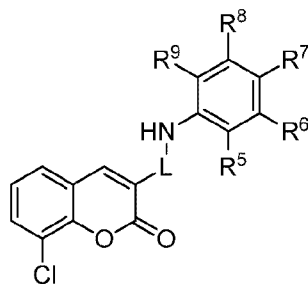
and pharmaceutically acceptable salts or prodrugs thereof. In this class of compounds, R¹ is hydrogen, halogen, hydroxyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted C₁₋₆ alkyl, or substituted or unsubstituted heterocycloalkyl; R² is hydrogen, halogen, hydroxyl, nitro, cyano, azido, thiocyanato, trifluoromethyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted carbonyl, or substituted or unsubstituted C₁₋₆ alkyl; R³ is hydrogen or substituted or unsubstituted C₁₋₆ alkyl; R⁴ is substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted

aryl, or substituted or unsubstituted heteroaryl; X is S or O; and Y is O or NCH₃. Optionally, the compound is selected from the group consisting of:



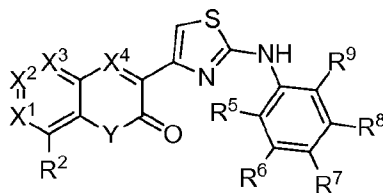
- 5 wherein R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from hydrogen, halogen, hydroxyl, substituted or unsubstituted alkoxy, cyano, nitro, trifluoromethyl, substituted or unsubstituted carbonyl, substituted or unsubstituted amino, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted sulfonamide, substituted or unsubstituted sulfonyl, or substituted or unsubstituted
- 10 thio. Optionally, R¹ and R², R⁵ and R⁶, R⁶ and R⁷, R⁷ and R⁸, or R⁸ and R⁹ combine to form a substituted or unsubstituted aryl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

A class of CFTR correctors includes compounds of the following formula:



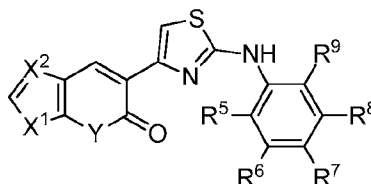
- 15 and pharmaceutically acceptable salts or prodrugs thereof. In this class of compounds, L is a heteroaryl; and R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from hydrogen and methoxy.

A class of CFTR correctors includes compounds of the following formula:



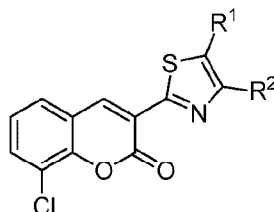
and pharmaceutically acceptable salts or prodrugs thereof. In this class of compounds, X^1 , X^2 , X^3 and X^4 are each independently selected from CH and N; Y is O or NR, where R is hydrogen or methyl; R^2 is hydrogen, C_{1-6} alkyl, halogen, or trifluoroalkyl; and R^5 , R^6 , R^7 , R^8 , and R^9 are each independently selected from hydrogen and methoxy.

5 A class of CFTR correctors includes compounds of the following formula:



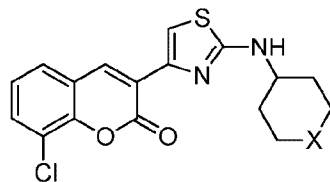
and pharmaceutically acceptable salts or prodrugs thereof. In this class of compounds, X^1 is O or NCH_3 ; X^2 is CH or N; Y is O, NH, or NCH_3 ; and R^5 , R^6 , R^7 , R^8 , and R^9 are each independently selected from hydrogen and methoxy.

10 A class of CFTR correctors includes compounds of the following formula:



and pharmaceutically acceptable salts or prodrugs thereof. In this class of compounds, R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted amino, and substituted or unsubstituted carbonyl.

15 A class of CFTR correctors includes compounds of the following formula:



and pharmaceutically acceptable salts or prodrugs thereof. In this class of compounds, X is CH_2 , NH, or O.

20 A method for the treatment of a hyperproliferative disease in a subject is also described herein. The method for the treatment of a hyperproliferative disease in a subject comprises administering to the subject an effective amount of a compound as described herein. Optionally, the hyperproliferative disease is cancer. Optionally the hyperproliferative disease is polycystic kidney disease. Optionally, the hyperproliferative disease is a fibrosis (e.g., idiopathic pulmonary fibrosis).

Also provided herein are methods of inhibiting the interaction between two or more heat shock protein chaperones in a cell. The methods of inhibiting the interaction between two or more heat shock protein chaperones in a cell comprise contacting a cell with a compound as described herein. Optionally, the two or more heat shock protein chaperones are selected from the group consisting of Hsp-90, Hsp-70, Hsc-70, and Hsp-40. Optionally, the method is performed *in vitro*. Optionally, the method is performed *in vivo*.

The details of one or more embodiments are set forth in the drawings and the description below. Other features, objects, and advantages will be apparent from the description and drawings, and from the claims.

DESCRIPTION OF DRAWINGS

Figure 1 contains a schematic showing a general approach for the growth curve assay for profiling the compounds (graph on the right), a picture of a primary human ADPKD hyperproliferative culture (photograph on the top left), and a picture of a metastatic ARCaP-M cell line (photograph on the bottom left).

Figure 2 is a plot showing the viability of **Compound DBM 228** in cystic ADPKD cells, in a prostate cancer line, and in a kidney cancer line.

Figure 3 is a plot showing the viability of **Compound DBM 101** in confluent cystic ADPKD cells, in proliferating cystic ADPKD cells, in confluent normal renal cells, and in proliferating normal renal cells.

Figure 4 is a plot showing the growth inhibition of myeloma cells treated with **Compound DBM 227, Compound DBM 228, Compound DBM 308, Compound DBM 318, Compound DBM 701, Compound DBM 707, Compound DBM 717, and Compound DBM 328.**

Figure 5A is a plot showing the growth inhibition of cloned polycystic kidney tissue cells treated with **Compound DBM 101 (001-2), Compound DBM 228 (N828), Compound DBM 308 (3-8Cl), and Compound DBM 328 (3-8COOH).**

Figure 5B is a plot showing the growth inhibition of cloned non-cystic kidney tissue cells treated with **Compound DBM 101 (001-2), Compound DBM 228 (N828), Compound DBM 308 (3-8Cl), and Compound DBM 328 (3-8COOH).**

Figure 6 is a plot showing the growth inhibition of primary human idiopathic pulmonary fibrosis myofibroblasts treated with **Compound DBM 228, Compound DBM 308, Compound**

DBM 318, Compound DBM 701, Compound DBM 707, Compound DBM 715, and Compound DBM 328.

5 Figure 7 is a plot showing the growth inhibition of primary human idiopathic pulmonary fibrosis myofibroblasts and primary human chronic obstructive pulmonary disease (COPD) fibroblasts treated with **Compound DBM 701**.

Figure 8 is a plot showing the growth inhibition of primary human idiopathic pulmonary fibrosis myofibroblasts treated with **Compound DBM 701**.

10 Figure 9 is a graph showing the inhibition of the multi-drug resistant NCI/ADR-RES ovarian carcinoma cell line after treatment with paclitaxel, vincristine, and **Compound DBM 228**.

Figure 10 is a graph showing the neurosphere growth of primary human glioblastoma multiforme cells after treatment with various doses of **Compound DBM 308** (30 nM, 300 nM, and 3 μ M), temozolomide (TMZ) (500 μ M), and DMSO.

15 Figure 11A contains graphs showing U251MG glioblastoma cells tested with increasing concentrations of **Compound DBM 228** (upper left panel: control; upper right panel: 40 nM **Compound DBM 228**; lower left panel: 100 nM **Compound DBM 228**; lower right panel: 400 nM **Compound DBM 228**).

Figure 11B is a graph showing the percent change in caspase 3/7 activation in U251MG cells treated with **Compound DBM 228, Compound DBM 318, and Compound DBM 328**.

20 Figure 11C is a graph showing the inhibition of biochemical tubulin polymerization after treatment with paclitaxel, vincristine, a control (**Compound DBM 328**), **Compound DBM 227, Compound DBM 228, Compound DBM 308, Compound DBM 318, Compound DBM 701, Compound DBM 707, and Compound DBM 715**.

25 Figure 12 contains the results of an intracellular signaling molecule phosphor-array for human hyperproliferative GBM cancer cells after treatment with **Compound DBM 228, Compound DBM 328, Compound DBM 308, or a DMSO vehicle control** (upper left panel); a plot of the percent phosphorylation vs. vehicle control for **Compound DBM 228 (002-N8-28), Compound DBM 308 (003-8Cl), and Compound DBM 328 (003-8COOH)** for p38 α , JNK pan, and c-Jun phosphorylation (lower left panel); a dose-response effect is provided for **Compound DBM 228 (002-N8-28)** for potentiation of c-Jun phosphorylation (upper right panel); and a plot of the time dependence of the effect for **Compound DBM 228's (002-N8-28)** potentiation of c-Jun phosphorylation.

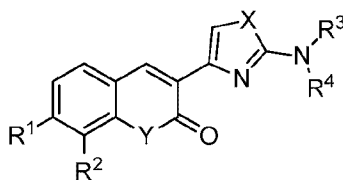
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DETAILED DESCRIPTION

The coumarin derivative compounds and methods described herein are useful in the treatment of hyperproliferative diseases. As used herein, a hyperproliferative disease is any disorder or condition that involves dis-regulated or unregulated but accelerated cell growth (versus the normal condition of cells in normal tissues) that impacts the health of a subject. Such dis-regulated or unregulated and accelerated cell growth may result in the death of the subject. The compounds and methods described herein are useful for treating hyperproliferative disorders that include, but are not limited to, cancer, polycystic kidney disease, and fibrosis (e.g., idiopathic pulmonary fibrosis).

I. Compounds

A class of coumarin derivatives described herein is represented by **Formula I**:



I

and pharmaceutically acceptable salts or prodrugs thereof.

In **Formula I**, R^1 is hydrogen, halogen, hydroxyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted C_{1-6} alkyl, or substituted or unsubstituted heterocycloalkyl.

Also, in **Formula I**, R^2 is hydrogen, halogen, hydroxyl, nitro, cyano, azido, thiocyanato, trifluoromethyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted carbonyl, or substituted or unsubstituted C_{1-6} alkyl.

Additionally, in **Formula I**, R^3 is hydrogen or substituted or unsubstituted C_{1-6} alkyl.

Further, in **Formula I**, R^4 is substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

Also, in **Formula I**, X is S or O.

Additionally, in **Formula I**, Y is O, NH, or NCH_3 .

As used herein, the terms alkyl and alkenyl include straight- and branched-chain monovalent substituents. Examples include methyl, ethyl, isobutyl, and the like. Ranges of these groups useful with the compounds and methods described herein include C_1 - C_8 alkyl and C_3 - C_8 alkenyl.

Heteroalkyl and heteroalkenyl are defined similarly as alkyl and alkenyl, but can contain O, S, or N heteroatoms or combinations thereof within the backbone. Ranges of these groups

useful with the compounds and methods described herein include C₁-C₈ heteroalkyl and C₃-C₈ heteroalkenyl.

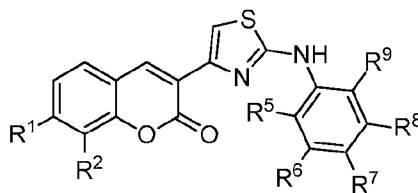
The term cycloalkyl includes cyclic alkyl groups having a single cyclic ring or multiple condensed rings. Examples include cyclohexyl, cyclopentylethyl, and adamantanyl. A range of these groups useful with the compounds and methods described herein includes C₃-C₉ cycloalkyl.

The term heterocycloalkyl is defined similarly as cycloalkyl, but can contain O, S, or N heteroatoms or combinations thereof within the cyclic backbone. A range of these groups useful with the compounds and methods described herein includes C₄-C₉ heterocycloalkyl.

Aryl groups include, for example, phenyl and substituted phenyl. Heteroaryl groups contain O, N, or S heteroatoms, either alone or in combination in five or six membered rings. Examples of heteroaryl groups with one heteroatom include pyridyl, thienyl, and furyl substituted on or joined by any of the available carbon atoms. Examples of heteroaryl groups with more than one heteroatom include pyrimidinyl, oxazolyl, and thiazolyl substituted on or joined by any of the available carbon atoms. Aryl and heteroaryl groups can include additional fused rings. Examples of such groups include indanyl, naphthyl, benzothieryl, quinolinyl, and isomers thereof substituted on or joined by any of the available carbon atoms.

All groups mentioned above can be unsubstituted or substituted with one or more of the following which may be the same or different. Examples of appropriate substituents include, but are not limited to, the following: alkoxy (e.g., methoxy), alkyl, aryl, carboxylate, carboxylate ester, cyano, halogen (e.g., chloro, bromo, fluoro, iodo), heteroaryl, nitro, amino, alkylsulfonyl, sulfonamide, reverse sulfonamide, and thio.

In some examples, **Formula I** is represented by **Structure I-A**:

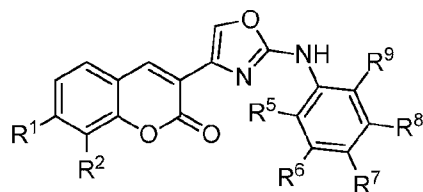


In **Structure I-A**, R¹ and R² are as defined above for **Formula I**.

Also in **Structure I-A**, R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from hydrogen, halogen, hydroxyl, substituted or unsubstituted alkoxy, cyano, nitro, trifluoromethyl, substituted or unsubstituted carbonyl, substituted or unsubstituted amino, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted sulfonamide, substituted or unsubstituted sulfonyl, or

substituted or unsubstituted thio. The carbonyl can be a carboxylic acid or an acid derivative. As used herein, an acid derivative refers to a functional derivative of a carboxylic acid such as, for example, an ester or an amide.

In some examples, **Formula I** is represented by **Structure I-B**:

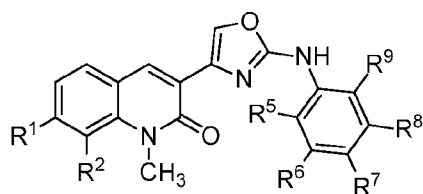


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In **Structure I-B**, R^1 and R^2 are as defined above for **Formula I**.

Also in **Structure I-B**, R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above for **Structure I-A**.

In some examples, **Formula I** is represented by **Structure I-C**:

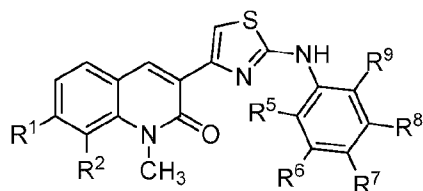


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In **Structure I-C**, R^1 and R^2 are as defined above for **Formula I**.

Also in **Structure I-C**, R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above for **Structure I-A**.

In some examples, **Formula I** is represented by **Structure I-D**:



In **Structure I-D**, R^1 and R^2 are as defined above for **Formula I**.

15

Also in **Structure I-D**, R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above for **Structure I-A**.

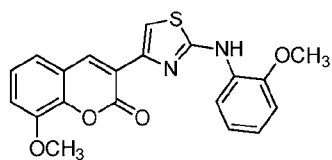
Optionally, adjacent R groups in **Structures I-A**, **I-B**, **I-C**, and **I-D**, e.g., R^1 and R^2 , R^5 and R^6 , R^6 and R^7 , R^7 and R^8 , or R^8 and R^9 can be combined to form a substituted or unsubstituted aryl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

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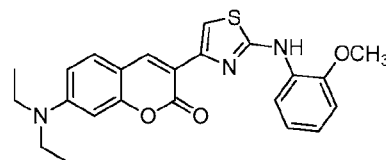
Examples of **Formula I** include the following compounds:

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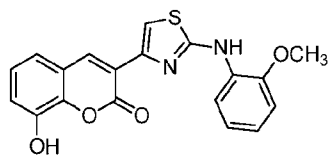
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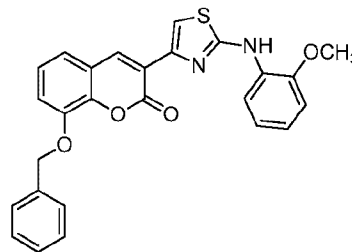
43H11 (DBM 101) (001_2)



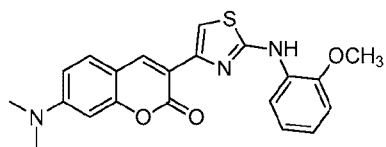
001_5



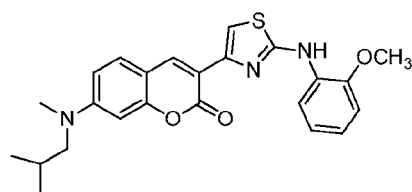
001_6



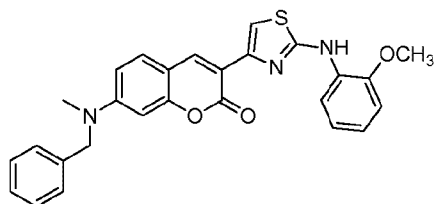
001_7



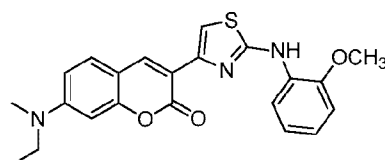
002_N7_11



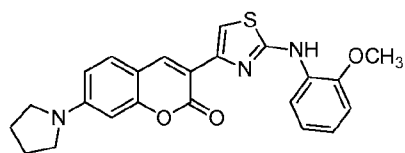
002_N7_13



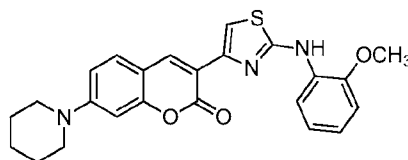
002_N7_14



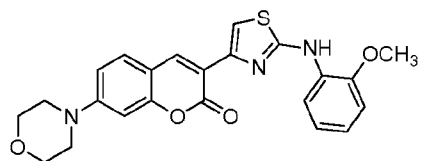
002_N7_21



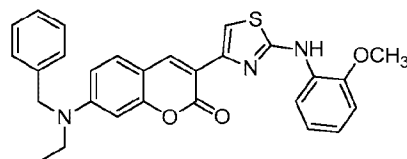
002_N7_22



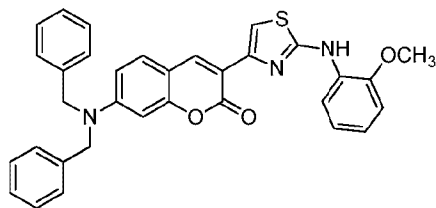
002_N7_23



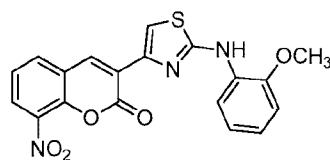
002_N7_26



002_N7_29

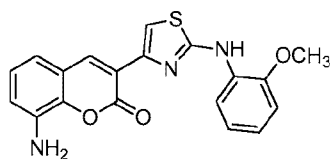


002_N7_31

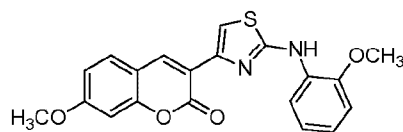


002_N8_27 (DBM227)

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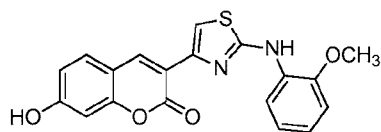


002_N8_28 (DBM228)

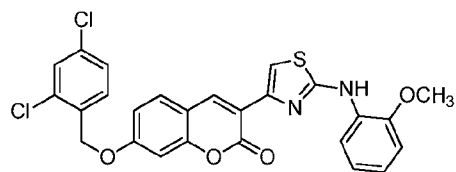


002_07_1

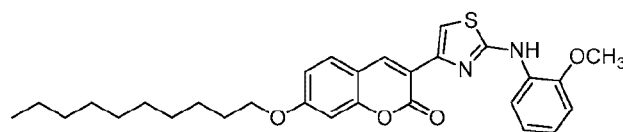
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002_07_11

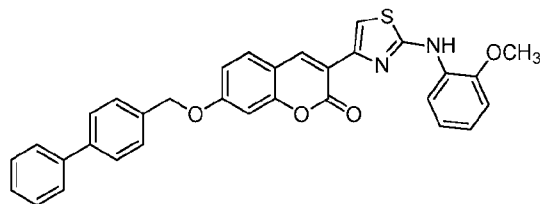


002_07_12

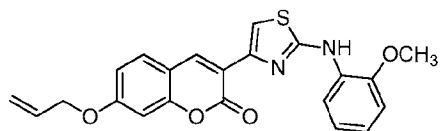


002_07_13

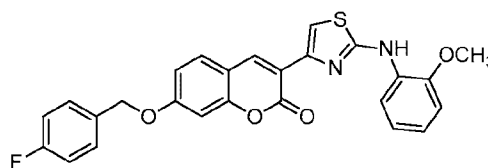
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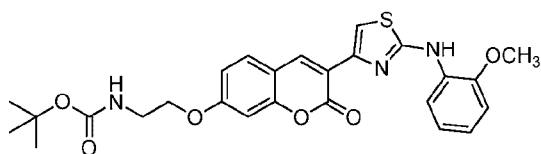
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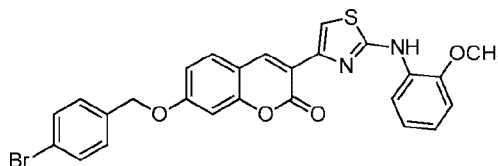
002_07_15



002_07_17

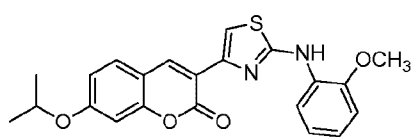


002_07_18

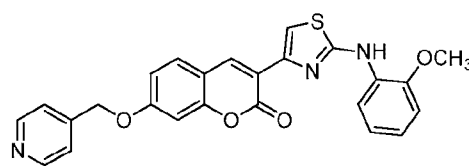


002_07_19

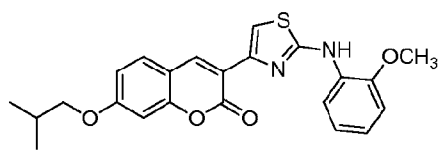
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002_07_2



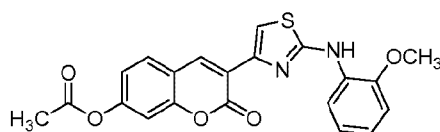
002_07_20



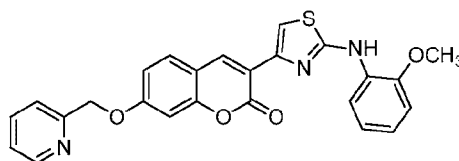
002_07_3



002_07_4

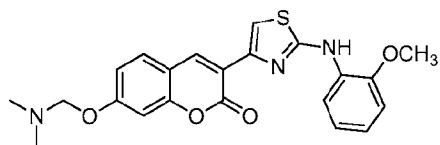


002_07_6

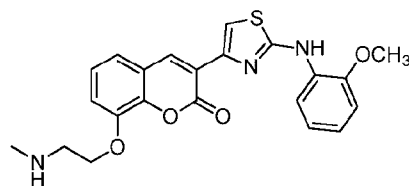


002_07_7

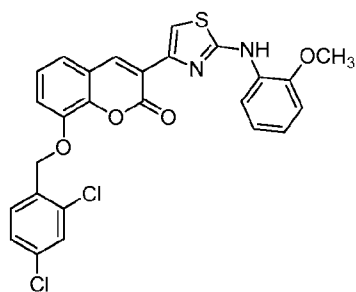
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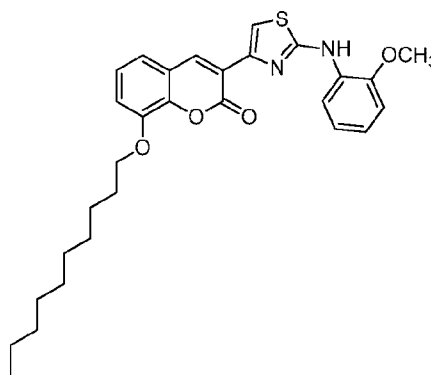
002_07_8



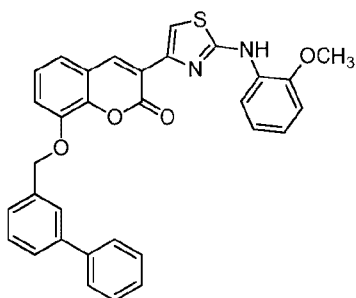
002_08_10



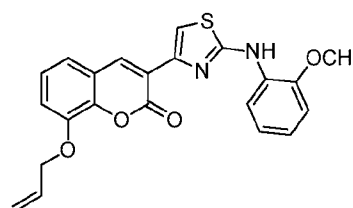
002_08_12



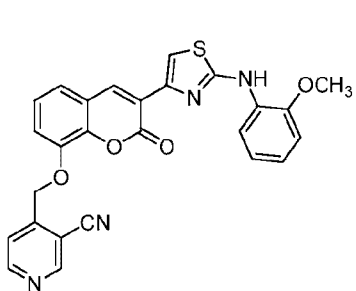
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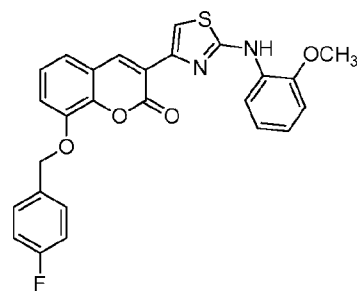
002_08_14



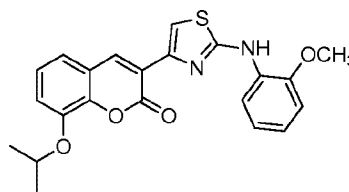
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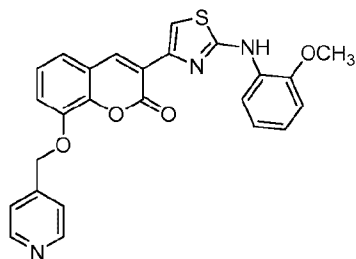
002_08_16



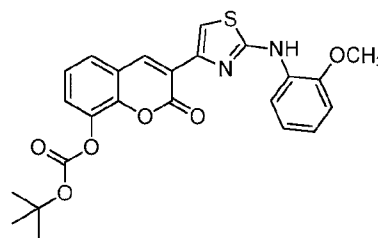
002_08_17



002_08_2



002_08_20

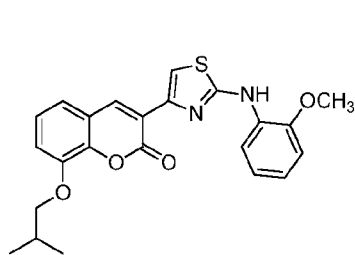


002_08_21

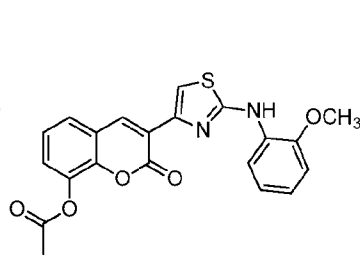
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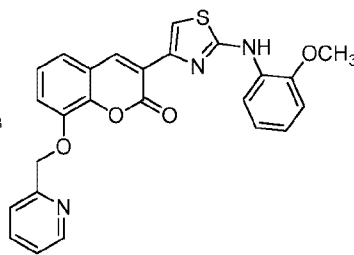
PCT/US2014/027154



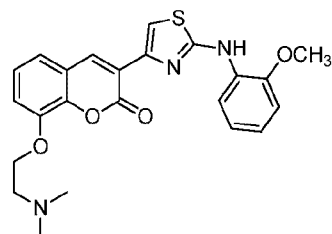
002_08_3



002_08_6

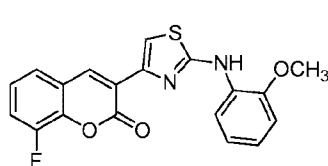


002_08_7

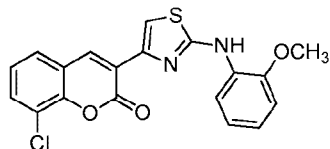


002_08_8

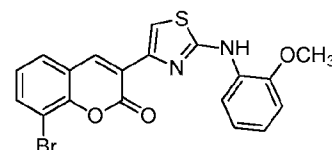
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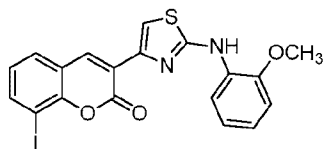
DBM-003-8F



