

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(10) International Publication Number  
**WO 2013/056067 A1**

(43) International Publication Date  
**18 April 2013 (18.04.2013)**

(51) International Patent Classification:  
**A61K 31/519 (2006.01) A61P 35/00 (2006.01)**

(21) International Application Number:  
**PCT/US2012/059976**

(22) International Filing Date:  
**12 October 2012 (12.10.2012)**

(25) Filing Language:  
**English**

(26) Publication Language:  
**English**

(30) Priority Data:  
**61/546,612 13 October 2011 (13.10.2011) US**

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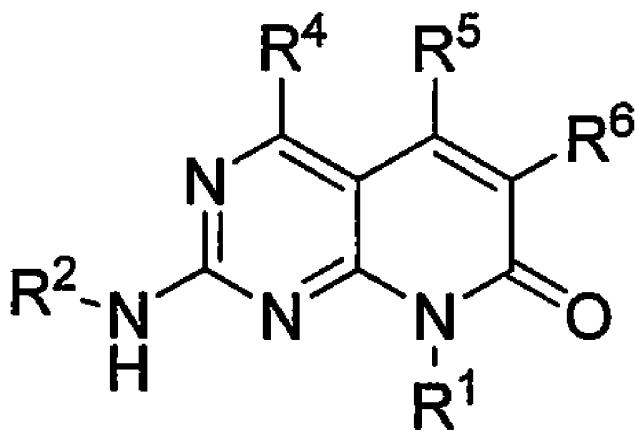
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: COMPOUNDS FOR USE IN THE TREATMENT OF BASAL CELL CARCINOMA



(57) Abstract: The invention provides a method for treating BCC in a patient in need of such treatment, comprising administering a therapeutically effective amount a compound of formula IIa.

IIa.

## COMPOUNDS FOR USE IN THE TREATMENT OF BASAL CELL CARCINOMA

## CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of U.S. Provisional Application No. 61/546,612, filed, October 13, 2011, the entire contents of which is incorporated herein by reference.

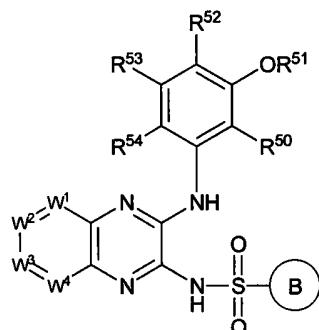
## BACKGROUND

[0002] Basal Cell Carcinoma (BCC) is one of the most common human cancers, accounting for approximately one third of all cancers in the United States, with an incidence that is increasing by 4-5% per year. With its high prevalence and morbidity, it is estimated that the annual cost to Medicare alone of treatment of this tumor exceeds \$400 million {Rigel, 2008 #1}. Sporadic BCCs usually develop in small numbers (i.e. 1-2), from the fifth or sixth decade of life, whereas an estimated 1 in 60,000 individuals have the heritable disease, basal cell nevus syndrome (BCNS, Gorlin syndrome) and develop multiple BCCs from puberty and throughout their lifetime. As a result, a need remains for new therapeutic options for the treatment of BCCs.

## SUMMARY

[0003] Accordingly, methods are provided for treating basal cell carcinoma comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula I or of formula II or a single isomer thereof or optionally as a pharmaceutically acceptable salt, tautomer, hydrate, or solvate thereof:

(a) where the compound of formula I is:



I

wherein:

$W^1$ ,  $W^2$ ,  $W^3$ , and  $W^4$  are  $-C(R^1)=$ ; or one or two of  $W^1$ ,  $W^2$ ,  $W^3$ , and  $W^4$  are independently  $-N=$  and the remaining are  $-C(R^1)=$ ; and where each  $R^1$  is independently hydrogen, alkyl, haloalkyl, nitro, alkoxy, haloalkoxy, halo, hydroxy, cyano, amino, alkylamino, or dialkylamino;

$R^{51}$  is hydrogen or alkyl;

$R^{52}$  is hydrogen or halo;

$R^{50}$ ,  $R^{53}$ , and  $R^{54}$  are independently hydrogen, alkyl, alkenyl, halo, haloalkyl, haloalkenyl, hydroxy, alkoxy, alkenyloxy, haloalkoxy, nitro, amino, alkylamino, dialkylamino,  $-N(R^{55})C(O)-C_1-C_6$ -alkylene- $N(R^{55a})R^{55b}$ , alkylcarbonyl, alkenylcarbonyl, carboxy, alkoxycarbonyl, cyano, alkylthio,  $-S(O)_2NR^{55}R^{55a}$ , or alkylcarbonylamino and where  $R^{55}$  and  $R^{55b}$  are independently hydrogen, alkyl, or alkenyl and  $R^{55a}$  is hydrogen, alkyl, alkenyl, hydroxy, or alkoxy; or  $R^{53}$  and  $R^{54}$  together with the carbons to which they are attached form a 5- or 6-membered heteroaryl or 5- or 6-membered heterocycloalkyl;

B is phenyl substituted with  $R^{3a}$  and optionally further substituted with one, two, or three  $R^3$ ;  
or

B is heteroaryl optionally substituted with one, two, or three  $R^3$ ;

$R^{3a}$  is cyano, hydroxyamino, carboxy, alkoxycarbonyl, alkylamino, dialkylamino, alkylcarbonyl, haloalkoxy, alkylsulfonyl, aminoalkyloxy, alkylaminoalkyloxy, dialkylaminoalkyloxy, or

a)  $-N(R^7)C(O)-C_1-C_6$ -alkylene- $N(R^{7a})(R^{7b})$  where  $R^7$  is hydrogen, alkyl, or alkenyl and  $R^{7a}$  and  $R^{7b}$  are independently hydrogen, alkyl, alkenyl, hydroxyalkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, aryl, arylalkyl, or arylalkyloxy and where the aryl, cycloalkyl, heterocycloalkyl and heteroaryl rings in  $R^{7a}$  and  $R^{7b}$  (either alone or as part of arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl and heteroarylalkyl) are independently optionally substituted with 1, 2, or 3 groups independently selected from alkyl, amino, alkylamino, dialkylamino, hydroxy, halo, alkoxy, alkylthio, and oxo);

b)  $-C(O)NR^8R^{8a}$  where  $R^8$  is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, haloalkyl, or haloalkoxy and  $R^{8a}$  is hydrogen, alkyl, alkenyl, hydroxyalkyl, cyanoalkyl, alkoxyalkyl, alkylthioalkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, aryl, or arylalkyl and where the aryl, cycloalkyl, heteroaryl, and heterocycloalkyl rings in  $R^{8a}$  (either alone or as part of arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl and heteroarylalkyl) are

independently optionally substituted with 1, 2, or 3 groups independently selected from alkyl, alkenyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, hydroxyalkyl, oxo, amino, alkylamino, dialkylamino, alkylcarbonyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxycarbonyl, and -C(O)H;

- c) -NR<sup>9</sup>C(O)R<sup>9a</sup> where R<sup>9</sup> is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, haloalkyl, or haloalkoxy and R<sup>9a</sup> is hydrogen, C<sub>2</sub>-C<sub>6</sub>-alkyl, alkenyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, aryl, or arylalkyl; where the aryl, cycloalkyl, heteroaryl, and heterocycloalkyl rings in R<sup>9a</sup> (either alone or as part of arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl and heteroarylalkyl) are independently optionally substituted with 1, 2, or 3 groups independently selected from alkyl, alkenyl, alkoxy, hydroxy, hydroxyalkyl, halo, haloalkyl, haloalkoxy, oxo, amino, alkylamino, dialkylamino, alkylcarbonyl, alkoxycarbonyl, -C(O)H, aryl (optionally substituted with one or two halo), arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, and cycloalkylcarbonyl;
- d) -C(O)N(R<sup>10</sup>)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>10a</sup>)R<sup>10b</sup> where R<sup>10a</sup> is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, haloalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, or hydroxyalkyl and R<sup>10</sup> and R<sup>10b</sup> are independently hydrogen, alkyl, alkenyl, haloalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, or hydroxyalkyl;
- e) -NR<sup>11</sup>C(O)NR<sup>11a</sup>R<sup>11b</sup> where R<sup>11a</sup> is hydrogen, alkyl, alkenyl, hydroxy, or alkoxy and R<sup>11</sup> and R<sup>11b</sup> are independently hydrogen, alkyl, alkenyl, aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl;
- f) -C(O)R<sup>12</sup> where R<sup>12</sup> is heterocycloalkyl optionally substituted with 1, 2, or 3 groups selected from alkyl, oxo, amino, alkylamino, and heterocycloalkylalkyl;
- g) -NR<sup>13</sup>C(O)OR<sup>13a</sup> where R<sup>13</sup> is hydrogen, alkyl, or alkenyl and R<sup>13a</sup> is aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aryl, or arylalkyl;
- h) -C(O)N(R<sup>14</sup>)N(R<sup>14a</sup>)(R<sup>14b</sup>) where R<sup>14</sup>, R<sup>14a</sup>, and R<sup>14b</sup> are independently hydrogen, alkyl, or alkenyl;
- i) -S(O)<sub>2</sub>N(R<sup>15</sup>)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>15a</sup>)R<sup>15b</sup> where R<sup>15</sup>, R<sup>15a</sup>, and R<sup>15b</sup> are independently hydrogen, alkyl, or alkenyl;
- j) -C(O)N(R<sup>16</sup>)-C<sub>1</sub>-C<sub>6</sub>-alkylene-C(O)OR<sup>16a</sup> where R<sup>16</sup> is hydrogen, alkyl, or alkenyl and R<sup>16a</sup> is alkyl or alkenyl;
- k) heteroaryl optionally substituted with one or two aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl;

- l)  $-\text{N}(\text{R}^{17})\text{-C}(=\text{N}(\text{R}^{17b})(\text{R}^{17a}))(\text{NR}^{17c}\text{R}^{17d})$  where  $\text{R}^{17}$ ,  $\text{R}^{17a}$ ,  $\text{R}^{17b}$ ,  $\text{R}^{17c}$ , and  $\text{R}^{17d}$  are independently hydrogen, alkyl, or alkenyl;
- m)  $-\text{N}(\text{R}^{18})\text{C}(\text{O})\text{-C}_1\text{-C}_6\text{-alkylene-N}(\text{R}^{18b})\text{C}(\text{O})\text{R}^{18a}$  where  $\text{R}^{18a}$  is hydrogen, alkyl, alkenyl, or alkoxy and  $\text{R}^{18}$  and  $\text{R}^{18b}$  are independently hydrogen, alkyl, or alkenyl;
- n)  $-\text{C}(\text{O})\text{N}(\text{R}^{19})\text{-C}_1\text{-C}_6\text{-alkylene-C}(\text{O})\text{R}^{19a}$  where  $\text{R}^{19}$  is hydrogen, alkyl, or alkenyl and  $\text{R}^{19a}$  is amino, alkylamino, dialkylamino, or heterocycloalkyl;
- o)  $-\text{N}(\text{R}^{20})\text{C}(\text{O})\text{-C}_1\text{-C}_6\text{-alkylene-C}(\text{O})\text{R}^{20a}$  where  $\text{R}^{20}$  is hydrogen, alkyl, or alkenyl and  $\text{R}^{20a}$  is cycloalkyl or heterocycloalkyl;
- p)  $-\text{NR}^{21}\text{S}(\text{O})_2\text{-C}_1\text{-C}_6\text{-alkylene-N}(\text{R}^{21b})\text{R}^{21a}$  where  $\text{R}^{21}$  is hydrogen, alkyl, or alkenyl and  $\text{R}^{21a}$  and  $\text{R}^{21b}$  are independently hydrogen, alkyl, or alkenyl;
- q)  $-\text{N}(\text{R}^{22})\text{C}(\text{O})\text{-C}_1\text{-C}_6\text{-alkylene-N}(\text{R}^{22b})\text{-N}(\text{R}^{22c})(\text{R}^{22a})$  where  $\text{R}^{22}$ ,  $\text{R}^{22a}$  and  $\text{R}^{22b}$  are independently hydrogen, alkyl, or alkenyl;
- r)  $-\text{C}_0\text{-C}_6\text{-alkylene-N}(\text{R}^{23})\text{-C}_1\text{-C}_6\text{-alkylene-N}(\text{R}^{23b})\text{R}^{23a}$  where  $\text{R}^{23}$ ,  $\text{R}^{23a}$  and  $\text{R}^{23b}$  are independently hydrogen, alkyl, or alkenyl; or
- s)  $-\text{NR}^{24}\text{C}(\text{O})\text{-C}_1\text{-C}_6\text{-alkylene-OR}^{24a}$  where  $\text{R}^{24}$  is hydrogen, alkyl, or alkenyl and  $\text{R}^{24a}$  is alkoxyalkyl or aryl optionally substituted with one or two halo or alkyl; and

where each of the alkylene in  $\text{R}^{3a}$  is independently optionally further substituted with 1, 2, 3, 4, or 5 groups selected from halo, hydroxy, amino, alkylamino, and dialkylamino; and each  $\text{R}^3$  (when  $\text{R}^3$  is present) is independently alkyl; alkenyl; alkynyl; halo; hydroxy; oxo; alkoxy; cyano; hydroxyamino; carboxy; alkoxy carbonyl; amino; alkylamino; dialkylamino; alkylcarbonyl; haloalkoxy; alkylsulfonyl; aminoalkyloxy; alkylaminoalkyloxy; dialkylaminoalkyloxy; or

- a)  $-\text{N}(\text{R}^7)\text{C}(\text{O})\text{-C}_1\text{-C}_6\text{-alkylene-N}(\text{R}^{7a})(\text{R}^{7b})$  where  $\text{R}^7$  is hydrogen, alkyl, or alkenyl and  $\text{R}^{7a}$  and  $\text{R}^{7b}$  are independently hydrogen, alkyl, alkenyl, hydroxyalkyl, haloalkyl, alkoxy, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, aryl, arylalkyl, or arylalkyloxy and where the aryl, cycloalkyl, heterocycloalkyl and heteroaryl rings in  $\text{R}^{7a}$  and  $\text{R}^{7b}$  (either alone or as part of arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl and heteroarylalkyl) are independently optionally substituted with 1, 2, or 3 groups independently selected from alkyl, amino, alkylamino, dialkylamino, hydroxy, halo, alkoxy, alkylthio, and oxo);
- b)  $-\text{C}(\text{O})\text{NR}^8\text{R}^{8a}$  where  $\text{R}^8$  is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, haloalkyl, or haloalkoxy and  $\text{R}^{8a}$  is hydrogen, alkyl, alkenyl, hydroxyalkyl, cyanoalkyl, alkoxyalkyl, alkylthioalkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkyl,

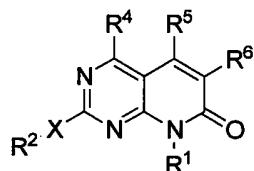
- cycloalkylalkyl, heteroaryl, heteroarylalkyl, aryl, or arylalkyl and where the aryl, cycloalkyl, heteroaryl, and heterocycloalkyl rings in R<sup>8a</sup> (either alone or as part of arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl and heteroarylalkyl) are independently optionally substituted with 1, 2, or 3 groups independently selected from alkyl, alkenyl, alkoxy, halo, haloalkyl, haloalkoxy, hydroxy, hydroxylalkyl, oxo, amino, alkylamino, dialkylamino, alkylcarbonyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxycarbonyl, and -C(O)H;
- c) -NR<sup>9</sup>C(O)R<sup>9a</sup> where R<sup>9</sup> is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, haloalkyl, or haloalkoxy and R<sup>9a</sup> is hydrogen, C<sub>2</sub>-C<sub>6</sub>-alkyl, alkenyl, hydroxylalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, aryl, or arylalkyl; where the aryl, cycloalkyl, heteroaryl, and heterocycloalkyl rings in R<sup>9a</sup> (either alone or as part of arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl and heteroarylalkyl) are independently optionally substituted with 1, 2, or 3 groups independently selected from alkyl, alkenyl, alkoxy, hydroxy, hydroxylalkyl, halo, haloalkyl, haloalkoxy, oxo, amino, alkylamino, dialkylamino, alkylcarbonyl, alkoxycarbonyl, -C(O)H, aryl (optionally substituted with one or two halo), arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, and cycloalkylcarbonyl;
  - d) -C(O)N(R<sup>10</sup>)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>10a</sup>)R<sup>10b</sup> where R<sup>10a</sup> is hydrogen, hydroxy, alkoxy, alkyl, alkenyl, haloalkyl, or hydroxylalkyl and R<sup>10</sup> and R<sup>10b</sup> are independently hydrogen, alkyl, alkenyl, haloalkyl, or hydroxylalkyl;
  - e) -NR<sup>11</sup>C(O)NR<sup>11a</sup>R<sup>11b</sup> where R<sup>11a</sup> is hydrogen, alkyl, alkenyl, hydroxy, or alkoxy and R<sup>11</sup> and R<sup>11b</sup> are independently hydrogen, alkyl, alkenyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl;
  - f) -C(O)R<sup>12</sup> where R<sup>12</sup> is heterocycloalkyl optionally substituted with 1, 2, or 3 groups selected from alkyl, oxo, amino, alkylamino, and heterocycloalkylalkyl;
  - g) -NR<sup>13</sup>C(O)OR<sup>13a</sup> where R<sup>13</sup> is hydrogen, alkyl, or alkenyl and R<sup>13a</sup> is aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aryl, or arylalkyl;
  - h) -C(O)N(R<sup>14</sup>)N(R<sup>14a</sup>)(R<sup>14b</sup>) where R<sup>14</sup>, R<sup>14a</sup>, and R<sup>14b</sup> are independently hydrogen, alkyl, or alkenyl;
  - i) -S(O)<sub>2</sub>N(R<sup>15</sup>)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>15a</sup>)R<sup>15b</sup> where R<sup>15</sup>, R<sup>15a</sup>, and R<sup>15b</sup> are independently hydrogen, alkyl, or alkenyl;
  - j) -C(O)N(R<sup>16</sup>)-C<sub>1</sub>-C<sub>6</sub>-alkylene-C(O)OR<sup>16a</sup> where R<sup>16</sup> is hydrogen, alkyl, or alkenyl and R<sup>16a</sup> is alkyl or alkenyl;

- k) heteroaryl optionally substituted with one or two aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl;
- l)  $-\text{N}(\text{R}^{17})\text{-C}(=\text{N}(\text{R}^{17b})(\text{R}^{17a}))(\text{NR}^{17c}\text{R}^{17d})$  where  $\text{R}^{17}$ ,  $\text{R}^{17a}$ ,  $\text{R}^{17b}$ ,  $\text{R}^{17c}$ , and  $\text{R}^{17d}$  are independently hydrogen, alkyl, or alkenyl;
- m)  $-\text{N}(\text{R}^{18})\text{C(O)-C}_1\text{-C}_6\text{-alkylene-N}(\text{R}^{18b})\text{C(O)R}^{18a}$  where  $\text{R}^{18a}$  is hydrogen, alkyl, alkenyl, or alkoxy and  $\text{R}^{18}$  and  $\text{R}^{18b}$  are independently hydrogen, alkyl, or alkenyl;
- n)  $-\text{C(O)N}(\text{R}^{19})\text{-C}_1\text{-C}_6\text{-alkylene-C(O)R}^{19a}$  where  $\text{R}^{19}$  is hydrogen, alkyl, or alkenyl and  $\text{R}^{19a}$  is amino, alkylamino, dialkylamino, or heterocycloalkyl;
- o)  $-\text{N}(\text{R}^{20})\text{C(O)-C}_1\text{-C}_6\text{-alkylene-C(O)R}^{20a}$  where  $\text{R}^{20}$  is hydrogen, alkyl, or alkenyl and  $\text{R}^{20a}$  is cycloalkyl or heterocycloalkyl;
- p)  $-\text{NR}^{21}\text{S(O)}_2\text{-C}_1\text{-C}_6\text{-alkylene-N}(\text{R}^{21b})\text{R}^{21a}$  where  $\text{R}^{21}$  is hydrogen, alkyl, or alkenyl and  $\text{R}^{21a}$  and  $\text{R}^{21b}$  are independently hydrogen, alkyl, or alkenyl;
- q)  $-\text{N}(\text{R}^{22})\text{C(O)-C}_1\text{-C}_6\text{-alkylene-N}(\text{R}^{22b})\text{-N}(\text{R}^{22c})(\text{R}^{22a})$ , where  $\text{R}^{22}$ ,  $\text{R}^{22a}$  and  $\text{R}^{22b}$  are independently hydrogen, alkyl, or alkenyl;
- r)  $-\text{C}_0\text{C}_6\text{-alkylene-N}(\text{R}^{23})\text{-C}_1\text{-C}_6\text{-alkylene-N}(\text{R}^{23b})\text{R}^{23a}$  where  $\text{R}^{23}$ ,  $\text{R}^{23a}$  and  $\text{R}^{23b}$  are independently hydrogen, alkyl, or alkenyl; or
- s)  $-\text{NR}^{24}\text{C(O)-C}_1\text{C}_6\text{-alkylene-OR}^{24a}$  where  $\text{R}^{24}$  is hydrogen, alkyl, or alkenyl and  $\text{R}^{24a}$  is alkoxyalkyl or aryl optionally substituted with one or two halo or alkyl;

wherein each of the alkylene in  $\text{R}^3$  is independently optionally further substituted with 1, 2, 3,

4, or 5 groups selected from halo, hydroxy, amino, alkylamino, and dialkylamino; and provided that when  $\text{R}^{50}$  and  $\text{R}^{52}$  are hydrogen,  $\text{R}^{51}$  is hydrogen or methyl,  $\text{R}^{53}$  is hydrogen or methoxy, and  $\text{R}^{54}$  is hydrogen or methoxy, then B is not 2,3-dihydro-1,4-benzodioxinyl, thien-2-yl, or thien-2-yl substituted with one  $\text{R}^3$  where  $\text{R}^3$  is halo; and

(b) where the compound of formula II is:



II

wherein:

$\text{R}^1$  is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heterocycloalkyl, optionally substituted

heterocycloalkylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl;

$R^2$  is hydrogen or alkyl where the alkyl is optionally substituted with 1, 2, 3, 4, or 5  $R^8$  groups;

$X$  is  $-NR^3-$ ;

$R^3$  is hydrogen;

$R^4$  is optionally substituted alkyl;

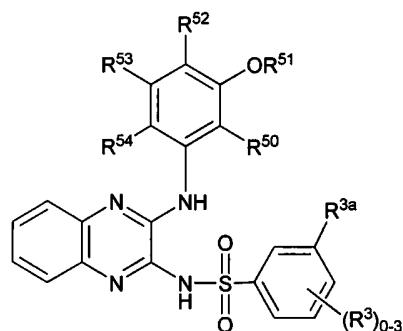
$R^5$  is hydrogen; and

$R^6$  is phenyl, acyl, or heteroaryl wherein the phenyl and heteroaryl are optionally substituted with 1, 2, 3, 4, or 5  $R^9$  groups;

each  $R^8$ , when present, is independently hydroxy, halo, alkoxy, haloalkoxy, amino, alkylamino, dialkylaminoalkyl, or alkoxyalkylamino; and

each  $R^9$ , when present, is independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, amino, alkylamino, dialkylamino, alkoxyalkyl, carboxyalkyl, alcoxycarbonyl, aminoalkyl, cycloalkyl, aryl, arylalkyl, aryloxy, heterocycloalkyl, or heteroaryl, and where the cycloalkyl, aryl, heterocycloalkyl, and heteroaryl, each either alone or as part of another group within  $R^9$ , are independently optionally substituted with 1, 2, 3, or 4 groups selected from halo, alkyl, haloalkyl, hydroxy, alkoxy, haloalkoxy, amino, alkylamino, and dialkylamino.

**[0004]** In one embodiment, the compound of formula I is a compound of formula Ia:



Ia

or a single stereoisomer or mixture of stereoisomers thereof and optionally as a pharmaceutically acceptable salt, tautomer, hydrate, or solvate thereof, wherein:

$R^{50}$  is hydrogen;

$R^{51}$  is methyl;

$R^{52}$  is hydrogen;

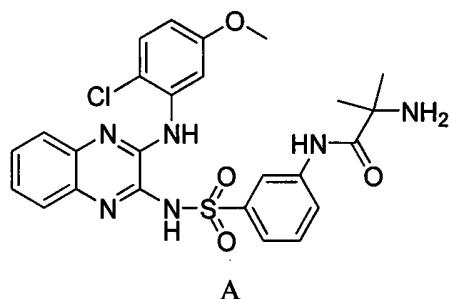
$R^{53}$  is hydrogen or alkoxy; and

$R^{54}$  is hydrogen, alkyl, alkoxy, or halo; or  $R^{53}$  and  $R^{54}$  together with the carbons to which they are attached form a 6-membered heteroaryl; and

$R^3$  is halo or methyl; and

$R^{3a}$  is  $-N(R^7)C(O)-C_1-C^6\text{-alkylene-}N(R^{7a})(R^{7b})$  where  $R^7$  is hydrogen and  $R^{7a}$  and  $R^{7b}$  are independently hydrogen, alkyl, aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl.

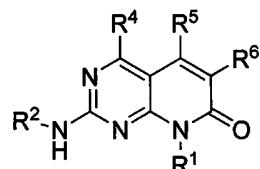
[0005] In one embodiment, the compound of formula I and of formula Ia is compound A:



or a tautomer, zwitterion, or pharmaceutically salt thereof.

[0006] Compound A is known by its chemical name N-(3-{[(3-{[2-chloro-5-(methoxy)phenyl]amino}quinoxalin-2-yl)amino]sulfonyl}phenyl)-2-methylalaninamide.

[0007] In one embodiment, the compound of formula II is a compound of formula IIa:



or a pharmaceutically acceptable salt thereof, wherein:

$R^1$  is alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl;

$R^2$  is hydrogen or alkyl;

$R^4$  is alkyl;

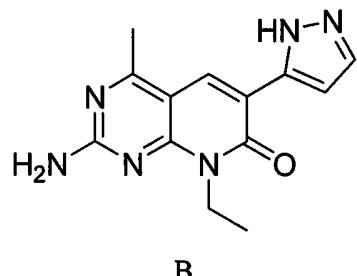
$R^5$  is hydrogen;

$R^6$  is phenyl, acyl, or heteroaryl wherein the phenyl and heteroaryl are optionally substituted with 1, 2, 3, 4, or 5  $R^9$  groups; and

each  $R^9$ , when present, is independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, amino, alkylamino, dialkylamino, alkoxyalkyl, carboxyalkyl, alkoxy carbonyl, aminoalkyl, cycloalkyl, aryl, arylalkyl, aryloxy, heterocycloalkyl, or heteroaryl and where the cycloalkyl, aryl, heterocycloalkyl, and heteroaryl, each either alone or as part of another

group within R<sup>9</sup>, are independently optionally substituted with 1, 2, 3, or 4 groups selected from halo, alkyl, haloalkyl, hydroxy, alkoxy, haloalkoxy, amino, alkylamino, and dialkylamino.

[0008] In another embodiment, the compound of formula II is compound B.



[0009] Compound B is known by its name 2-amino-8-ethyl-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one. Compound B is disclosed in WO 2007/044813, the entire contents of which are incorporated herein by reference.

#### BRIEF SUMMARY OF THE FIGURES

[0010] Figure 1 provides a Principal Component Analysis of the gene expression array data showing that 10 M tazarotene treatment of ASZ001 cells significantly altered the gene expression profiles at both 10 hours and 24 hours.

[0011] Figure 2 shows the validation of the Affymetrix gene expression data by real-time qPCR.

[0012] Figure 3 provides a bioinformatic analysis using Ingenuity software suggested that a possible downstream pathway that thea number of 10 DE genes had in common was one the PI3K/Akt pathway.

[0013] Figure 4 shows immunohistochemistry with phosphorylated Akt1 (p-Akt) antisera on untreated visible BCC that grew on *Ptch1*<sup>+/−</sup>, basal keratinocyte-deleted p53 mice.

[0014] Figure 5 shows an over-expression of AKT1 in ASZ001 cells reduces the in vitro anti-BCC effect of tazarotene.

[0015] Figure 6 shows the potential of compound A and compound B as therapies for treating BCC.

[0016] Figure 7 depicts the in vivo treatment with PI3K inhibitors: Microscopic and visible BCC assessment at age 21 and 28 weeks respectively, after 8 weeks of drug treatment.

## DETAILED DESCRIPTION

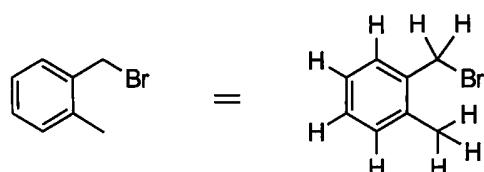
### Abbreviations and Definitions

[0017] The following abbreviations and terms have the indicated meanings throughout:

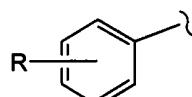
Abbreviation	Meaning
Ac	Acetyl
br	Broad
°C	Degrees Celsius
c-	Cyclo
CBZ	CarboBenZoxy = benzyloxycarbonyl
d	Doublet
dd	Doublet of doublet
dt	Doublet of triplet
DCM	Dichloromethane
DMA	Dimethylacetamide
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	Dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphano)ferrocene
EI	Electron Impact ionization
g	Gram(s)
h or hr	Hour(s)
HPLC	High pressure liquid chromatography
L	Liter(s)
M	Molar or molarity
m	Multiplet
mg	Milligram(s)
MHz	megahertz (frequency)
Min	minute(s)
mL	milliliter(s)
μL	microliter(s)
μM	Micromole(s) or micromolar
mM	Millimolar
mmol	Millimole(s)
mol	Mole(s)
MS	Mass spectral analysis
N	Normal or normality
nM	Nanomolar
NMR	Nuclear magnetic resonance spectroscopy
q	Quartet
RT	Room temperature
s	Singlet
t or tr	Triplet
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography

**[0018]** The symbol “-” means a single bond, “=” means a double bond, “≡” means a triple bond, “—” means a single or double bond. The symbol “~” refers to a group on a double-bond as occupying either position on the terminus of a double bond to which the symbol is attached; that is, the geometry, E- or Z-, of the double bond is ambiguous. When a group is depicted removed from its parent formula, the “~” or “—|” symbol will be used at the end of the bond which was theoretically cleaved in order to separate the group from its parent structural formula.

**[0019]** When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four. For example, in the structure on the left-hand side of the schematic below there are nine hydrogens implied. The nine hydrogens are depicted in the right-hand structure. Sometimes a particular atom in a structure is described in textual formula as having a hydrogen or hydrogens as substitution (expressly defined hydrogen), for example, -CH<sub>2</sub>CH<sub>2</sub>- . It is understood by one of ordinary skill in the art that the aforementioned descriptive techniques are common in the chemical arts to provide brevity and simplicity to description of otherwise complex structures.

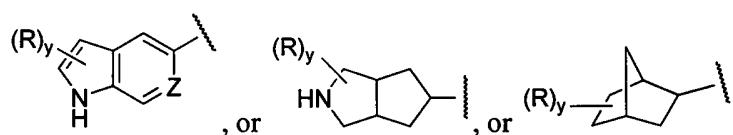


**[0020]** If a group “R” is depicted as “floating” on a ring system, as for example in the formula:



then, unless otherwise defined, a substituent “R” may reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

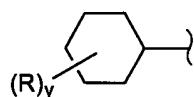
**[0021]** If a group “R” is depicted as floating on a fused ring system, as for example in the formulae:



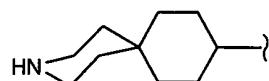
then, unless otherwise defined, a substituent “R” may reside on any atom of the fused ring system, assuming replacement of a depicted hydrogen (for example the -NH- in the formula

above), implied hydrogen (for example as in the formula above, where the hydrogens are not shown but understood to be present), or expressly defined hydrogen (for example where in the formula above, “Z” equals =CH-) from one of the ring atoms, so long as a stable structure is formed. In the example depicted, the “R” group may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula depicted above, when y is 2 for example, then the two “R’s” may reside on any two atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

**[0022]** When a group “R” is depicted as existing on a ring system containing saturated carbons, as for example in the formula:



where, in this example, “y” can be more than one, assuming each replaces a currently depicted, implied, or expressly defined hydrogen on the ring; then, unless otherwise defined, where the resulting structure is stable, two “R’s” may reside on the same carbon. A simple example is when R is a methyl group; there can exist a geminal dimethyl on a carbon of the depicted ring (an “annular” carbon). In another example, two R’s on the same carbon, including that carbon, may form a ring, thus creating a spirocyclic ring (a “spirocyclyl” group) structure with the depicted ring as for example in the formula:



**[0023]** “Acyl” means a -C(O)R radical where R is optionally substituted alkyl, optionally substituted alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylalkyl, as defined herein, e.g., acetyl, trifluoromethylcarbonyl, or 2-methoxyethylcarbonyl, and the like.

**[0024]** “Acylamino” means a -NRR’ radical where R is hydrogen, hydroxy, alkyl, or alkoxy and R’ is acyl, as defined herein.

**[0025]** “Acyloxy” means an -OR radical where R is acyl, as defined herein, e.g. cyanomethylcarbonyloxy, and the like.

**[0026]** “Administration” and variants thereof (e.g., “administering” a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents, “administration” and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

[0027] “Alkenyl” means a means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to 6 carbon atoms which radical contains at least one double bond, e.g., ethenyl, propenyl, 1-but-3-enyl, and 1-pent-3-enyl, and the like.

[0028] “Alkoxy” means an -OR group where R is alkyl group as defined herein. Examples include methoxy, ethoxy, propoxy, isopropoxy, and the like.

[0029] “Alkoxyalkyl” means an alkyl group, as defined herein, substituted with at least one, preferably one, two, or three, alkoxy groups as defined herein. Representative examples include methoxymethyl and the like.

[0030] “Alkoxyalkylamino” means an -NRR’ group where R is hydrogen, alkyl, or alkoxyalkyl and R’ is alkoxyalkyl, as defined herein.

[0031] “Alkoxyalkylaminoalkyl” means an alkyl group substituted with at least one, specifically one or two, alkoxyalkylamino group(s), as defined herein.

[0032] “Alkoxycarbonyl” means a -C(O)R group where R is alkoxy, as defined herein.

[0033] “Alkyl” means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to 6 carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, butyl (including all isomeric forms), or pentyl (including all isomeric forms), and the like.

[0034] “Alkylamino” means an -NHR group where R is alkyl, as defined herein.

[0035] “Alkylaminoalkyl” means an alkyl group substituted with one or two alkylamino groups, as defined herein.

[0036] “Alkylaminoalkyloxy” means an -OR group where R is alkylaminoalkyl, as defined herein.

[0037] “Alkylcarbonyl” means a -C(O)R group where R is alkyl, as defined herein.

[0038] “Alkynyl” means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to 6 carbon atoms which radical contains at least one triple bond, e.g., ethynyl, propynyl, butynyl, pentyN-2-yl and the like.

[0039] “Amino” means -NH<sub>2</sub>.

[0040] “Aminoalkyl” means an alkyl group substituted with at least one, specifically one, two or three, amino groups.

[0041] “Aminoalkyloxy” means an -OR group where R is aminoalkyl, as defined herein.

[0042] “Aryl” means a monovalent six- to fourteen-membered, mono- or bi-carbocyclic ring, wherein the monocyclic ring is aromatic and at least one of the rings in the bicyclic ring

is aromatic. Unless stated otherwise, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. Representative examples include phenyl, naphthyl, and indanyl, and the like.

[0043] “Arylalkyl” means an alkyl radical, as defined herein, substituted with one or two aryl groups, as defined herein, e.g., benzyl and phenethyl, and the like.

[0044] “Aryloxy” means an -OR group where R is aryl, as defined herein.

[0045] “Carboxyalkyl” means an alkyl group, as defined herein, substituted with at least one, specifically one or two, -C(O)OH group(s).

[0046] “Cycloalkyl” means a monocyclic or fused bicyclic, saturated or partially unsaturated (but not aromatic), monovalent hydrocarbon radical of three to ten carbon ring atoms. Fused bicyclic hydrocarbon radical includes bridged ring systems. Unless stated otherwise, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. One or two ring carbon atoms may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. More specifically, the term cycloalkyl includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexyl, or cyclohex-3-enyl, and the like.

[0047] “Cycloalkylalkyl” means an alkyl group substituted with at least one, specifically one or two, cycloalkyl group(s) as defined herein.