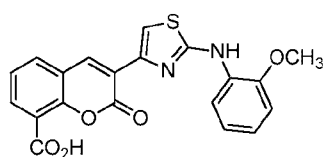
DBM-003-8Cl (DBM 308)



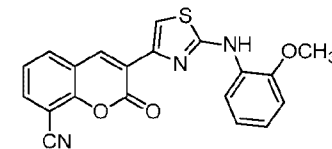
DBM-003-8Br (DBM 318)



DBM-003-8I

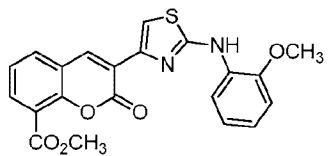
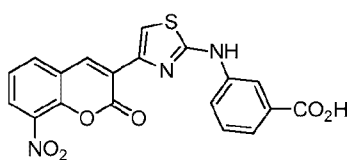


DBM-003-8COOH (DBM 328)

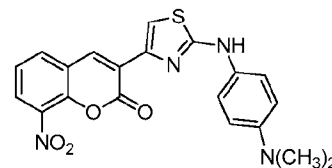


DBM-003-8CN

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DBM-003-8COOCH₃

DBM-003-TU4

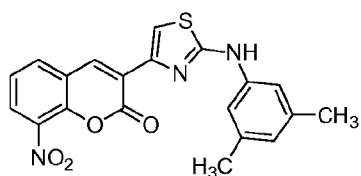
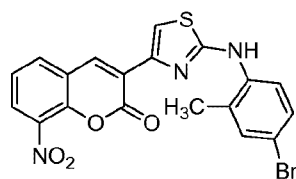
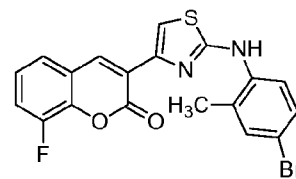
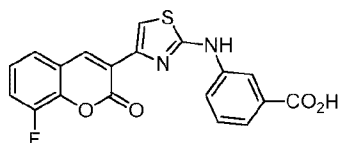
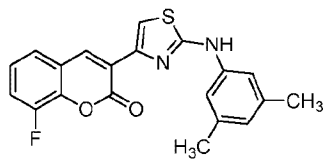
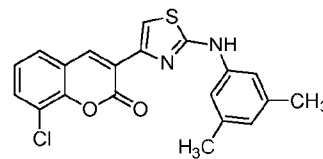
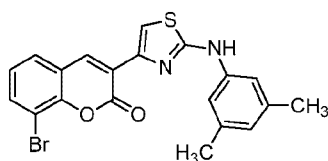
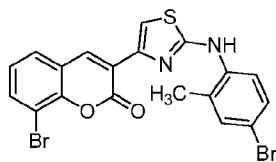
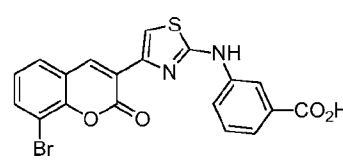


DBM-003-TU31

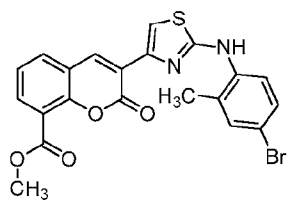
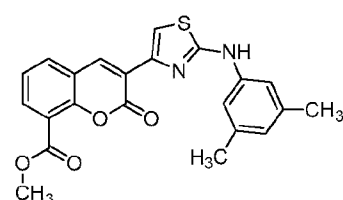
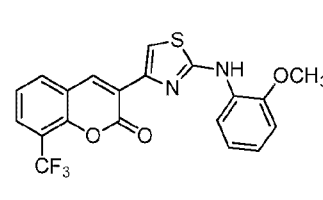
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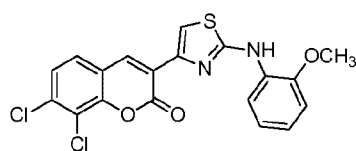
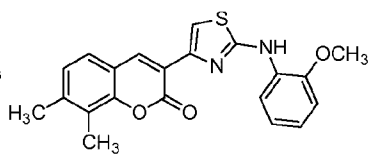
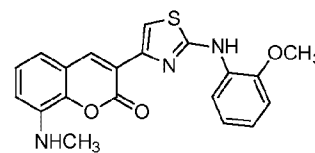
PCT/US2014/027154

**DBM-003-TU16****DBM-003-TU21****DBM-003-TU21-F**5 **DBM-003-TU4-F****DBM-003-TU16-F****DBM-003-TU16-Cl****DBM-003-TU16-Br****DBM-003-TU21-Br****DBM-003-TU4-Br**

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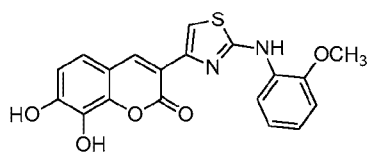
**DBM-003-TU21-COOCH₃****DBM-003-TU16-COOCH₃****007-01 (DBM-701)**

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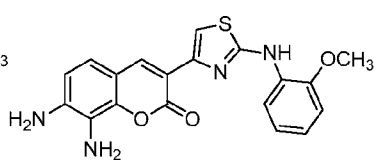
**007-02****007-03****004-04**

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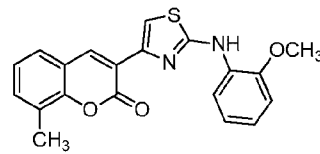
PCT/US2014/027154



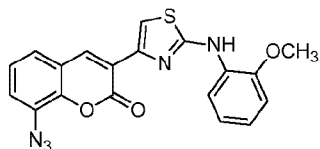
004-05



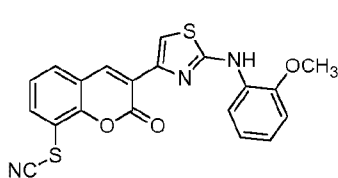
004-06



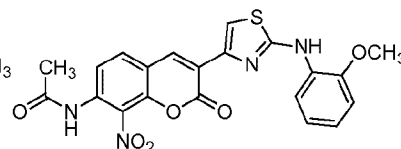
004-07 (DBM 707)



004-09

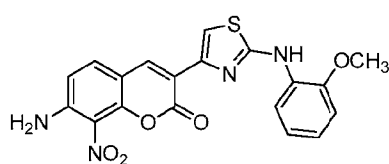


004-10

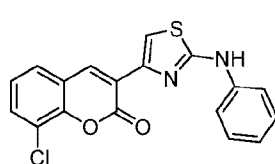


004-14

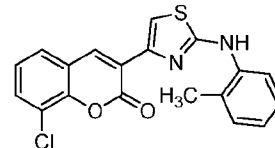
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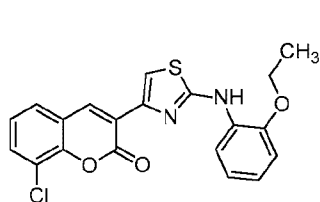
004-15 (DBM 715)



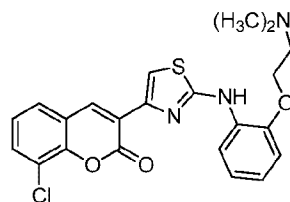
DBM-E-01



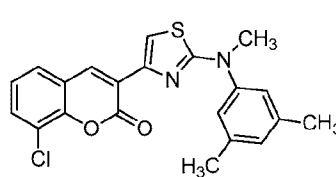
DBM-E-02



DBM E-03

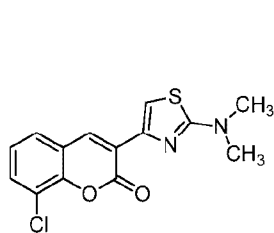


DBM-E-04

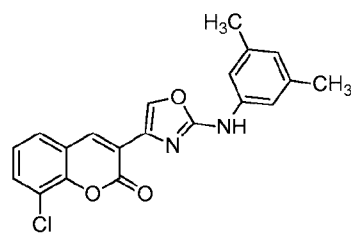


DBM-E-05

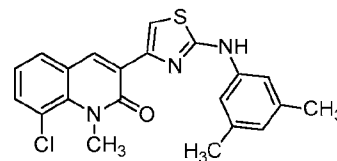
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DBM-E-05.1



DBM-E-06

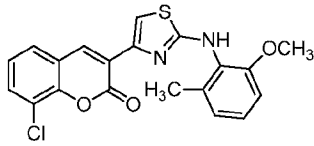


DBM-E-07

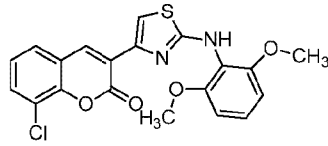
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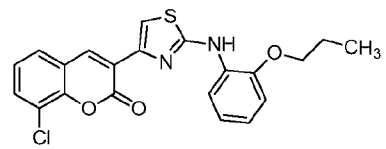
PCT/US2014/027154



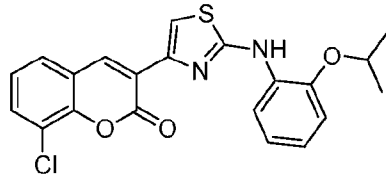
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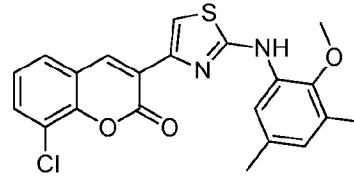
DBM-E-12



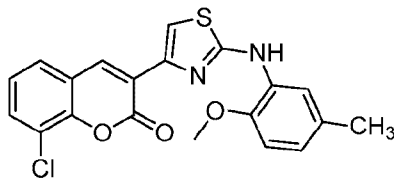
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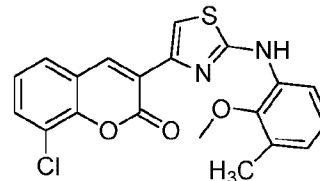
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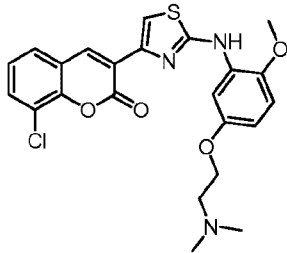
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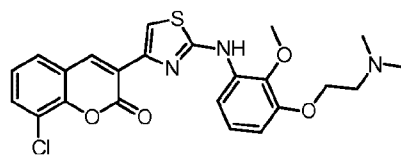
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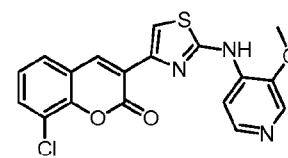
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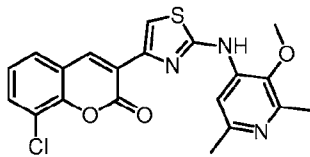
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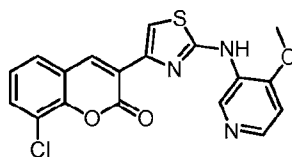
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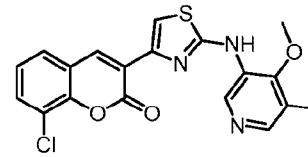
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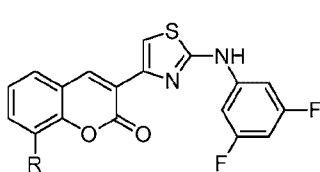
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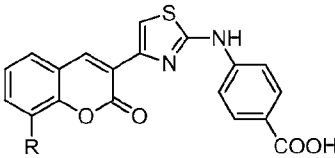
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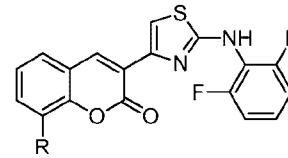
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P1



P2



P3

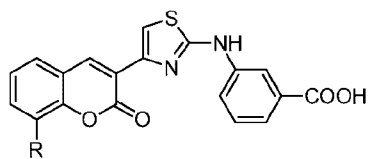
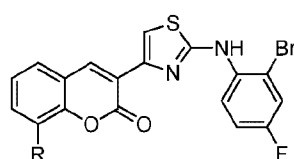
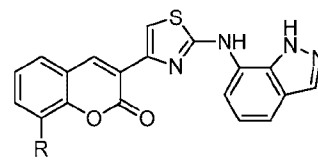
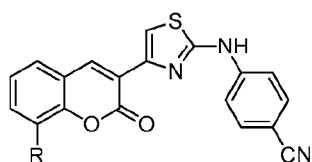
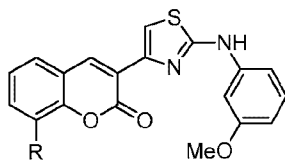
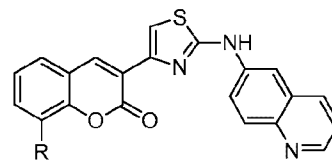
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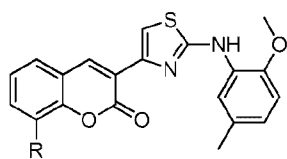
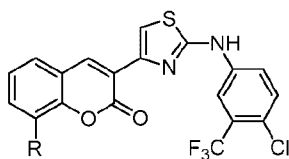
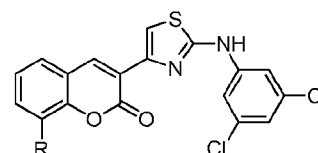
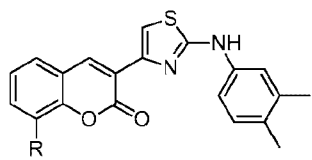
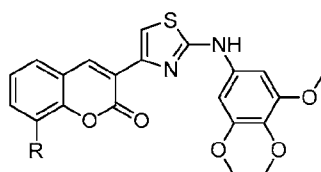
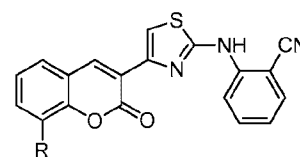
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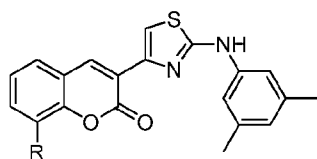
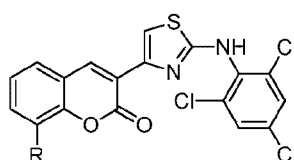
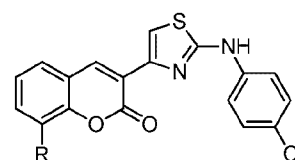
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**P4****P5****P6****P7****P8****P9**

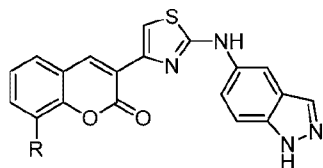
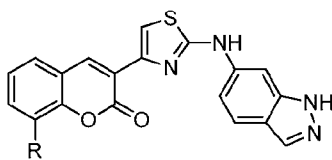
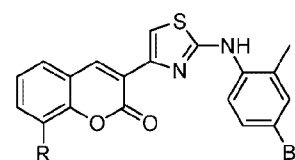
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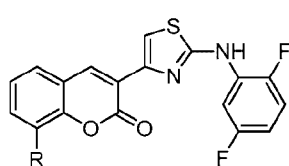
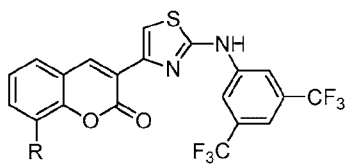
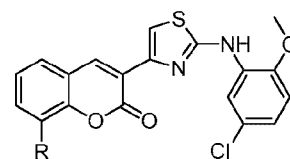
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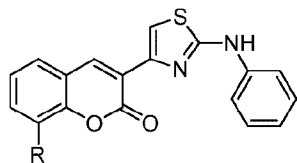
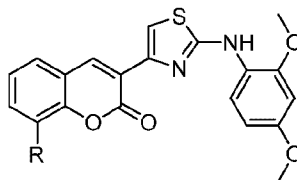
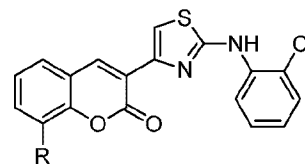
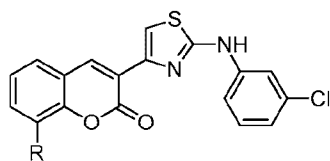
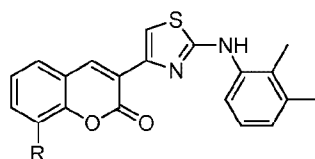
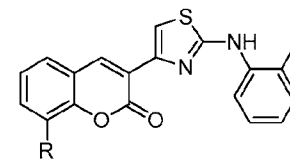
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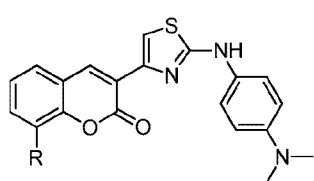
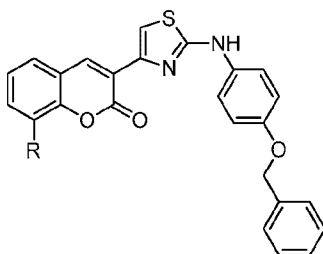
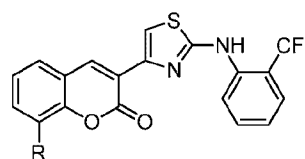
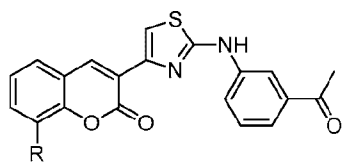
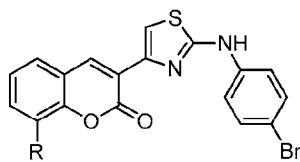
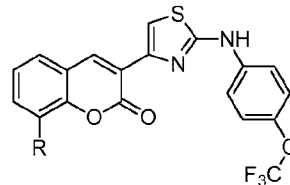
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**P22****P23****P24**

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**P25****P26****P27****P28****P29****P30**

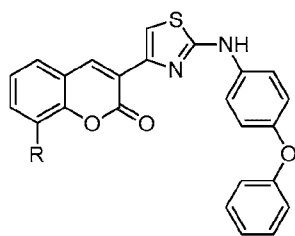
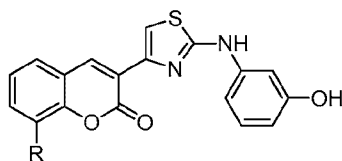
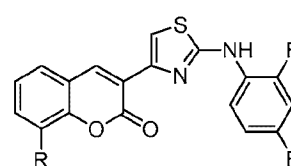
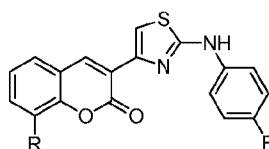
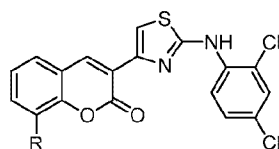
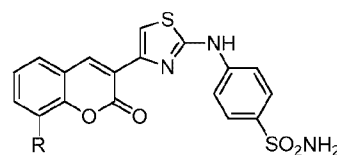
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**P31****P32****P33****P34****P35****P36**

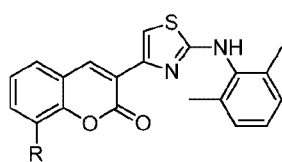
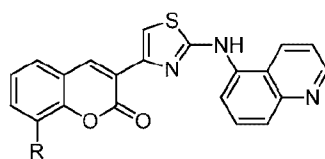
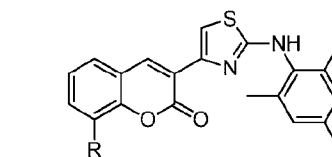
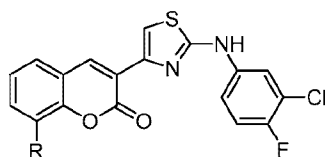
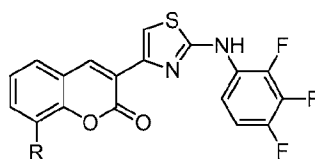
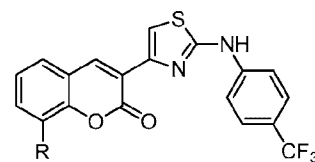
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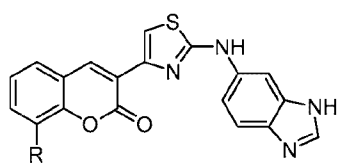
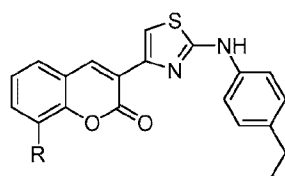
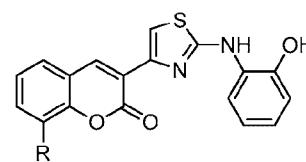
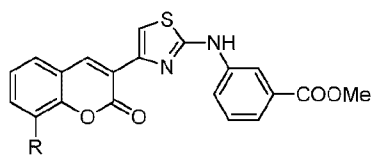
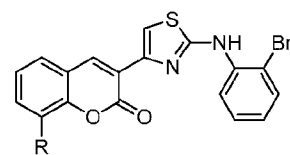
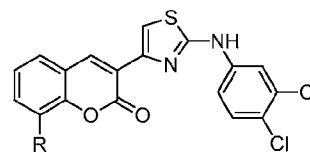
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**P37****P38****P39****P40****P41****P42**

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**P43****P44****P45****P46****P47****P48**

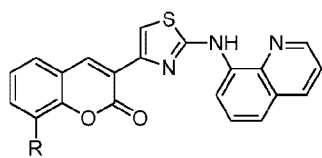
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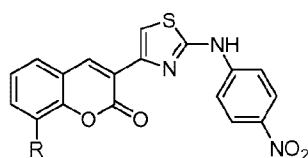
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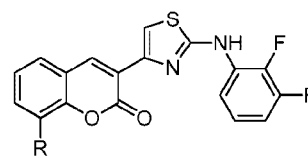
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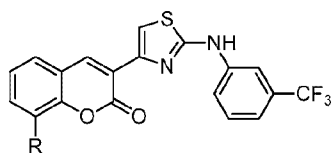
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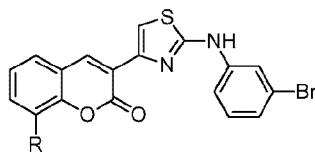
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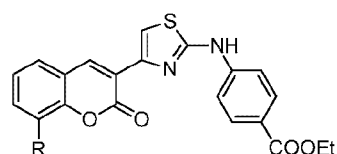
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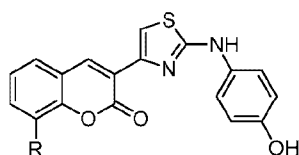


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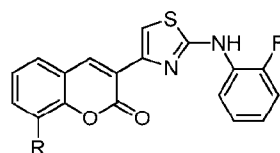


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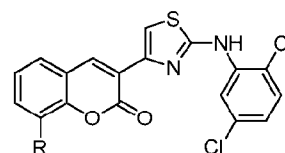
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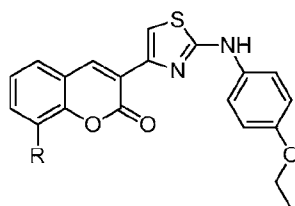
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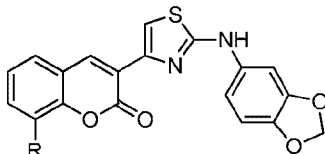
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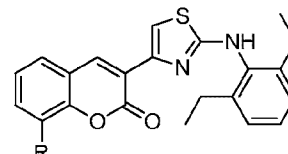
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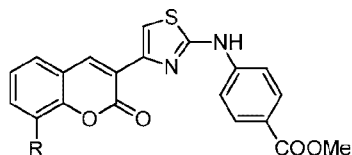


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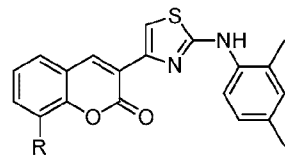


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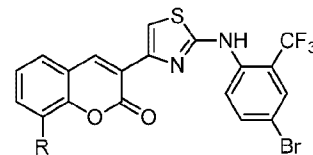
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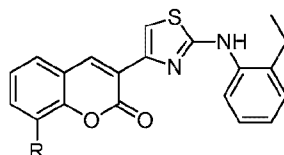


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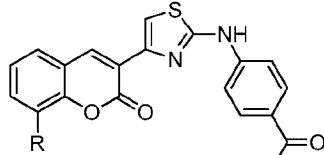


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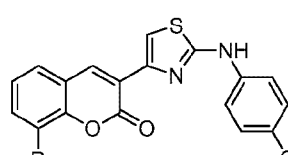
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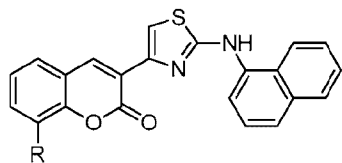
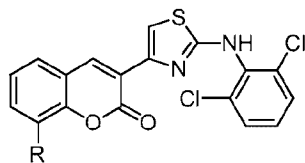
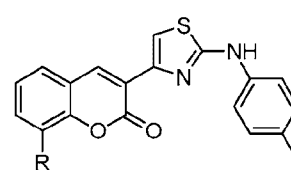
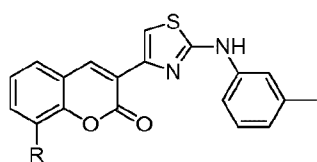
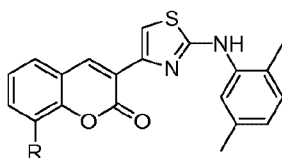
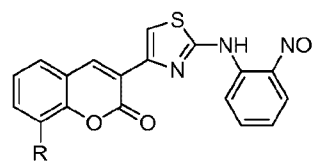
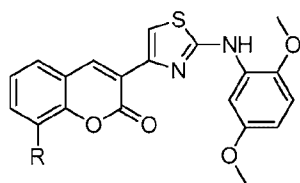
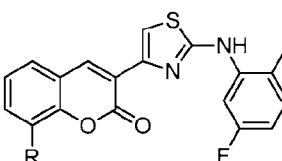
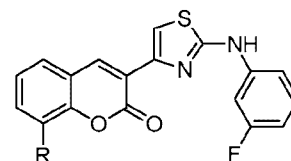
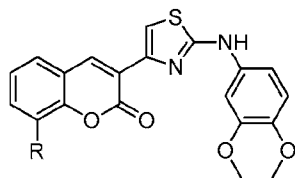
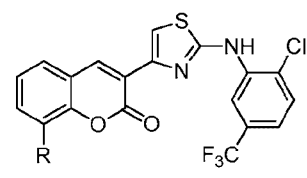
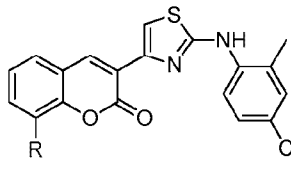
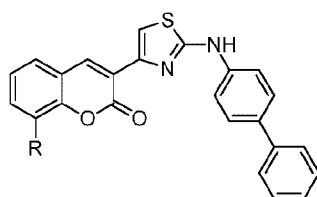
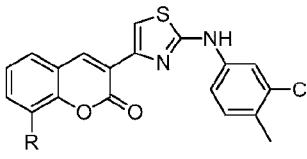
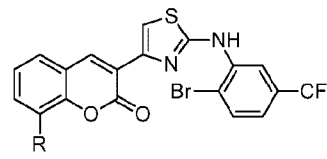
P70



P71

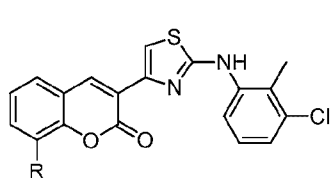
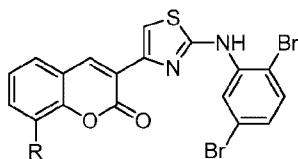
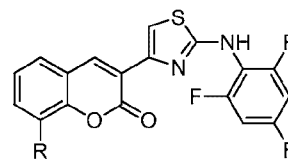
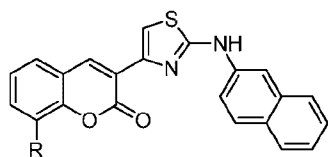
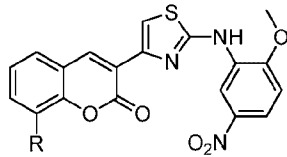
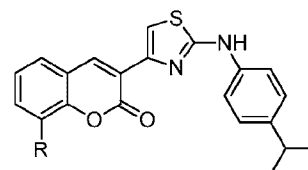
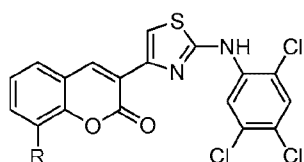
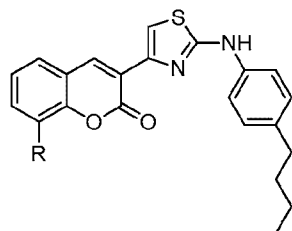
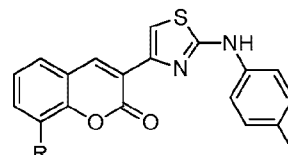
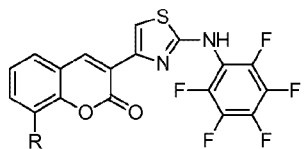
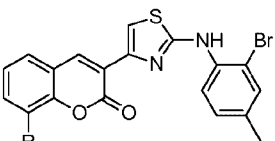
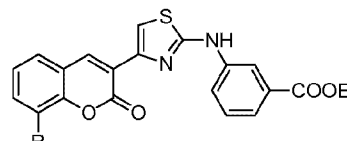
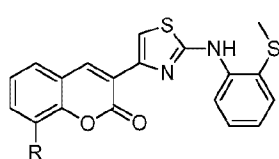
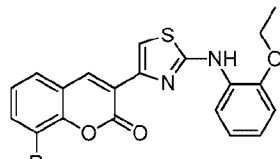
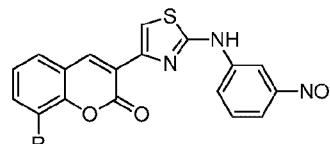


P72

**P73****P74****P75****P76****P77****P78****P79****P80****P81****P82****P83****P84****P85****P86****P87**

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**P88****P89****P90****P91****P92****P93****P94****P95****P96****P97****P98****P99****P100****P101****P102**

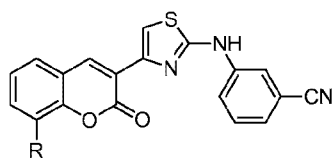
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10

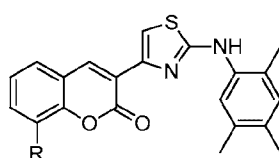
15

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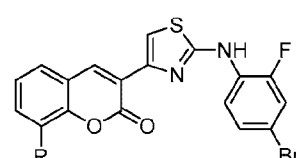
PCT/US2014/027154



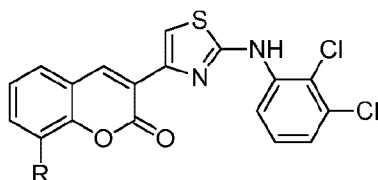
P103



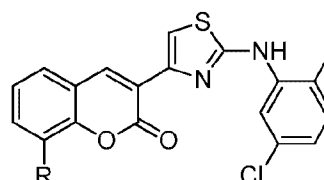
P104



P105



P106

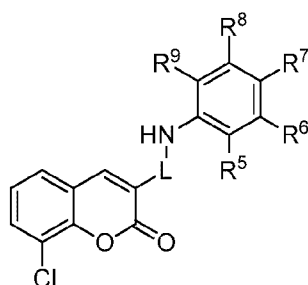


P107

5

In **Compounds P1** through **P107**, R can be halogen (e.g., chloro). In some embodiments, the compound is not **Compound DBM 328**.