[0048] “Dialkylamino” means a -NRR’ radical where R and R’ are alkyl as defined herein, or an N-oxide derivative, or a protected derivative thereof, e.g., dimethylamino, diethylamino, *N,N*-methylpropylamino or *N,N*-methylethylamino, and the like.

[0049] “Dialkylaminoalkyl” means an alkyl group substituted with one or two dialkylamino groups, as defined herein.

[0050] “Dialkylaminoalkyloxy” means an -OR group where R is dialkylaminoalkyl, as defined herein. Representative examples include 2-(*N,N*-diethylamino)-ethoxy, and the like.

[0051] “Fused-polycyclic” or “fused ring system” means a polycyclic ring system that contains bridged or fused rings; that is, where two rings have more than one shared atom in their ring structures. In this application, fused-polycyclics and fused ring systems are not necessarily all aromatic ring systems. Typically, but not necessarily, fused-polycyclics share a vicinal set of atoms, for example naphthalene or 1,2,3,4-tetrahydro-naphthalene. A spiro ring system is not a fused-polycyclic by this definition, but fused polycyclic ring systems of the invention may themselves have spiro rings attached thereto via a single ring atom of the fused-polycyclic. In some examples, as appreciated by one of ordinary skill in the art, two adjacent groups on an aromatic system may be fused together to form a ring structure. The

fused ring structure may contain heteroatoms and may be optionally substituted with one or more groups. It should additionally be noted that saturated carbons of such fused groups (*i.e.* saturated ring structures) can contain two substitution groups.

[0052] “Halogen” or “halo” refers to fluorine, chlorine, bromine or iodine.

[0053] “Haloalkoxy” means an -OR’ group where R’ is haloalkyl as defined herein, e.g., trifluoromethoxy or 2,2,2-trifluoroethoxy, and the like.

[0054] “Haloalkyl” mean an alkyl group substituted with one or more halogens, specifically one to five halo atoms, e.g., trifluoromethyl, 2-chloroethyl, and 2,2-difluoroethyl, and the like.

[0055] “Heteroaryl” means a monocyclic, fused bicyclic, or fused tricyclic, monovalent radical of 5 to 14 ring atoms containing one or more, specifically one, two, three, or four ring heteroatoms independently selected from -O-, -S(O)<sub>n</sub>. (n is 0, 1, or 2), -N-, -N(R<sup>x</sup>)-, and the remaining ring atoms being carbon, wherein the ring comprising a monocyclic radical is aromatic and wherein at least one of the fused rings comprising a bicyclic or tricyclic radical is aromatic. One or two ring carbon atoms of any nonaromatic rings comprising a bicyclic or tricyclic radical may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. R<sup>x</sup> is hydrogen, alkyl, hydroxy, alkoxy, acyl, or alkylsulfonyl. Fused bicyclic radical includes bridged ring systems. Unless stated otherwise, the valency may be located on any atom of any ring of the heteroaryl group, valency rules permitting. When the point of valency is located on the nitrogen, R<sup>x</sup> is absent. More specifically, the term heteroaryl includes, but is not limited to, 1,2,4-triazolyl, 1,3,5-triazolyl, phthalimidyl, pyridinyl, pyrrolyl, imidazolyl, thienyl, furanyl, indolyl, 2,3-dihydro-1*H*-indolyl (including, for example, 2,3-dihydro-1*H*-indol-2-yl or 2,3-dihydro-1*H*-indol-5-yl, and the like), isoindolyl, indolinyl, isoindolinyl, benzimidazolyl, benzodioxol-4-yl, benzofuranyl, cinnolinyl, indolizinyl, naphthyridin-3-yl, phthalazin-3-yl, phthalazin-4-yl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, tetrazoyl, pyrazoyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isooxazolyl, oxadiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl (including, for example, tetrahydroisoquinolin-4-yl or tetrahydroisoquinolin-6-yl, and the like), pyrrolo[3,2-c]pyridinyl (including, for example, pyrrolo[3,2-c]pyridin-2-yl or pyrrolo[3,2-c]pyridin-7-yl, and the like), benzopyranyl, thiazolyl, isothiazolyl, thiadiazolyl, benzothiazolyl, benzothienyl, and the derivatives thereof, or N-oxide or a protected derivative thereof.

[0056] “Heteroarylalkyl” means an alkyl group, as defined herein, substituted with at least one, specifically one or two heteroaryl group(s), as defined herein.

[0057] “Heteroatom” refers to O, S, N, or P.

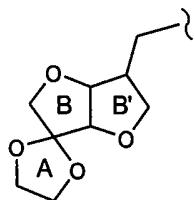
[0058] “Heterocycloalkyl” means a saturated or partially unsaturated (but not aromatic) monovalent monocyclic group of 3 to 8 ring atoms or a saturated or partially unsaturated (but not aromatic) monovalent fused bicyclic group of 5 to 12 ring atoms in which one or more, specifically one, two, three, or four ring heteroatoms independently selected from O, S(O)<sub>n</sub> (n is 0, 1, or 2), N, N(R<sup>y</sup>) (where R<sup>y</sup> is hydrogen, alkyl, hydroxy, alkoxy, acyl, or alkylsulfonyl), the remaining ring atoms being carbon. One or two ring carbon atoms may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. Fused bicyclic radical includes bridged ring systems. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. When the point of valency is located on a nitrogen atom, R<sup>y</sup> is absent. More specifically the term heterocycloalkyl includes, but is not limited to, azetidinyl, pyrrolidinyl, 2-oxopyrrolidinyl, 2,5-dihydro-1*H*-pyrrolyl, piperidinyl, 4-piperidonyl, morpholinyl, piperazinyl, 2-oxopiperazinyl, tetrahydropyranyl, 2-oxopiperidinyl, thiomorpholinyl, thiamorpholinyl, perhydroazepinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, oxazolinyl, oxazolidinyl, isoxazolidinyl, thiazolinyl, thiazolidinyl, quinuclidinyl, isothiazolidinyl, octahydroindolyl, octahydroisoindolyl, decahydroisoquinolyl, tetrahydrofuryl, and tetrahydropyranyl, and the derivatives thereof and N-oxide or a protected derivative thereof.

[0059] “Heterocycloalkylalkyl” means an alkyl radical, as defined herein, substituted with one or two heterocycloalkyl groups, as defined herein, e.g., morpholinylmethyl, *N*-pyrrolidinylethyl, and 3-(*N*-azetidinyl)propyl, and the like.

[0060] “Heterocycloalkylalkyloxy means an -OR group where R is heterocycloalkylalkyl, as defined herein.

[0061] “Saturated bridged ring system” refers to a bicyclic or polycyclic ring system that is not aromatic. Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may have aromatic substitution thereon). For example, hexahydro-furo[3,2-*b*]furan, 2,3,3a,4,7,7a-hexahydro-1*H*-indene, 7-aza-bicyclo[2.2.1]heptane, and 1,2,3,4,4a,5,8,8a-octahydro-naphthalene are all included in the class “saturated bridged ring system.”

[0062] “Spirocyclyl” or “spirocyclic ring” refers to a ring originating from a particular annular carbon of another ring. For example, as depicted below, a ring atom of a saturated bridged ring system (rings B and B’), but not a bridgehead atom, can be a shared atom between the saturated bridged ring system and a spirocyclyl (ring A) attached thereto. A spirocyclyl can be carbocyclic or heteroalicyclic.



**[0063]** “Optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. One of ordinary skill in the art would understand that with respect to any molecule described as containing one or more optional substituents, only sterically practical and/or synthetically feasible compounds are meant to be included. “Optionally substituted” refers to all subsequent modifiers in a term. So, for example, in the term “optionally substituted arylC<sub>1-8</sub> alkyl,” optional substitution may occur on both the “C<sub>1-8</sub> alkyl” portion and the “aryl” portion of the molecule may or may not be substituted. A list of exemplary optional substitutions is presented below in the definition of “substituted.”

**[0064]** “Optionally substituted alkoxy” means an -OR group where R is optionally substituted alkyl, as defined herein.

**[0065]** “Optionally substituted alkyl” means an alkyl radical, as defined herein, optionally substituted with one or more group(s), specifically one, two, three, four, or five groups, independently selected from alkylcarbonyl, alkenylcarbonyl, cycloalkylcarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, amino, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cyano, cyanoalkylaminocarbonyl, alkoxy, alkenyloxy, hydroxy, hydroxyalkoxy, halo, carboxy, alkylcarbonylamino, alkylcarbonyloxy, alkyl-S(O)<sub>0-2-</sub>, alkenyl-S(O)<sub>0-2-</sub>, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl-NR<sup>c</sup>- (where R<sup>c</sup> is hydrogen, alkyl, optionally substituted alkenyl, hydroxy, alkoxy, alkenyloxy, or cyanoalkyl), alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylaminoalkyloxy, dialkylaminoalkyloxy, alkoxycarbonyl, alkenyloxycarbonyl, alkoxycarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkoxyalkyloxy, and -C(O)NR<sup>a</sup>R<sup>b</sup> (where R<sup>a</sup> and R<sup>b</sup> are independently hydrogen, alkyl, optionally substituted alkenyl, hydroxy, alkoxy, alkenyloxy, or cyanoalkyl).

**[0066]** “Optionally substituted alkenyl” means an alkyl radical, as defined herein, optionally substituted with one or more group(s), specifically one, two, three, four, or five groups, independently selected from alkylcarbonyl, alkenylcarbonyl, cycloalkylcarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, amino, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cyano, cyanoalkylaminocarbonyl, alkoxy,

alkenyloxy, hydroxy, hydroxyalkoxy, halo, carboxy, alkylcarbonylamino, alkylcarbonyloxy, alkyl-S(O)<sub>0-2-</sub>, alkenyl-S(O)<sub>0-2-</sub>, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl-NR<sup>c</sup>- (where R<sup>c</sup> is hydrogen, alkyl, optionally substituted alkenyl, hydroxy, alkoxy, alkenyloxy, or cyanoalkyl), alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylaminoalkyloxy, dialkylaminoalkyloxy, alcoxycarbonyl, alkenyloxycarbonyl, alcoxycarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkoxyalkyloxy, and -C(O)NR<sup>a</sup>R<sup>b</sup> (where R<sup>a</sup> and R<sup>b</sup> are independently hydrogen, alkyl, optionally substituted alkenyl, hydroxy, alkoxy, alkenyloxy, or cyanoalkyl).

[0067] “Optionally substituted amino” refers to the group -N(H)R or -N(R)R where each R is independently selected from the group: optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, acyl, carboxy, alcoxycarbonyl, -S(O)<sub>2</sub>-(optionally substituted alkyl), -S(O)<sub>2</sub>-optionally substituted aryl), -S(O)<sub>2</sub>-(optionally substituted heterocycloalkyl), -S(O)<sub>2</sub>-(optionally substituted heteroaryl), and -S(O)<sub>2</sub>-(optionally substituted heteroaryl). For example, “optionally substituted amino” includes diethylamino, methylsulfonylamino, and furanyl-oxy-sulfonamino.

[0068] “Optionally substituted aminoalkyl” means an alkyl group, as defined herein, substituted with at least one, specifically one or two, optionally substituted amino group(s), as defined herein.

[0069] “Optionally substituted aryl” means an aryl group, as defined herein, optionally substituted with one, two, or three substituents independently selected from acyl, acylamino, acyloxy, optionally substituted alkyl, optionally substituted alkenyl, alkoxy, alkenyloxy, halo, hydroxy, alcoxycarbonyl, alkenyloxycarbonyl, amino, alkylamino, dialkylamino, nitro, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, aminoalkoxy, or aryl is pentafluorophenyl. Within the optional substituents on “aryl”, the alkyl and alkenyl, either alone or as part of another group (including, for example, the alkyl in alcoxycarbonyl), are independently optionally substituted with one, two, three, four, or five halo.

[0070] “Optionally substituted arylalkyl” means an alkyl group, as defined herein, substituted with optionally substituted aryl, as defined herein.

[0071] “Optionally substituted cycloalkyl” means a cycloalkyl group, as defined herein, substituted with one, two, or three groups independently selected from acyl, acyloxy, acylamino, optionally substituted alkyl, optionally substituted alkenyl, alkoxy, alkenyloxy,

alkoxycarbonyl, alkenyloxycarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, halo, hydroxy, amino, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, nitro, alkoxyalkyloxy, aminoalkoxy, alkylaminoalkoxy, dialkylaminoalkoxy, carboxy, and cyano. Within the above optional substituents on “cycloalkyl”, the alkyl and alkenyl, either alone or as part of another substituent on the cycloalkyl ring, are independently optionally substituted with one, two, three, four, or five halo, e.g. haloalkyl, haloalkoxy, haloalkyloxy, or haloalkylsulfonyl.

[0072] “Optionally substituted cycloalkylalkyl” means an alkyl group substituted with at least one, specifically one or two, optionally substituted cycloalkyl groups, as defined herein.

[0073] “Optionally substituted heteroaryl” means a heteroaryl group optionally substituted with one, two, or three substituents independently selected from acyl, acylamino, acyloxy, optionally substituted alkyl, optionally substituted alkenyl, alkoxy, alkenyloxy, halo, hydroxy, alkoxy carbonyl, alkenyloxycarbonyl, amino, alkylamino, dialkylamino, nitro, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, aminoalkoxy, alkylaminoalkoxy, and dialkylaminoalkoxy. Within the optional substituents on “heteroaryl”, the alkyl and alkenyl, either alone or as part of another group (including, for example, the alkyl in alkoxy carbonyl), are independently optionally substituted with one, two, three, four, or five halo.

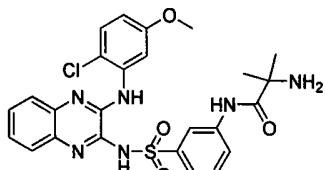
[0074] “Optionally substituted heteroarylalkyl” means an alkyl group, as defined herein, substituted with at least one, specifically one or two, optionally substituted heteroaryl group(s), as defined herein.

[0075] “Optionally substituted heterocycloalkyl” means a heterocycloalkyl group, as defined herein, optionally substituted with one, two, or three substituents independently selected from acyl, acylamino, acyloxy, optionally substituted alkyl, optionally substituted alkenyl, alkoxy, alkenyloxy, halo, hydroxy, alkoxy carbonyl, alkenyloxycarbonyl, amino, alkylamino, dialkylamino, nitro, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, aminoalkoxy, or aryl is pentafluorophenyl. Within the optional substituents on “heterocycloalkyl”, the alkyl and alkenyl, either alone or as part of another group (including, for example, the alkyl in alkoxy carbonyl), are independently optionally substituted with one, two, three, four, or five halo.

[0076] “Optionally substituted heterocycloalkylalkyl” means an alkyl group, as defined herein, substituted with at least one, specifically one or two, optionally substituted heterocycloalkyl group(s) as defined herein.

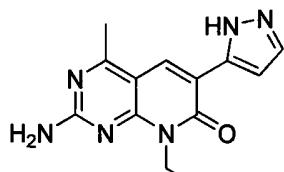
[0077] “Pharmaceutical composition” comprises 1) a compound of formula I or a single isomer thereof where the compound is optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof; and 2) a pharmaceutically acceptable carrier, excipient, or diluent.

[0078] As used herein, “compound A,” which is a compound of formula I and of formula



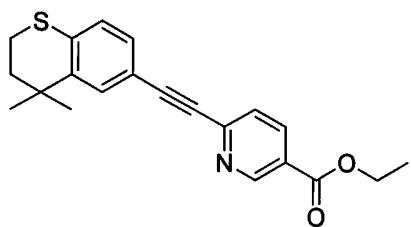
Ia, has the following structure . Compound A is known by its chemical name N-(3-{[(3-{[2-chloro-5-(methoxy)phenyl]amino}quinoxalin-2-yl)amino]sulfonyl}phenyl)-2-methylalaninamide. As discussed in more detail below, the compound may exist in several tautomeric forms. Accordingly, as used herein the terms “compound A” and “N-(3-{[(3-{[2-chloro-5-(methoxy)phenyl]amino}quinoxalin-2-yl)amino]sulfonyl}phenyl)-2-methylalaninamide” encompass all possible tautomeric and zwitterionic forms of the compound.

[0079] As used herein, “compound B,” which is a compound of formula II and of



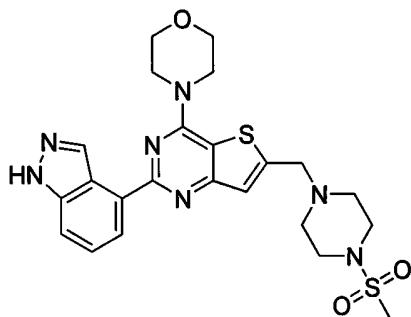
formula IIa has the following structure . Compound B is known by its chemical name 2-amino-8-ethyl-4-methyl-6-(1H-pyrazol-5-yl)pyrido[2,3-d]pyrimidin-7(8H)-one. The compound of formula II that is compound B is disclosed in WO 07/044813, the entire contents of which is incorporated herein by reference.

[0080] Tazarotene (Tazorac; CAS Number 118292-40-3) has the following structure



. Tazarotene is also known by its chemical name ethyl 6-[2-(4,4-dimethyl-3,4-dihydro-2H-1-benzothiopyran-6-yl)ethynyl]pyridine-3-carboxylate.

[0081] GDC0941 (CAS No. 957054-30-7) is a PI3K inhibitor from Genetech which has



the following structure . GDC0941 is also known by its chemical name 2-(1H-indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1- ylmethyl)-4-morpholin-4-yl-thieno[3,2-d]pyrimidine and is administered as the bimesylate salt.

[0082] “Yield” for each of the reactions described herein is expressed as a percentage of the theoretical yield.

[0083] “Patient” for the purposes of the present invention includes humans and other animals, particularly mammals, and other organisms. Thus the methods are applicable to both human therapy and veterinary applications. In a preferred embodiment the patient is a mammal, and in a most preferred embodiment the patient is human.

[0084] The terms “effective amount,” “pharmaceutically effective amount,” and “therapeutically effective amount” refer to a sufficient amount of an agent to provide the desired biological, therapeutic, and/or prophylactic result. That result can be reduction, amelioration, palliation, lessening, delaying, and/or alleviation of one or more of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. In reference to cancer, an effective amount comprises an amount sufficient to cause a tumor to shrink and/or to decrease the growth rate of the tumor (such as to suppress tumor growth) or to prevent or delay other unwanted cell proliferation. In some embodiments, an effective amount is an amount sufficient to delay development. In some embodiments, an effective amount is an amount sufficient to prevent or delay recurrence. An effective amount can be administered in one or more administrations. The effective amount of the combination or drug or composition may: (i) reduce the number of cancer cells; (ii) reduce tumor size; (iii) inhibit, retard, slow to some extent, and preferably stop cancer cell infiltration into peripheral organs; (iv) inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; (v) inhibit tumor growth; (vi) prevent or delay occurrence and/or recurrence of tumor; and/or (vii) relieve to some extent one or more of the symptoms associated with the cancer. For example, an “effective amount” for therapeutic uses is the amount of compound A or B, or a metabolite thereof, a pharmaceutically acceptable salt or solvate thereof, or a composition comprising

compound A or B or a metabolite thereof, or a pharmaceutically acceptable salt thereof, required to provide a clinically significant decrease in the progression of BCC.

[0085] A “pharmaceutically acceptable salt” of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17<sup>th</sup> ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference or S. M. Berge, et al., “Pharmaceutical Salts,” *J. Pharm. Sci.*, 1977;66:1-19 both of which are incorporated herein by reference.

[0086] Examples of pharmaceutically acceptable acid addition salts include those formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, 3-(4-hydroxybenzoyl)benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, p-toluenesulfonic acid, and salicylic acid, and the like.

[0087] Examples of a pharmaceutically acceptable base addition salts include those formed when an acidic proton present in the parent compound is replaced by a metal ion, such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferable salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Examples of organic bases include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine,

tromethamine, *N*-methylglucamine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine.

[0088] “Prodrug” refers to compounds that are transformed (typically rapidly) *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. Common examples include, but are not limited to, ester and amide forms of a compound having an active form bearing a carboxylic acid moiety. Examples of pharmaceutically acceptable esters of the compounds of this invention include, but are not limited to, alkyl esters (for example with between about one and about six carbons) the alkyl group is a straight or branched chain. Acceptable esters also include cycloalkyl esters and arylalkyl esters such as, but not limited to benzyl. Examples of pharmaceutically acceptable amides of the compounds of this invention include, but are not limited to, primary amides, and secondary and tertiary alkyl amides (for example with between about one and about six carbons). Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, “Pro-drugs as Novel Delivery Systems,” Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

[0089] “Metabolite” refers to the break-down or end product of a compound or its salt produced by metabolism or biotransformation in the animal or human body; for example, biotransformation to a more polar molecule such as by oxidation, reduction, or hydrolysis, or to a conjugate (see Goodman and Gilman, "The Pharmacological Basis of Therapeutics" 8.sup.th Ed., Pergamon Press, Gilman et al. (eds), 1990 for a discussion of biotransformation). As used herein, the metabolite of a compound of the invention or its salt may be the biologically active form of the compound in the body. In one example, a prodrug may be used such that the biologically active form, a metabolite, is released *in vivo*. In another example, a biologically active metabolite is discovered serendipitously, that is, no prodrug design *per se* was undertaken. An assay for activity of a metabolite of a compound of the present invention is known to one of skill in the art in light of the present disclosure.

[0090] Unless otherwise indicated, “treating” or “treatment” of a disease, disorder, or syndrome, as used herein, means inhibiting the disease, disorder, or syndrome, that is, arresting its development; and relieving the disease, disorder, or syndrome, that is, causing regression of the disease, disorder, or syndrome. As is known in the art, in the context of

treatment, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by one of ordinary skill in the art.

[0091] “Prevention” means preventing the disease, disorder, or syndrome from occurring in a human, i.e. causing the clinical symptoms of the disease, disorder, or syndrome not to develop in an animal that may be exposed to or predisposed to the disease, disorder, or syndrome but does not yet experience or display symptoms of the disease, disorder, or syndrome.

### **Embodiments**

[0092] The following paragraphs present a number of embodiments that can be used to practice the invention. In each instance, the embodiment includes both the recited compounds as well as individual isomers and mixtures of isomers. In addition, in each instance, the embodiment includes the pharmaceutically acceptable salts, hydrates, and/or solvates of the recited compounds and any individual isomers or mixture of isomers thereof.

[0093] In one embodiment, methods are provided for treating cancer which method comprises administering to a patient an effective amount of a compound of formula I or II or a pharmaceutical composition comprising a compound of formula I or II.

[0094] In another embodiment, methods are provided for treating cancer which method comprises administering to a patient an effective amount of a compound of formula I or II or a pharmaceutical composition comprising a compound of formula I where the cancer is basal cell carcinoma.

[0095] Any of the following embodiments, including the representative compounds described below, may be used to practice any of the methods disclosed herein.

### **Compounds of Formula I**

[0096] The compound of formula I is selected from any of the following embodiments, including from the Representative compounds in the associated Table.

[0097] One embodiment (A) of the compound of formula I is where  $W^1$ ,  $W^2$ ,  $W^3$ , and  $W^4$  are  $-C(R^1)=$ ; or one or two of  $W^1$ ,  $W^2$ ,  $W^3$ , and  $W^4$  are independently  $-N=$  and the remaining are  $-C(R^1)=$ ; where each  $R^1$  is independently hydrogen, alkyl, haloalkyl, nitro, alkoxy, haloalkoxy, halo, hydroxy, cyano, amino, alkylamino, or dialkylamino; and all other groups

are as defined in the Summary of the Invention. In another embodiment, W<sup>1</sup>, W<sup>2</sup>, W<sup>3</sup>, and W<sup>4</sup> are -C(R<sup>1</sup>)= and each R<sup>1</sup> is independently hydrogen or alkyl; or one of W<sup>1</sup> and W<sup>4</sup> is -N= and the other is -C(H)=. In another embodiment, W<sup>1</sup>, W<sup>2</sup>, W<sup>3</sup>, and W<sup>4</sup> are -C(R<sup>1</sup>)= where each R<sup>1</sup> is independently hydrogen or alkyl. In another embodiment, R<sup>1</sup> is hydrogen.

[0098] Another embodiment (B) of a compound of formula I is where R<sup>50</sup> is hydrogen, alkyl, alkenyl, halo, haloalkyl, haloalkenyl, hydroxy, alkoxy, alkenyloxy, haloalkoxy, nitro, amino, alkylamino, dialkylamino, -N(R<sup>55</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>55a</sup>)R<sup>55b</sup>, alkylcarbonyl, alkenylcarbonyl, carboxy, alkoxycarbonyl, cyano, alkylthio, -S(O)<sub>2</sub>NR<sup>55</sup>R<sup>55a</sup>, or alkylcarbonylamino; where R<sup>55</sup> and R<sup>55b</sup> are independently hydrogen, alkyl, or alkenyl and R<sup>55a</sup> is hydrogen, alkyl, alkenyl, hydroxy, or alkoxy; and all other groups are as defined in the Summary of the Invention. In another embodiment, R<sup>50</sup> is hydrogen.

[0099] Another embodiment (C) of a compound of formula I is where R<sup>51</sup> is hydrogen or alkyl; and all other groups are as defined in the Summary of the Invention. In another embodiment, R<sup>51</sup> is alkyl, In another embodiment, R<sup>51</sup> is methyl.

[00100] Another embodiment (D) of a compound of formula I is where R<sup>52</sup> is hydrogen or halo; and all other groups are as defined in the Summary of the Invention. In another embodiment R<sup>52</sup> is hydrogen or fluoro. In another embodiment, R<sup>52</sup> is hydrogen.

[00101] Another embodiment (E) of a compound of formula I is where R<sup>53</sup> is hydrogen, alkyl, alkenyl, halo, haloalkyl, haloalkenyl, hydroxy, alkoxy, alkenyloxy, haloalkoxy, nitro, amino, alkylamino, dialkylamino, -N(R<sup>55</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>55a</sup>)R<sup>55b</sup>, alkylcarbonyl, alkenylcarbonyl, carboxy, alkoxycarbonyl, cyano, alkylthio, -S(O)<sub>2</sub>NR<sup>55</sup>R<sup>55a</sup>, or alkylcarbonylamino; where R<sup>55</sup> and R<sup>55b</sup> are independently hydrogen, alkyl, or alkenyl and R<sup>55a</sup> is hydrogen, alkyl, alkenyl, hydroxy, or alkoxy; and all other groups are as defined in the Summary of the Invention. In another embodiment, R<sup>53</sup> is hydrogen, alkoxy, nitro, amino, or -N(R<sup>55</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>55a</sup>)R<sup>55b</sup>. In another embodiment, R<sup>53</sup> is hydrogen, methoxy, nitro, amino, or -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>. In another embodiment, R<sup>53</sup> is hydrogen or methoxy.

[00102] Another embodiment (F) of a compound of formula I is where R<sup>54</sup> is hydrogen, alkyl, alkenyl, halo, haloalkyl, haloalkenyl, hydroxy, alkoxy, alkenyloxy, haloalkoxy, nitro, amino, alkylamino, dialkylamino, -N(R<sup>55</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>55a</sup>)R<sup>55b</sup>, alkylcarbonyl, alkenylcarbonyl, carboxy, alkoxycarbonyl, cyano, alkylthio, -S(O)<sub>2</sub>NR<sup>55</sup>R<sup>55a</sup>, or alkylcarbonylamino; where R<sup>55</sup> and R<sup>55b</sup> are independently hydrogen, alkyl, or alkenyl and R<sup>55a</sup> is hydrogen, alkyl, alkenyl, hydroxy, or alkoxy; and all other groups are as defined in the Summary of the Invention. In another embodiment, R<sup>54</sup> is hydrogen, alkyl, alkoxy, or halo.

In another embodiment, R<sup>54</sup> is hydrogen, methyl, methoxy, bromo, or chloro. In another embodiment, R<sup>54</sup> is hydrogen, methoxy, or chloro.

**[00103]** Another embodiment (G) is directed to a compound of formula I where R<sup>50</sup>, R<sup>52</sup>, and R<sup>53</sup> are hydrogen and R<sup>54</sup> is halo or alkoxy; R<sup>50</sup>, R<sup>52</sup>, and R<sup>54</sup> are hydrogen and R<sup>53</sup> is alkoxy; or R<sup>50</sup> and R<sup>52</sup> are hydrogen and R<sup>53</sup> and R<sup>54</sup> together with the carbons to which they are attached form a 6-membered heteroaryl; and all other groups are as defined in the Summary of the Invention. In another embodiment, R<sup>50</sup>, R<sup>52</sup>, and R<sup>53</sup> are hydrogen and R<sup>54</sup> is chloro or methoxy; R<sup>50</sup>, R<sup>52</sup>, and R<sup>54</sup> are hydrogen and R<sup>53</sup> is methoxy; or R<sup>50</sup> and R<sup>52</sup> are hydrogen and R<sup>53</sup> and R<sup>54</sup> together with the carbons to which they are attached form pyridinyl. Even more specifically, R<sup>50</sup>, R<sup>52</sup>, and R<sup>53</sup> are hydrogen and R<sup>54</sup> is chloro or methoxy; or R<sup>50</sup>, R<sup>52</sup>, and R<sup>54</sup> are hydrogen and R<sup>53</sup> is methoxy.

**[00104]** In another embodiment (G1) of embodiment G is a compound of formula I where R<sup>51</sup> is methyl.

**[00105]** Another embodiment (J), B is heteroaryl optionally substituted with one, two, or three R<sup>3</sup>. In another embodiment, B is thien-3-yl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, oxazolyl, isoxazolyl, pyrrolyl, imidazolyl, pyrazolyl, or thiazolyl, each of which is optionally substituted with one or two R<sup>3</sup>. In another embodiment, B is thien-3-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, imidazol-2-yl, pyrrol-2-yl, pyrrol-3-yl, imidazol-4-yl, imidazol-5-yl, pyrazol-3-yl, pyrazol-4-yl, or pyrazol-5-yl, each of which is optionally substituted with one or two R<sup>3</sup>. In another embodiment, B is thien-3-yl, pyridin-3-yl, pyridin-4-yl, isoxazol-4-yl, or pyrazol-4-yl, each of which is optionally substituted with one or two R<sup>3</sup>. In another embodiment, B is pyridin-3-yl, 2-hydroxy-pyridin-5-yl, isoxazol-4-yl, or pyrazol-4-yl, each of which is optionally substituted with one or two R<sup>3</sup>.

**[00106]** Another embodiment (K), R<sup>3a</sup> is cyano; hydroxyamino; carboxy; alkylsulfonyl, aminoalkyloxy; alkylaminoalkyloxy; dialkylaminoalkyloxy; -N(R<sup>7</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>7a</sup>)(R<sup>7b</sup>); -C(O)NR<sup>8</sup>R<sup>8a</sup>; -NR<sup>9</sup>C(O)R<sup>9a</sup>; -C(O)N(R<sup>10</sup>)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>10a</sup>)R<sup>10b</sup>; -NR<sup>11</sup>C(O)NR<sup>11a</sup>R<sup>11b</sup> where R<sup>11a</sup>; -C(O)R<sup>12</sup>; -NR<sup>13</sup>C(O)OR<sup>13a</sup>; -C(O)N(R<sup>14</sup>)N(R<sup>14a</sup>)(R<sup>14b</sup>); -S(O)<sub>2</sub>N(R<sup>15</sup>)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>15a</sup>)R<sup>15b</sup>; -C(O)N(R<sup>16</sup>)-C<sub>1</sub>-C<sub>6</sub>-alkylene-C(O)OR<sup>16a</sup>; heteroaryl optionally substituted with one or two aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl; -N(R<sup>17</sup>)-C(=N(R<sup>17b</sup>)(R<sup>17a</sup>))(NR<sup>17c</sup>R<sup>17d</sup>); -N(R<sup>18</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>18b</sup>)C(O)R<sup>18a</sup>; -C(O)N(R<sup>19</sup>)-C<sub>1</sub>-C<sub>6</sub>-alkylene-C(O)R<sup>19a</sup>; -N(R<sup>22</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>22b</sup>)-N(R<sup>22c</sup>)(R<sup>22a</sup>); -C<sub>0</sub>C<sub>6</sub>-alkylene-N(R<sup>23</sup>)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>23b</sup>)R<sup>23a</sup>; or -NR<sup>24</sup>C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-OR<sup>24a</sup>; where each of the alkylene in R<sup>3a</sup> is independently optionally further

substituted with 1, 2, 3, 4, or 5 groups selected from halo, hydroxy, amino, alkylamino, and dialkylamino; and all other groups are as defined in the Summary of the Invention.

[00107] In another embodiment, R<sup>3a</sup> is:-NHC(O)CH<sub>2</sub>NH(CH<sub>3</sub>), -NHC(O)CH<sub>2</sub>NH(CH<sub>2</sub>CH<sub>3</sub>), -NHC(O)CH(CH<sub>3</sub>)NH<sub>2</sub>, -NHC(O)C(CH<sub>3</sub>)<sub>2</sub>NH<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH(NH<sub>2</sub>)CH<sub>2</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH(CH<sub>3</sub>)NH(CH<sub>3</sub>), -NHC(O)CH<sub>2</sub>NH<sub>2</sub>, -NHC(O)H, -NHC(O)CH<sub>2</sub>(azetidin-1-yl), -NHC(O)(pyrrolidin-2-yl), -NHC(O)CH(NH<sub>2</sub>)CH<sub>2</sub>OH, -NHC(O)(azetidin-4-yl), -NHC(O)C(CH<sub>3</sub>)<sub>2</sub>NH(CH<sub>3</sub>), -NH<sub>2</sub>, -NHC(O)CH<sub>2</sub>NH(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), -NHC(O)CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, -NHOH, -NHC(O)(piperidin-3-yl), -NHC(O)CH<sub>2</sub>(4-methyl-1,4-diazepan-1-yl), -NHC(O)CH(NH<sub>2</sub>)(CH<sub>2</sub>CH<sub>3</sub>), -NHC(O)CH<sub>2</sub>NH(CH<sub>2</sub>CH(OH)(CH<sub>3</sub>)), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>CH<sub>2</sub>F, -NHC(O)CH<sub>2</sub>NH(OCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), -NHC(O)(1-aminocycloprop-1-yl), -NHC(O)CH<sub>2</sub>NH(CH<sub>2</sub>cyclopropyl), -NHC(O)CH<sub>2</sub>(3-(dimethylamino)-azetidin-1-yl), -NHC(O)(piperidin-2-yl), -NHC(O)(morpholin-4-yl), -NHC(O)CH<sub>2</sub>(pyrrolidin-1-yl), -NHC(O)CH(NH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>), -NHC(O)CH<sub>2</sub>(imidazol-5-yl), -NHC(O)(1-aminocyclopent-1-yl), -NHC(O)CH<sub>2</sub>NH(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>), -NHC(O)(N-(imidazol-4-ylmethyl)-azetidin-3-yl), -NHC(O)(N-ethyl-azetidin-3-yl), -NHCH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)(N-methyl-pyrrolidin-3-yl), -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>), -NHC(O)CH<sub>2</sub>(3-hydroxy-pyrrolidin-1-yl), -NHC(O)(1-amino-cyclobut-1-yl), -NHC(O)CH<sub>2</sub>NH(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>(3-piperidin-1-ylazetidin-1-yl), -NHC(O)NH<sub>2</sub>, -NHC(O)(1-hydroxycyclopropyl), -NHC(O)CH<sub>2</sub>NHN(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)NH(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>OH, -NHC(O)(pyridazin-4-yl), -NHC(O)(N-methyl-piperidin-4-yl), -NHC(O)CH<sub>2</sub>NH(CH<sub>3</sub>)<sub>3</sub>, -NHC(O)(imidazol-2-yl), -NHC(O)(imidazol-4-yl), -NHC(O)(1,2-oxazol-5-yl), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>CF<sub>3</sub>, -NHC(O)CH<sub>2</sub>CH<sub>2</sub>(piperidin-1-yl), -NHC(O)(3-oxo-cyclopent-1-yl), -NHC(O)(2-hydroxy-pyridin-6-yl), -NHC(O)CH<sub>2</sub>NH(3-fluoro-4-hydroxyphenyl), -NHC(O)(CH<sub>2</sub>)<sub>3</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)(1-(furan-2-ylmethyl)-azetidin-3-yl), -NHC(O)(pyrimidin-5-yl), -NHC(O)(pyrrol-2-yl), -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>(3-methyl-1,2-oxazol-5-yl), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>(3-hydroxyphenyl), -NHC(O)(N-methyl-pyrrol-2-yl), -NHC(O)(2-amino-tetrahydropyran-2-yl), -NHC(O)CH<sub>2</sub>(4-methylamino-piperidin-1-yl), -NHC(O)(piperidin-1-yl), -NHC(O)(N-methyl-pyrrolidin-2-yl), -NHC(O)(thien-3-yl),