A class of coumarin derivatives described herein is represented by **Formula II**:



II

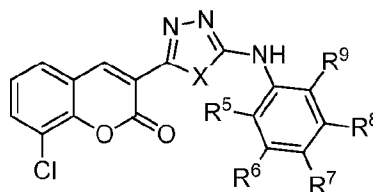
10

15 and pharmaceutically acceptable salts or prodrugs thereof.

In **Formula II**, L is a heteroaryl.

Also, in **Formula II**, R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from hydrogen and methoxy.

In some examples, **Formula II** is represented by **Structure II-A**:

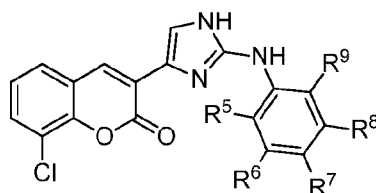


20

In **Structure II-A**, X is NH or O.

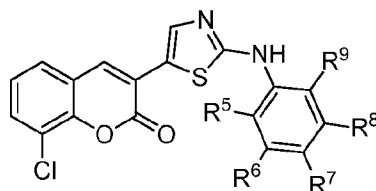
Also in **Structure II-A**, R⁵, R⁶, R⁷, R⁸, and R⁹ are as defined above for **Formula II**.

In some examples, **Formula II** is represented by **Structure II-B**:



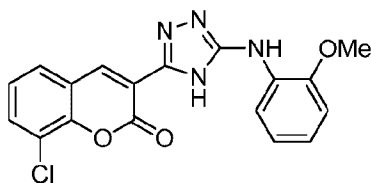
In **Structure II-B**, R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above for **Formula II**.

In some examples, **Formula II** is represented by **Structure II-C**:

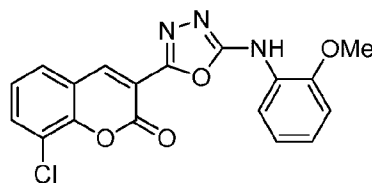


5 In **Structure II-C**, R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above for **Formula II**.

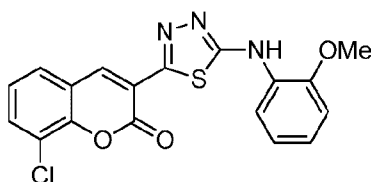
Examples of **Formula II** include the following compounds:



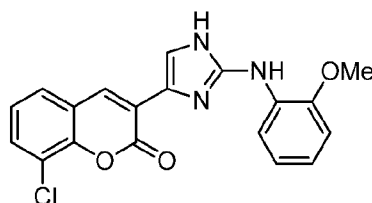
Compound II-1



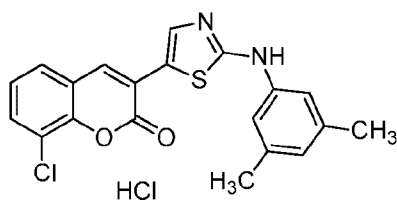
Compound II-2



10 **Compound II-3**

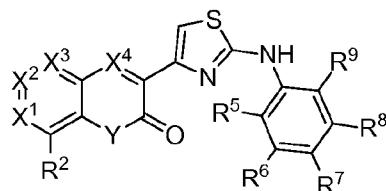


Compound II-4



DBM-E-10

A class of coumarin derivatives described herein is represented by **Formula III**:



III

and pharmaceutically acceptable salts or prodrugs thereof.

In **Formula III**, X^1 , X^2 , X^3 and X^4 are each independently selected from CH and N.

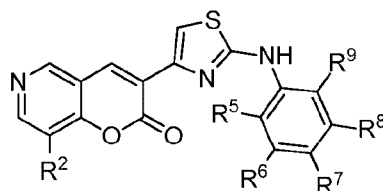
Also, in **Formula III**, Y is O or NR, where R is hydrogen or methyl.

Additionally, in **Formula III**, R^2 is hydrogen, C_{1-6} alkyl, halogen, or trifluoroalkyl.

Optionally, R^2 is Cl or methyl.

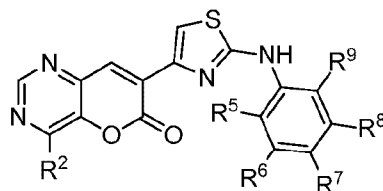
5 Further, in **Formula III**, R^5 , R^6 , R^7 , R^8 , and R^9 are each independently selected from hydrogen and methoxy.

In some examples, **Formula III** is represented by **Structure III-A**:



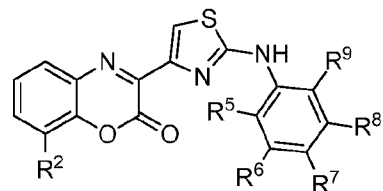
In **Structure III-A**, R^2 , R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above for **Formula III**.

10 In some examples, **Formula III** is represented by **Structure III-B**:



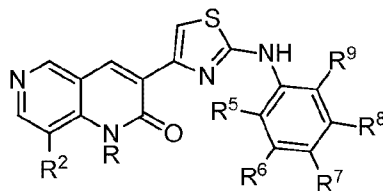
In **Structure III-B**, R^2 , R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above for **Formula III**.

In some examples, **Formula III** is represented by **Structure III-C**:



15 In **Structure III-C**, R^2 , R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above for **Formula III**.

In some examples, **Formula III** is represented by **Structure III-D**:



In **Structure III-D**, R is hydrogen or methyl.

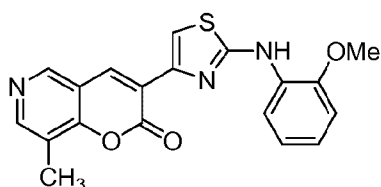
Also, in **Structure III-D**, R^2 , R^5 , R^6 , R^7 , R^8 , and R^9 are as defined above for **Formula**

20 **III**.

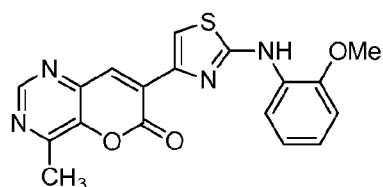
Examples of **Formula III** include the following compounds:

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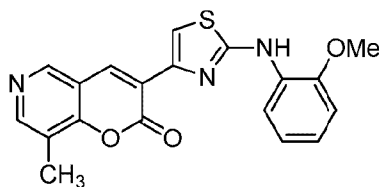
PCT/US2014/027154



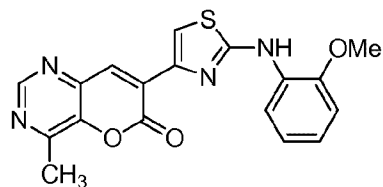
Compound III-1



Compound III-2

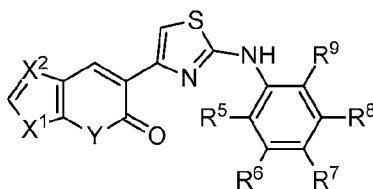


Compound III-3



Compound III-4

A class of coumarin derivatives described herein is represented by **Formula IV**:



IV

and pharmaceutically acceptable salts or prodrugs thereof.

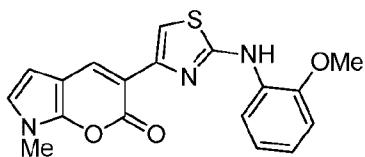
In **Formula IV**, X^1 is O or NCH_3 .

Also, in **Formula IV**, X^2 is CH or N.

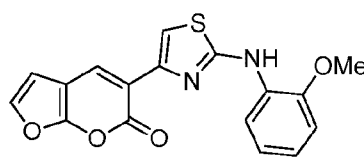
Additionally, in **Formula IV**, Y is O, NH, or NCH_3 .

Further, in **Formula IV**, R^5 , R^6 , R^7 , R^8 , and R^9 are each independently selected from hydrogen and methoxy.

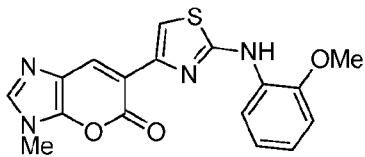
Examples of **Formula IV** include the following compounds:



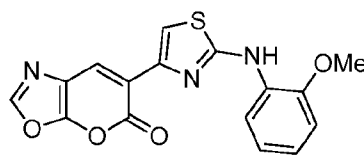
Compound IV-1



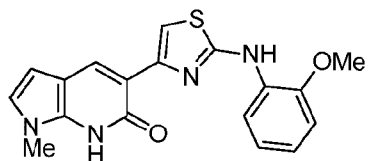
Compound IV-2



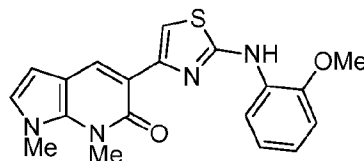
Compound IV-3



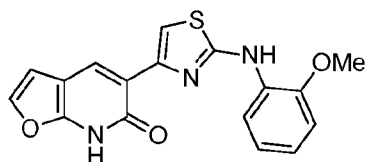
Compound IV-4



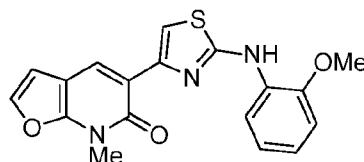
Compound IV-5



Compound IV-6

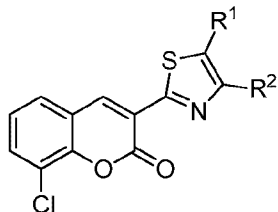


Compound IV-7



Compound IV-8

A class of coumarin derivatives described herein is represented by **Formula V**:

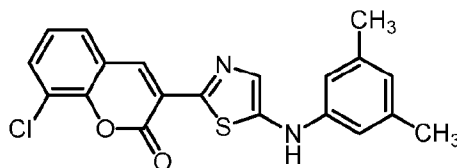


V

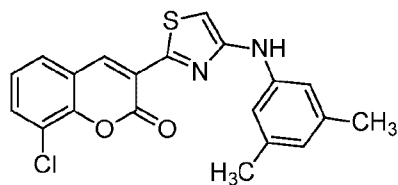
and pharmaceutically acceptable salts or prodrugs thereof.

In **Formula V**, R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted amino, and substituted or unsubstituted carbonyl.

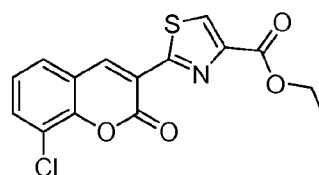
Examples of **Formula V** include the following compounds:



DBM-E-08

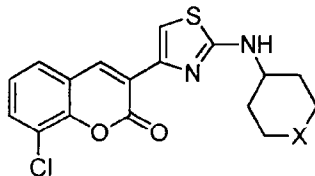


DBM-E-09



DBM-E-09.1

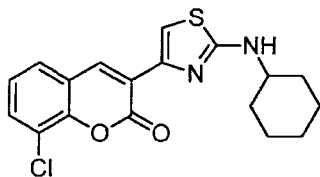
A class of coumarin derivatives described herein is represented by **Formula VI**:



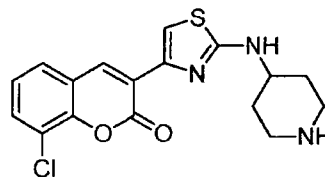
5 and pharmaceutically acceptable salts or prodrugs thereof.

In **Formula VI**, X is CH₂, NH, or O.

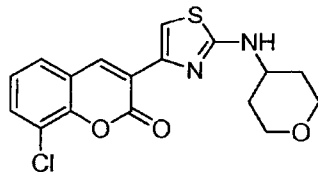
Examples of **Formula VI** include the following compounds:



Compound VI-1



Compound VI-2



Compound VI-3

10 II. Methods of Making the Compounds

The compounds described herein can be prepared in a variety of ways. The compounds can be synthesized using various synthetic methods. At least some of these methods are known
 15 in the art of synthetic organic chemistry. The compounds described herein can be prepared from readily available starting materials. Optimum reaction conditions can vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Variations on **Formulas I-VI** include the addition, subtraction, or movement of the
 20 various constituents as described for each compound. Similarly, when one or more chiral centers are present in a molecule, all possible chiral variants are included. Additionally, compound synthesis can involve the protection and deprotection of various chemical groups. The use of protection and deprotection, and the selection of appropriate protecting groups can be determined by one skilled in the art. The chemistry of protecting groups can be found, for
 25 example, in Greene, et al., *Protective Groups in Organic Synthesis*, 2d. Ed., Wiley & Sons, 1991.

Reactions to produce the compounds described herein can be carried out in solvents, which can be selected by one of skill in the art of organic synthesis. Solvents can be substantially nonreactive with the starting materials (reactants), the intermediates, or products under the conditions at which the reactions are carried out, i.e., temperature and pressure.

5 Reactions can be carried out in one solvent or a mixture of more than one solvent. Product or intermediate formation can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^1H or ^{13}C) infrared spectroscopy, spectrophotometry (e.g., UV-visible), or mass spectrometry, or by chromatography such as high performance liquid
10 chromatography (HPLC) or thin layer chromatography.

III. Pharmaceutical Formulations

The compounds described herein or derivatives thereof can be provided in a pharmaceutical composition. The pharmaceutical compositions are administered in a number of ways depending on whether local or systemic treatment is desired, and on the area to be treated.
15 The pharmaceutical compositions are administered via any of several routes of administration, including topically, orally, parenterally, intravenously, intra-articularly, intraperitoneally, intramuscularly, subcutaneously, intradermally, intracavity (e.g., rectal, intravesical, lumen of vesical organs), transdermally, intrahepatically, intracranially, nebulization/inhalation, or by installation via bronchoscopy. Intradermal administration includes administration at a site that is
20 afferent to the site of lymphatic transport dysfunction. Optionally, the pharmaceutical composition is administered by oral inhalation, nasal inhalation, intranasal mucosal administration, or suppository. The pharmaceutical composition can also be injected or infused, for example, at a site of inflammation, such as, for example, an inflamed joint. Administration of the pharmaceutical compositions by inhalant can be through the nose or mouth via delivery
25 by spraying or droplet mechanism, for example, in the form of an aerosol.

Depending on the intended mode of administration, the pharmaceutical composition can be in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, or suspensions, preferably in unit dosage form suitable for single administration of a precise dosage. The compositions will include a
30 therapeutically effective amount of the compound described herein or derivatives thereof in combination with a pharmaceutically acceptable carrier and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, or diluents. By pharmaceutically acceptable is meant a material that is not biologically or otherwise undesirable, which can be administered

to an individual along with the selected compound without causing unacceptable biological effects or interacting in a deleterious manner with the other components of the pharmaceutical composition in which it is contained.

As used herein, the term carrier encompasses any excipient, diluent, filler, salt, buffer, stabilizer, solubilizer, lipid, stabilizer, or other material well known in the art for use in pharmaceutical formulations. The choice of a carrier for use in a composition will depend upon the intended route of administration for the composition. The preparation of pharmaceutically acceptable carriers and formulations containing these materials is described in, e.g., Remington's Pharmaceutical Sciences, 21st Edition, ed. University of the Sciences in Philadelphia, Lippincott, Williams & Wilkins, Philadelphia Pa., 2005. Examples of physiologically acceptable carriers include buffers, such as phosphate buffers, citrate buffer, and buffers with other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers, such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates, including glucose, mannose, or dextrans; chelating agents, such as EDTA; sugar alcohols, such as mannitol or sorbitol; salt-forming counterions, such as sodium; and/or nonionic surfactants, such as TWEEN® (ICI, Inc.; Bridgewater, New Jersey), polyethylene glycol (PEG), and PLURONICSTM (BASF; Florham Park, NJ).

Compositions containing the compound described herein or derivatives thereof suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), 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 a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants, such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be promoted by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. Isotonic agents, for example, sugars, sodium chloride, and the like may also be included. Prolonged absorption of the injectable pharmaceutical form can be

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

Solid dosage forms for oral administration of the compounds described herein or derivatives thereof include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds described herein or derivatives thereof is admixed with at least one inert customary excipient (or carrier), such as sodium citrate or dicalcium phosphate, or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (e) solution retarders, as for example, paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms 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 sugar as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others known in the art. They may contain opacifying agents and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions that can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration of the compounds described herein or derivatives thereof include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, sesame oil,

glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, and fatty acid esters of sorbitan, or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include additional agents, such as wetting, emulsifying, suspending, sweetening, flavoring, or perfuming agents.

5 Suspensions, in addition to the active compounds, may contain additional agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

10 Compositions of the compounds described herein or derivatives thereof for rectal administrations are optionally suppositories, which can be prepared by mixing the compounds with suitable non-irritating excipients or carriers, such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and, therefore, melt in the rectum or vaginal cavity and release the active component.

15 Dosage forms for topical administration of the compounds described herein or derivatives thereof include ointments, powders, sprays, and inhalants. The compounds described herein or derivatives thereof are admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, ointments, powders, and solutions are also contemplated as being within the scope of the compositions.

20 The compositions can include one or more of the compounds described herein and a pharmaceutically acceptable carrier. As used herein, the term pharmaceutically acceptable salt refers to those salts of the compound described herein or derivatives thereof that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of subjects without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable
25 benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds described herein. The term salts refers to the relatively non-toxic, inorganic and organic acid addition salts of the compounds described herein. These salts can be prepared in situ during the isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and
30 isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate, methane sulphonate, and laurylsulphonate salts, and the

like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See S.M. Barge et al., J. Pharm. Sci. (1977) 66, 1.)

Administration of the compounds and compositions described herein or pharmaceutically acceptable salts thereof can be carried out using therapeutically effective amounts of the compounds and compositions described herein or pharmaceutically acceptable salts thereof as described herein for periods of time effective to treat a disorder. The effective amount of the compounds and compositions described herein or pharmaceutically acceptable salts thereof as described herein may be determined by one of ordinary skill in the art and includes exemplary dosage amounts for a mammal of from about 0.5 to about 200mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. Alternatively, the dosage amount can be from about 0.5 to about 150mg/kg of body weight of active compound per day, about 0.5 to 100mg/kg of body weight of active compound per day, about 0.5 to about 75mg/kg of body weight of active compound per day, about 0.5 to about 50mg/kg of body weight of active compound per day, about 0.5 to about 25mg/kg of body weight of active compound per day, about 1 to about 20mg/kg of body weight of active compound per day, about 1 to about 10mg/kg of body weight of active compound per day, about 20mg/kg of body weight of active compound per day, about 10mg/kg of body weight of active compound per day, or about 5mg/kg of body weight of active compound per day. Those of skill in the art will understand that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition.

IV. Methods of Use

The methods described herein include a method of treating hyperproliferative diseases in a subject. These methods include the step of administering to the subject an effective amount of a compound as described herein, or a pharmaceutically salt or prodrug thereof. The expression

“effective amount,” when used to describe an amount of compound in a method, refers to the amount of a compound that achieves the desired pharmacological effect or other effect, for example, an amount that results in tumor growth rate reduction. Additional steps can be included in the method described herein. For example, the methods can further include the steps of selecting a subject with a hyperproliferative disease, and administering to the subject one or more of the compounds as described herein. The compounds and compositions described herein or pharmaceutically acceptable salts thereof are useful for treating hyperproliferative diseases in humans, including, without limitation, pediatric and geriatric populations, and in animals, e.g., veterinary applications. Optionally, the hyperproliferative disease is cancer. Optionally, the hyperproliferative disease is polycystic kidney disease. Optionally, the hyperproliferative disease is idiopathic pulmonary fibrosis.

As described above, the compounds described herein are useful in the treatment of hyperproliferative diseases, including cancer, polycystic kidney disease, and fibrosis. The compounds described herein do not significantly inhibit cellular proliferation in normal cell types or in non-proliferating cells.

Optionally, the cancer is bladder cancer, brain cancer, breast cancer, colorectal cancer, cervical cancer, gastrointestinal cancer, genitourinary cancer, head and neck cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, skin cancer, or testicular cancer.

Optionally, the polycystic kidney disease is autosomal dominant polycystic kidney disease (ADPKD) or autosomal recessive polycystic kidney disease (ARPKD). The methods of treating a polycystic kidney disease in a subject can further include treating or preventing symptoms of polycystic kidney disease. The symptoms can be related to ADPKD or ARPKD. For example, the symptoms can include brain aneurysms, cysts in the liver, pancreas, and testes, urinary tract infections, high blood pressure and diverticula of the colon.

Optionally, the fibrosis is pulmonary fibrosis, idiopathic pulmonary fibrosis, cirrhosis, endomyocardial fibrosis, mediastinal fibrosis, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis, nephrogenic systemic fibrosis, Crohn's Disease, keloid, old myocardial infarction, scleroderma/systemic sclerosis, arthrofibrosis, and adhesive capsulitis of the breast, prostate, blood, brain, kidney, liver or skin. In a further embodiment, the fibrosis is idiopathic pulmonary fibrosis.

In the methods described herein, the subjects treated can be further treated with one or more additional agents. The one or more additional agents and the compounds described herein or pharmaceutically acceptable salts or prodrugs thereof can be administered together in a single

composition (e.g., as an admixture) or in separate compositions in any order, including simultaneous administration, as well as temporally spaced order of up to several days apart. The methods can also include more than a single administration of the one or more additional agents and/or the compounds described herein or pharmaceutically acceptable salts or prodrugs thereof.

5 The administration of the one or more additional agents and the compounds described herein or pharmaceutically acceptable salts or prodrugs thereof can be by the same or different routes and concurrently or sequentially.

Therapeutic agents include, but are not limited to, chemotherapeutic agents. A chemotherapeutic agent is a compound or composition effective in inhibiting or arresting the

10 growth of an abnormally growing cell. Thus, such an agent may be used therapeutically to treat cancer as well as other diseases marked by abnormal cell growth. Illustrative examples of chemotherapeutic compounds include, but are not limited to, bexarotene, gefitinib, erlotinib, gemcitabine, paclitaxel, docetaxel, topotecan, irinotecan, temozolomide, carmustine, vinorelbine, capecitabine, leucovorin, oxaliplatin, bevacizumab, cetuximab, panitumumab,

15 bortezomib, oblimersen, hexamethylmelamine, ifosfamide, CPT-11, deflunomide, cycloheximide, dicarbazine, asparaginase, mitotant, vinblastine sulfate, carboplatin, colchicine, etoposide, melphalan, 6-mercaptopurine, teniposide, vinblastine, antibiotic derivatives (e.g. anthracyclines such as doxorubicin, liposomal doxorubicin, and diethylstilbestrol doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens (e.g., tamoxifen); antimetabolites

20 (e.g., fluorouracil (FU), 5-FU, methotrexate, floxuridine, interferon alpha-2B, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine); cytotoxic agents (e.g., carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cisplatin, vincristine and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol

25 acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephalen, chlorambucil, mechlorethamine (nitrogen mustard) and thiotepa); and steroids (e.g., bethamethasone sodium phosphate).

Therapeutic agents can also include, but are not limited to, pain medications (e.g., NSAIDs, tramadol, clonidine, narcotics, and opioids), agents that reduce blood pressure (e.g., antihypertensives or diuretics), and antibiotics. Therapeutic agents can further include

30 prednisone, azathioprine, and N-acetylcysteine.

Any of the aforementioned therapeutic agents can be used in any combination with the compositions described herein. Combinations are administered either concomitantly (e.g., as an

admixture), separately but simultaneously (e.g., via separate intravenous lines into the same subject), or sequentially (e.g., one of the compounds or agents is given first followed by the second). Thus, the term combination is used to refer to concomitant, simultaneous, or sequential administration of two or more agents.

5 The methods and compounds as described herein are useful for both prophylactic and therapeutic treatment. For prophylactic use, a therapeutically effective amount of the compounds and compositions or pharmaceutically acceptable salts thereof as described herein are administered to a subject prior to onset (e.g., before obvious signs of a hyperproliferative disease), during early onset (e.g., upon initial signs and symptoms of a hyperproliferative
10 disease), or after the development of a hyperproliferative disease. Prophylactic administration can occur for several days to years prior to the manifestation of symptoms of a hyperproliferative disease. Therapeutic treatment involves administering to a subject a therapeutically effective amount of the compounds and compositions or pharmaceutically acceptable salts thereof as described herein after a hyperproliferative disease is diagnosed.

15 The methods and compounds described herein are also useful in inhibiting the interaction between two or more heat shock protein chaperones in a cell. The methods of inhibiting the interaction between two or more heat shock protein chaperones in a cell comprise contacting a cell with a compound as described herein. Optionally, the two or more heat shock protein chaperones are selected from the group consisting of Hsp-90, Hsp-70, Hsc-70, and Hsp-40.
20 Optionally, the method is performed *in vitro*. Optionally, the method is performed *in vivo*.

 Optionally, the methods and compounds described herein can be used to regulate kinases involved in the phosphorylation of vimentin. For example, the methods and compounds described herein can be used to regulated cyclin dependent kinases (cdk), including Cdk5. Optionally, the regulation of kinases involved in the phosphorylation of vimentin using the
25 methods and compounds described herein can result in vimentin filament disassembly. Optionally, the vimentin filament disassembly can result in increased apoptosis of cancer cells.

 The methods herein for prophylactic and therapeutic treatment optionally comprise selecting a subject with or at risk of developing a hyperproliferative disease. A skilled artisan can make such a determination using, for example, a variety of prognostic and diagnostic
30 methods, including, for example, a personal or family history of the disease or condition, clinical tests (e.g., imaging, biopsy, genetic tests), and the like.