-NHC(O)(*N*-(cyclopropylcarbonyl)azetidin-3-yl), -NHC(O)CH<sub>2</sub>(4-methylpiperazin-1-yl),  
-NHC(O)(*N*-benzylazetidin-3-yl), -NHC(O)(2-chloro-pyridin-3-yl), -NHC(O)CH<sub>2</sub>(pyridin-4-yl), -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)(CH<sub>2</sub>CH=CH<sub>2</sub>), -NHC(O)CH<sub>2</sub>NH(benzyl), -NHC(O)CH<sub>2</sub>OCH<sub>3</sub>,  
-NHC(O)[1-(C(O)CH<sub>2</sub>CH<sub>3</sub>)-azetidin-3-yl], -NHC(O)(pyridin-3-yl), -  
NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -NHC(O)(1-[C(O)CH<sub>3</sub>]piperidin-4-yl), -NHC(O)CH<sub>2</sub>(2-methyl-pyrrolidin-1-yl), -NHC(O)(furan-3-yl), -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)(2-chloropyridin-5-yl), -NHC(O)(2-chlorophenyl), -NHC(O)CH<sub>2</sub>(pyridin-2-yl), -NHC(O)CH<sub>2</sub>(3-dimethylamino-azetidin-1-yl), -NHC(O)CH<sub>2</sub>(pyridin-3-yl), -NHC(O)CH<sub>2</sub>(2-chlorophenyl),  
-NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>OH,  
-NHC(O)CH<sub>2</sub>(2-benzyl-pyrrolidin-1-yl), -NHC(O)(furan-2-yl), -NHC(O)(2-chloro-pyridin-4-yl), -NHC(O)CH<sub>2</sub>NHC(O)CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -NHC(O)(4-chlorophenyl),  
-NHC(O)(4-methyl-phenyl), -NHC(O)CH<sub>2</sub>NHC(O)O(CH<sub>3</sub>)<sub>3</sub>, -NHC(O)(benzo[d][1,3]dioxol-5-yl), -NHC(O)CH<sub>2</sub>NHOCH<sub>2</sub>(2-methoxyphenyl), -NHC(O)(pyridin-4-yl), -NHC(O)CH<sub>2</sub>[4-(3,4-dichlorophenyl)-piperazin-1-yl], -NHC(O)CH<sub>2</sub>CH<sub>2</sub>(pyridin-3-yl),  
-NHC(O)(tetrahydrofuran-3-yl), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>(2-methylphenyl),  
-NHC(O)CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>(3-fluorophenyl), -NHC(O)CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>phenyl,  
-NHC(O)(2-methyl-cycloprop-1-yl), -NHC(O)(2-methyl-4-methoxyphenyl), -NHC(O)(2-methylpyridin-3-yl), -NHC(O)(4-methoxyphenyl), -NHC(O)CH<sub>2</sub>(4-ethylpiperazin-1-yl),  
-NHC(O)(thien-2-yl), -NHC(O)(3-fluoro-2-methylphenyl), -NHC(O)(2-bromo-thien-3-yl),  
-NHC(O)(4-fluorophenyl), -NHC(O)CH<sub>2</sub>(3-methylpiperidin-1-yl), -NHC(O)CH(CH<sub>3</sub>)<sub>2</sub>, -  
NHC(O)(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>NH(2-fluorophenyl),  
-NHC(O)(3-dimethylaminophenyl), -NHC(O)CH<sub>2</sub>(4-methylpiperidin-1-yl),  
-NHC(O)CH<sub>2</sub>NH(2-*n*-propylphenyl), -NHC(O)phenyl, -NHC(O)(pyrazin2-yl), -NHC(O)(3-fluoro-4-methoxyphenyl), -NHC(O)C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>O(4-fluorophenyl),  
-NHC(O)(1-methylcarbonyl-azetidin-3-yl), -NHC(O)CH<sub>2</sub>NH(4-methylphenyl),  
-NHC(O)CH<sub>2</sub>NH(phenyl), -NHC(O)CH<sub>2</sub>(4-allyl-piperazin-1-yl), -NHC(O)(2-methylphenyl),  
-NHC(O)CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -NHC(O)(3-methyl-furan-2-yl), -NHC(O)C(CH<sub>3</sub>)<sub>3</sub>, -  
NHC(O)CH<sub>2</sub>NHObenzyl, -NHC(O)CH<sub>2</sub>NH(3-chlorophenyl), --NHC(O)cyclobutyl,  
-NHC(O)CH<sub>2</sub>(3-methoxyphenyl), -NHC(O)(1-methylcycloprop-1-yl), -  
NHC(O)(3-fluorophenyl), -NHC(O)(4-dimethylaminophenyl), -NHC(O)(3,4-dichlorophenyl),  
-NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>(2-methylthiophenyl), -NHC(O)CH<sub>2</sub>(2-fluorophenyl), -  
NHC(O)CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)CH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)(thiazol-4-yl), -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)benzyl, -  
NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>(thien-2-yl), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>(pyridin-2-yl), -NHC(O)(3-methoxyphenyl), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>(3-chloro-4-methylphenyl), -

NHC(O)CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>(4-chlorophenyl), -NHC(O)(3-fluoro-4-methylphenyl), -NHC(O)CH<sub>2</sub>O(2-methylphenyl), -NHC(O)CH<sub>2</sub>(cyclohexyl), -NHC(O)(2-phenyl-cycloprop-1-yl), -NHC(O)(3-chlorophenyl), -NHC(O)CH<sub>2</sub>(2-methoxyphenyl), -NHC(O)CH<sub>2</sub>CH<sub>2</sub>(3-methoxyphenyl), -NHC(O)CH<sub>2</sub>NH(2-fluoro-4-methyl-phenyl), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>(3-fluoro-phenyl), -NHC(O)CH<sub>2</sub>(4-methoxy-phenyl), -NHC(O)benzyl, -NHC(O)(2,4-dichlorophenyl), -NHC(O)(3-oxo-cyclohex-1-yl), -NHC(O)CH<sub>2</sub>NH(3-fluorophenyl), -NHC(O)CH<sub>2</sub>(3-chlorophenyl), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>CH(CH<sub>3</sub>)phenyl, -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>(2,4-dimethylphenyl), -NHC(O)CH<sub>2</sub>(2-methyl-piperidin-1-yl), -NHC(O)CH<sub>2</sub>NH(2-methoxyphenyl), -NHC(O)CH<sub>2</sub>(1,2,3,4-tetrahydroisoquinolin-2-yl), -NHC(O)CH<sub>2</sub>CH<sub>2</sub>CH=CH<sub>2</sub>, -NHC(O)CH<sub>2</sub>NH(2-methylphenyl), -NHC(O)CH<sub>2</sub>(4-oxo-piperidin-1-yl), -NHC(O)(2-fluorophenyl), -NHC(O)CH<sub>2</sub>NHCH(CH<sub>3</sub>)phenyl, -NHC(O)(2-fluoro-6-methoxyphenyl), -NHC(O)CH<sub>2</sub>NH(2-isopropylphenyl), -NHC(O)CH<sub>2</sub>CH<sub>2</sub>(2-methoxyphenyl), -NHC(O)CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>(2-phenyl-morpholin-4-yl), -NHC(O)CH<sub>2</sub>CH<sub>2</sub>(4-methoxyphenyl), -NHC(O)CH<sub>2</sub>N(allyl)cyclopentyl, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -NHC(O)CH<sub>2</sub>CH<sub>2</sub>C(O)cyclopropyl, NHC(O)CH<sub>2</sub>NH(3-*tert*-butylphenyl), -NHC(O)CH<sub>2</sub>N(*n*-propyl)(cyclopropylmethyl), -NHC(O)CH<sub>2</sub>(2-oxo-cyclopentyl), -NHC(O)CH<sub>2</sub>NH(4-chlorophenyl), -NHC(O)CH<sub>2</sub>(4-piperidin-1-yl)piperidin-1-yl), -NHC(O)CH<sub>2</sub>(4-cyclopentylpiperazin-1-yl), -NHC(O)CH<sub>2</sub>(2-methylphenyl), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>(3-fluoro-6-methylphenyl), -NHC(O)CH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>, -NHC(O)CH<sub>2</sub>NH(2-chlorophenyl), -NHC(O)(3-fluoro-6-methylphenyl), -NHC(O)(4-fluoro-3-methylphenyl), -NHC(O)(2,3-dichlorophenyl), -NHC(O)CH<sub>2</sub>Ophenyl, -NHC(O)CH<sub>2</sub>NH(2,3-dimethylphenyl), -NHC(O)(2-fluoro-5-methylphenyl), -NHC(O)CH<sub>2</sub>NHOCH<sub>2</sub>(4-methylphenyl), -NHC(O)CH<sub>2</sub>(4-isopropylpiperazin-1-yl), -NHC(O)CH<sub>2</sub>(4-fluorophenyl), -NHC(O)CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)(2-methoxy-4-methylphenyl), -NHC(O)CH<sub>2</sub>(4-*n*-propylpiperidin-1-yl), -NHC(O)CH<sub>2</sub>O(3-methylphenyl), -NHC(O)(tetrahydrofuran-2-yl), -NHC(O)CH<sub>2</sub>(3-hydroxymethylpiperidin-1-yl), -NHC(O)(1-*tert*-butoxycarbonylpiperidin-2-yl), -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>(pyridin-3-yl), -NHC(O)CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)phenyl, -NHC(O)CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -NHC(O)CH<sub>2</sub>CH<sub>2</sub>(cyclopentyl), -NHC(O)(2,5-dichlorophenyl), -NHC(O)CH<sub>2</sub>(4-methylcarbonylpiperazin-1-yl), -NHC(O)(5-fluoro-2-methoxyphenyl), -NHC(O)CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)cyclohexyl, -NHC(O)(5-methyl-1,2-oxazol-3-yl), -NHC(O)(3-methylpyridin-3-yl), -NHC(O)(2-methoxypyridin-3-yl), -NHC(O)(3,5-dichlorophenyl), -NHC(O)CH<sub>2</sub>(thiazolidin3-yl), -NHC(O)CH<sub>2</sub>(4-[C(O)H]-piperazin-1-yl), -NHC(O)CH<sub>2</sub>(2-pyridin-4-ylpiperidin-1-yl), -NHC(O)(2-methoxyphenyl), -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>(4-[C(O)H]-homopiperazin-1-yl),

-NHC(O)(1-phenylcycloprop-1-yl), -NHC(O)CH<sub>2</sub>(2,6-dimethylmorpholin-4-yl), NHC(O)CH<sub>2</sub>(2-phenylpyrrolidin-1-yl), -NHC(O)CH<sub>2</sub>(morpholin-4-yl), -C(O)NHCH(CH<sub>3</sub>)CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -C(O)NH(pyrrolidin-3-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>(pyrrolidin-1-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, -C(O)N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -C(O)NHCH<sub>2</sub>(piperidin-2-yl), -C(O)NH(1-methylazetidin-3-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>(piperidin-1-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -C(O)NH(1-methylpiperidin-3-yl), -C(O)NH(piperidin-3-yl), -C(O)NHCH<sub>2</sub>(1-methylpiperidin-3-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>OH)<sub>2</sub>, -C(O)NH(1-ethylpiperidin-3-yl), -C(O)NH<sub>2</sub>, -C(O)(3-aminopyrrolidin-1-yl), -C(O)(3-methylaminopyrrolidin-1-yl), -C(O)OH, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>(morpholin-4-yl), -C(O)NHCH<sub>2</sub>(1-ethylpyrrolidin-2-yl), -C(O)(4-amino-3-oxo-pyrazolidin-1-yl), -C(O)NHCH<sub>3</sub>, -C(O)(3-aminocyclobut-1-yl), -C(O)NHCH<sub>2</sub>(pyridin-3-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>OH, -C(O)NH(3-oxo-pyrazolidin-4-yl), -NHCH<sub>2</sub>CH<sub>2</sub>(imidazol-4-yl), -C(O)(3-dimethylaminopyrrolidin-1-yl), -C(O)NHCH<sub>2</sub>(pyridin-4-yl), -C(O)N(CH<sub>3</sub>)(1-methyl-pyrrolidin-3-yl), -C(O)(3-diethylaminopyrrolidin-1-yl), -C(O)NH(pyrrol-1-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>(pyrrolidin-1-yl), -C(O)N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CN, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -C(O)N(CH<sub>2</sub>CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CN, -C(O)(3-aminopiperidin-1-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -C(O)NH(morpholin-4-yl), -C(O)NHN(CH<sub>3</sub>)<sub>2</sub>, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>(imidazol-1-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CN, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>C(O)OCH<sub>3</sub>, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>SCH<sub>3</sub>, -(O)NHCH<sub>2</sub>CH<sub>2</sub>SCH<sub>2</sub>CH<sub>3</sub>, -C(O)N(CH<sub>2</sub>CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>(2-oxo-pyrrolidin-1-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>(pyridin-4-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>(morpholin-4-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -C(O)N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>C(O)OCH<sub>2</sub>CH<sub>3</sub>, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OCH(CH<sub>3</sub>)<sub>2</sub>, -C(O)NHC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>(piperidin-1-yl), -C(O)N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -C(O)NH(piperidin-1-yl), -C(O)NHCH(CH<sub>3</sub>)CH<sub>2</sub>OCH<sub>3</sub>, -C(O)NHC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>(morpholin-4-yl), -C(O)(2-dimethylaminomethyl)piperidin-1-yl), -C(O)NH(CH<sub>2</sub>)<sub>3</sub>O(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -C(O)NHCH(CH<sub>3</sub>)(CH<sub>2</sub>)<sub>3</sub>N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -C(O)NHC(CH<sub>3</sub>)<sub>2</sub>C(O)(piperidin-1-yl), -C(O)(4-methylpiperazin-1-yl), -C(O)(2-piperidin-1-ylmethyl-piperidin-1-yl), cyano, -NHCH<sub>3</sub>, -CH(CH<sub>3</sub>)NHCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -C(O)CH<sub>3</sub>, -S(O)<sub>2</sub>NHCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -S(O)<sub>2</sub>NH(CH<sub>2</sub>)<sub>3</sub>N(CH<sub>3</sub>)<sub>2</sub>, 5-(N,N-dimethylaminomethyl)-1,3,4-oxadiazol-2-yl, -NHCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -OCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC[N(CH<sub>3</sub>)<sub>2</sub>][=N(CH<sub>3</sub>)<sub>2</sub>], -OCF<sub>2</sub>, -S(O)<sub>2</sub>CH<sub>3</sub>, -OCF<sub>3</sub>, or -NHC(O)CH<sub>2</sub>(4-dimethylaminopiperidin-1-yl).

**[00108]** In another embodiment (L), R<sup>3a</sup> is hydroxyamino, -N(R<sup>7</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>7a</sup>)(R<sup>7b</sup>), -C(O)NR<sup>8</sup>R<sup>8a</sup>, -NR<sup>9</sup>C(O)R<sup>9a</sup>, -C(O)N(R<sup>10</sup>)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>10a</sup>)R<sup>10b</sup>, -NR<sup>11</sup>C(O)NR<sup>11a</sup>R<sup>11b</sup>, -N(R<sup>22</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>22b</sup>)-N(R<sup>22c</sup>)(R<sup>22a</sup>), -NR<sup>13</sup>C(O)OR<sup>13a</sup>, -N(R<sup>18</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>18b</sup>)C(O)R<sup>18a</sup>, -NR<sup>24</sup>C(O)-C<sub>1</sub>.C<sub>6</sub>-alkylene-OR<sup>24a</sup>, or -N(R<sup>20</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-C(O)R<sup>20a</sup>; where each of the alkylene in R<sup>3a</sup> is independently optionally further substituted with 1, 2, 3, 4, or 5 groups selected from halo, hydroxy, and amino; and all other groups are as defined in the Summary of the Invention. In another embodiment, R<sup>3a</sup> is -NHC(O)CH<sub>2</sub>NH(CH<sub>3</sub>), -NHC(O)CH(CH<sub>3</sub>)NH<sub>2</sub>, -NHC(O)C(CH<sub>3</sub>)<sub>2</sub>NH<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH(NH<sub>2</sub>)CH<sub>2</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH(CH<sub>3</sub>)NH(CH<sub>3</sub>), -NHC(O)H, -NHC(O)CH<sub>2</sub>(azetidin-1-yl), -NHC(O)(pyrrolidin-2-yl), -NHC(O)CH(NH<sub>2</sub>)CH<sub>2</sub>OH, -NHC(O)(azetidin-4-yl), -NHC(O)C(CH<sub>3</sub>)<sub>2</sub>NH(CH<sub>3</sub>), -NH<sub>2</sub>, -NHC(O)CH<sub>2</sub>NH(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), -NHC(O)CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, -NHOH, or -NHC(O)(piperidin-3-yl).

**[00109]** In another embodiment (M), R<sup>3a</sup> -N(R<sup>7</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>7a</sup>)(R<sup>7b</sup>); and R<sup>7</sup> is hydrogen or alkyl and R<sup>7a</sup> and R<sup>7b</sup> are independently hydrogen, alkyl, aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl; and all other groups are as defined in the Summary of the Invention. In another embodiment, R<sup>3a</sup> is -NHC(O)CH<sub>2</sub>NH(CH<sub>3</sub>), -NHC(O)CH(CH<sub>3</sub>)NH<sub>2</sub>, -NHC(O)C(CH<sub>3</sub>)<sub>2</sub>NH<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH(NH<sub>2</sub>)CH<sub>2</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, or -NHC(O)CH(CH<sub>3</sub>)NH(CH<sub>3</sub>).

**[00110]** Embodiment (N) provides a compound of formula I where each R<sup>3</sup> is independently halo; cyano; alkyl; alkenyl; alkoxy; hydroxyamino; carboxy; alkylsulfonyl, aminoalkyloxy; alkylaminoalkyloxy; dialkylaminoalkyloxy; -N(R<sup>7</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>7a</sup>)(R<sup>7b</sup>); -C(O)NR<sup>8</sup>R<sup>8a</sup>, -NR<sup>9</sup>C(O)R<sup>9a</sup>; -C(O)N(R<sup>10</sup>)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>10a</sup>)R<sup>10b</sup>; -NR<sup>11</sup>C(O)NR<sup>11a</sup>R<sup>11b</sup> where R<sup>11a</sup>; -C(O)R<sup>12</sup>; -NR<sup>13</sup>C(O)OR<sup>13a</sup>; -C(O)N(R<sup>14</sup>)N(R<sup>14a</sup>)(R<sup>14b</sup>); -S(O)<sub>2</sub>N(R<sup>15</sup>)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>15a</sup>)R<sup>15b</sup>; -C(O)N(R<sup>16</sup>)-C<sub>1</sub>-C<sub>6</sub>-alkylene-C(O)OR<sup>16a</sup>; heteroaryl optionally substituted with one or two aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl; -N(R<sup>17</sup>)-C(=N(R<sup>17b</sup>)(R<sup>17a</sup>))(NR<sup>17c</sup>R<sup>17d</sup>); -N(R<sup>18</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>18b</sup>)C(O)R<sup>18a</sup>; -C(O)N(R<sup>19</sup>)-C<sub>1</sub>-C<sub>6</sub>-alkylene-C(O)R<sup>19a</sup>; -N(R<sup>22</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>22b</sup>)-N(R<sup>22c</sup>)(R<sup>22a</sup>); -C<sub>0</sub>-C<sub>6</sub>-alkylene-N(R<sup>23</sup>)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>23b</sup>)R<sup>23a</sup>; or -NR<sup>24</sup>C(O)-C<sub>1</sub>.C<sub>6</sub>-alkylene-OR<sup>24a</sup>; where each of the alkylene in R<sup>3</sup> is independently optionally further substituted with 1, 2, 3, 4, or 5 groups selected from halo, hydroxy, amino, alkylamino, and dialkylamino; and all other groups are as defined in the Summary of the Invention.

In another embodiment, each R<sup>3</sup> is independently methyl, bromo, chloro, fluoro, -NHC(O)CH<sub>2</sub>NH(CH<sub>3</sub>), -NHC(O)CH<sub>2</sub>NH(CH<sub>2</sub>CH<sub>3</sub>), -NHC(O)CH(CH<sub>3</sub>)NH<sub>2</sub>, -NHC(O)C(CH<sub>3</sub>)<sub>2</sub>NH<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH(NH<sub>2</sub>)CH<sub>2</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH(CH<sub>3</sub>)NH(CH<sub>3</sub>), -NHC(O)CH<sub>2</sub>NH<sub>2</sub>, -NHC(O)H, -NHC(O)CH<sub>2</sub>(azetidin-1-yl), -NHC(O)(pyrrolidin-2-yl), -NHC(O)CH(NH<sub>2</sub>)CH<sub>2</sub>OH, -NHC(O)(azetidin-4-yl), -NHC(O)C(CH<sub>3</sub>)<sub>2</sub>NH(CH<sub>3</sub>), -NH<sub>2</sub>, -NHC(O)CH<sub>2</sub>NH(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), -NHC(O)CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, -NHOH, -NHC(O)(piperidin-3-yl), -NHC(O)CH<sub>2</sub>(4-methyl-1,4-diazepan-1-yl), -NHC(O)CH(NH<sub>2</sub>)(CH<sub>2</sub>CH<sub>3</sub>), -NHC(O)CH<sub>2</sub>NH(CH<sub>2</sub>CH(OH)(CH<sub>3</sub>)), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>CH<sub>2</sub>F, -NHC(O)CH<sub>2</sub>NH(OCH<sub>2</sub>CH(CH<sub>3</sub>))<sub>2</sub>, -NHC(O)(1-aminocycloprop-1-yl), -NHC(O)CH<sub>2</sub>NH(CH<sub>2</sub>cyclopropyl), -NHC(O)CH<sub>2</sub>(3-(dimethylamino)-azetidin-1-yl), -NHC(O)(piperidin-2-yl), -NHC(O)(morpholin-4-yl), -NHC(O)CH<sub>2</sub>(pyrrolidin-1-yl), -NHC(O)CH(NH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>), -NHC(O)CH<sub>2</sub>(imidazol-5-yl), -NHC(O)(1-aminocyclopent-1-yl), -NHC(O)CH<sub>2</sub>NH(CH<sub>2</sub>CH(CH<sub>3</sub>))<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>), -NHC(O)(N-(imidazol-4-ylmethyl)-azetidin-3-yl), -NHC(O)(N-ethyl-azetidin-3-yl), -NHCH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)(N-methyl-pyrrolidin-3-yl), -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>))<sub>2</sub>, -NHC(O)CH<sub>2</sub>(3-hydroxy-pyrrolidin-1-yl), -NHC(O)(1-amino-cyclobut-1-yl), -NHC(O)CH<sub>2</sub>NH(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>(3-piperidin-1-ylazetidin-1-yl), -NHC(O)NH<sub>2</sub>, -NHC(O)(1-hydroxycyclopropyl), -NHC(O)CH<sub>2</sub>NHN(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)NH(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>OH, -NHC(O)(pyridazin-4-yl), -NHC(O)(N-methyl-piperidin-4-yl), -NHC(O)CH<sub>2</sub>NHCH(CH<sub>3</sub>)<sub>3</sub>, -NHC(O)CH<sub>2</sub>(3-dimethylamino-pyrrolidin-1-yl), -NHC(O)CH<sub>2</sub>NH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)(1-cyclopropylmethyl-azetidin-3-yl), -NHC(O)CH<sub>2</sub>NH(CH<sub>3</sub>)<sub>3</sub>, -NHC(O)(imidazol-2-yl), -NHC(O)(imidazol-4-yl), -NHC(O)(1,2-oxazol-5-yl), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>CF<sub>3</sub>, -NHC(O)CH<sub>2</sub>CH<sub>2</sub>(piperidin-1-yl), -NHC(O)(3-oxo-cyclopent-1-yl), -NHC(O)(2-hydroxy-pyridin-6-yl), -NHC(O)CH<sub>2</sub>NH(3-fluoro-4-hydroxyphenyl), -NHC(O)(CH<sub>2</sub>)<sub>3</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)(1-(furan-2-ylmethyl)-azetidin-3-yl), -NHC(O)(pyrimidin-5-yl), -NHC(O)(pyrrol-2-yl), -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>(3-methyl-1,2-oxazol-5-yl), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>(3-hydroxyphenyl), -NHC(O)(N-methyl-pyrrol-2-yl), -NHC(O)(2-amino-tetrahydropyran-2-yl), -NHC(O)CH<sub>2</sub>(4-methylamino-piperidin-1-yl), -NHC(O)(piperidin-1-yl), -NHC(O)(N-methyl-pyrrolidin-2-yl), -NHC(O)(thien-3-yl), -NHC(O)(N-(cyclopropylcarbonyl)azetidin-3-yl), -NHC(O)CH<sub>2</sub>(4-methylpiperazin-1-yl), -NHC(O)(N-benzylazetidin-3-yl), -NHC(O)(2-chloro-pyridin-3-yl), -NHC(O)CH<sub>2</sub>(pyridin-4-

yl), -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)(CH<sub>2</sub>CH=CH<sub>2</sub>), -NHC(O)CH<sub>2</sub>NH(benzyl), -NHC(O)CH<sub>2</sub>OCH<sub>3</sub>, -NHC(O)[1-(C(O)CH<sub>2</sub>CH<sub>3</sub>)-azetidin-3-yl], -NHC(O)(pyridin-3-yl), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -NHC(O)(1-[C(O)CH<sub>3</sub>]piperidin-4-yl), -NHC(O)CH<sub>2</sub>(2-methyl-pyrrolidin-1-yl), -NHC(O)(furan-3-yl), -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)(2-chloropyridin-5-yl), -NHC(O)(2-chlorophenyl), -NHC(O)CH<sub>2</sub>(pyridin-2-yl), -NHC(O)CH<sub>2</sub>(3-dimethylamino-azetidin-1-yl), -NHC(O)CH<sub>2</sub>(pyridin-3-yl), -NHC(O)CH<sub>2</sub>(2-chlorophenyl), -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>OH, -NHC(O)CH<sub>2</sub>(2-benzyl-pyrrolidin-1-yl), -NHC(O)(furan-2-yl), -NHC(O)(2-chloro-pyridin-4-yl), -NHC(O)CH<sub>2</sub>NHC(O)CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -NHC(O)(4-chlorophenyl), -NHC(O)(4-methyl-phenyl), -NHC(O)CH<sub>2</sub>NHC(O)O(CH<sub>3</sub>)<sub>3</sub>, -NHC(O)(benzo[d][1,3]dioxol-5-yl), -NHC(O)CH<sub>2</sub>NHOCH<sub>2</sub>(2-methoxyphenyl), -NHC(O)(pyridin-4-yl), -NHC(O)CH<sub>2</sub>[4-(3,4-dichlorophenyl)-piperazin-1-yl], -NHC(O)CH<sub>2</sub>CH<sub>2</sub>(pyridin-3-yl), -NHC(O)(tetrahydrofuran-3-yl), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>(2-methylphenyl), -C(O)CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>(3-fluorophenyl), -NHC(O)CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>phenyl, -NHC(O)(2-methyl-cycloprop-1-yl), -NHC(O)(2-methyl-4-methoxyphenyl), -NHC(O)(2-methylpyridin-3-yl), -NHC(O)(4-methoxyphenyl), -NHC(O)CH<sub>2</sub>(4-ethylpiperazin-1-yl), -NHC(O)(thien-2-yl), -NHC(O)(3-fluoro-2-methylphenyl), -NHC(O)(2-bromo-thien-3-yl), -NHC(O)(4-fluorophenyl), -NHC(O)CH<sub>2</sub>(3-methylpiperidin-1-yl), -NHC(O)CH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>NH(2-fluorophenyl), -NHC(O)(3-dimethylaminophenyl), -NHC(O)CH<sub>2</sub>(4-methylpiperidin-1-yl), -NHC(O)CH<sub>2</sub>NH(2-n-propylphenyl), -NHC(O)phenyl, -NHC(O)(pyrazin2-yl), -NHC(O)(3-fluoro-4-methoxyphenyl), -NHC(O)C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>O(4-fluorophenyl), -NHC(O)(1-methylcarbonyl-azetidin-3-yl), -NHC(O)CH<sub>2</sub>NH(4-methylphenyl), -NHC(O)CH<sub>2</sub>NH(phenyl), -NHC(O)CH<sub>2</sub>(4-allyl-piperazin-1-yl), -NHC(O)(2-methylphenyl), -NHC(O)CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -NHC(O)(3-methyl-furan-2-yl), -NHC(O)C(CH<sub>3</sub>)<sub>3</sub>, -NHC(O)CH<sub>2</sub>NHObenzyl, -NHC(O)CH<sub>2</sub>NH(3-chlorophenyl), -NHC(O)cyclobutyl, -NHC(O)CH<sub>2</sub>(3-methoxyphenyl), -NHC(O)(1-methylcycloprop-1-yl), -NHC(O)(3-fluorophenyl), -NHC(O)(4-dimethylaminophenyl), -NHC(O)(3,4-dichlorophenyl), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>(2-methylthiophenyl), -NHC(O)CH<sub>2</sub>(2-fluorophenyl), -NHC(O)CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)CH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)(thiazol-4-yl), -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)benzyl, -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>(thien-2-yl), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>(pyridin-2-yl), -NHC(O)(3-methoxyphenyl), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>(3-chloro-4-methylphenyl), -NHC(O)CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>(4-chlorophenyl), -NHC(O)(3-fluoro-4-methylphenyl), -NHC(O)CH<sub>2</sub>O(2-methylphenyl),

-NHC(O)CH<sub>2</sub>(cyclohexyl), -NHC(O)(2-phenyl-cycloprop-1-yl), -NHC(O)(3-chlorophenyl), -NHC(O)CH<sub>2</sub>(2-methoxyphenyl), -NHC(O)CH<sub>2</sub>CH<sub>2</sub>(3-methoxyphenyl), -NHC(O)CH<sub>2</sub>NH(2-fluoro-4-methyl-phenyl), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>(3-fluoro-phenyl), -NHC(O)CH<sub>2</sub>(4-methoxy-phenyl), -NHC(O)benzyl, -NHC(O)(2,4-dichlorophenyl), -NHC(O)(3-oxo-cyclohex-1-yl), -NHC(O)CH<sub>2</sub>NH(3-fluorophenyl), -NHC(O)CH<sub>2</sub>(3-chlorophenyl), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>CH(CH<sub>3</sub>)phenyl, -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>(2,4-dimethylphenyl), -NHC(O)CH<sub>2</sub>(2-methyl-piperidin-1-yl), -NHC(O)CH<sub>2</sub>NH(2-methoxyphenyl), -NHC(O)CH<sub>2</sub>(1,2,3,4-tetrahydroisoquinolin-2-yl), -NHC(O)CH<sub>2</sub>CH<sub>2</sub>CH=CH<sub>2</sub>, -NHC(O)CH<sub>2</sub>NH(2-methylphenyl), -NHC(O)CH<sub>2</sub>(4-oxo-piperidin-1-yl), -NHC(O)(2-fluorophenyl), -NHC(O)CH<sub>2</sub>NHCH(CH<sub>3</sub>)phenyl, -NHC(O)(2-fluoro-6-methoxyphenyl), -NHC(O)CH<sub>2</sub>NH(2-isopropylphenyl), -NHC(O)CH<sub>2</sub>CH<sub>2</sub>(2-methoxyphenyl), -NHC(O)CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>(2-phenyl-morpholin-4-yl), -NHC(O)CH<sub>2</sub>CH<sub>2</sub>(4-methoxyphenyl), -NHC(O)CH<sub>2</sub>N(allyl)cyclopentyl, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -NHC(O)CH<sub>2</sub>CH<sub>2</sub>C(O)cyclopropyl, -NHC(O)CH<sub>2</sub>NH(3-*tert*-butylphenyl), -NHC(O)CH<sub>2</sub>N(*n*-propyl)(cyclopropylmethyl), -NHC(O)CH<sub>2</sub>(2-oxo-cyclopentyl), -NHC(O)CH<sub>2</sub>NH(4-chlorophenyl), -NHC(O)CH<sub>2</sub>(4-piperidin-1-yl)piperidin-1-yl), -NHC(O)CH<sub>2</sub>(4-cyclopentylpiperazin-1-yl), -NHC(O)CH<sub>2</sub>(2-methylphenyl), -NHC(O)CH<sub>2</sub>NHCH<sub>2</sub>(3-fluoro-6-methylphenyl), -NHC(O)CH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>, -NHC(O)CH<sub>2</sub>NH(2-chlorophenyl), -NHC(O)(3-fluoro-6-methylphenyl), -NHC(O)(4-fluoro-3-methylphenyl), -NHC(O)(2,3-dichlorophenyl), -NHC(O)CH<sub>2</sub>Ophenyl, -NHC(O)CH<sub>2</sub>NH(2,3-dimethylphenyl), -NHC(O)(2-fluoro-5-methylphenyl), -NHC(O)CH<sub>2</sub>NHOCH<sub>2</sub>(4-methylphenyl), -NHC(O)CH<sub>2</sub>(4-isopropylpiperazin-1-yl), -NHC(O)CH<sub>2</sub>(4-fluorophenyl), -NHC(O)CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)(2-methoxy-4-methylphenyl), -NHC(O)CH<sub>2</sub>(4-*n*-propylpiperidin-1-yl), -NHC(O)CH<sub>2</sub>O(3-methylphenyl), -NHC(O)(tetrahydrofuran-2-yl), -NHC(O)CH<sub>2</sub>(3-hydroxymethylpiperidin-1-yl), -NHC(O)(1-*tert*-butoxycarbonylpiperidin-2-yl), -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>(pyridin-3-yl), -NHC(O)CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)phenyl, -NHC(O)CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -NHC(O)CH<sub>2</sub>CH<sub>2</sub>(cyclopentyl), -NHC(O)(2,5-dichlorophenyl), -NHC(O)CH<sub>2</sub>(4-methylcarbonylpiperazin-1-yl), -NHC(O)(5-fluoro-2-methoxyphenyl), -NHC(O)CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)cyclohexyl, -NHC(O)(5-methyl-1,2-oxazol-3-yl), -NHC(O)(3-methylpyridin-3-yl), -NHC(O)(2-methoxypyridin-3-yl), -NHC(O)(3,5-dichlorophenyl), -NHC(O)CH<sub>2</sub>(thiazolidin3-yl), -NHC(O)CH<sub>2</sub>(4-[C(O)H]-piperazin-1-yl), -NHC(O)CH<sub>2</sub>(2-pyridin-4-yl)piperidin-1-yl), -NHC(O)(2-methoxyphenyl), -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>(4-[C(O)H]-homopiperazin-1-yl), -NHC(O)(1-phenylcycloprop-1-yl), -NHC(O)CH<sub>2</sub>(2,6-dimethylmorpholin-4-yl),