V. Kits

Also provided herein are kits for treating or preventing hyperproliferative diseases in a subject. A kit can include any of the compounds or compositions described herein. For example, a kit can include a compound of **Formula I**, **Formula II**, **Formula III**, **Formula IV**,
5 **Formula V**, **Formula VI**, or combinations thereof. A kit can further include one or more additional agents, such as chemotherapeutic agents, pain medications, agents that reduce blood pressure (e.g., antihypertensives or diuretics), antibiotics, prednisone, azathioprine, and N-acetylcysteine. A kit can include an oral formulation of any of the compounds or compositions described herein. A kit can include an intravenous formulation of any of the compounds or
10 compositions described herein. A kit can additionally include directions for use of the kit (e.g., instructions for treating a subject), a container, a means for administering the compounds or compositions (e.g., a syringe), and/or a carrier.

VI. Methods of Screening

Methods of screening for a compound for treating a hyperproliferative disease are
15 provided. Such methods involve the steps of contacting a cell with the candidate compound to be screened and determining the effect of the candidate compound on proliferation of hyperproliferating cells. The method can be performed *in vitro* or *in vivo*. The method provides an effective and reliable means of screening for compounds capable of treating a disease or condition caused, at least in part, by hyperproliferative cells.

20 Optionally, the method can include contacting a hyperproliferative cell with a candidate agent; obtaining a measurement indicative of cell growth, such as, but not limited to, cell number, cell viability, cell cycle progression, apoptotic frequency or activity of an enzyme involved in the apoptotic process; and identifying the candidate agent as a putative agent if the measurement of the property is significantly less than the baseline value of the property.

25 In one embodiment, such a screening assay can be performed, for example, by determining in an appropriate model system (such as, but not limited to, those systems described herein) the amount of inhibition of a measurement indicative of cell growth and detecting a difference in the level or activity of the foregoing in the presence of as compared to the absence of candidate compound.

30 The various screening assays may be combined with an *in vivo* assay entailing measuring the effect of the test compound on the symptoms the disease states and conditions discussed herein.

Suitable test compounds for use in the screening assays can be obtained from any suitable source, such as conventional compound libraries. The test compounds can also be obtained using any of the numerous approaches in combinatorial library methods known in the art, including biological libraries, spatially addressable parallel solid phase or solution phase libraries, synthetic library methods requiring deconvolution, the “one-bead one-compound” library method, and synthetic library methods using affinity chromatography selection. The biological library approach includes peptide libraries, while the other four approaches include peptide, non-peptide oligomer, or small molecule libraries of compounds. Accordingly, virtually any number of chemical extracts or compounds can be screened using the methods described herein. Examples of such extracts or compounds include, but are not limited to, plant-, fungal-, prokaryotic- or animal-based extracts, fermentation broths, and synthetic compounds, as well as modifications of existing compounds. Numerous methods are also available for generating random or directed synthesis (e.g., semi-synthesis or total synthesis) of any number of chemical compounds, including, but not limited to, saccharide-, lipid-, peptide-, polypeptide- and nucleic acid-based compounds. Synthetic compound libraries and libraries of natural compounds in the form of bacterial, fungal, plant, and animal extracts are commercially available. In addition, natural and synthetically produced libraries are generated, if desired, according to methods known in the art, e.g., by standard extraction and fractionation methods. Furthermore, if desired, any library or compound is readily modified using standard chemical, physical, or biochemical methods.

Examples of methods for the synthesis of molecular libraries can be found in the art. Libraries of compounds may be presented in solution or on beads, bacteria, spores, plasmids or phage.

A screening assay of the disclosure is particularly amenable to a high throughput format, thereby providing a means to screen, for example, a combinatorial library of small organic molecules, peptides, nucleic acid molecules, and the like.

As used herein the terms treatment, treat, or treating refer to a method of reducing one or more symptoms of a disease or condition. Thus in the disclosed method, treatment can refer to a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% reduction in the severity of one or more symptoms of the disease or condition. For example, a method for treating a disease is considered to be a treatment if there is a 10% reduction in one or more symptoms or signs (e.g., size of the tumor or rate of tumor growth) of the disease in a subject as compared to a control. As used herein, control refers to the untreated condition (e.g., the tumor cells not treated with the

compounds and compositions described herein). Thus the reduction can be a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or any percent reduction in between 10% and 100% as compared to native or control levels. It is understood that treatment does not necessarily refer to a cure or complete ablation of the disease, condition, or symptoms of the disease or condition.

5 As used herein, the terms prevent, preventing, and prevention of a disease or disorder refer to an action, for example, administration of a composition or therapeutic agent, that occurs before or at about the same time a subject begins to show one or more symptoms of the disease or disorder, which inhibits or delays onset or severity of one or more symptoms of the disease or disorder.

10 As used herein, references to decreasing, reducing, or inhibiting include a change of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater as compared to a control level. Such terms can include, but do not necessarily include, complete elimination.

15 As used herein, subject means both mammals and non-mammals. Mammals include, for example, humans; non-human primates, e.g., apes and monkeys; cattle; horses; sheep; rats; mice; pigs; and goats. Non-mammals include, for example, fish and birds.

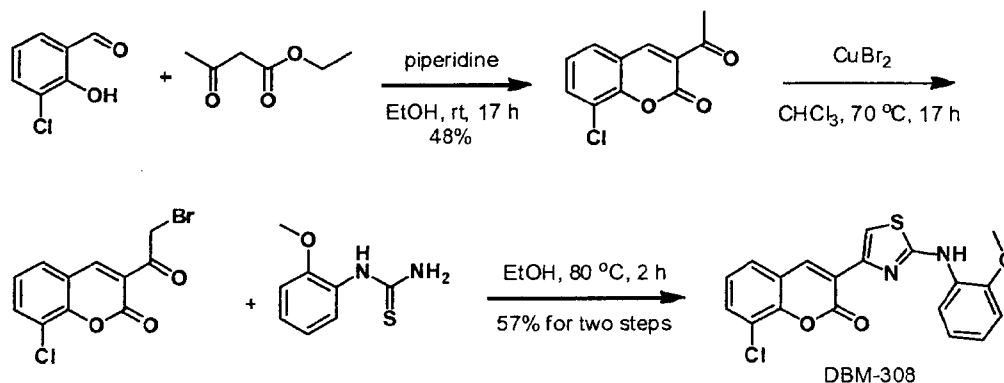
The examples below are intended to further illustrate certain aspects of the methods and compositions described herein, and are not intended to limit the scope of the claims.

EXAMPLES

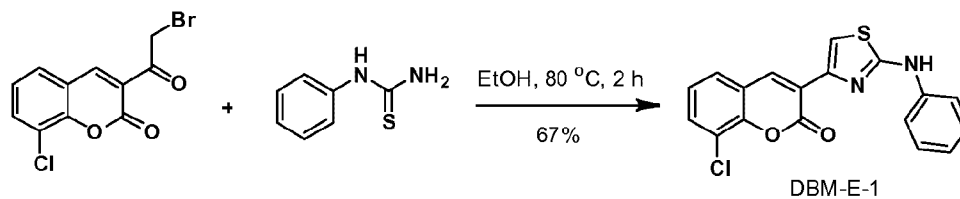
Example 1: Synthesis

A synthetic scheme for **DBM-308** is shown in **Scheme 1**.

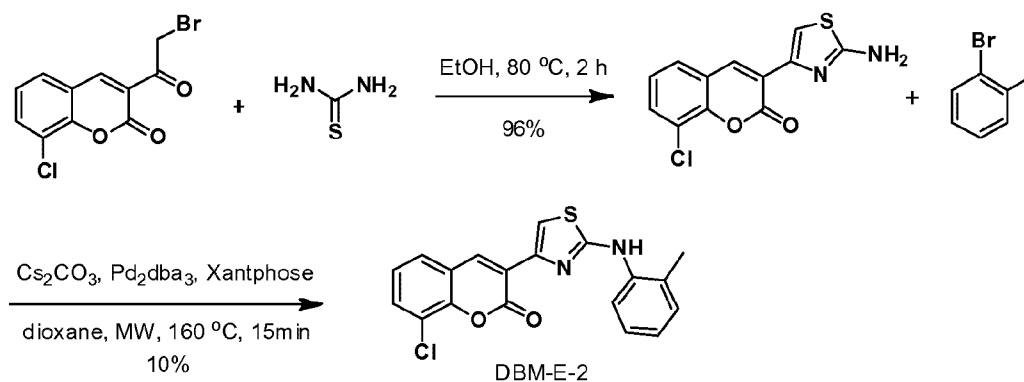
Scheme 1:



A synthetic scheme for **DBM-E-1** is shown in **Scheme 2**.

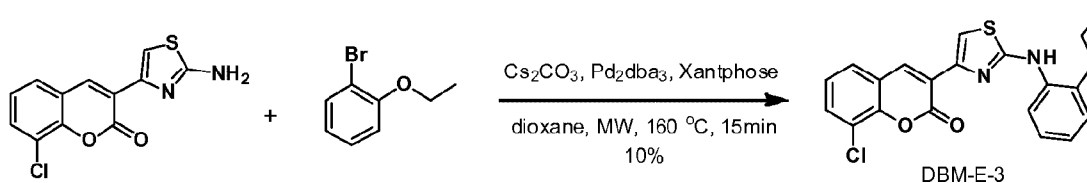
Scheme 2:

A synthetic scheme for **DBM-E-2** is shown in **Scheme 3**.

Scheme 3:

5

DBM-E-3 was prepared according to the procedure listed below and the synthetic scheme shown in **Scheme 4**.

Scheme 4:

10

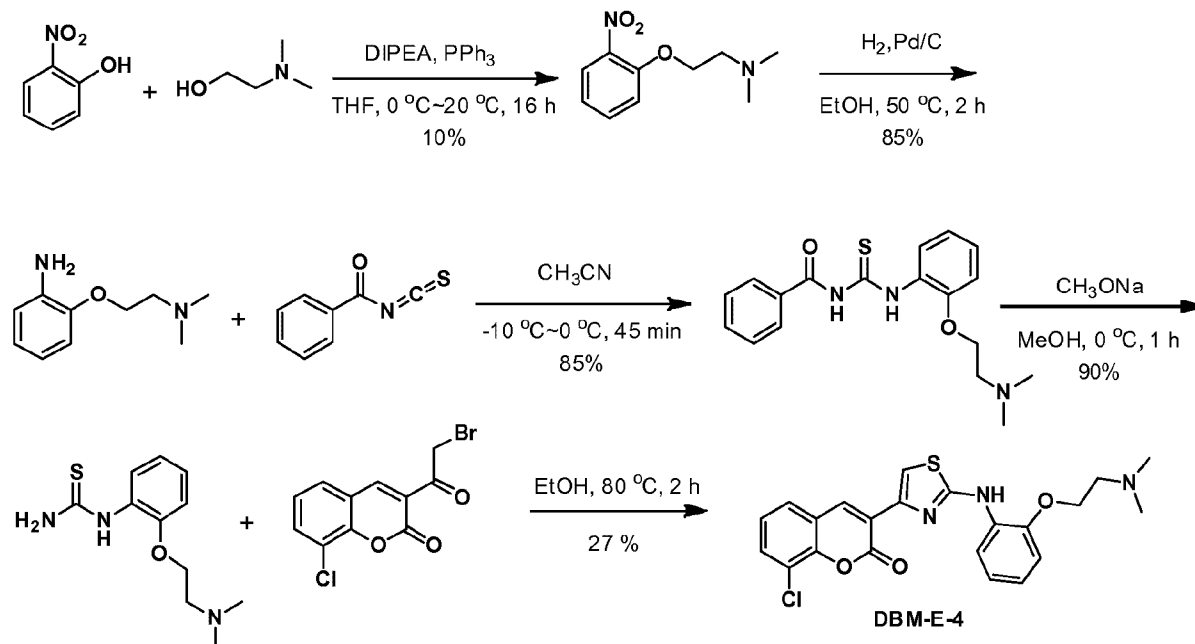
3-(2-bromoacetyl)-8-chloro-2H-chromen-2-one (150 mg, 0.54 mmol) and 1-bromo-2-ethoxybenzene (108 mg, 0.54 mmol) were reacted in a microwave in the presence of Cs_2CO_3 (528 mg, 1.62 mmol), $\text{Pd}_2(\text{dba})_3$ (40mg, 0.054mmol.), xantphos (60mg, 0.108mmol), and dioxane (2 mL) at 160°C for 15 minutes. The resulting product was then purified by pre-HPLC to yield 8-chloro-3-(2-(2-ethoxyphenylamino)thiazol-4-yl)-2H-chromen-2-one (20 mg, 10%) as a yellow solid. ESI-MS (EI^+ , m/z): 399.1 $[\text{M}+1]^+$; ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 1.40 (t, $J = 7$ Hz, 3H), 4.14 (q, $J = 7$ Hz, 2H), 6.99-7.05 (m, 3H), 7.39 (t, $J = 8$ Hz, 1H), 7.76-7.79 (m, 2H), 7.93 (t, $J = 7$ Hz, 1H), 8.48-8.49 (m, 1H), 8.65 (s, 1H), 9.54 (s, 1H).

15

DBM-E-4 was prepared according to the procedure listed below and the synthetic scheme shown in **Scheme 5**.

20

Scheme 5:

*Step 1: N,N-dimethyl-2-(2-nitrophenoxy)ethanamine:*

5 To a solution of 2-nitrophenol (13.9 g, 10 mmol), 2-(dimethylamino)ethanol (10.7g, 12mmol), and PPh₃ (29 g, 11 mmol) in dry THF (200 mL) was added DIAD (22 g, 11 mmol) dropwise at 0 °C. Then, the mixture was stirred at rt for 17 hrs. The solvent was removed. The residue was dissolved in 1 N HCl aq. and washed with EtOAc. The water layer was neutralized with saturated NaHCO₃ and extracted with EtOAc (2x). The organic layers were collected,
10 washed with brine, dried (Na₂SO₄), and concentrated to afford *N,N*-dimethyl-2-(2-nitrophenoxy)ethanamine (2.1 g, 10%) as a yellow oil. ESI-MS (EI⁺, *m/z*): 211.0 [M+1]⁺.

Step 2: 2-(2-(dimethylamino)ethoxy)aniline:

To a solution of *N,N*-dimethyl-2-(2-nitrophenoxy)ethanamine (1.0 g, 4.76mmol) in EtOH (10 mL) was added Pd/C (800 mg, 10%). The mixture was stirred at 50 °C for 2 hrs under H₂.
15 The reaction mixture was cooled down to rt and then filtered. The filtrate was concentrated to afford 2-(2-(dimethylamino)ethoxy)aniline (730 mg, 85%) as a yellow oil. ESI-MS (EI⁺, *m/z*): 181.0 [M+1]⁺.

Step 3: N-(2-(2-(dimethylamino)ethoxy)phenyl)benzamide:

2-(2-(dimethylamino)ethoxy)aniline (550 mg, 3 mmol) and benzoyl isothiocyanate (727
20 mg, 3.6 mmol) were reacted. The resulting mixture was then purified by filtration to provide *N*-(2-(2-(dimethylamino)ethoxy)phenyl)benzamide (360 mg, 35%) as a white solid. ESI-MS (EI⁺, *m/z*): 344.0 [M+1]⁺.

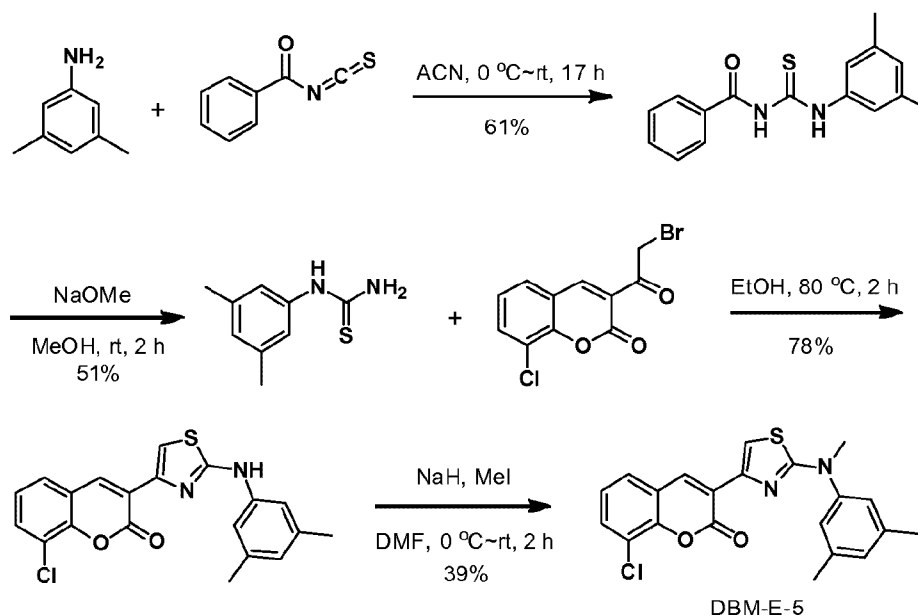
Step 4: 1-(2-(2-(dimethylamino)ethoxy)phenyl)thiourea:

N-(2-(2-(dimethylamino)ethoxy)phenyl)carbamothioyl)benzamide (343 mg, 1.0 mmol) was reacted with a solution of NaOMe in MeOH (1 mL, 30%), and the resulting mixture was purified by filtration to provide 1-(2-(2-(dimethylamino)ethoxy)-phenyl)thiourea (160 mg, 67%) as a white solid. ESI-MS (EI^+ , m/z): 240.0 $[\text{M}+1]^+$.

Step 5: 8-chloro-3-(2-(2-(2-(dimethylamino)ethoxy)phenylamino)thiazol-4-yl)-2H-chromen-2-one:

3-(2-bromoacetyl)-8-chloro-2H-chromen-2-one (~279 mg, 50%, 0.53 mmol) and 1-(2-(2-(dimethylamino)ethoxy)phenyl)thiourea (106 mg, 0.44 mmol) were reacted in ethanol at 80 °C. The product was then purified by filtration to provide 8-chloro-3-(2-(2-(2-(dimethylamino)ethoxy)phenylamino)thiazol-4-yl)-2H-chromen-2-one (60 mg, 31%) as a yellow solid. ESI-MS (EI^+ , m/z): 442.0 $[\text{M}+1]^+$; ^1H NMR (500 MHz, CF_3COOD): δ 3.64 (s, 6H), 4.27 (s, 2H), 5.02 (s, 2H), 7.65 (d, $J = 8.0$ Hz, 1H), 7.75 (t, $J = 8.0$ Hz, 1H), 7.94-7.99 (m, 2H), 8.12 (s, 1H), 8.14 (d, $J = 8.0$ Hz, 1H), 8.20 (d, $J = 7.5$ Hz, 1H), 8.33 (d, $J = 7.5$ Hz, 1H), 9.03 (s, 1H)

DBM-E-5 was prepared according to the procedure listed below and the synthetic scheme shown in **Scheme 6**.

Scheme 6:*Step 1: N-(3,5-dimethylphenylcarbamothioyl)benzamide:*

3,5-dimethylaniline (2.42 g, 20 mmol) and benzoyl isothiocyanate (4.24 g, 26 mmol) in acetonitrile were reacted at a temperature of from 0 °C to room temperature over 17 hours. The resulting mixture was then purified by filtration to provide *N*-(3,5-

dimethylphenylcarbamothioyl)benzamide (3.5 g, 61%) as a white solid. ESI-MS (EI^+ , m/z): 285.1 $[\text{M}+1]^+$.

Step 2: 1-(3,5-dimethylphenyl)thiourea:

N-(3,5-dimethylphenylcarbamothioyl)benzamide (3.5 g, 12.3mmol) and a solution of NaOMe in MeOH (4 mL, 30%) were mixed at room temperature for two hours. The resulting mixture was then purified by filtration to provide 1-(3,5-dimethylphenyl)thiourea (1.1 g, 51%) as a white solid. ESI-MS (EI^+ , m/z): 181.0 $[\text{M}+1]^+$.

Step 3: 8-chloro-3-(2-(3,5-dimethylphenylamino)thiazol-4-yl)-2H-chromen-2-one:

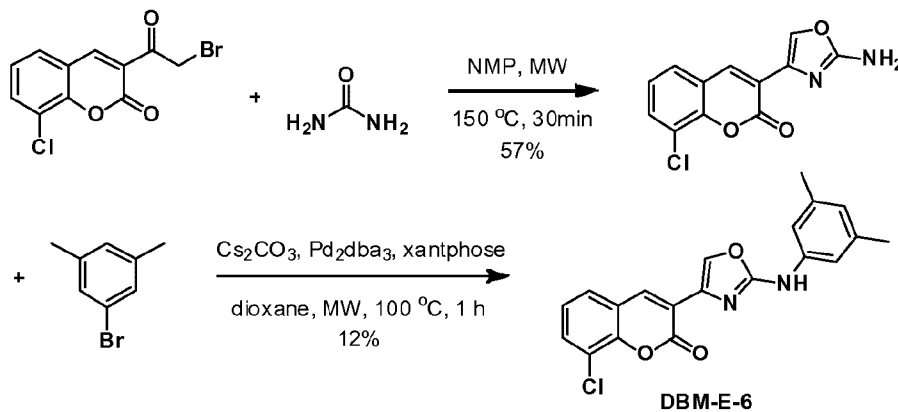
3-(2-bromoacetyl)-8-chloro-2H-chromen-2-one (~1 g, 50%, 1.67 mmol) and 1-(3,5-dimethylphenyl)thiourea (600 mg, 3.33mmol) were reacted in ethanol at 80 °C. The product was then purified by filtration to provide 8-chloro-3-(2-(3,5-dimethylphenylamino)thiazol-4-yl)-2H-chromen-2-one (500 mg, 78%) as a yellow solid. ESI-MS (EI^+ , m/z): 383.0 $[\text{M}+1]^+$;

Step 4: 8-chloro-3-(2-((3,5-dimethylphenyl)(methyl)amino)thiazol-4-yl)-2H-chromen-2-one:

To a solution of 8-chloro-3-(2-(3,5-dimethylphenylamino)thiazol-4-yl)-2H-chromen-2-one (150 mg, 0.39 mmol) in dry DMF (10mL) was added NaH (31 mg, 60%, 0.78mmol) at 0 °C. The mixture was then stirred at 0 °C for 15 min. MeI (56 mg, 0.39mmol) was added and the mixture was stirred at rt for 2 hrs. The reaction solution was quenched with saturated NH_4Cl solution, diluted with EtOAc (80 mL), washed with H_2O (2x) and brine (2x), dried (Na_2SO_4), filtered, and concentrated to give 8-chloro-3-(2-((3,5-dimethylphenyl)(methyl)amino)thiazol-4-yl)-2H-chromen-2-one (60 mg, 39%) as a yellow solid. ESI-MS (EI^+ , m/z): 397.0 $[\text{M}+1]^+$; ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 2.31 (s, 6H), 3.56 (s, 3H), 6.98 (s, 1H), 7.13 (s, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.63 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 7.5 Hz, 1H), 8.69 (s, 1H).

DBM-E-6 was prepared according to the procedure listed below and the synthetic scheme shown in **Scheme 7**.

Scheme 7:



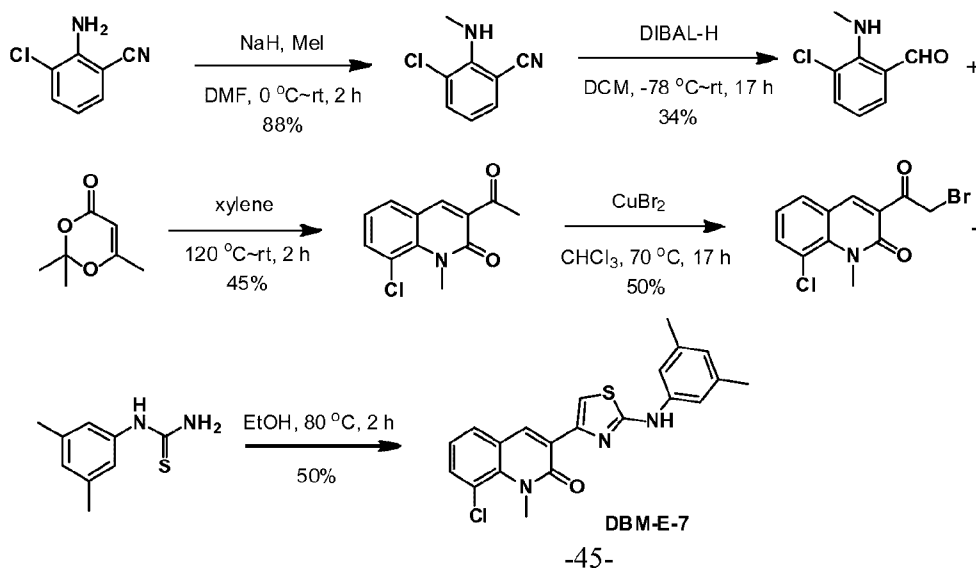
Step 1: 3-(2-aminoxazol-4-yl)-8-chloro-2H-chromen-2-one:

To an oven-dried microwave vial was added 3-(2-bromoacetyl)-8-chloro-2H-chromen-2-one (600 mg, 50%, 1 mmol), urea (90 mg, 1.5 eq), and dry NMP (2 mL). The vial was capped and purged with nitrogen. The reaction mixture was heated to 150 °C for 30 minutes under
 5 microwave irradiation. Then, the mixture was allowed to cool and purified by pre-HPLC to afford 3-(2-aminoxazol-4-yl)-8-chloro-2H-chromen-2-one (150 mg, 57%) as a pale yellow solid. ESI-MS (EI^+ , m/z): 263.0 $[\text{M}+1]^+$

Step 2: 8-chloro-3-(2-(3,5-dimethylphenylamino)oxazol-4-yl)-2H-chromen-2-one:

To an oven-dried microwave vial was added 3-(2-aminoxazol-4-yl)-8-chloro-2H-
 10 chromen-2-one (100 mg, 0.38 mmol), 1-bromo-3,5-dimethylbenzene (702 mg, 3.8 mmol), Cs_2CO_3 (249 mg, 0.76mmol), $\text{Pd}_2(\text{dba})_3$ (35 mg, 0.038mmol), xantphose (44mg, 0.076mmol), and dry dioxane (3 mL). The vial was capped and purged with nitrogen. The reaction mixture was heated to 100 °C for 1 hour under microwave irradiation. The mixture was allowed to cool and diluted with EtOAc (100mL), washed with H_2O (2x) and brine (2x), dried (Na_2SO_4),
 15 filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/PE=0~10%) to get a crude product. The crude product was purified by pre-HPLC to afford 8-chloro-3-(2-(3,5-dimethylphenylamino)-oxazol-4-yl)-2H-chromen-2-one (17 mg, 12%) as a yellow solid. ESI-MS (EI^+ , m/z): 367.1 $[\text{M}+1]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 2.30 (s, 6H), 6.64 (s, 1H), 7.34 (s, 1H), 7.41(t, $J = 8.0$ Hz, 2H), 7.77-7.79 (m, 1H), 7.95(d, $J = 7$ Hz, 1H),
 20 8.20 (s, 1H), 8.50 (s, 1H), 10.18 (s, 1H).

DBM-E-7 was prepared according to the procedure listed below and the synthetic scheme shown in **Scheme 8**.

Scheme 8:

Step 1: 3-chloro-2-(methylamino)benzotrile:

To a solution of 2-amino-3-chlorobenzotrile (5.0 g, 32.9 mmol) in dry DMF (60 mL) was added NaH (1.97 g, 60%, 49.3 mmol) at 0 °C. Then, the mixture was stirred at 0 °C for 15 min. MeI (4.67 g, 32.9 mmol) was added and the mixture was stirred at rt for 2 hrs. The reaction
5 solution was quenched with saturated NH₄Cl solution, diluted with EtOAc (200 mL), washed with H₂O (2x) and brine (2x), dried (Na₂SO₄), filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/PE=0~5%) to give 3-chloro-2-(methylamino)benzotrile (4.8 g, 88%) as a white solid. ESI-MS (EI⁺, *m/z*): 167.0 [M+1]⁺.

Step 2: 3-chloro-2-(methylamino)benzaldehyde:

To a solution of 3-chloro-2-(methylamino)benzotrile (4 g, 24 mmol) in dry DCM (50 mL) was added DIBAL-H (1M, 36 mL, 36mmol) at -78 °C. Then, the mixture was stirred at rt for 17 hrs. The reaction mixture was quenched with a saturated citric acid solution, diluted with DCM (150 mL), washed with H₂O (2x) and brine (2x), dried (Na₂SO₄), filtered, and
15 concentrated. The residue was purified by silica gel column chromatography (EtOAc/PE=0~3%) to give 3-chloro-2-(methylamino)benzaldehyde (1.4g, 34%) as a yellow oil. ESI-MS (EI⁺, *m/z*): 170.0 [M+1]⁺.