NHC(O)CH<sub>2</sub>(2-phenylpyrrolidin-1-yl), -NHC(O)CH<sub>2</sub>(morpholin-4-yl),  
 -C(O)NHCH(CH<sub>3</sub>)CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -C(O)NH(pyrrolidin-3-yl),  
 -C(O)NHCH<sub>2</sub>CH<sub>2</sub>(pyrrolidin-1-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>,  
 -C(O)N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -C(O)NHCH<sub>2</sub>(piperidin-2-yl), -C(O)NH(1-methylazetidin-3-yl),  
 -C(O)NHCH<sub>2</sub>CH<sub>2</sub>(piperidin-1-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -C(O)NH(1-methylpiperidin-3-yl),  
 -C(O)NH(piperidin-3-yl), -C(O)NHCH<sub>2</sub>(1-methylpiperidin-3-yl),  
 -C(O)NHCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>OH)<sub>2</sub>, -C(O)NH(1-ethylpiperidin-3-yl), -C(O)NH<sub>2</sub>, -C(O)(3-aminopyrrolidin-1-yl),  
 -C(O)(3-methylaminopyrrolidin-1-yl), -C(O)OH, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>(morpholin-4-yl), -C(O)NHCH<sub>2</sub>(1-ethylpyrrolidin-2-yl), -C(O)(4-amino-3-oxo-pyrazolidin-1-yl), -C(O)NHCH<sub>3</sub>, -C(O)(3-aminocyclobut-1-yl), -C(O)NHCH<sub>2</sub>(pyridin-3-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>OH, -C(O)NH(3-oxo-pyrazolidin-4-yl), -NHCH<sub>2</sub>CH<sub>2</sub>(imidazol-4-yl),  
 -C(O)(3-dimethylaminopyrrolidin-1-yl), -C(O)NHCH<sub>2</sub>(pyridin-4-yl), -C(O)N(CH<sub>3</sub>)(1-methyl-pyrrolidin-3-yl), -C(O)(3-diethylaminopyrrolidin-1-yl), -C(O)NH(pyrrol-1-yl),  
 -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>(pyrrolidin-1-yl), -C(O)N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CN, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>,  
 -C(O)N(CH<sub>2</sub>CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CN, -C(O)(3-aminopiperidin-1-yl),  
 -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -C(O)NH(morpholin-4-yl), -C(O)NHN(CH<sub>3</sub>)<sub>2</sub>, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>(imidazol-1-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>,  
 -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CN, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>C(O)OCH<sub>3</sub>, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>SCH<sub>3</sub>,  
 -C(O)NHCH<sub>2</sub>CH<sub>2</sub>SCH<sub>2</sub>CH<sub>3</sub>, -C(O)N(CH<sub>2</sub>CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>(2-oxo-pyrrolidin-1-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>(pyridin-4-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>(morpholin-4-yl), -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>,  
 -C(O)N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>,  
 -C(O)NHCH<sub>2</sub>CH<sub>2</sub>C(O)OCH<sub>2</sub>CH<sub>3</sub>, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OCH(CH<sub>3</sub>)<sub>2</sub>, -C(O)NHC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>(piperidin-1-yl), -C(O)N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -C(O)NH(piperidin-1-yl),  
 -C(O)NHCH(CH<sub>3</sub>)CH<sub>2</sub>OCH<sub>3</sub>, -C(O)NHC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>(morpholin-4-yl), -C(O)(2-dimethylaminomethyl)piperidin-1-yl), -C(O)NH(CH<sub>2</sub>)<sub>3</sub>O(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -C(O)NHCH(CH<sub>3</sub>)(CH<sub>2</sub>)<sub>3</sub>N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -C(O)NHC(CH<sub>3</sub>)<sub>2</sub>C(O)(piperidin-1-yl), -C(O)(4-methylpiperazin-1-yl), -C(O)(2-piperidin-1-ylmethyl-piperidin-1-yl), cyano, -NHCH<sub>3</sub>,  
 -CH(CH<sub>3</sub>)NHCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -C(O)CH<sub>3</sub>, -S(O)<sub>2</sub>NHCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>,  
 -S(O)<sub>2</sub>NH(CH<sub>2</sub>)<sub>3</sub>N(CH<sub>3</sub>)<sub>2</sub>, 5-(N,N-dimethylaminomethyl)-1,3,4-oxadiazol-2-yl,  
 -NHCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>3</sub>)<sub>2</sub>, -OCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC[N(CH<sub>3</sub>)<sub>2</sub>][=N(CH<sub>3</sub>)<sub>2</sub>], -OCHF<sub>2</sub>,  
 -CF<sub>3</sub>, -S(O)<sub>2</sub>CH<sub>3</sub>, -OCF<sub>3</sub>, -NHC(O)CH<sub>2</sub>(4-dimethylaminopiperidin-1-yl), or methoxy.

**[00111]** In another embodiment (P), R<sup>3</sup> is independently halo, alkyl, hydroxyamino, -N(R<sup>7</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>7a</sup>)(R<sup>7b</sup>), -C(O)NR<sup>8</sup>R<sup>8a</sup>, -NR<sup>9</sup>C(O)R<sup>9a</sup>, -C(O)N(R<sup>10</sup>)-C<sub>1</sub>-C<sub>6</sub>-

alkylene-N(R<sup>10a</sup>)R<sup>10b</sup>-NR<sup>11</sup>C(O)NR<sup>11a</sup>R<sup>11b</sup>, -N(R<sup>22</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>22b</sup>)-N(R<sup>22c</sup>)(R<sup>22a</sup>), -NR<sup>13</sup>C(O)OR<sup>13a</sup>, -N(R<sup>18</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>18b</sup>)C(O)R<sup>18a</sup>, -NR<sup>24</sup>C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-OR<sup>24a</sup>, or -N(R<sup>20</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-C(O)R<sup>20a</sup>; where each of the alkylene in R<sup>3</sup> is independently optionally further substituted with 1, 2, 3, 4, or 5 groups selected from halo, hydroxy, and amino; and all other groups are as defined in the Summary of the Invention. In another embodiment, each R<sup>3</sup> is independently methyl, chloro, -NHC(O)CH<sub>2</sub>NH(CH<sub>3</sub>), -NHC(O)CH(CH<sub>3</sub>)NH<sub>2</sub>, -NHC(O)C(CH<sub>3</sub>)<sub>2</sub>NH<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH(NH<sub>2</sub>)CH<sub>2</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH(CH<sub>3</sub>)NH(CH<sub>3</sub>), -NHC(O)H, -NHC(O)CH<sub>2</sub>(azetidin-1-yl), -NHC(O)(pyrrolidin-2-yl), -NHC(O)CH(NH<sub>2</sub>)CH<sub>2</sub>OH, -NHC(O)(azetidin-4-yl), -NHC(O)C(CH<sub>3</sub>)<sub>2</sub>NH(CH<sub>3</sub>), -NH<sub>2</sub>, -NHC(O)CH<sub>2</sub>NH(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), -NHC(O)CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, -NHOH, or -NHC(O)(piperidin-3-yl).

[00112] In another embodiment (Q), R<sup>3</sup> is alkyl or -N(R<sup>7</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>7a</sup>)(R<sup>7b</sup>); and R<sup>7</sup> is hydrogen or alkyl and R<sup>7a</sup> and R<sup>7b</sup> are independently hydrogen, alkyl, aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl; and all other groups are as defined in the Summary of the Invention. In another embodiment, each R<sup>3</sup> is independently methyl, -NHC(O)CH<sub>2</sub>NH(CH<sub>3</sub>), -NHC(O)CH(CH<sub>3</sub>)NH<sub>2</sub>, -NHC(O)C(CH<sub>3</sub>)<sub>2</sub>NH<sub>2</sub>, -NHC(O)-CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH(NH<sub>2</sub>)CH<sub>2</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, or -NHC(O)CH(CH<sub>3</sub>)NH(CH<sub>3</sub>).

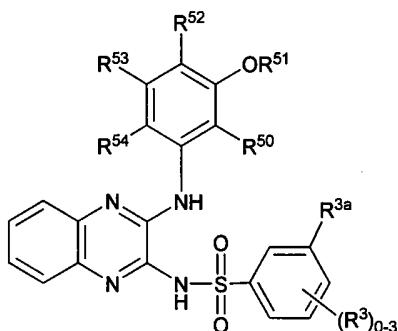
[00113] In another embodiment (R), B is phenyl, R<sup>3</sup> is not present or R<sup>3</sup> is halo, alkyl, or alkoxy; R<sup>3a</sup> is -C(O)NR<sup>8</sup>R<sup>8a</sup>, -NR<sup>9</sup>C(O)R<sup>9a</sup>, -N(R<sup>7</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>7a</sup>)(R<sup>7b</sup>), or -C(O)N(R<sup>10</sup>)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>10a</sup>)R<sup>10b</sup> where each of the alkylene in R<sup>3a</sup> is independently optionally further substituted with 1, 2, 3, 4, or 5 groups selected from halo, hydroxy, and amino; and all other groups are as defined in the Summary of the Invention.

[00114] In another embodiment (R1) of embodiment R, R<sup>50</sup>, R<sup>52</sup>, and R<sup>53</sup> are hydrogen and R<sup>54</sup> is halo or alkoxy; R<sup>50</sup>, R<sup>52</sup>, and R<sup>54</sup> are hydrogen and R<sup>53</sup> is alkoxy; or R<sup>50</sup> and R<sup>52</sup> are hydrogen and R<sup>53</sup> and R<sup>54</sup> together with the carbons to which they are attached form a 6-membered heteroaryl; and all other groups are as defined in the Summary of the Invention. In another embodiment, R<sup>50</sup>, R<sup>52</sup>, and R<sup>53</sup> are hydrogen and R<sup>54</sup> is halo or alkoxy; or R<sup>50</sup>, R<sup>52</sup>, and R<sup>54</sup> are hydrogen and R<sup>53</sup> is alkoxy.

[00115] In another embodiment of (R2) of embodiment R, R<sup>51</sup> is methyl.

### Compounds of Formula Ia

[00116] In another embodiment, the compound of formula I is a compound of formula Ia:

**Ia**

or a pharmaceutically acceptable salt, tautomer, hydrate, or solvate thereof, wherein:

R<sup>50</sup> is hydrogen;

R<sup>51</sup> is methyl;

R<sup>52</sup> is hydrogen;

R<sup>53</sup> is hydrogen or alkoxy;

R<sup>54</sup> is hydrogen, alkyl, alkoxy, or halo; or R<sup>53</sup> and R<sup>54</sup> together with the carbons to which they are attached form a 6-membered heteroaryl;

R<sup>3</sup> is halo or methyl; and

R<sup>3a</sup> is -N(R<sup>7</sup>)C(O)-C<sub>1</sub>-C<sup>6</sup>-alkylene-N(R<sup>7a</sup>)(R<sup>7b</sup>) where R<sup>7</sup> is hydrogen and R<sup>7a</sup> and R<sup>7b</sup> are independently hydrogen, alkyl, aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl.

**[00117]** In one embodiment of the compound of formula Ia, R<sup>51</sup> is methyl; and R<sup>50</sup>, R<sup>52</sup>, and R<sup>53</sup> are hydrogen and R<sup>54</sup> is halo or alkoxy or R<sup>50</sup>, R<sup>52</sup>, and R<sup>54</sup> are hydrogen and R<sup>53</sup> is alkoxy; or a single stereoisomer or mixture of stereoisomers thereof.

**[00118]** In another embodiment, R<sup>3a</sup> is -NHC(O)CH<sub>2</sub>NH(CH<sub>3</sub>), -NHC(O)CH(CH<sub>3</sub>)NH<sub>2</sub>, -NHC(O)C(CH<sub>3</sub>)<sub>2</sub>NH<sub>2</sub>, -NHC(O)-CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH(NH<sub>2</sub>)CH<sub>2</sub>CH<sub>3</sub>, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, or -NHC(O)CH(CH<sub>3</sub>)NH(CH<sub>3</sub>).

**[00119]** In another embodiment, the compound of formula Ia is:

Structure	Name
	<i>N</i> -(3-{[(3-{[2-chloro-5-(methoxy)phenyl]amino}quinoxalin-2-yl)amino}sulfonyl]-phenyl)- <i>N</i> -2-methylglycinamide

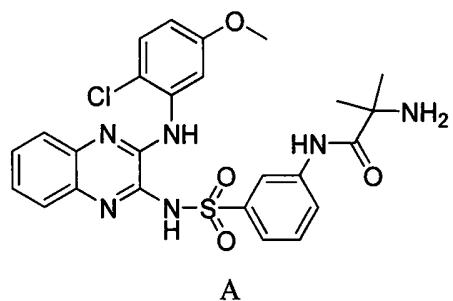
Structure	Name
	<i>N</i> -(3-{[(3,5-bis(methoxy)phenyl]amino}quinoxalin-2-yl)amino]sulfonyl}phenyl)- <i>N</i> -2-, <i>N</i> -2-dimethylglycinamide
	<i>N</i> -(3-{[(3-{[2-chloro-5-(methoxy)phenyl]amino}quinoxalin-2-yl)amino]sulfonyl}-4-methylphenyl)- <i>N</i> -2-, <i>N</i> -2-dimethylglycinamide
	<i>N</i> -(3-{[(3-{[2-chloro-5-(methoxy)phenyl]amino}quinoxalin-2-yl)amino]sulfonyl}phenyl)-L-alaninamide
	<i>N</i> -(3-{[(3-{[2-chloro-5-(methoxy)phenyl]amino}quinoxalin-2-yl)amino]sulfonyl}phenyl)-2-methylalaninamide
	<i>N</i> -(3-{[(3-{[2-chloro-5-(methoxy)phenyl]amino}quinoxalin-2-yl)amino]sulfonyl}phenyl)- <i>N</i> -2-[2-(dimethylamino)ethyl]- <i>N</i> -2-methylglycinamide

Structure	Name
	<i>N</i> -(3-{[(3-{[2-chloro-5-(methoxy)phenyl]amino}quinoxalin-2-yl)amino]sulfonyl}phenyl)- <i>N</i> -2-, <i>N</i> -2-dimethylglycinamide
	<i>N</i> -(3-{[(3-{[2-chloro-5-(methoxy)phenyl]amino}quinoxalin-2-yl)amino]sulfonyl}phenyl)glycinamide
	<i>N</i> -(2-chloro-5-{[(3-{[2-chloro-5-(methoxy)phenyl]amino}quinoxalin-2-yl)amino]sulfonyl}phenyl)- <i>N</i> -2-methylglycinamide
	<i>N</i> -(5-{[(3-{[3,5-bis(methoxy)phenyl]amino}quinoxalin-2-yl)amino]sulfonyl}-2-methylphenyl)glycinamide
	<i>N</i> -(5-{[(3-{[3,5-bis(methoxy)phenyl]amino}quinoxalin-2-yl)amino]sulfonyl}-2-methylphenyl)-beta-alaninamide

Structure	Name
	<i>N</i> -(5-{[(3-{[2-chloro-5-(methoxy)phenyl]amino}quinoxalin-2-yl)amino]sulfonyl}-2-methylphenyl)- <i>N</i> -2, <i>N</i> -2-dimethylglycinamide

or a pharmaceutically acceptable salt thereof.

[00120] In one embodiment, the compound of formula I and of formula Ia is compound A:



or a pharmaceutically salt, tautomer, hydrate, or solvate thereof.

### Compound of Formula II

[00121] In one embodiment, R<sup>1</sup> in the compound of formula II is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl. Specifically, R<sup>1</sup> is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalkyl, or optionally substituted heterocycloalkylalkyl. More specifically, R<sup>1</sup> is hydrogen, alkyl, alkyl substituted with one or two hydroxy, alkyl substituted with alkoxy, cycloalkyl, arylalkyl, or heterocycloalkylalkyl. Even more specifically, R<sup>1</sup> is hydrogen, methyl, ethyl, propyl, isopropyl, 2-hydroxypropyl, 3-hydroxypropyl, 2-ethoxyethyl, 3-methoxypropyl, 3-ethoxypropyl, 3-isopropoxypropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, or 2-piperidin-1-ylethyl. Yet even more specifically, R<sup>1</sup> is ethyl, isopropyl, cyclopentyl, or cyclohexyl. Yet even more specifically, R<sup>1</sup> is ethyl.

[00122] In another embodiment, R<sup>2</sup> is hydrogen or alkyl where the alkyl is optionally substituted with 1, 2, 3, 4, or 5 R<sup>8</sup> groups. Specifically, R<sup>2</sup> is hydrogen or alkyl where the

alkyl is optionally substituted with one, two, or three R<sup>8</sup> groups. More specifically, R<sup>2</sup> is hydrogen or alkyl where the alkyl is optionally substituted with one, two, or three R<sup>8</sup> groups; and each R<sup>8</sup>, when present, is independently selected from amino, alkylamino, dialkylamino, and halo. Even more specifically, R<sup>2</sup> is hydrogen, methyl, ethyl, propyl, isopropyl, *tert*-butyl, 3-aminopropyl, 3-(N-methylamino)-propyl, 3-(N,N-dimethylamino)-propyl, 2-fluoroethyl, or 2,2,2-trifluoroethyl. Yet even more specifically, R<sup>2</sup> is hydrogen or ethyl. Yet even more preferably, R<sup>2</sup> is ethyl.

[00123] In another embodiment, R<sup>2</sup> is hydrogen.

[00124] In another embodiment, R<sup>4</sup> is optionally substituted alkyl. Specifically, R<sup>4</sup> is methyl or ethyl. More specifically, R<sup>4</sup> is methyl.

[00125] In another embodiment, R<sup>6</sup> is acyl. More specifically, R<sup>6</sup> is alkylcarbonyl. Even more specifically, R<sup>6</sup> is acetyl.

[00126] In another embodiment, R<sup>6</sup> is phenyl optionally substituted with 1, 2, 3, 4, or 5 R<sup>9</sup> groups. Specifically, R<sup>6</sup> is phenyl optionally substituted with one or two R<sup>9</sup> groups; and each R<sup>9</sup>, when present, is independently selected from aryl, halo, alkoxy, aryloxy, and haloalkyl. More specifically, R<sup>6</sup> is phenyl optionally substituted with one or two R<sup>9</sup> groups; and each R<sup>9</sup>, when present, is independently selected from phenyl, fluoro, chloro, methoxy, phenoxy, and trifluoromethyl. Even more specifically, R<sup>6</sup> is phenyl, phenyl substituted with phenyl, fluorophenyl, difluorophenyl, chlorophenyl, dichlorophenyl, phenyl substituted with chloro and fluoro, methoxyphenyl, dimethoxyphenyl, phenoxyphenyl, or trifluoromethylphenyl. Yet even more specifically, R<sup>6</sup> is phenyl, 2-phenyl-phenyl, 3-phenyl-phenyl, 4-phenyl-phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,3-dimethoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 4-phenyloxyphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, or 4-trifluoromethylphenyl.

[00127] In another embodiment, R<sup>6</sup> is heteroaryl optionally substituted with 1, 2, 3, 4, or 5 R<sup>9</sup> groups.

[00128] In another embodiment, R<sup>6</sup> is a 6-membered heteroaryl optionally substituted with one or two R<sup>9</sup>. More specifically, R<sup>6</sup> is pyridinyl, pyrazinyl, pyrimidinyl, or pyridazinyl each of which is optionally substituted with one R<sup>9</sup> wherein R<sup>9</sup>, when present, is halo. Even more

specifically, R<sup>6</sup> is pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 3-fluoropyridin-4-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyridazin-3-yl, or pyridazin-4-yl, each of which is optionally substituted with one or two R<sup>9</sup>.