Step 3: 3-acetyl-8-chloro-1-methylquinolin-2(1H)-one:

A solution of 3-chloro-2-(methylamino)benzaldehyde (800mg, 4.7 mmol) in xylene (30 mL) at 120 °C was treated with 2,2,6-trimethyl-4H-1,3-dioxin-4-one (6.7 g, 47 mmol). The
20 reaction mixture was heated at 120 °C for 2 hrs and then cooled to rt. The solvent was removed and the residue was purified by silica gel column chromatography (EtOAc/PE=0~3%) to give 3-acetyl-8-chloro-1-methylquinolin-2(1H)-one (500mg, 45%) as a yellow solid. ESI-MS (EI⁺, *m/z*): 236.0 [M+1]⁺; ¹H NMR (500 MHz, DMSO-*d*₆): δ 2.61 (s, 3H), 3.86 (s, 3H), 7.31(t, *J* = 8 Hz, 1H), 7.79-7.81(m, 1H), 7.92-7.94(m, 1H), 8.41 (s, 1H).

Step 4: 3-(2-bromoacetyl)-8-chloro-1-methylquinolin-2(1H)-one:

To a solution of 3-acetyl-8-chloro-1-methylquinolin-2(1H)-one (432 mg, 1.84mmol) in CHCl₃ (20 mL) was added CuBr₂ (404 mg, 1.84 mmol) at rt. The mixture was stirred at 70 °C for 17 hrs. The solvent was evaporated, the crude product was diluted with EtOAc (100 mL), washed with water (2x), brine (2x), dried (Na₂SO₄), and concentrated to provide 3-(2-
30 bromoacetyl)-8-chloro-1-methylquinolin-2(1H)-one (~500 mg, 50%), which was used directly in the next step. ESI-MS (EI⁺, *m/z*): 313.9 [M+H]⁺.

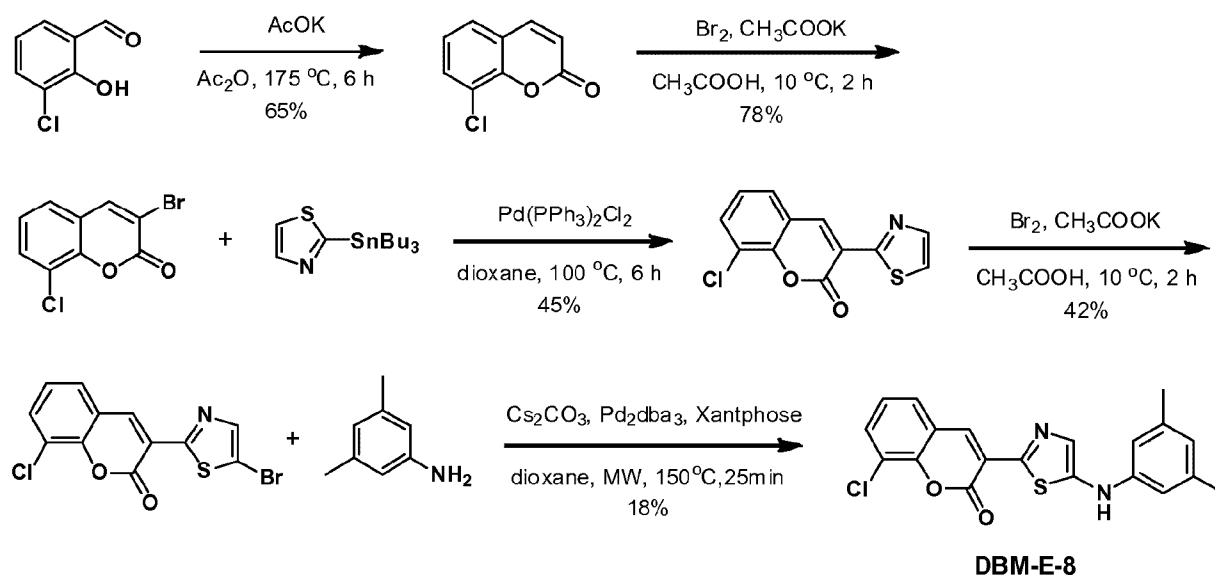
Step 5: 8-chloro-3-(2-(3,5-dimethylphenylamino)thiazol-4-yl)-1-methylquinolin-2(1H)-one:

3-(2-bromoacetyl)-8-chloro-1-methylquinolin-2(1H)-one (~200 mg, 50%, 0.32 mmol)

and 1-(3,5-dimethylphenyl)thiourea (115 mg, 0.64mmol) were reacted in ethanol at 80 °C. The product was then purified by filtration to provide 8-chloro-3-(2-(3,5-dimethylphenylamino)thiazol-4-yl)-1-methylquinolin-2(1H)-one (50 mg, 50%) as a yellow solid. ESI-MS (EI⁺, *m/z*): 396.0 [M+1]⁺; ¹HNMR (500 MHz, DMSO-*d*₆): δ 2.31 (s, 6H), 3.94 (s, 3H), 6.64 (s, 1H), 7.29-7.35(m, 3H), 7.69-7.71(m, 1H), 7.81(d, *J* = 7.0 Hz, 1H), 7.99 (s, 1H), 8.58 (s, 1H), 10.16 (s, 1H).

DBM-E-8 was prepared according to the procedure listed below and the synthetic scheme shown in **Scheme 9**.

Scheme 9:



Step 1: 8-chloro-2H-chromen-2-one:

A mixture of 3-chloro-2-hydroxybenzaldehyde (1 g, 6.4 mmol) and CH₃COOH (1.3 g, 12.8mmol) in Ac₂O (45 mL) was heated to 175 °C for 6 hrs. The mixture was then cooled down to rt. The precipitate which formed was collected to give 8-chloro-2H-chromen-2-one (1.02 g, 88%) as a brown solid. ESI-MS (EI⁺, *m/z*): 181.0 [M+1]⁺.

Step 2: 3-bromo-8-chloro-2H-chromen-2-one:

To a mixture of 8-chloro-2H-chromen-2-one (1 g, 5.56mmol) and CH₃COOK (1.09 g, 11.1 mmol) in CH₃COOH (30 mL) was added Br₂ (4.4 g, 27.8mmol). The mixture was stirred at 50 °C for 4 hrs. The reaction mixture was cooled to rt and poured into water (100 mL) and filtered to get a brown solid. The crude product was purified by silica gel column chromatography (EtOAc/PE=0~5%) to give 3-bromo-8-chloro-2H-chromen-2-one (640 mg, 45%) as a yellow solid. ESI-MS (EI⁺, *m/z*): 260.9 [M+1]⁺.

Step 3: 8-chloro-3-(thiazol-2-yl)-2H-chromen-2-one:

A mixture of 3-bromo-8-chloro-2H-chromen-2-one (620 mg, 2.4 mmol), 2-(tributylstannyl)thiazole (1.8 g, 4.8 mmol), and Pd(PPh₃)₄ (276 mg, 0.24 mmol) in dry dioxane (20 mL) was heated to 100 °C for 6 hrs. The reaction mixture was then cooled to rt and concentrated. The residue was purified by silica gel column chromatography (EtOAc/PE=0~30%) to give 8-chloro-3-(thiazol-2-yl)-2H-chromen-2-one (500 mg, 79%) as a yellow solid. ESI-MS (EI⁺, *m/z*): 264.0 [M+1]⁺.

Step 4: 3-(5-bromothiazol-2-yl)-8-chloro-2H-chromen-2-one:

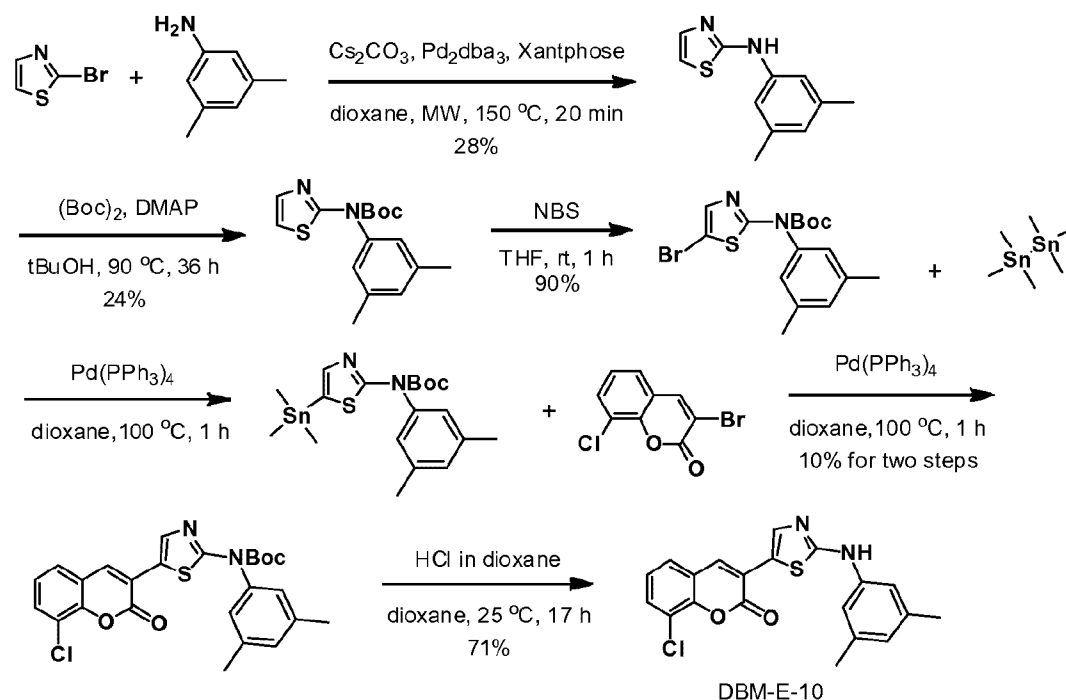
To a mixture of 8-chloro-3-(thiazol-2-yl)-2H-chromen-2-one (400 mg, 1.52 mmol) and CH₃COOK (447 mg, 4.56 mmol) in CH₃COOH (15ml) was added Br₂ (479 mg, 3.04 mmol). Then, the mixture was stirred at rt for 2 hrs. The reaction mixture was poured into water (100 mL) and filtered to get a brown solid. The crude product was purified by silica gel column chromatography (EtOAc/PE=0~20%) to give 3-(5-bromothiazol-2-yl)-8-chloro-2H-chromen-2-one (250 mg, 48%) as a yellow solid. ESI-MS (EI⁺, *m/z*): 342.0 [M+1]⁺.

Step 5: 8-chloro-3-(5-(3,5-dimethylphenylamino)thiazol-2-yl)-2H-chromen-2-one:

3-(5-bromothiazol-2-yl)-8-chloro-2H-chromen-2-one (100 mg, 0.3 mmol) and 3,5-dimethylaniline (182 mg, 1.5 mmol) were reacted in a microwave in the presence of Cs₂CO₃ (293 mg, 0.9 mmol), Pd₂(dba)₃ (21mg, 0.03 mmol.), xantphose (52mg, 0.09 mmol), and dioxane (2 mL) at 150°C for 25 minutes. The mixture was then purified by pre-HPLC to provide 8-chloro-3-(5-(3,5-dimethylphenylamino)thiazol-2-yl)-2H-chromen-2-one (25 mg, 22%) as a yellow solid. ESI-MS (EI⁺, *m/z*): 383.1 [M+1]⁺; ¹H NMR (500 MHz, DMSO-*d*₆): δ 2.25 (s, 6H), 6.56 (s, 1H), 6.74 (s, 2H), 7.43 (t, *J* = 8 Hz, 1H), 7.63 (s, 1H), 7.79-7.81 (m, 1H), 7.93-7.94 (m, 1H), 8.81 (s, 1H), 9.15 (s, 1H).

DBM-E-10 was prepared according to the procedure listed below and the synthetic scheme shown in **Scheme 10**.

Scheme 10:

Step 1: *N*-(3,5-dimethylphenyl)thiazol-2-amine:

2-Bromothiazole (3.26 g, 20 mmol), 3,5-dimethylaniline (3.6 g, 30 mmol) and *p*-toluenesulfonic acid (1.7 g, 10 mmol) were dissolved in *i*-propanol (50 mL). The mixture was stirred at 80 °C for 17 hrs. The reaction mixture was diluted with EtOAc (200mL), washed with H₂O (2x) and brine (2x), dried (Na₂SO₄), filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/PE=0~20%) to give *N*-(3,5-dimethylphenyl)thiazol-2-amine (1.1 g, 27%) as a white solid. ESI-MS (EI⁺, *m/z*): 205.0 [M+1]⁺.

Step 2: *tert*-butyl 3,5-dimethylphenyl(thiazol-2-yl)carbamate:

A mixture of *N*-(3,5-dimethylphenyl)thiazol-2-amine (1.02 g, 5 mmol), (Boc)₂O (5.45g, 25mmol) and DMAP (1.52g, 12.5mmol) in *t*-BuOH (20 mL) was heated to 80 °C for 36 hrs. The solvent was removed and the residue was purified by silica gel column chromatography (EtOAc/PE=0~5%) to give *tert*-butyl 3,5-dimethylphenyl(thiazol-2-yl)carbamate (360 mg, 24%) as a white solid. ESI-MS (EI⁺, *m/z*): 305.0 [M+1]⁺.

Step 3: *tert*-butyl 5-bromothiazol-2-yl(3,5-dimethylphenyl)carbamate:

To a mixture of *tert*-butyl 3,5-dimethylphenyl(thiazol-2-yl)carbamate (390 mg, 1.28 mmol) in THF (15mL) was added NBS (252 mg, 1.41mmol) at rt. Then the mixture was stirred at rt for 1 h. The solvent was removed and the residue was purified by silica gel column

chromatography (EtOAc/PE=0~5%) to give *tert*-butyl 5-bromothiazol-2-yl(3,5-dimethylphenyl)carbamate (445 mg, 90%) as a pale yellow solid. ESI-MS (EI^+ , m/z): 385.0 $[\text{M}+1]^+$.

Step 4: tert-butyl 3,5-dimethylphenyl(5-(trimethylstannyl)thiazol-2-yl)carbamate:

5 A mixture of *tert*-butyl 5-bromothiazol-2-yl(3,5-dimethylphenyl)carbamate (445mg, 1.17 mmol), 1,1,1,2,2,2-hexamethyldistannane (579 mg, 1.76 mmol), and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (83 mg, 0.12mmol) in dioxane (15mL) was stirred at 100 °C for 1 h. Then the mixture was cooled to rt and quenched with a saturated KF solution. The mixture was stirred at rt for 1 h, diluted with EtOAc (100 mL), washed with H_2O (2x) and brine (2x), dried (Na_2SO_4), filtered, and
10 concentrated. The crude product *tert*-butyl 3,5-dimethylphenyl(5-(trimethylstannyl)thiazol-2-yl)carbamate (~500 mg) was used directly in the next step. ESI-MS (EI^+ , m/z): 469.0 $[\text{M}+1]^+$.

Step5: tert-butyl-5-(8-chloro-2-oxo-2H-chromen-3-yl)thiazol-2-yl(3,5-dimethylphenyl)carbamate:

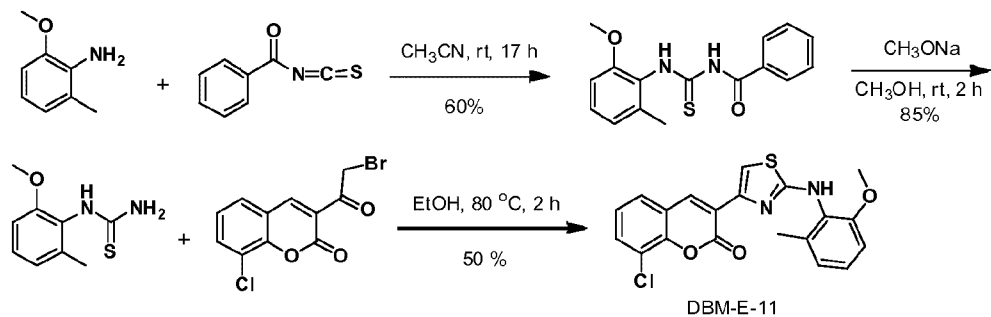
A mixture of *tert*-butyl 3,5-dimethylphenyl(5-(trimethylstannyl)thiazol-2-yl)
15 carbamate (~500 mg), 3-bromo-8-chloro-2H-chromen-2-one (300 mg, 1.16mmol), and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (83 mg, 0.12mmol) in dioxane (15mL) was stirred at 100 °C for 1 h. Then, the mixture was cooled to rt, diluted with EtOAc (100 mL), washed with H_2O (2x) and brine (2x), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by pre-HPLC to give *tert*-butyl-5-(8-chloro-2-oxo-2H-chromen-3-yl)thiazol-2-yl(3,5-dimethylphenyl)carbamate (30 mg,
20 10% for two steps) as a yellow solid. ESI-MS (EI^+ , m/z): 483.0 $[\text{M}+1]^+$.

Step5: 8-chloro-3-(2-(3,5-dimethylphenylamino)thiazol-5-yl)-2H-chromen-2-one:

To a solution of *tert*-butyl-5-(8-chloro-2-oxo-2H-chromen-3-yl)thiazol-2-yl(3,5-dimethylphenyl)carbamate (25 mg, 0.05mmol) in dioxane (2mL) was added a solution of HCl in dioxane (4M, 60mL). The mixture was stirred at 25 °C for 17 hrs. Then the solvent was
25 removed. The solid was washed with Et_2O to afford 8-chloro-3-(2-(3,5-dimethylphenylamino)thiazol-5-yl)-2H-chromen-2-one (17 mg, 71%) as a yellow solid. ESI-MS (EI^+ , m/z): 383.1 $[\text{M}+1]^+$; ^1H NMR (400 MHz, CF_3COOD): δ 2.91 (s, 6H), 7.58 (s, 2H), 7.71 (s, 1H), 7.96(t, $J = 8.0$ Hz, 1H), 8.16(d, $J = 8.0$ Hz, 1H), 8.30(d, $J = 8.0$ Hz, 1H), 8.61 (s, 1H), 8.82 (s, 1H).

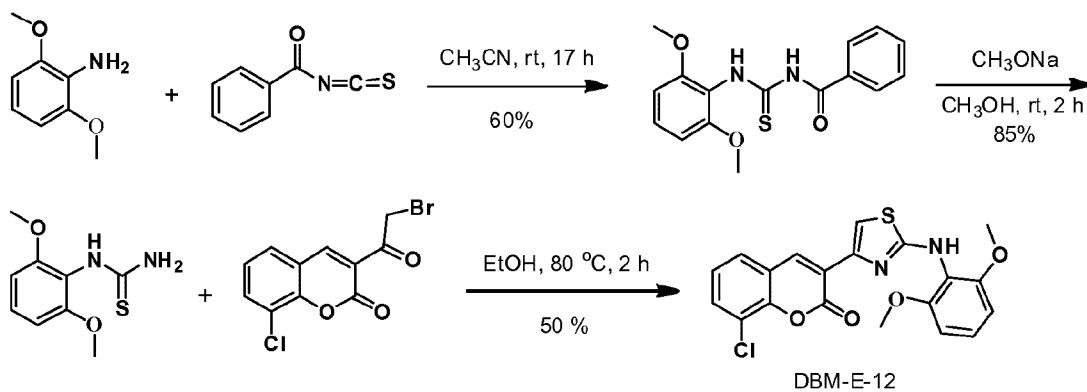
30 A synthetic scheme for **DBM-E-11** is shown in **Scheme 11**.

Scheme 11:



A synthetic scheme for **DBM-E-12** is shown in **Scheme 12**.

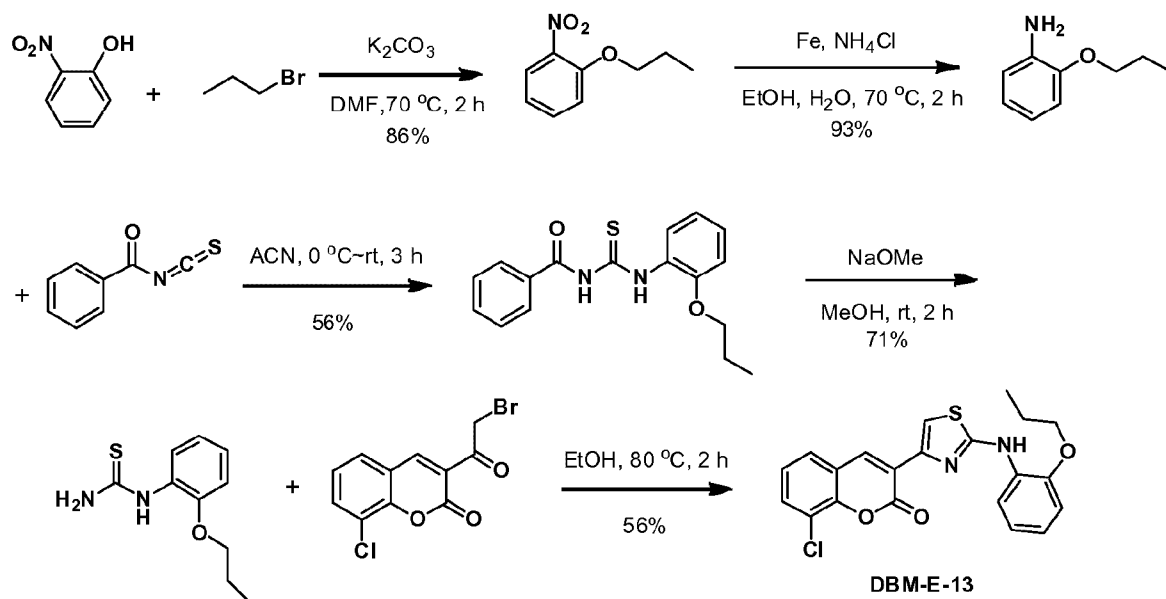
Scheme 12:



5

DBM-E-13 was prepared according to the procedure listed below and the synthetic scheme shown in **Scheme 13**.

Scheme 13:



10

Step 1: 1-nitro-2-propoxybenzene:

A mixture of 2-nitrophenol (3 g, 21.6 mmol), 1-bromopropane (3.9 g, 32.4 mmol), and K₂CO₃ (8.9 g, 64.8 mmol) in DMF (50 mL) was stirred at 70 °C for 2 hrs. The reaction mixture was cooled to rt, diluted with EtOAc (150 mL), washed with H₂O (2x) and brine (2x), dried (Na₂SO₄), filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/PE=0~3%) to give 1-nitro-2-propoxybenzene (3.36 g, 86%) as a yellow oil. ESI-MS (EI⁺, *m/z*): 182.0 [M+1]⁺.

Step 2: 2-propoxyaniline:

A mixture of 1-nitro-2-propoxybenzene (1.5 g, 8.3 mol), Fe (2.32 g, 41.5mmol), NH₄Cl (2.19 g, 41.5mmol) in EtOH (20mL) and H₂O (2 mL) was stirred at 90 °C for 2 hrs. The reaction mixture was filtered. The filtrate was concentrated and the residue was diluted with DCM (100mL), dried (Na₂SO₄), filtered, and concentrated to afford 2-propoxyaniline (1.16 g, 93%) as yellow oil. ESI-MS (EI⁺, *m/z*): 152.0 [M+1]⁺.

Step 3: N-(2-propoxyphenylcarbamothioyl)benzamide:

2-propoxyaniline (1.16 g, 7.68mmol) and benzoyl isothiocyanate (1.63 g, 10.0 mmol) were reacted in acetonitrile at a temperature of from 0 °C to room temperature over 3 hours. The mixture was then purified by filtration to provide *N*-(2-propoxyphenylcarbamothioyl)benzamide (1.36g, 56%) as a white solid. ESI-MS (EI⁺, *m/z*): 315.0 [M+1]⁺.

Step 4: 1-(2-propoxyphenyl)thiourea:

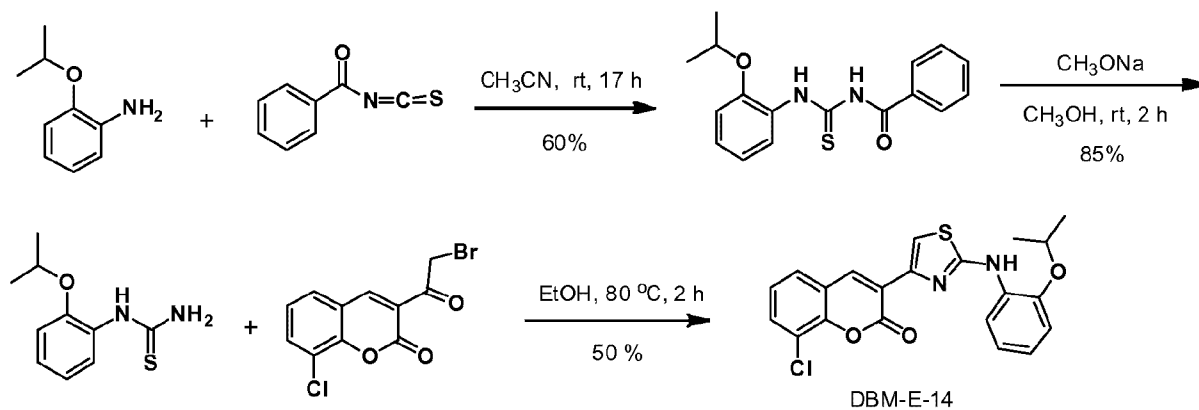
N-(2-propoxyphenylcarbamothioyl)benzamide (1.36 g, 4.3 mmol) was reacted with a solution of NaOMe in MeOH (4 mL, 30%). The resulting mixture was then purified by filtration to provide 1-(2-propoxyphenyl)thiourea (650 mg, 71%) as a white solid. ESI-MS (EI⁺, *m/z*): 211.0 [M+1]⁺.

Step 5: 8-chloro-3-(2-(2-propoxyphenylamino)thiazol-4-yl)-2H-chromen-2-one:

3-(2-bromoacetyl)-8-chloro-2H-chromen-2-one (~300 mg, 50%, 0.5 mmol) and 1-(2-propoxyphenyl)thiourea (158 mg, 0.75mmol) were reacted in ethanol at 80 °C. The product was then purified by filtration to provide 8-chloro-3-(2-(2-propoxyphenylamino)thiazol-4-yl)-2H-chromen-2-one (115 mg, 56%) as a yellow solid. ESI-MS (EI⁺, *m/z*): 413.0 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.99 (t, *J* = 7.2 Hz, 3H), 1.78-1.84 (m, 2H), 4.03 (t, *J* = 6.8 Hz, 2H), 7.01-7.05 (m, 3H), 7.39 (t, *J* = 8 Hz, 1H), 7.76-7.79 (m, 2H), 7.93 (d, *J* = 7.6 Hz, 1H), 8.41-8.44 (m, 1H), 8.64 (s, 1H), 9.49 (s, 1H).

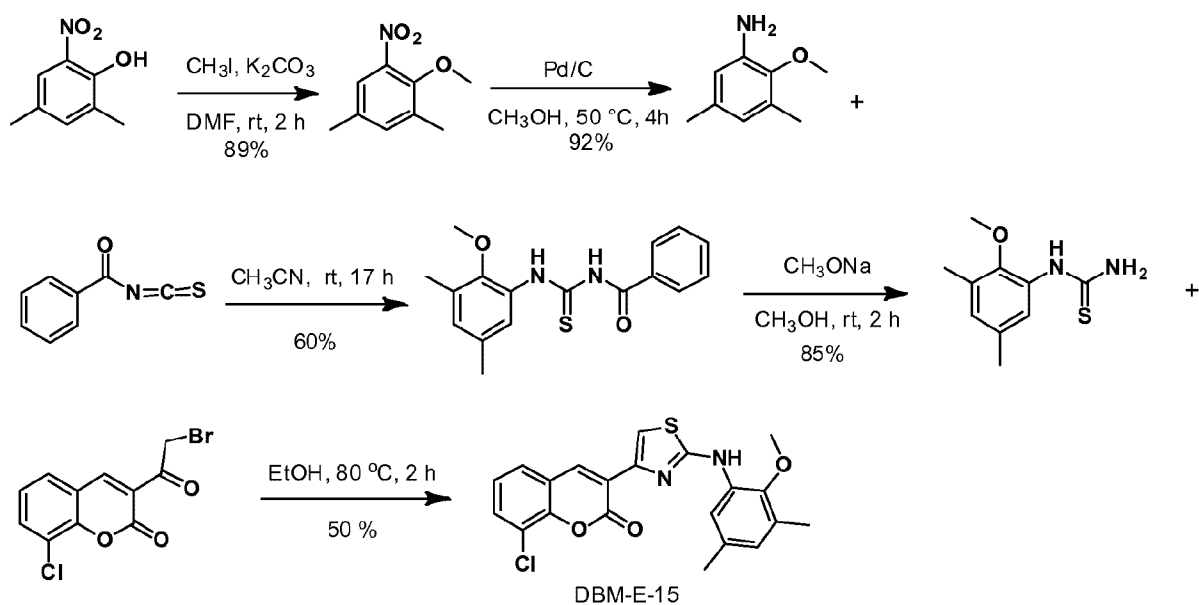
A synthetic scheme for **DBM-E-14** is shown in **Scheme 14**.

Scheme 14:



A synthetic scheme for **DBM-E-15** is shown in **Scheme 15**.

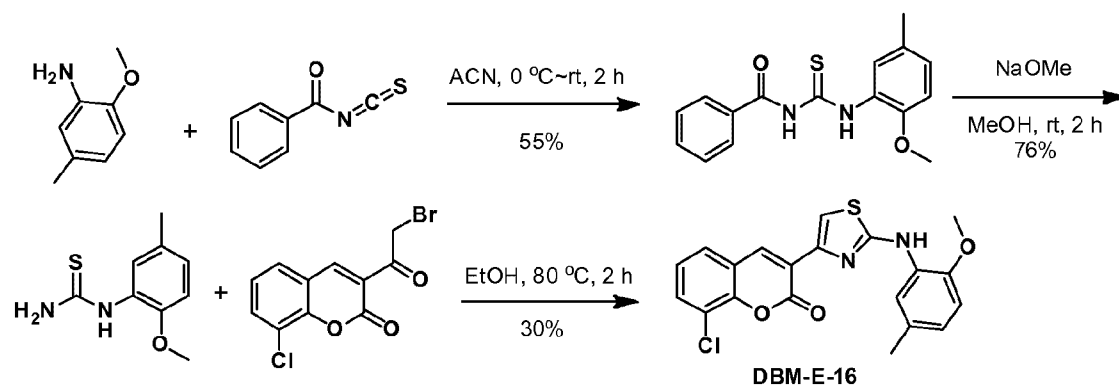
Scheme 15:



5

DBM-E-16 was prepared according to the procedure listed below and the synthetic scheme shown in **Scheme 16**.

Scheme 16:



Step 1: *N*-(2-methoxy-5-methylphenylcarbamoithioyl)benzamide:

2-methoxy-5-methylaniline (500 mg, 3.65 mmol) and benzoyl isothiocyanate (773 mg, 4.74 mmol) were reacted in acetonitrile at a temperature of from 0 °C to room temperature over 2 hours. The mixture was then purified by filtration to provide *N*-(2-methoxy-5-

5 methylphenylcarbamoithioyl)benzamide (600 mg, 55%) as a white solid. ESI-MS (EI⁺, *m/z*): 301.1 [M+1]⁺.

Step 2: 1-(2-methoxy-5-methylphenyl)thiourea:

N-(2-methoxy-5-methylphenylcarbamoithioyl)-benzamide (600 mg, 2 mmol) was reacted with a solution of NaOMe in MeOH (0.7 mL, 30%). The resulting mixture was then purified by

10 filtration to provide 1-(2-methoxy-5-methylphenyl)thiourea (300 mg, 76%) as a white solid. ESI-MS (EI⁺, *m/z*): 197.0 [M+1]⁺.

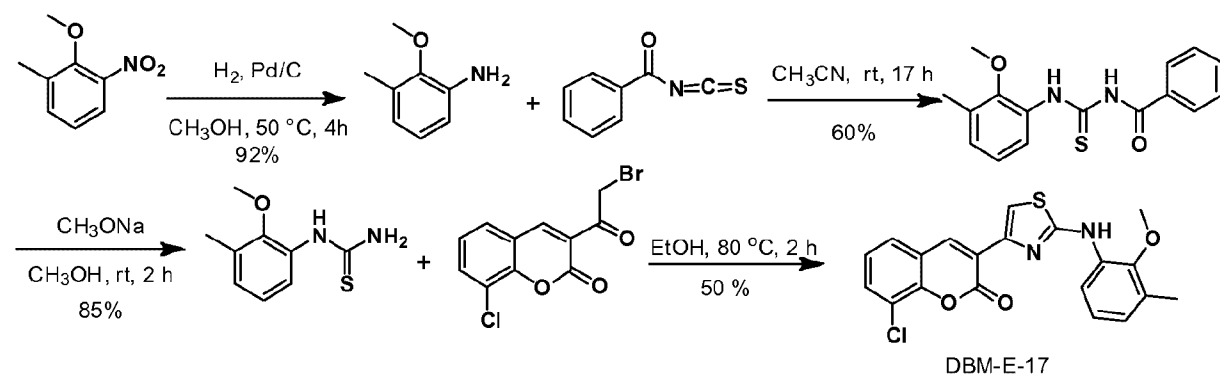
Step 3: 8-chloro-3-(2-(2-methoxy-5-methylphenylamino)thiazol-4-yl)-2H-chromen-2-one:

3-(2-bromoacetyl)-8-chloro-2H-chromen-2-one (~300 mg, 50%, 0.5 mmol) and 1-(2-methoxy-5-methylphenyl)thiourea (197 mg, 1 mmol) were reacted in ethanol at 80 °C. The

15 product was then purified by filtration to provide 8-chloro-3-(2-(2-methoxy-5-methylphenylamino)thiazol-4-yl)-2H-chromen-2-one (60 mg, 30%) as a yellow solid. ESI-MS (EI⁺, *m/z*): 399.0 [M+1]⁺; ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.36 (s, 3H), 3.84 (s, 3H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.75-7.77 (m, 2H), 7.83 (d, *J* = 7.6 Hz, 1H), 8.29 (s, 1H), 8.58 (s, 1H), 9.62 (s, 1H).

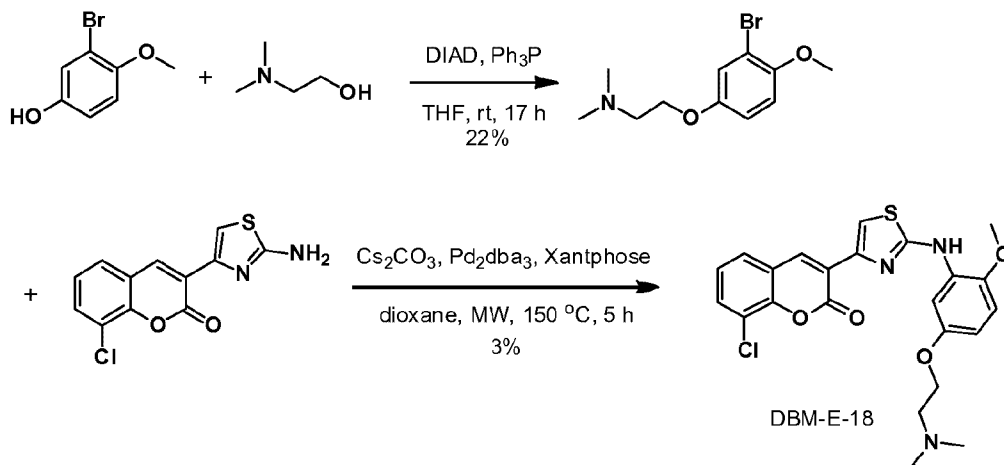
20 A synthetic scheme for **DBM-E-17** is shown in **Scheme 17**.

Scheme 17:



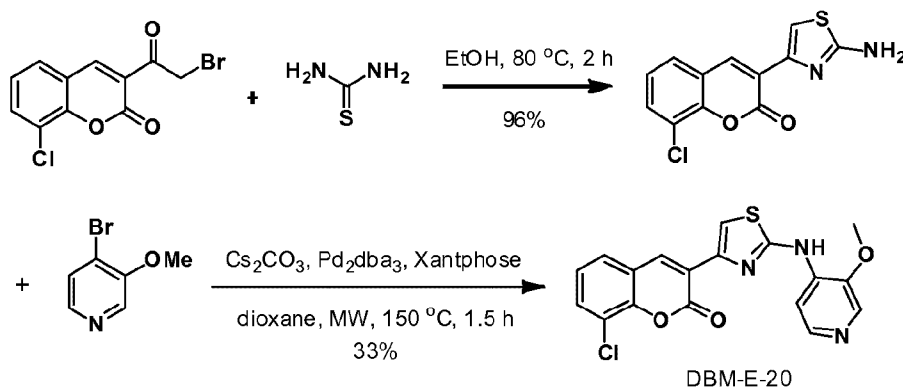
A synthetic scheme for **DBM-E-18** is shown in **Scheme 18**.

Scheme 18:



DBM-E-20 was prepared according to the procedure listed below and the synthetic scheme shown in Scheme 19.

5 Scheme 19:



Step 1: 3-(2-aminothiazol-4-yl)-8-chloro-2H-chromen-2-one:

A mixture of 3-(2-bromoacetyl)-8-chloro-2H-chromen-2-one (~1.4 g, 50%, 2.33 mmol) and thiourea (355 mg, 4.67 mmol) in EtOH (25 mL) was stirred at 80 °C for 2 hrs. The precipitate which formed was collected to give 3-(2-aminothiazol-4-yl)-8-chloro-2H-chromen-2-one (630 mg, 96%) as a yellow solid. ESI-MS (EI^+ , m/z): 279.0 $[\text{M}+1]^+$;

Step 2: 8-chloro-3-(2-(3-methoxypyridin-4-ylamino)thiazol-4-yl)-2H-chromen-2-one:

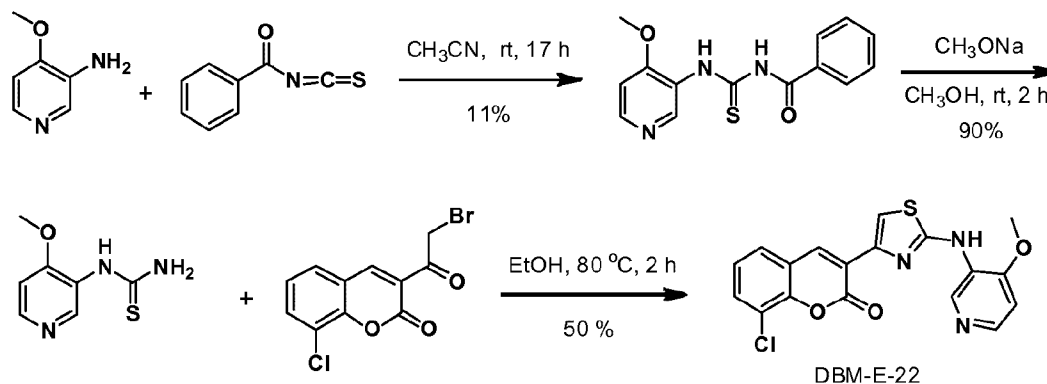
3-(2-aminothiazol-4-yl)-8-chloro-2H-chromen-2-one (100 mg, 0.36 mmol) and 4-bromo-3-methoxypyridine hydrochloride (80 mg, 0.36 mmol) were reacted in a microwave in the presence of Cs_2CO_3 (351 mg, 1.08 mmol), $\text{Pd}_2(\text{dba})_3$ (25 mg, 0.036 mmol), xantphos (41 mg, 0.072 mmol), and dry dioxane (2 mL) at 150 °C for 1.5 hr. The mixture was then purified by pre-HPLC to provide 8-chloro-3-(2-(3-methoxypyridin-4-ylamino)thiazol-4-yl)-2H-chromen-2-one (45 mg, 33%) as a yellow solid. ESI-MS (EI^+ , m/z): 386.1 $[\text{M}+1]^+$; $^1\text{H NMR}$ (400 MHz, DMSO-

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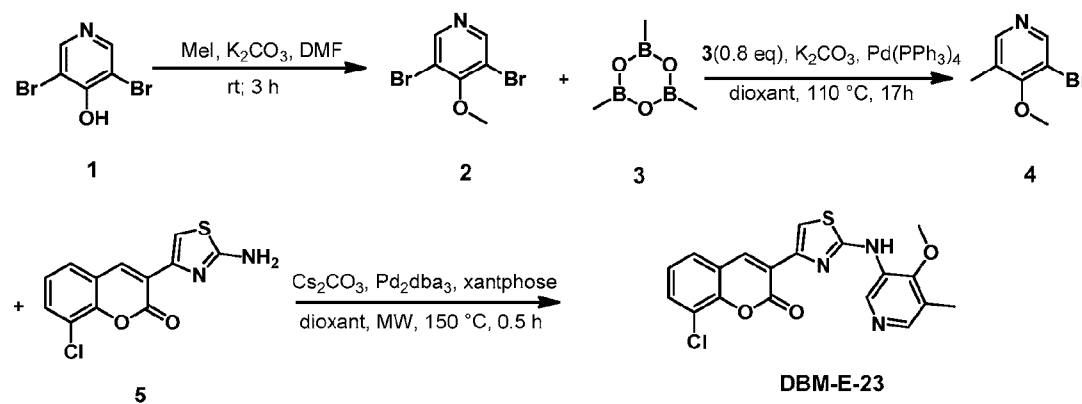
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d_6): δ 3.98 (s, 3H), 7.42 (t, $J = 8$ Hz, 1H), 7.77-7.79 (m, 1H), 7.92 (s, 1H), 8.00 (d, $J = 7$ Hz, 1H), 8.21-8.26 (m, 2H), 8.68-8.74 (m, 2H), 10.27 (s, 1H).

A synthetic scheme for **DBM-E-22** is shown in **Scheme 20**.

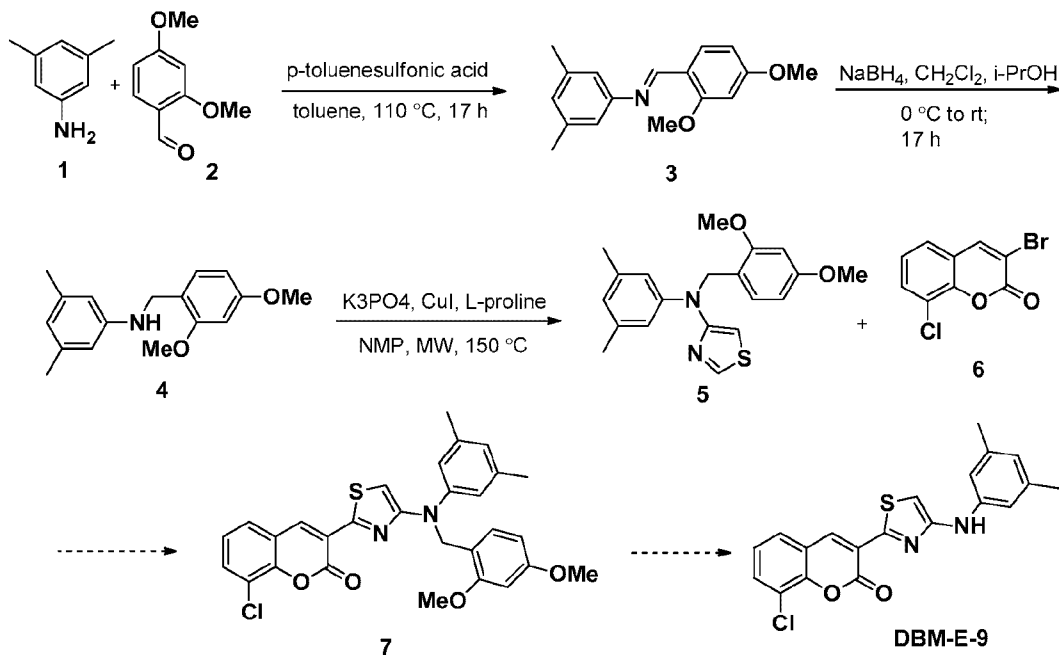
Scheme 20:

A synthetic scheme for **DBM-E-23** is shown in **Scheme 21**.

Scheme 21:

A synthetic scheme for **DBM-E-9** is shown in **Scheme 22**.

15

Scheme 22:**Example 2: Assay Design**

The compounds described herein are effective for inhibiting cellular proliferation in hyperproliferative cell types. To study the effects of these compounds, an assay was developed to differentiate the effects of the compounds on proliferating versus confluent cells. The assay design generates a proliferating density 24 hours after seeding and provides a 3-day active cell growth/doubling window in which to gauge the anti-proliferative effect of the compounds described herein. For studies of proliferating cells, a seeding density of 1,000 – 2,000 human hyperproliferative cells per well of 96-well full area well plates was shown to provide a linearity in the doubling of cell number across a 3-day (72 hour) active cell growth/doubling period after a 24-hour seeding period in which cells attach before starting to proliferate. In this 3-day growth window, cell number increases with daily doublings across the 72-hour period (see **Figure 1**).

In each assay design, compounds were added at the 24-hour timepoint after cell seeding. The effect of the compounds, relative to vehicle control and to VelCade (a proteasome inhibitor approved in the U.S. for treating relapsed multiple myeloma and mantle cell lymphoma) as a positive control, was assessed across the 3-day growth window for proliferating cells and on an already near confluent culture of cells for the same time period. Normal cells were handled in the same manner, with some adjustment of seeding density needed in select cases. This assay design holds for the data series presented below.

Cell number at the end of the assay was determined using the CELLTITER-GLO Luminescent Cell Viability Assay (Promega; Madison, WI). The CELLTITER-GLO Luminescent Cell Viability Assay is a homogeneous method of determining the number of viable cells in culture based on quantitation of the ATP present, an indicator of metabolically active cells. IC₅₀ values were calculated. Cell number (number of cells per well) was converted to the % of DMSO matched controls. Each measurement was performed in triplicate. Typical dosage ranges tested were from 250 picomolar to 50 micromolar.

Example 3:

The compounds described herein demonstrate nanomolar (nM) selectivity in causing growth arrest of hyperproliferative cancer cells but is without effect on growth and viability of 'normal' non-cancerous human cells until mid-micromolar (μ M) concentrations. Two early analogs, **Compound DBM 227** and **Compound DBM 228**, have been evaluated and validated externally by the NCI Developmental Therapeutics Program where they demonstrate nM potency with an average GI₅₀ of 250nM in the NCI-60 cell panel (22 cell lines had GI₅₀ values \leq 100nM). For example, **Compound DBM-228** was profiled on the NCI 60 human cancer cell line panel (see Table 1). GI₅₀ means the growth inhibition of 50%, and represents the drug concentration resulting in a 50% reduction in the net cytosolic ATP increase (as measured by CELLTITER-GLO[®] (Promega, Madison, WI)) in control cells during the drug incubation. TGI means the drug concentration resulting in total growth inhibition or "cytostasis." LC₅₀ is the concentration of drug resulting in a 50% reduction in the measured cytosolic ATP at the end of the drug treatment as compared to that at the beginning, indicating a net loss of cells following treatment (cytotoxicity).

Table 1:

Panel and Cell Lines	GI ₅₀	TGI	LC ₅₀
<i>Leukemia Lines</i>			
CCRF-CEM	177 nM	15.4 μ M	>100 μ M
HL-60	34 nM	137 nM	825 nM
K-562	43 nM	16.1 μ M	>100 μ M
MOLT-4	168 nM	17.8 μ M	>100 μ M
RPMI-8226	238 nM	43.9 μ M	>100 μ M
<i>Non-Small Cell Lung Cancer Lines</i>			
A549	97 nM	22.6 μ M	>100 μ M
HOP-62	537 nM	44.8 μ M	>100 μ M
HOP-92	1.45 μ M	24.7 μ M	>100 μ M
NCI-H226	11.2 μ M	37.2 μ M	>100 μ M
NCI-H23	504 nM	15.8 μ M	63.1 μ M

NCI-H322M	672 nM	25.9 uM	93.3 uM
NCI-H460	91.2 nM	14.2 uM	>100 uM
NCI-H522	24.7 nM	94 nM	>100 uM
<i>Colon Cancer Lines</i>			
COLO 205	337 nM	1.8 uM	>100 uM
HCC-2998	1.05 uM	16.5 uM	>100 uM
HCT-116	79.5 nM	10 uM	>100 uM
HCT-15	128 nM	17.3 uM	>100 uM
HT29	308 nM	1.6 uM	24.7 uM
KM12	70.5 nM	13.4 uM	>100 uM
SW-620	64 nM	>100 uM	>100 uM
<i>CNS Cancer Lines</i>			
SF-268	770 nM	55.3 uM	>100 uM
SF-295	42.4 nM	1.49 uM	41.5 uM
SF-539	109 nM	850 nM	29.8 uM
SNB-19	182 nM	35 uM	>100 uM
SNB-75	48.1 nM	ND	>100 uM
U251	46.8 nM	10.6 uM	35.7 uM
<i>Melanoma Lines</i>			
LOX IMVI	900 nM	50.8 uM	>100 uM
MALME-3M	16.8 uM	49.6 uM	>100 uM
M14	70.8 nM	ND	49.9 uM
MDA-MB-435	23.1 nM	67.9 nM	69.5 uM
SK-MEL-2	86 nM	28.4 uM	99.5 uM
SK-MEL-28	88.9 nM	31 uM	99.3 uM
SK-MEL-5	76.8 nM	2.3 uM	26.8 uM
UACC-257	ND	33.7 uM	>100 uM
UACC-62	51.1 nM	28.2 uM	>100 uM
<i>Ovarian Cancer Lines</i>			
IGROV1	1.23 uM	23.4 uM	>100 uM
OVCAR-3	45.6 nM	322 nM	24.2 uM
OVCAR-4	1.35 uM	25 uM	>100 uM
OVCAR-5	592 nM	15.7 uM	51.9 uM
OVCAR-8	310 nM	13.2 uM	>100 uM
NCI/ADR-RES	45.9 nM	327 nM	>100 uM
SK-OV-3	410 nM	22 uM	>100 uM
<i>Renal Cancer Lines</i>			
786-0	709 nM	15.9 uM	89.4 uM
A498	35.4 nM	4.42 uM	>100 uM
ACHN	1.49 uM	15.9 uM	42.7 uM
CAKI-1	115 nM	27.9 uM	>100 uM
RXF 393	218 nM	15.2 uM	52.6 uM
SN12C	526 nM	>100 uM	>100 uM
TK-10	10 uM	23.5 uM	55 uM

UO-31	1.46 uM	43 uM	>100 uM
<i>Prostate Cancer Lines</i>			
PC-3	270 nM	36 uM	>100 uM
DU-145	356 nM	5.31 uM	41 uM
<i>Breast Cancer Lines</i>			
MCF7	54.5 nM	>100 uM	>100 uM
MDA-MB-231	1.37 uM	12 uM	>100 uM
HS 578T	13.7 uM	>100 uM	>100 uM
BT-549	239 nM	12.3 uM	>100 uM
T-47D	ND	55.9 uM	>100 uM
MDA-MB-468	47.1 nM	800 nM	60.9 uM
Complementary DBM In Vitro Profiling Data			
	<u>GI50</u>	<u>TGI</u>	<u>LC50</u>
<i>CNS Cancer Lines</i>			
T98G	467 nM	3.97 uM	17.6 uM
U251MG	197 nM	>30 uM	>30 uM
U118MG	2.71 uM	7.85 uM	>30 uM
<i>Hematologic Cancer Lines</i>			
ARH-77	154 nM	339 nM	>30 uM
RPMI-8826	271 nM	312 nM	>30 uM
U266	79.6 nM	116 nM	161 nM
<i>Ovarian Cancer Lines</i>			
SK-OV-3	845 nM	>30 uM	>30 uM
<i>Renal Cancer Lines</i>			
CAKI-1	142 nM	1.92 uM	5.21 uM
<i>Hypopharyngeal Cancer Lines</i>			
FaDu	1.4 uM	8.74 uM	27.5 uM

Example 4: Effect of Compound DBM 228 on Human Hyperproliferative Cell Platforms

The compounds as described herein were tested on primary human ADPKD cystic epithelial cell lines as well as two common cancer cell lines from the prostate (ARCaP-M) and kidney (CAKI-1). See **Figure 2**. The nanomolar ranges generates a cytostatic CRC where the cells are growth arrested but not killed. At and around the 1 micromolar dose in this extended 12-point CRC, there is a cytostatic plateau. At higher mid-micromolar concentrations, there is a cytotoxic effect.

Example 5: Effect of Compound DBM 101 on Proliferating versus Confluent Human Cystic ADPKD and Non-Cystic Renal Epithelial Cells *In Vitro*

The compounds as described herein were tested on confluent cystic ADPKD cells, proliferating cystic ADPKD cells, confluent normal renal cells, and proliferating normal renal cells. See **Figure 3**.

As shown in **Figure 3**, the cytostatic effects of the compounds described herein are selective for hyperproliferative ‘diseased’ cells at potent nanomolar doses. In sharp contrast, confluent diseased cells and proliferating and confluent normal cells were only partially affected and at mid-micromolar doses.

5 **Example 6: Potency and Efficiency of Compounds**

The compounds described herein demonstrate significant potency and efficacy (1 μ M GI₅₀). For a typical screening experiment to identify the compounds, cells were seeded into 96- or 384-well microtiter plates at plating densities pre-determined for each cell line to ensure drug exposure occurs during the proliferative phase well before confluency is reached. After seeding, cells were incubated for 24h prior to addition of experimental drugs. After 24h, a test plate was assayed (CellTiterGlo – measurement of cytosolic ATP) to determine a baseline measurement of the cell population for each cell line at the time of drug addition. Experimental drugs were then added and cells were cultured for a 48h drug exposure window. After 48h, cells were assayed and three dose-response parameters were calculated for each experimental agent: (1) growth inhibition of 50% (GI₅₀) is the drug concentration resulting in a 50% reduction in the net cytosolic ATP increase (as measured by CellTiterGlo) in control cells during the drug incubation, (2) the drug concentration resulting in total growth inhibition (TGI) or “cytostasis”, and (3) LC₅₀ or the concentration of drug resulting in a 50% reduction in the measured cytosolic ATP at the end of the drug treatment as compared to that at the beginning indicating a net loss of cells following treatment (“cytotoxicity”). Values were calculated for each of these three parameters if the level of activity was reached; however, if the effect was not reached or was exceeded, the value for that parameter was expressed as greater or less than the maximum or minimum concentration tested. Results are shown in **Figure 4** and **Table 2**.

Table 2:

nM	DBM 227	DBM 228	DBM 308	DBM 318	DBM 701	DBM 707	DBM 717	DBM 328
GI ₅₀	137	160	166	133	122	131	135	2106
TGI	404	271	247	164	153	183	232	>4,000
LC ₅₀	>4,000	>4,000	>4,000	226	193	544	>4,000	>4,000

25

As demonstrated in **Figure 4**, **Compounds DBM 308, DBM 318, DBM 701, DBM 707, and DBM 715** display significant efficacy and potency. Furthermore, these compounds were designed to remove problematic functional groups which may have hampered successful drug development. A dramatic difference in effect was observed when primary normal human cells

(i.e., respiratory and renal epithelial cells, dermal keratinocytes, liver hepatocytes, and brain astrocytes) were treated in parallel with these anti-proliferative compounds. The cytostatic effect was not observed in the nM range with any of the best in-class analogs and did not emerge until low μM ; cytotoxicity did not occur until the mid-to-high μM range. Given that the most potent analogs have an average GI_{50} of ~ 250 nM across the NCI-60 panel, there is at least a 2-log separation in effect, or selectivity, on these hyperproliferative cancer cells versus 'normal' human cells.

Example 7: Concentration-Response Effects of Compounds

The concentration-response effects of **Compound DBM 228**, **Compound DBM 308**, **Compound DBM 101**, and **Compound DBM 328** were determined in primary cultures derived as 'clones' from cystic versus non-cystic kidney tissue. CRC graphs, IC_{50} values, and the percent maximum inhibition versus lowest doses without effect were calculated with GraphPad Prism software. **Compound DBM 308** emerged as a potent and effective analog in this 72 hour treatment and in terms of cytostatic effect. There was also a marked separation in effect between hyperproliferative PKD cells (**Figure 5A** and **Table 3**) and WT cells (**Figure 5B** and **Table 4**).

Table 3:

Drug	IC_{50} (μM)	Max inhibition
001-2 (DBM 101)	7.2	77 %
N828 (DBM 308)	0.69	61 %
3-8Cl (DBM 308)	0.54	84 %
3-8COOH (DBM 328)	78	48 %

Table 4:

Drug	IC_{50} (μM)	Max inhibition
001-2 (DBM 101)	> 100	48 %
N828 (DBM 308)	> 100	49 %
3-8Cl (DBM 308)	> 100	52 %
3-8COOH (DBM 328)	> 100	28 %

Example 8: Effects of Compounds on the Growth of Primary Human Idiopathic Pulmonary Fibrosis Myfibroblasts *In Vitro*

The anti-proliferative effects of **Compounds DBM 228**, **DBM 308**, **DBM 318**, **DBM 701**, **DBM 707**, **DBM 715**, and **DBM 328** were determined on human idiopathic pulmonary fibrosis myofibroblasts. Compound DBM 328 served as a negative control and was without effect throughout the CRC. The results are shown in **Figure 6**.

Example 9: Effects of Compound DBM 701 on the Growth of Primary Human Idiopathic Pulmonary Fibrosis Myfibroblasts *In Vitro* versus Primary Human COPD Fibroblasts

The separation in effect of **Compound DBM 701** on the growth of primary human idiopathic pulmonary fibrosis (IPF) myofibroblasts was determined and compared to that of primary human COPD fibroblasts. The results are shown in **Figure 7** and **Table 5**. There was less separation in effect between IPF hyperproliferative myofibroblasts and fibroblasts isolated from COPD lungs; however, a significant separation was observed.

Table 5:

	GI₅₀ (μM)	TGI (μM)	LC₅₀ (μM)
IPF	0.109	0.450	> 30
COPD	0.318	5.9	> 30

The 'double' CRC was observed with **Compound DBM 701** on the growth of primary human idiopathic pulmonary fibrosis (IPF) myofibroblasts. Growth inhibition and cytostasis was observed in the nanomolar range up to 1 micromolar and cytotoxicity was starting to emerge in the micromolar range for **Compound DBM 701** (**Figure 8**).

Example 10: *In Vitro* Anti-Proliferative Efficacy against Multi-Drug Resistant Cancer

A major limitation with the anti-mitotic drugs in particular and in conventional chemotherapeutics in general, is their susceptibility to cellular mechanisms of adaptive/intrinsic multi-drug resistance (i.e., MDR efflux pumps such as p-glycoprotein, MRP1). The compounds described herein, however, including **Compound DBM 227** and **Compound DBM 228**, demonstrated superior potency in the NCI-ADR/RES cell line (100 nM and 44.5 nM, respectively). This cell line expresses high levels of MDR1 and P-glycoprotein and represents a good model for profiling compounds in an *in vitro* cell model of cancer multi-drug resistance. In drug-responsive cells found within the NCI-60 panel, agents such as paclitaxel and vincristine demonstrate potent cytotoxicity with GI₅₀ values often in the range of 1-10 nM. However, in the multi-drug resistant NCI-ADR/RES cell line, the potency of these common drugs is significantly right-shifted, whereas **Compound DBM 228** remained potent (**Figure 9**). The compound also displayed significant potency in the OVCAR-3 and SK-OV-3 cell lines (50 nM and 330 nM GI₅₀, respectively) which are known to demonstrate resistance to several clinically relevant drugs including adriamycin, melphalan and cisplatin. Thus, the compounds described herein can be effective in treating multi-drug resistant cancer.

Example 11: Dose-dependent Growth Arrest to Cytotoxic Effect on Primary Human Glioblastoma Multiforme (GBM) Cells

The compounds described herein are much more potent than known first-line anti-cancer drugs, such as temozolomide (TMZ) which was only cytotoxic and at high micromolar doses.

5 As shown in **Figure 10**, **Compound DBM 308** demonstrates a dose-dependent growth arrest to cytotoxic effect on primary human glioblastoma multiforme (GBM) cells grown *in vitro* on 3D neurospheres. **Compound DBM 308** has a cytostatic effect at nanomolar doses and an equivalent cytotoxic effect to TMZ (but at 3 micromolar versus 500 micromolar). Data are expressed as mean \pm SEM and represent at least two independent experiments with sample
10 replicates.

Example 12: Cell Cycle Arrest

Cell cycle analysis was performed on U251-MG cells to determine at what point in the cell cycle the compounds described herein were acting. U251MG glioblastoma cells were treated for 24h with increasing concentrations of **Compound DBM 228**. Propidium iodide-
15 based cell cycle analysis revealed G2/M arrest (see **Figure 11A** and **Table 6**).

Table 6:

	Control (DMSO)	40 nM	100 nM	400 nM
Pre-G₀/G₁	1.7 %	3.2 %	13.6 %	43.1 %
G₀/G₁	54.1 %	52.2 %	19.7 %	1.8 %
S	13.3 %	14.4 %	25.6 %	5.8 %
G₂/M	30.9 %	30.2 %	41.1 %	49.3 %

Table 6 shows the percentage of cells identified in different phases of the cell cycle. Increased percentages of cells were observed in G2/M phase, indicating G2/M phase block. However, at
20 higher nM doses, the cells appear to progress toward apoptosis and programmed cell death, given the higher % of cells in pre-G0/G1.

Following 24 hours of treatment with **Compound DBM 228**, **Compound DBM 318**, and **Compound DBM 328**, caspase 3/7 activation in U251MG cells was determined. The detection of caspase 3/7 activation in U251MG cells indicates activation of apoptosis. The
25 results are shown in **Figure 11B**. Tubulin polymerization was determined for **Compounds DBM 227**, **DBM 228**, **DBM 308**, **DBM 318**, **DBM 701**, **DBM 707**, **DBM 715**, paclitaxel, vincristine, and negative control **Compound DBM 328**. Biochemical tubulin polymerization was modestly inhibited by **Compounds DBM 227**, **DBM 228**, **DBM 308**, **DBM 318**, **DBM 701**, **DBM 707**, and **DBM 715**. Paclitaxel served as polymerization enhancer control and

vincristine served as polymerization inhibitor control. The negative control, **DBM 328**, also inhibited microtubule polymerization.

Example 13: Intracellular Signaling Molecule Phospho-Array in Drug-treated versus Vehicle-treated Human Hyperproliferative GBM Cancer Cells.

5 An intracellular signaling molecule phospho-array was performed in compound-treated human hyperproliferative GBM cancer cells and in vehicle-treated human hyperproliferative GBM cancer cells. The tested compounds included **Compound DBM 228 (002-N8-28)**, **Compound DBM 328 (003-8COOH)**, and **Compound DBM 308 (003-8CI)**. DMSO served as the vehicle control. The results are shown in **Figure 12**. The numbers reflect pairs of spots in the typical dot blots that correspond to major kinases and other signaling proteins. **Compound DBM 328 (003-8COOH)** is a negative control for this array experiment to complement the DMSO vehicle control. A dose-response effect is provided for **Compound DBM 228 (002-N8-28)** for potentiation of c-Jun phosphorylation (see top right panel of **Figure 12**) as well as the time-dependence of the effect requiring 24 hours (see bottom right panel of **Figure 12**).

10 **Example 14: Vimentin Phosphorylation and Disassembly in Human Hyperproliferative Diseases**

Vimentins are a class of intermediate filaments that are widely expressed in a variety of cultured cells, including mesenchymal and tumor cells. They constitute part of the cytoskeleton's scaffolding network, where their roles include maintenance of cell shape, division, migration, secretion, signaling molecule distribution, wound healing, and smooth muscle force development. The intracellular organization of filamentous vimentin networks is regulated by phosphorylation events by a series of protein kinases and phosphatases.

20 In particular, vimentin phosphorylation has a role in regulating spatial reorganization via disassembly of vimentin filaments *in vitro*. Disassembly of vimentin filaments also leads to an increase in single 'activated' subunits, which signal caspase-dependent apoptotic events.

Vimentin represents the most common intermediate filament present in mitosis, where hyperphosphorylation of vimentin is observed. For example, phosphorylation of vimentin at specific serine residues has been demonstrated to occur at the cleavage furrow during cytokinesis.

30 Specific kinases and phosphatases are implicated in vimentin regulation. For example, P21-activated kinases and cyclin dependent kinases (cdk) regulate vimentin at S56. In addition, Cdk5 mediates vimentin phosphorylation at Ser-56, where vimentin participates in GTP-induced secretion by neutrophils.

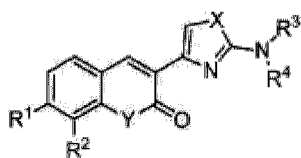
A custom, high sensitivity and comprehensive proteomics study was performed to analyze the effect of **Compound DBM 308** on vimentin. Vehicle and **Compound DBM 328** (an inactive analog) controls were performed in parallel. The proteomics data showed a 24.22 fold up-regulation in vimentin phosphorylated at a critical serine residue 56. The DMSO vehicle control was 1.0 and the inactive analog **Compound DBM 308** control was 1.4 (P=0.0006 – most significant change in the data – 99% of proteins in the proteomics array were unaffected). The proteomics data revealed that several kinases, such as Cdk5, were differentially regulated in **Compound DBM 308** treated cells versus the controls.

10

15

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A compound of the following formula for treating a hyperproliferative disease in a subject:



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is hydrogen, halogen, substituted or unsubstituted amino, or substituted or unsubstituted C₁₋₆ alkyl;

R² is halogen, nitro, trifluoromethyl, substituted or unsubstituted amino, or substituted or unsubstituted C₁₋₆ alkyl;

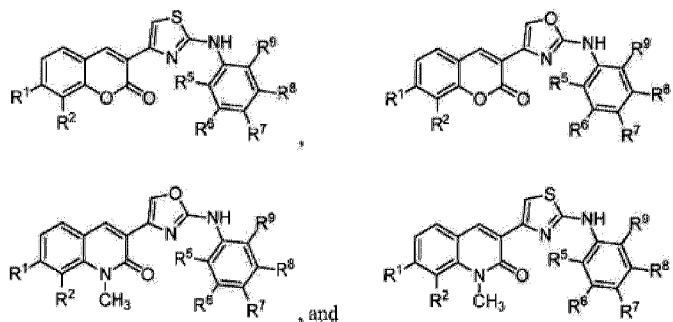
R³ is hydrogen or substituted or unsubstituted C₁₋₆ alkyl;

R⁴ is substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

X is S or O; and

Y is O, NH, or NCH₃.

2. A compound for treating a hyperproliferative disease in a subject selected from the group consisting of:



or a pharmaceutically acceptable salt thereof, wherein:

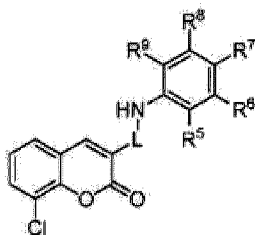
R¹ is hydrogen, halogen, substituted or unsubstituted amino, or substituted or unsubstituted C₁₋₆ alkyl;

R² is halogen, nitro, trifluoromethyl, substituted or unsubstituted amino, or substituted or unsubstituted C₁₋₆ alkyl;

R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from hydrogen, halogen, hydroxyl, substituted or unsubstituted alkoxy, cyano, nitro, trifluoromethyl, substituted or unsubstituted carbonyl, substituted or unsubstituted amino, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted sulfonamide, substituted or unsubstituted sulfonyl, or substituted or unsubstituted thio; and

optionally R¹ and R², R⁵ and R⁶, R⁶ and R⁷, R⁷ and R⁸, or R⁸ and R⁹ combine to form a substituted or unsubstituted aryl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

3. A compound of the following formula for treating a hyperproliferative disease in a subject:

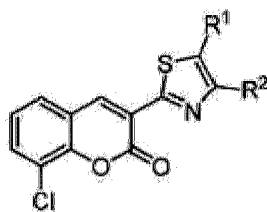


or a pharmaceutically acceptable salt thereof, wherein:

L is a heteroaryl; and

R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from hydrogen and methoxy.

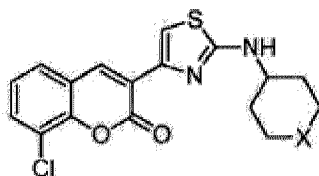
4. A compound of the following formula for treating a hyperproliferative disease in a subject:



or a pharmaceutically acceptable salt thereof, wherein:

R¹ and R² are each independently selected from hydrogen, substituted or unsubstituted amino, and substituted or unsubstituted carbonyl.

5. A compound of the following formula for treating a hyperproliferative disease in a subject:



or a pharmaceutically acceptable salt thereof, wherein:

X is CH₂, NH, or O.

6. The compound according to any one of claims 1 to 5, wherein the hyperproliferative disease is cancer.

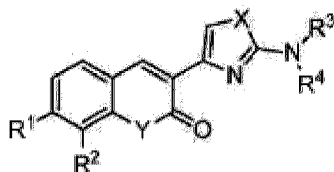
7. The compound according to any one of claims 1 to 5, wherein the hyperproliferative disease is polycystic kidney disease.

8. The compound according to any one of claims 1 to 5, wherein the hyperproliferative disease is a fibrosis.

9. The compound according to claim 8, wherein the fibrosis is idiopathic pulmonary fibrosis.

10. An *in vitro* method of inhibiting an interaction between two or more heat shock protein chaperones in a cell, comprising:

contacting a cell with an effective amount of a compound of the following formula:



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is hydrogen, halogen, substituted or unsubstituted amino, or substituted or unsubstituted C₁₋₆ alkyl;

R² is halogen, nitro, trifluoromethyl, substituted or unsubstituted amino, or substituted or unsubstituted C₁₋₆ alkyl;

R³ is hydrogen or substituted or unsubstituted C₁₋₆ alkyl;

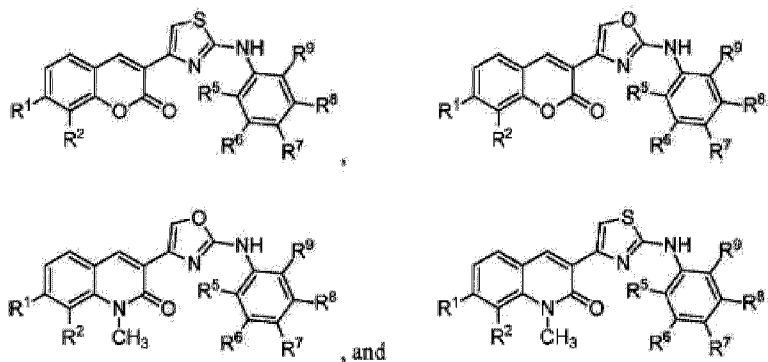
R⁴ is substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

X is S or O; and

Y is O, NH, or NCH₃.

11. An *in vitro* method of inhibiting an interaction between two or more heat shock protein chaperones in a cell, comprising:

contacting a cell with an effective amount of a compound selected from the group consisting of:



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is hydrogen, halogen, substituted or unsubstituted amino, or substituted or unsubstituted C₁₋₆ alkyl;

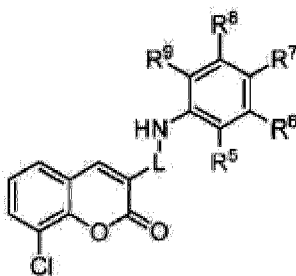
R² is halogen, nitro, trifluoromethyl, substituted or unsubstituted amino, or substituted or unsubstituted C₁₋₆ alkyl;

R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from hydrogen, halogen, hydroxyl, substituted or unsubstituted alkoxy, cyano, nitro, trifluoromethyl, substituted or unsubstituted carbonyl, substituted or unsubstituted amino, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted sulfonamide, substituted or unsubstituted sulfonyl, or substituted or unsubstituted thio; and

wherein optionally R¹ and R², R⁵ and R⁶, R⁶ and R⁷, R⁷ and R⁸, or R⁸ and R⁹ combine to form a substituted or unsubstituted aryl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

12. An *in vitro* method of inhibiting an interaction between two or more heat shock protein chaperones in a cell, comprising:

contacting a cell with an effective amount of a compound of the following formula:



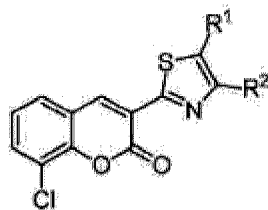
or a pharmaceutically acceptable salt thereof, wherein:

L is a heteroaryl; and

R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from hydrogen and methoxy.

13. An *in vitro* method of inhibiting an interaction between two or more heat shock protein chaperones in a cell, comprising:

contacting a cell with an effective amount of a compound of the following formula:

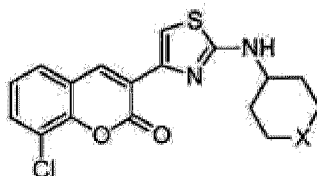


or a pharmaceutically acceptable salt thereof, wherein:

R¹ and R² are each independently selected from hydrogen, substituted or unsubstituted amino, and substituted or unsubstituted carbonyl.

14. An *in vitro* method of inhibiting the interaction between two or more heat shock protein chaperones in a cell, comprising:

contacting a cell with an effective amount of a compound of the following formula:

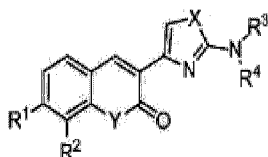


or a pharmaceutically acceptable salt thereof, wherein:

X is CH₂, NH, or O.

15. The *in vitro* method according to any one of claims 10 to 14, wherein the two or more heat shock protein chaperones are selected from the group consisting of Hsp-90, Hsp-70, Hsc-70, and Hsp-40.

16. A use of a compound in the manufacture of a medicament for the treatment of a hyperproliferative disease in a subject, said compound having the following formula:



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is hydrogen, halogen, substituted or unsubstituted amino, or substituted or unsubstituted C₁₋₆ alkyl;

R² is halogen, nitro, trifluoromethyl, substituted or unsubstituted amino, or substituted or unsubstituted C₁₋₆ alkyl;

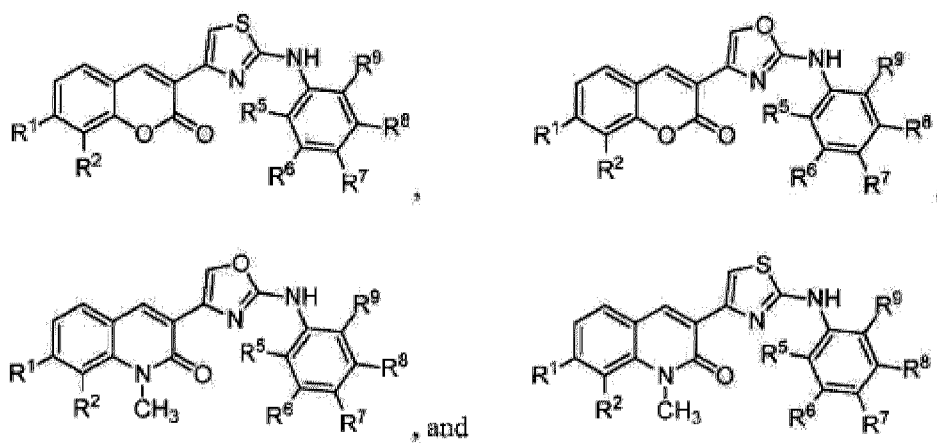
R³ is hydrogen or substituted or unsubstituted C₁₋₆ alkyl;

R⁴ is substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

X is S or O; and

Y is O, NH, or NCH₃.

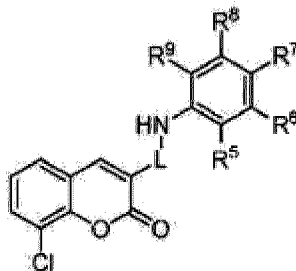
17. The use according to claim 16, wherein the compound is selected from the group consisting of:



wherein R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from hydrogen, halogen, hydroxyl, substituted or unsubstituted alkoxy, cyano, nitro, trifluoromethyl, substituted or unsubstituted carbonyl, substituted or unsubstituted amino, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted sulfonamide, substituted or unsubstituted sulfonyl, or substituted or unsubstituted thio; and

wherein optionally R¹ and R², R⁵ and R⁶, R⁶ and R⁷, R⁷ and R⁸, or R⁸ and R⁹ combine to form a substituted or unsubstituted aryl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

18. A use of a compound in the manufacture of a medicament for the treatment of a hyperproliferative disease in a subject, said compound having the following formula:



or a pharmaceutically acceptable salt thereof, wherein:

L is a heteroaryl; and

R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently selected from hydrogen and methoxy.

19. The use according to any one of claims 16 to 18, wherein the hyperproliferative disease is cancer.

20. The use according to any one of claims 16 to 18, wherein the hyperproliferative disease is polycystic kidney disease.

21. The use according to any one of claims 16 to 18, wherein the hyperproliferative disease is a fibrosis.

22. The use according to claim 21, wherein the fibrosis is idiopathic pulmonary fibrosis.

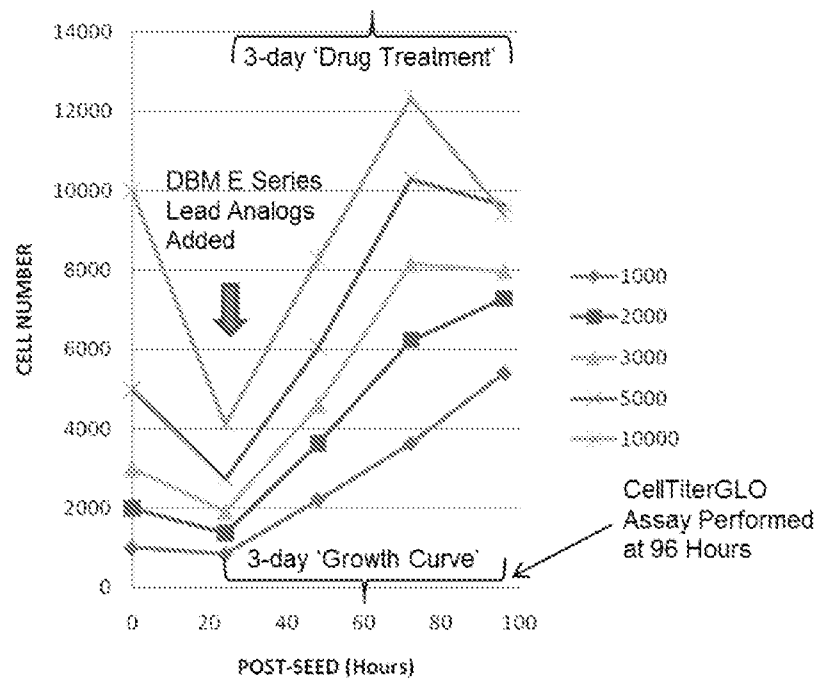
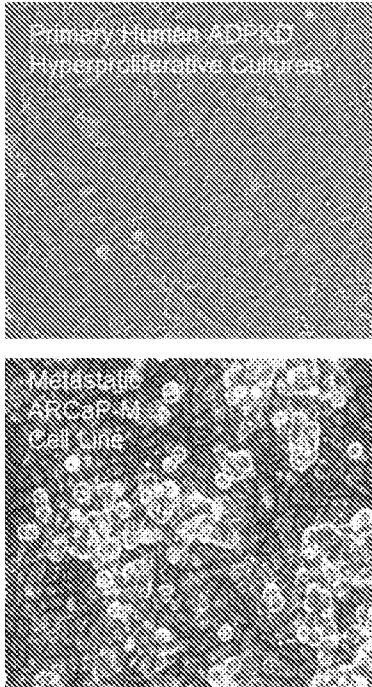


Figure 1

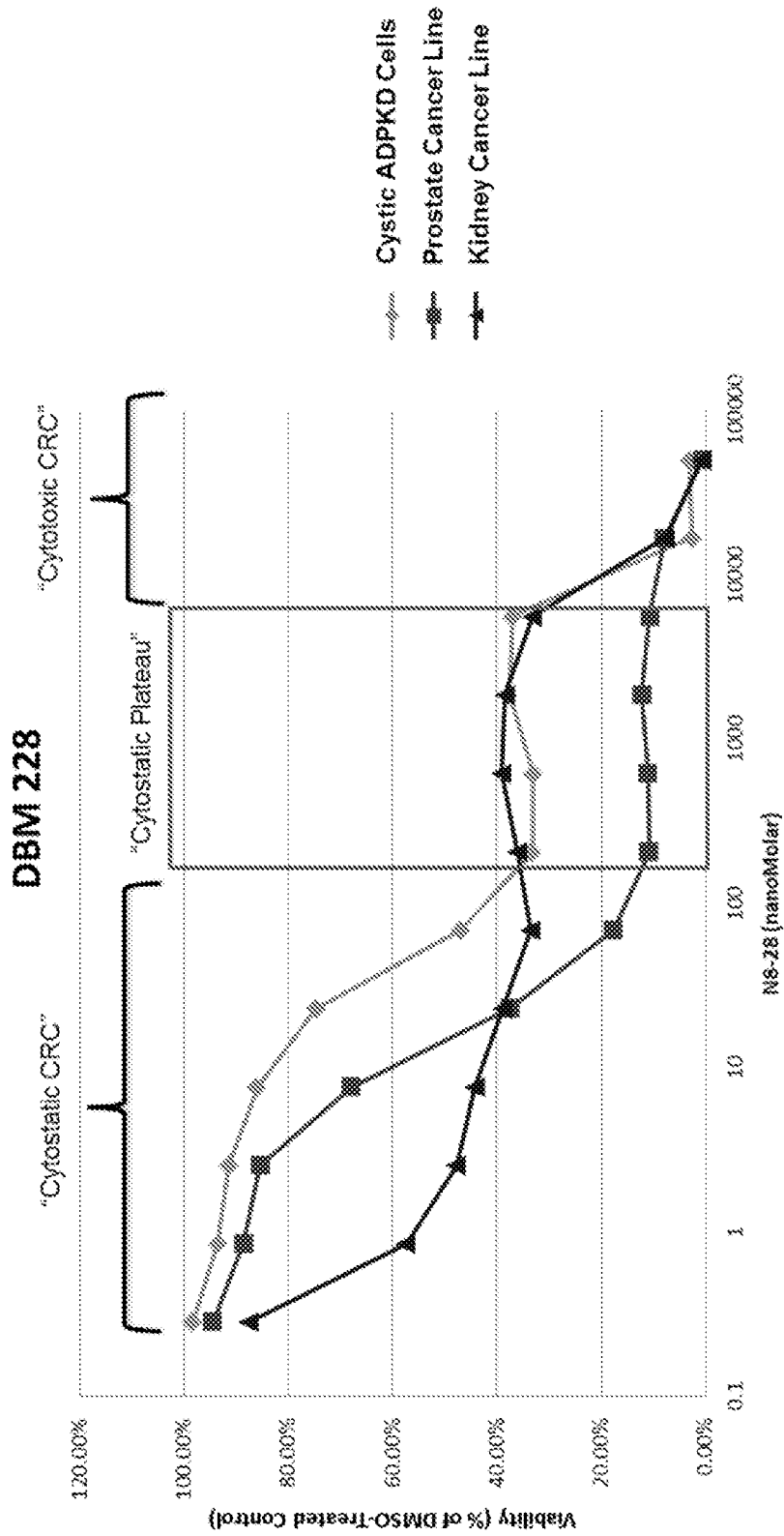


Figure 2

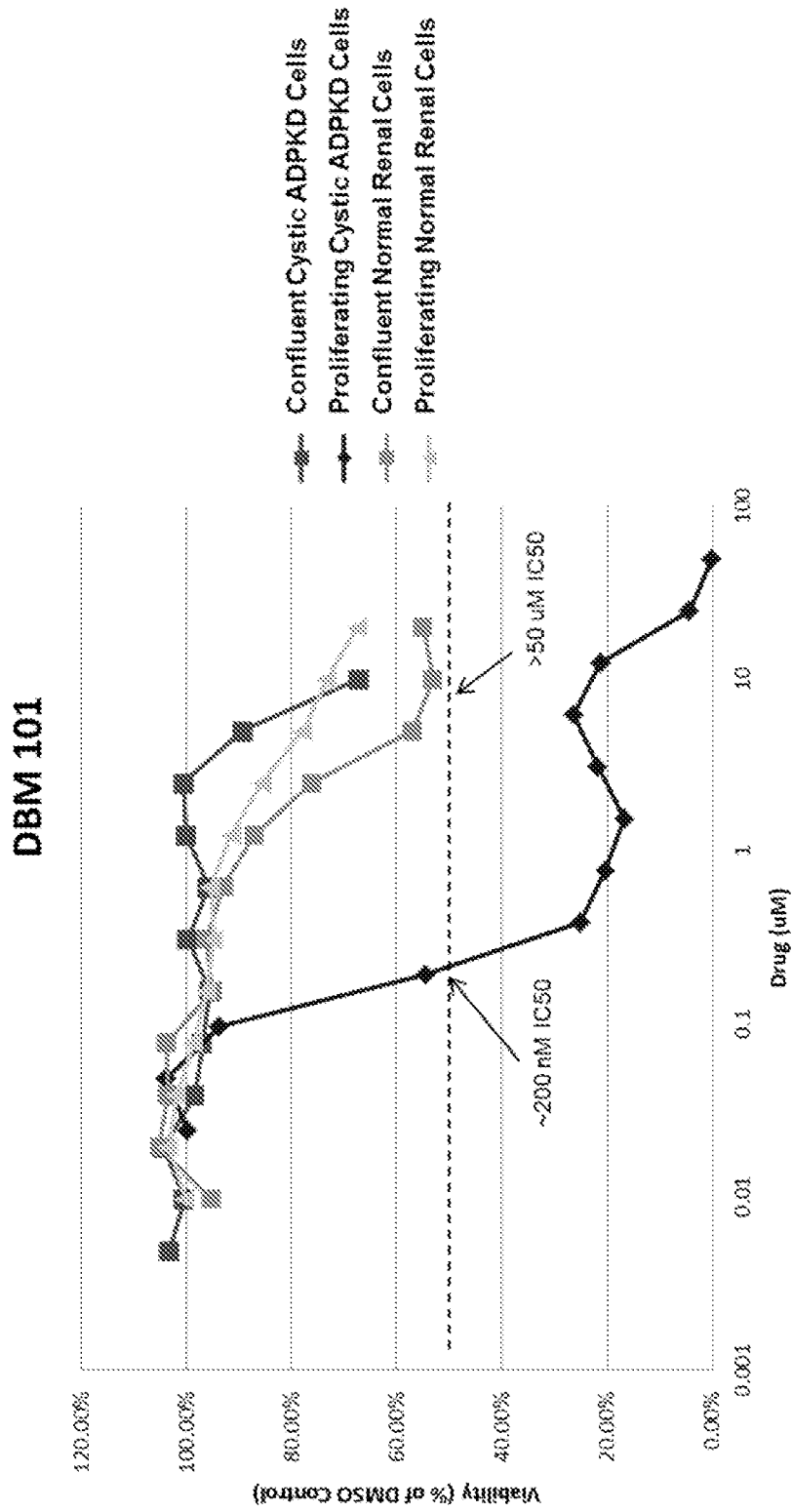


Figure 3

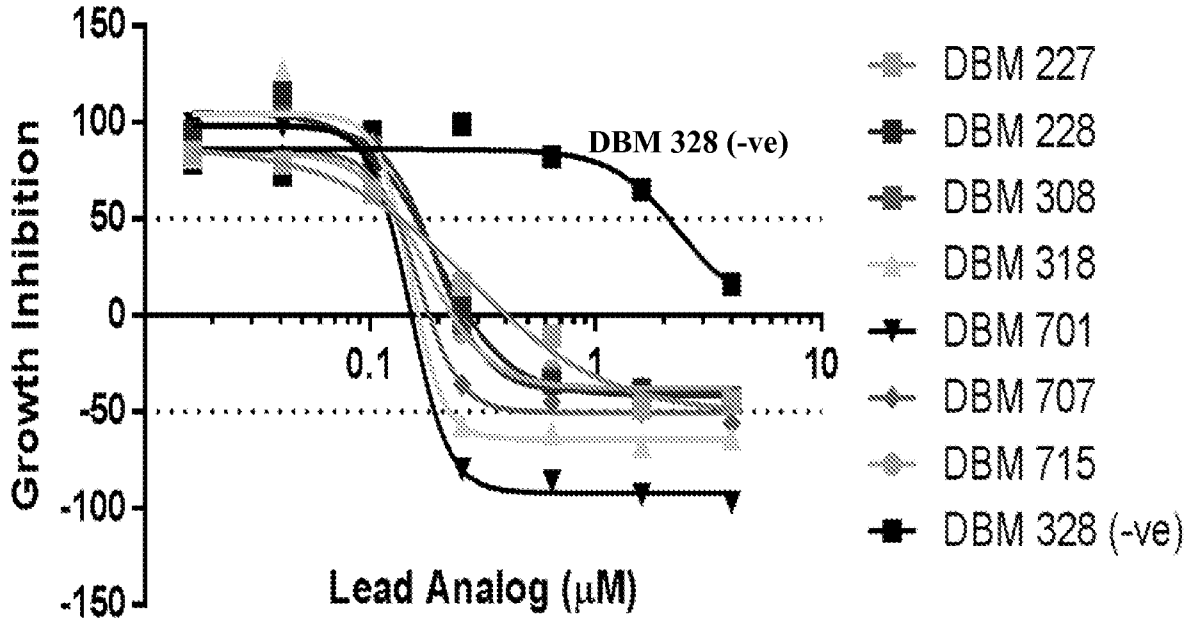


Figure 4

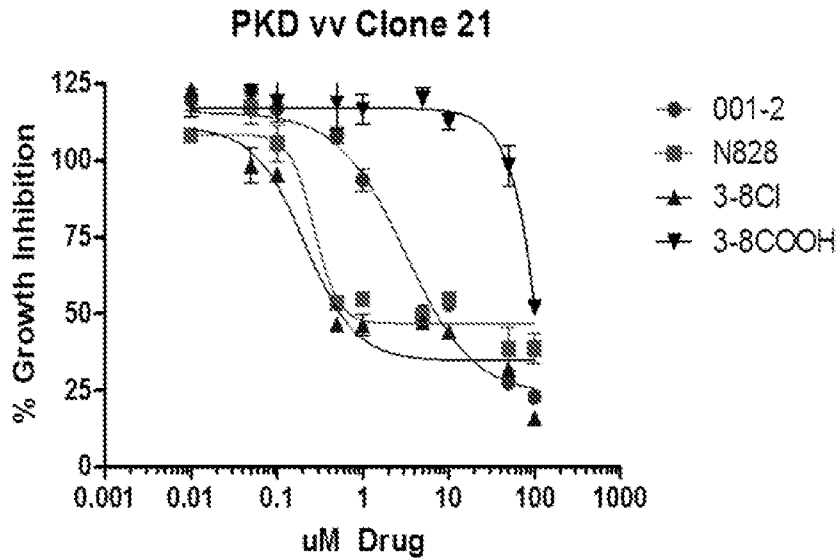


Figure 5A

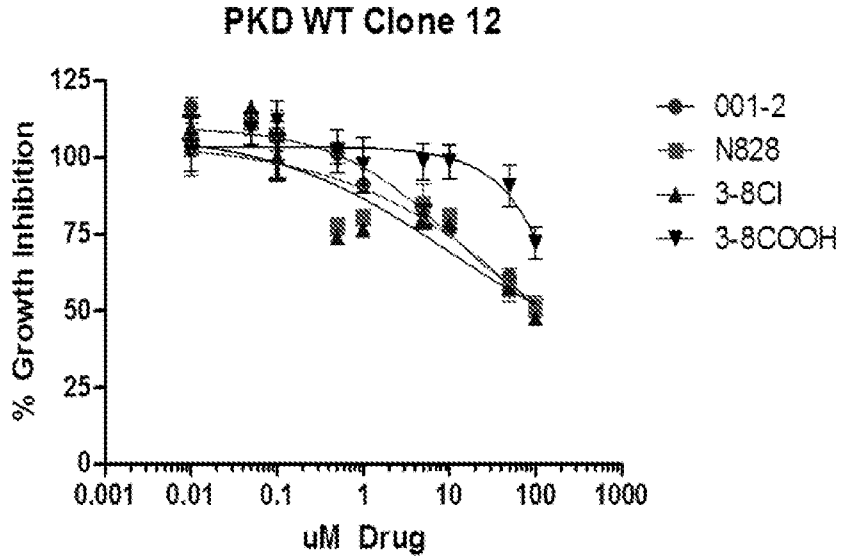


Figure 5B

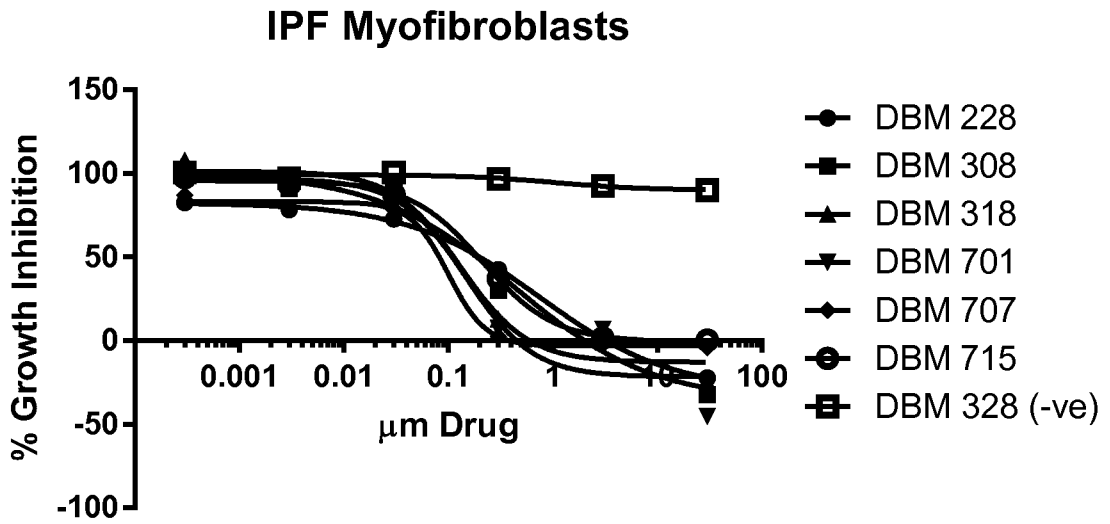


Figure 6

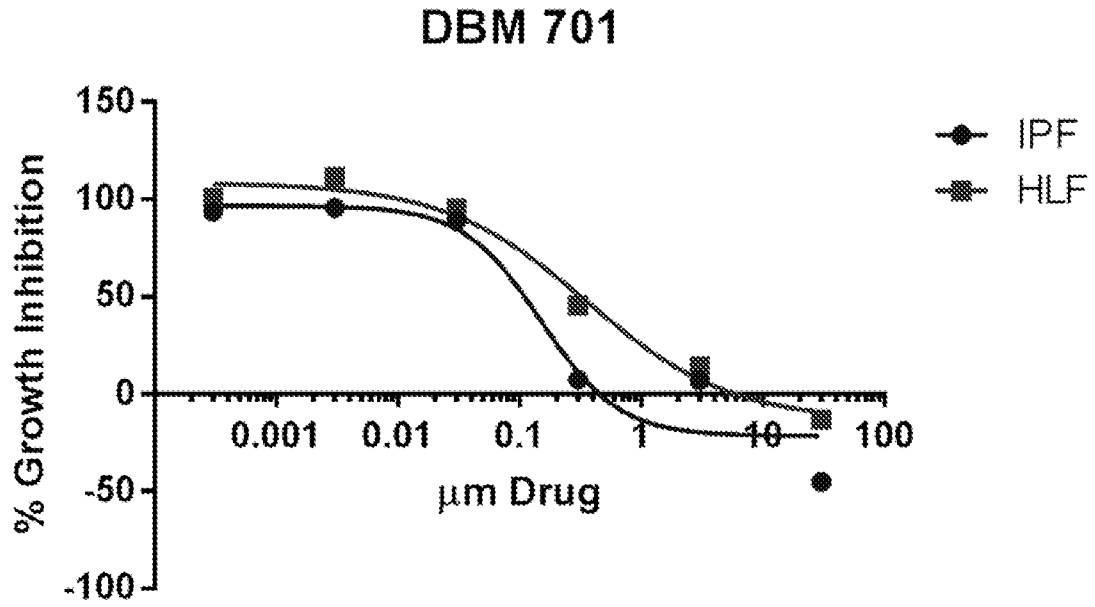


Figure 7

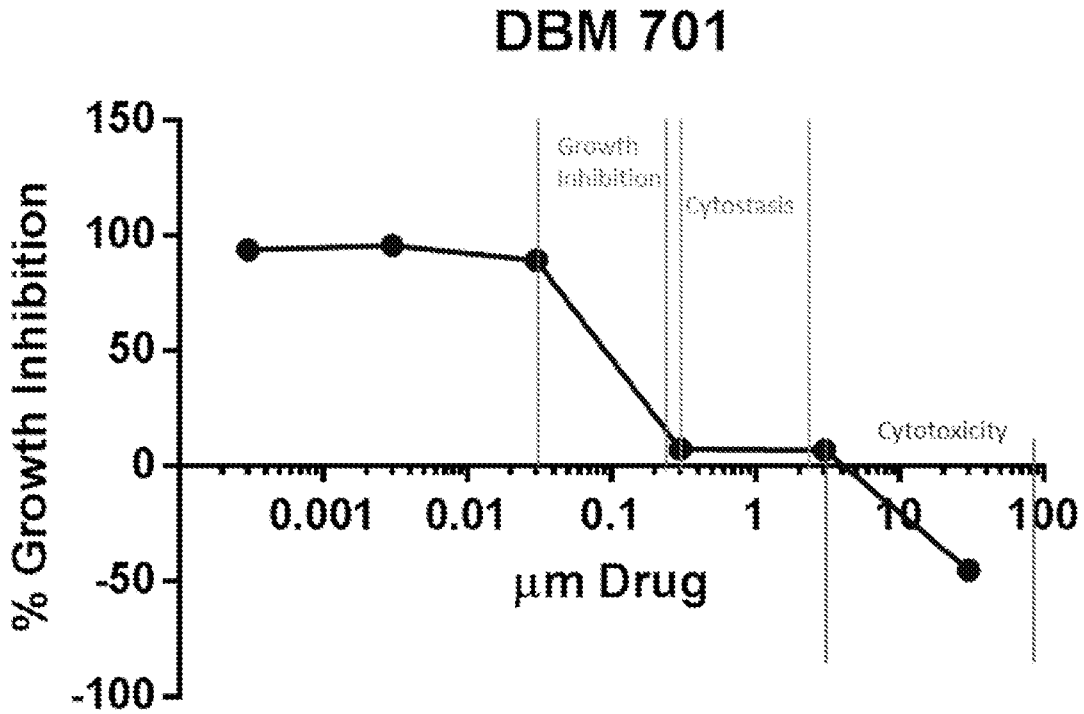


Figure 8

NCI/ADR-RES

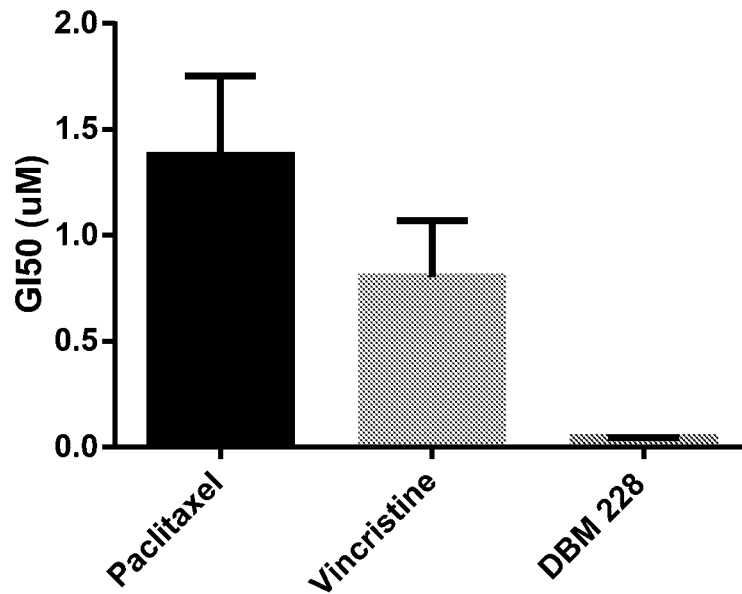


Figure 9

Figure 4 - DBM 308 Inhibits Neurosphere Growth of a Primary Human Glioblastoma Xenograft

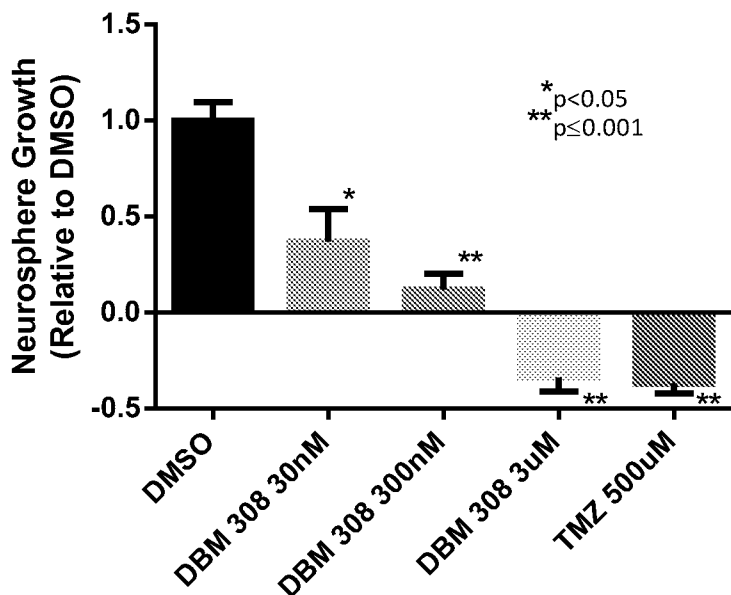


Figure 10

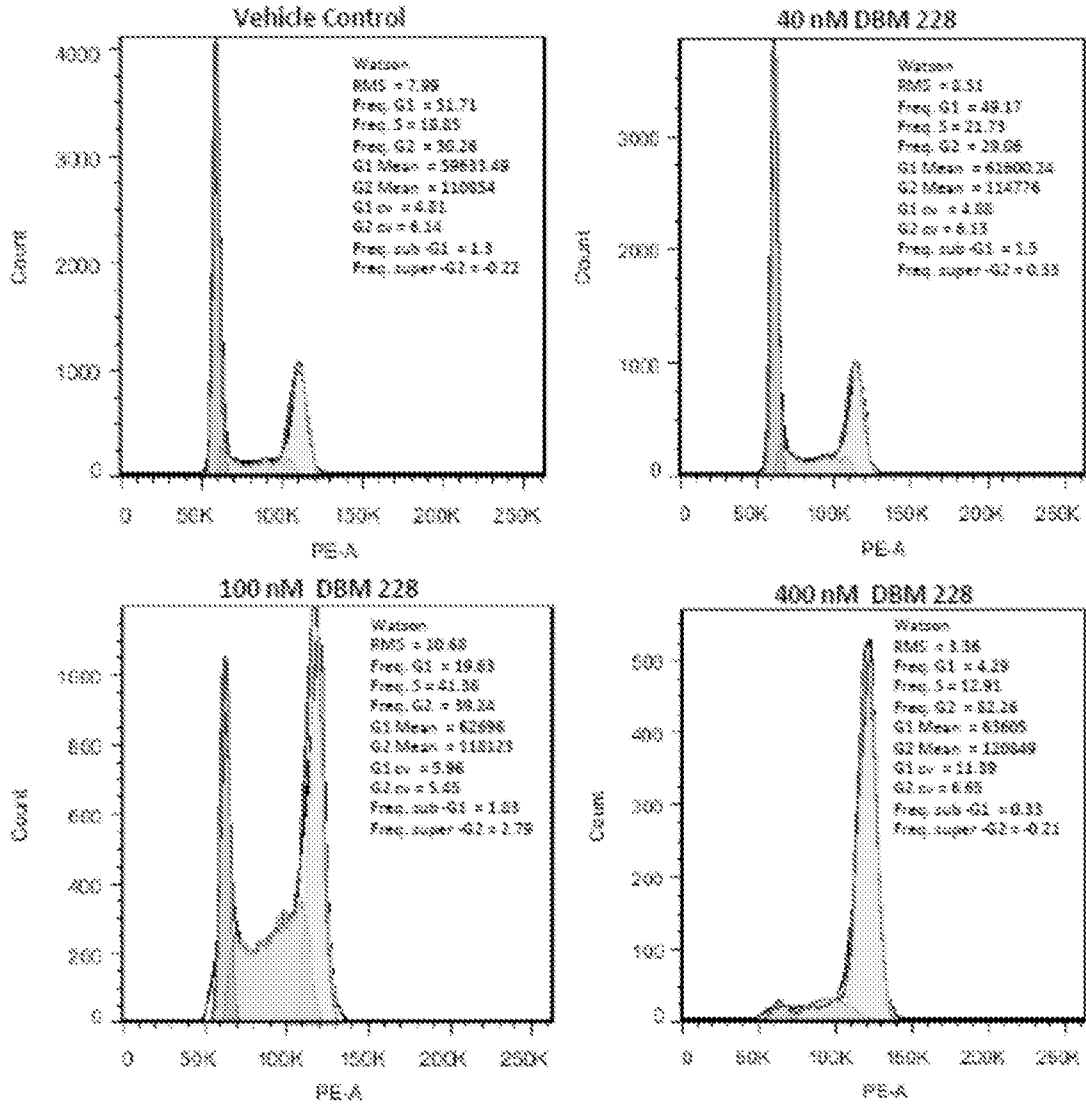


Figure 11A

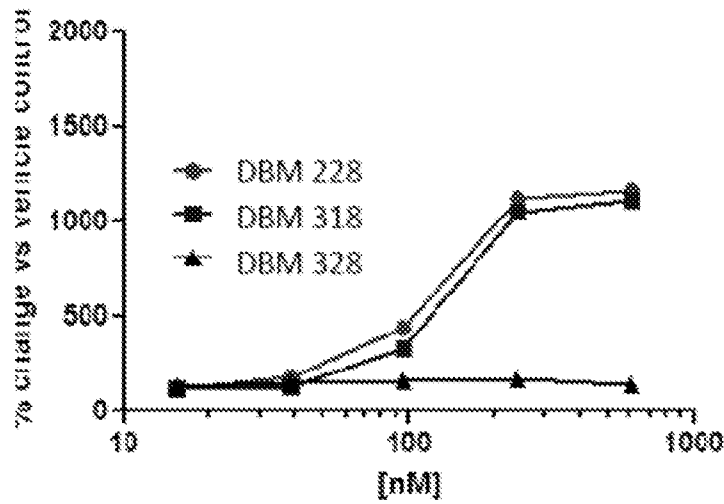


Figure 11B

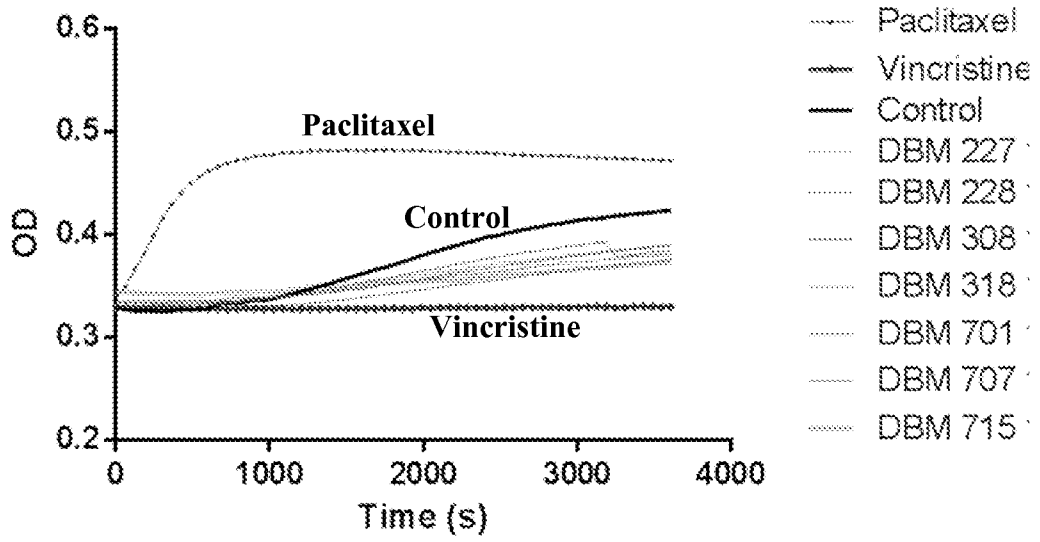


Figure 11C

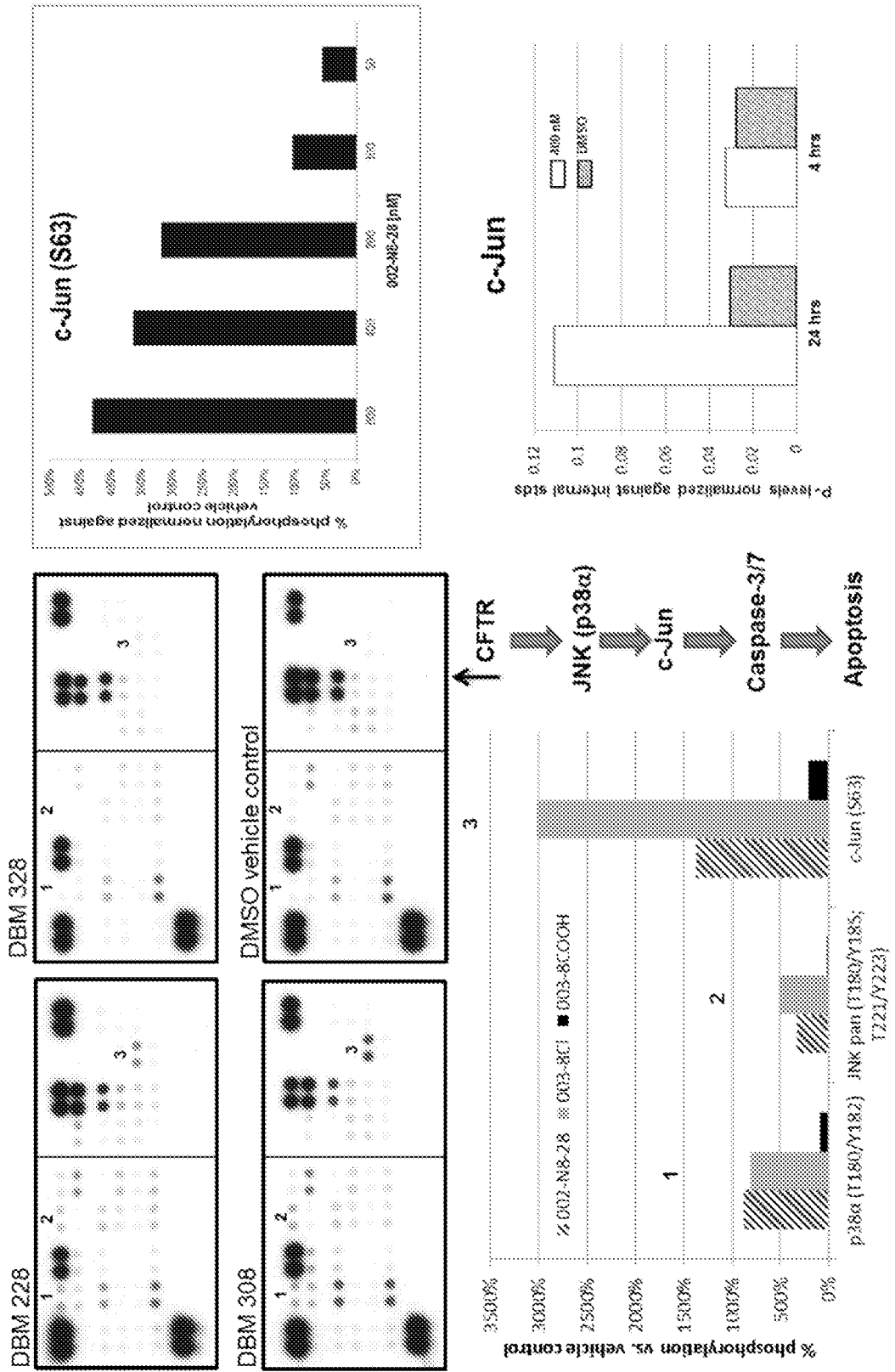


Figure 12