[00129] In another embodiment, R<sup>6</sup> is pyrazinyl, pyrimidinyl, or pyridazinyl, each of which is optionally substituted with one R<sup>9</sup> wherein R<sup>9</sup>, when present, is halo. Even more specifically, R<sup>6</sup> is pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyridazin-3-yl, or pyridazin-4-yl.

[00130] In another embodiment, R<sup>6</sup> is a 5-membered heteroaryl optionally substituted with one or two R<sup>9</sup>. Specifically R<sup>6</sup> is pyrazolyl, imidazolyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, furanyl, pyrrolyl, triazolyl, or tetrazolyl, each of which is optionally substituted with one R<sup>9</sup> wherein R<sup>9</sup>, when present, is alkyl, arylalkyl, cyano, aryl, alkoxy carbonyl, or halo. More specifically, R<sup>6</sup> is pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, thien-2-yl, thien-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, furan-2-yl, furan-3-yl, pyrrol-1-yl, pyrrol-2-yl, pyrrol-3-yl, triazol-1-yl, triazol-4-yl, triazol-5-yl, tetrazol-1-yl, or tetrazol-5-yl; each of which is optionally substituted with one R<sup>9</sup> wherein R<sup>9</sup>, when present, is methyl, benzyl, cyano, phenyl, N-*tert*-butoxycarbonyl, or chloro. Even more specifically, R<sup>6</sup> is pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, thien-2-yl, thien-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, furan-2-yl, furan-3-yl, pyrrol-2-yl, pyrrol-3-yl, triazol-4-yl, triazol-5-yl, or tetrazol-5-yl; each of which is optionally substituted with one R<sup>9</sup> wherein R<sup>9</sup>, when present, is methyl, benzyl, cyano, phenyl, N-*tert*-butoxycarbonyl, or chloro.

[00131] In another embodiment, R<sup>6</sup> is thienyl, pyrrolyl, furanyl, pyrazolyl, thiazolyl, isoxazolyl, imidazolyl, triazolyl, or tetrazolyl, each of which is optionally substituted with one R<sup>9</sup> wherein R<sup>9</sup>, when present, is methyl, benzyl, cyano, phenyl, N-*tert*-butoxycarbonyl, or chloro. Specifically, R<sup>6</sup> is thien-2-yl, thien-3-yl, pyrrol-2-yl, furan-2-yl, furan-3-yl, pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, thiazol-2-yl, thiazol-5-yl, isoxazol-4-yl, imidazol-5-yl, triazol-5-yl, tetrazol-5-yl, each of which is optionally substituted with one R<sup>9</sup> wherein R<sup>9</sup>, when present, is methyl, benzyl, cyano, phenyl, N-*tert*-butoxycarbonyl, or chloro. More specifically, R<sup>6</sup> is thien-2-yl, thien-3-yl, 5-cyano-thien-2-yl, 4-methyl-thien-2-yl, 4-methyl-

thien-3-yl, 5-chloro-thien-5-yl, 5-phenyl-thien-2-yl, pyrrol-2-yl, *N*-*tert*-butoxycarbonyl-pyrrol-2-yl, *N*-methyl-pyrrol-2-yl, furan-2-yl, furan-3-yl, pyrazol-3-yl, pyrazol-4-yl, *N*-benzyl-pyrazol-4-yl, pyrazol-5-yl, thiazol-2-yl, thiazol-5-yl, isoxazol-4-yl, imidazol-5-yl, triazol-5-yl, or tetrazol-5-yl.

[00132] In another embodiment, R<sup>6</sup> is thien-2-yl, thien-3-yl, pyrrol-2-yl, furan-2-yl, furan-3-yl, pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, thiazol-2-yl, thiazol-5-yl, isoxazol-4-yl, imidazol-5-yl, triazol-5-yl, or tetrazol-5-yl, each of which is optionally substituted with one R<sup>9</sup> wherein R<sup>9</sup>, when present, is methyl, benzyl, cyano, phenyl, *N*-*tert*-butoxycarbonyl, or chloro.

[00133] In another embodiment, R<sup>6</sup> is indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, or benzoisoxazolyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 R<sup>9</sup> groups. Specifically, R<sup>6</sup> is indol-2-yl, indol-3-yl, indol-4-yl, indol-5-yl, indol-6-yl, indol-7-yl, benzimidazol-2-yl, benzimidazol-4-yl, benzimidazol-5-yl, benzimidazol-6-yl, benzimidazol-7-yl, benzofuran-2-yl, benzofuran-3-yl, benzofuran-4-yl, benzofuran-5-yl, benzofuran-6-yl, benzofuran-7-yl, benzoxazol-2-yl, benzoxazol-4-yl, benzoxazol-5-yl, benzoxazol-6-yl, benzoxazol-7-yl, benzoisoxazol-3-yl, benzoisoxazol-4-yl, benzoisoxazol-5-yl, benzoisoxazol-6-yl, or benzoisoxazol-7-yl; each of which is optionally substituted with 1, 2, 3, 4, or 5 R<sup>9</sup> groups. More specifically, R<sup>6</sup> is indol-6-yl.

[00134] In another embodiment, R<sup>1</sup> is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkylalkyl, or optionally substituted arylalkyl; X is -NH-; R<sup>2</sup> is hydrogen or alkyl where the alkyl is optionally substituted with one or two R<sup>8</sup> groups; R<sup>4</sup> is alkyl; R<sup>5</sup> is hydrogen; R<sup>6</sup> is phenyl or heteroaryl wherein the phenyl and heteroaryl are optionally substituted with one, two, or three R<sup>9</sup> groups; each R<sup>8</sup>, when present, is independently amino, alkylamino, dialkylamino, or halo; and each R<sup>9</sup>, when present, is independently alkyl, arylalkyl, cyano, aryl, alkoxy carbonyl, or halo.

[00135] In another embodiment, R<sup>6</sup> is pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, thien-2-yl, thien-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, furan-2-yl, furan-3-yl, pyrrol-2-yl, pyrrol-3-yl, triazol-4-yl, triazol-5-yl, or tetrazol-5-yl; each of which is optionally substituted with 1, 2, 3, 4, or 5 R<sup>9</sup> groups.

[00136] In another embodiment, R<sup>1</sup> is alkyl or cycloalkyl; R<sup>4</sup> is methyl; and R<sup>6</sup> is heteroaryl optionally substituted with one or two R<sup>9</sup> groups. Specifically, each R<sup>9</sup>, when present, is independently alkyl, arylalkyl, cyano, aryl, alkoxy carbonyl, or halo. Specifically,

$R^6$  is pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, thien-2-yl, thien-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, furan-2-yl, furan-3-yl, pyrrol-2-yl, pyrrol-3-yl, triazol-4-yl, triazol-5-yl, or tetrazol-5-yl; each of which is optionally substituted with one  $R^9$  wherein  $R^9$ , when present, is methyl, benzyl, cyano, phenyl, or *N*-*tert*-butoxycarbonyl.

[00137] In another embodiment,  $R^2$  is hydrogen.

[00138] In another embodiment,  $R^2$  is methyl or ethyl.

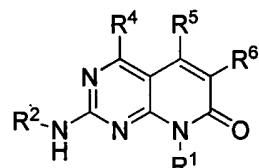
[00139] In another embodiment,  $R^1$  is alkyl or cycloalkyl;  $R^4$  is methyl; and  $R^6$  is phenyl optionally substituted with one or two  $R^9$  groups. Specifically each  $R^9$ , when present, is independently halo, alkoxy, or haloalkyl.

[00140] In another embodiment,  $R^1$  is alkyl or cycloalkyl;  $R^4$  is methyl; and  $R^2$  is hydrogen.

In another embodiment,  $R^1$  is alkyl or cycloalkyl;  $R^4$  is methyl; and  $R^2$  is optionally substituted alkyl.

### Compounds of Formula IIa

[00141] In another embodiment, the compound of formula I is a compound of formula IIa:



IIa

or a pharmaceutically acceptable salt thereof, wherein:

$R^1$  is alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl;

$R^2$  is hydrogen or alkyl;

$R^4$  is alkyl;

$R^5$  is hydrogen;

$R^6$  is phenyl, acyl, or heteroaryl wherein the phenyl and heteroaryl are optionally substituted with 1, 2, 3, 4, or 5  $R^9$  groups; and

each  $R^9$ , when present, is independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, amino, alkylamino, dialkylamino, alkoxyalkyl, carboxyalkyl, alkoxy carbonyl,

aminoalkyl, cycloalkyl, aryl, arylalkyl, aryloxy, heterocycloalkyl, or heteroaryl and where the cycloalkyl, aryl, heterocycloalkyl, and heteroaryl, each either alone or as part of another group within R<sup>9</sup>, are independently optionally substituted with 1, 2, 3, or 4 groups selected from halo, alkyl, haloalkyl, hydroxy, alkoxy, haloalkoxy, amino, alkylamino, and dialkylamino.

[00142] In one embodiment, R<sup>1</sup> is alkyl, cycloalkyl, heterocycloalkylalkyl, or arylalkyl; R<sup>2</sup> is hydrogen or alkyl; R<sup>4</sup> is alkyl; R<sup>5</sup> is hydrogen; R<sup>6</sup> is phenyl or heteroaryl wherein the phenyl and heteroaryl are optionally substituted with one, two, or three R<sup>9</sup> groups;

[00143] In another embodiment, R<sup>4</sup> is methyl.

[00144] In another embodiment, R<sup>1</sup> is alkyl, cycloalkyl, or heterocycloalkyl.

[00145] In another embodiment, R<sup>1</sup> is alkyl.

[00146] In another embodiment, R<sup>6</sup> is heteroaryl optionally substituted with 1, 2, or 3 R<sup>9</sup> groups.

[00147] In another embodiment, each R<sup>9</sup>, when present, is independently alkyl, arylalkyl, cyano, aryl, alkoxy carbonyl, or halo.

[00148] In another embodiment, R<sup>6</sup> is pyrazolyl, imidazolyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, furanyl, pyrrolyl, triazolyl, or tetrazolyl; each of which is optionally substituted with 1, 2, or 3 R<sup>9</sup> groups.

[00149] In another embodiment, R<sup>6</sup> is pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, thien-2-yl, thien-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, furan-2-yl, furan-3-yl, pyrrol-2-yl, pyrrol-3-yl, triazol-4-yl, triazol-5-yl, or tetrazol-5-yl; each of which is optionally substituted with 1, 2, or 3 R<sup>9</sup> groups.

[00150] In another embodiment, R<sup>6</sup> is pyrazinyl, pyrimidinyl, or pyridazinyl each of which is optionally substituted with 1, 2, or 3 R<sup>9</sup> groups and R<sup>4</sup> is methyl.

[00151] In another embodiment, R<sup>2</sup> is hydrogen, R<sup>4</sup> is methyl, R<sup>1</sup> is optionally substituted alkyl, cycloalkyl, or heterocycloalkyl, and R<sup>6</sup> is heteroaryl optionally substituted with 1, 2, or 3 R<sup>9</sup> groups.

[00152] In another embodiment, the compound of formula IIa is selected from:

2-amino-8-ethyl-4-methyl-6-(1H-pyrazol-5-yl)pyrido[2,3-d]pyrimidin-7(8H)-one;

2-amino-8-cyclopentyl-4-methyl-6-(1H-pyrazol-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one;

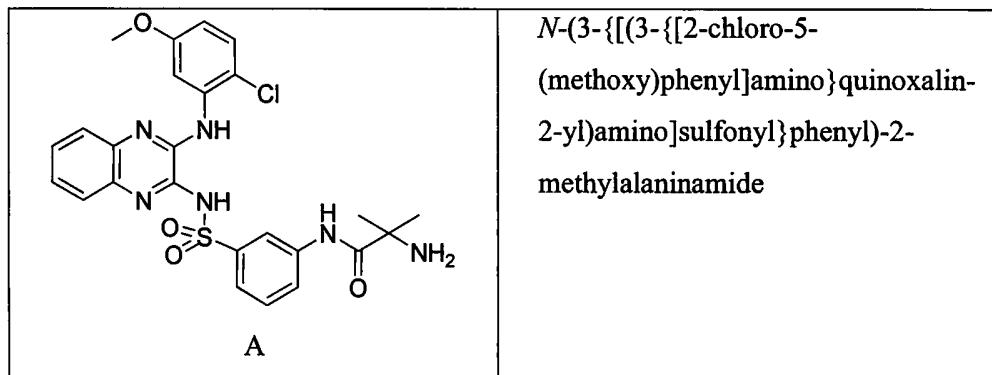
2-amino-4-methyl-8-(1-methylethyl)-6-(1H-pyrazol-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one;

2-amino-4-methyl-8-(phenylmethyl)-6-(1 <i>H</i> -pyrazol-3-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-4-methyl-6-(4-methyl-3-thienyl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-4-methyl-6-(2-thienyl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-4-methyl-6-(3-thienyl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-6-furan-3-yl-4-methylpyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-4-methyl-6-phenylpyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-6-isoxazol-4-yl-4-methylpyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-6-furan-2-yl-4-methylpyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
5-(2-amino-8-ethyl-4-methyl-7-oxo-7,8-dihydropyrido[2,3- <i>d</i> ]pyrimidin-6-yl)thiophene-2-carbonitrile;
2-amino-8-ethyl-4-methyl-6-pyrimidin-5-ylpyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-6-(1 <i>H</i> -imidazol-5-yl)-4-methylpyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-4-methyl-6-(1 <i>H</i> -1,2,3-triazol-5-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-4-methyl-6-(1 <i>H</i> -pyrazol-4-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-4-methyl-6-(1,3-thiazol-2-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-4-methyl-6-(1 <i>H</i> -tetrazol-5-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-4-methyl-6-(1-methyl-1 <i>H</i> -pyrrol-2-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-4,8-diethyl-6-(1 <i>H</i> -pyrazol-5-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one; and
2-amino-8-cyclopentyl-4-methyl-6-(1,3-thiazol-5-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one.

[00153] In another embodiment, the compound of formula IIa is compound B, which is 2-amino-8-ethyl-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (compound B) or a pharmaceutically acceptable salt thereof.

#### Compound A Additional Embodiments

[00154] In one embodiment, the invention provides a method of treating BCC in a patient in need of such treatment, comprising administering to the patient an effective amount of letrozole in combination with:



or a pharmaceutically acceptable salt, tautomer, hydrate, or solvate thereof.

[00155] In another embodiment, the compound A is administered as a capsule or tablet pharmaceutical composition.

[00156] In another embodiment, the amount of compound A in the tablet or capsule formulation is sufficient to produce saturation of absorption when administered once daily.

[00157] In another embodiment, about 100 mg to about 800 mg of compound A is administered as a capsule composition once daily.

[00158] In another embodiment, about 200 mg to about 700 mg of compound A is administered as a capsule composition once daily.

[00159] In another embodiment, about 500 mg to about 700 mg of compound A is administered as a capsule composition once daily.

[00160] In another embodiment, about 100 mg to about 800 mg of compound A is administered as a tablet composition once daily.

[00161] In another embodiment, about 200 mg to about 700 mg of compound A is administered as a tablet composition once daily.

[00162] In another embodiment, about 300 mg to about 500 mg of compound A is administered as a tablet composition once daily.

[00163] In another embodiment, about 400 mg of compound A is administered as a tablet composition once daily.

[00164] In another embodiment, compound A is administered as a capsule consisting of Size 0 capsules filled with drug substance only. There are no additional excipients other than the capsule gelatin and coloring agents. The composition of the hard gelatin capsule shell and color demarcation are presented in the table below.

### Gelatin Capsule Composition

Component	Swedish Orange Opaque Capsule (for 100-mg strength)
FDA/E171 titanium dioxide	0.4902%
FDA/E172 red iron dioxide	1.4706%
Gelatin	qsp 100%

FDA, Food and Drug Administration; qsp, quantity sufficient for 100%.

[00165] In another embodiment, compound A is administered as a 100, 150, or 200 mg tablet. The tablet strength will be distinguishable by shape and/or size. The tablet formulation contains compound A, silicified microcrystalline cellulose, partially pregelatinized maize starch, sodium starch glycolate, hypromellose, colloidal silicon dioxide, stearic acid, and magnesium stearate. All three tablet strengths are manufactured from a common blend with the composition listed in the following Table.

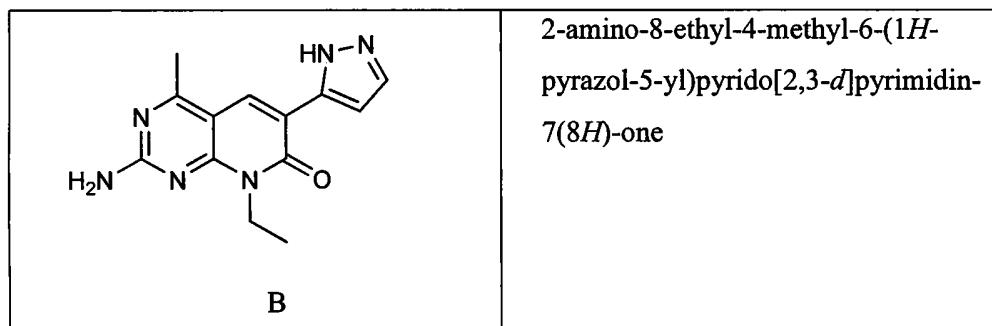
### Composition of the Compound 100-, 150-, and 200-mg Tablets

Ingredient	Batch Formula (% w/w)
Compound A	50.00
Silicified Microcrystalline Cellulose	14.75
Partially Pregelatinized Maize Starch	20.00
Sodium Starch Glycolate	7.00
Hypromellose 2910	6.00
Colloidal Silicon Dioxide	1.00
Stearic Acid	1.00
Magnesium Stearate	0.25
Purified Water	a

<sup>a</sup> Essentially removed during manufacture.

### Compound B Additional Embodiments

[00166] In one embodiment, the invention provides a method of treating BCC in a patient in need of such treatment, comprising administering to the patient an effective amount of letrozole in combination with:



or a pharmaceutically acceptable salt thereof.

[00167] In another embodiment, the compound B is administered as a capsule or tablet pharmaceutical composition.

[00168] In another embodiment, the amount of compound B in the tablet or capsule formulation is sufficient to produce saturation of absorption when administered once daily.

[00169] In another embodiment, the amount of compound B in the tablet or capsule formulation is sufficient to produce saturation of absorption when administered twice daily.

[00170] In another embodiment, about 10 mg to about 100 mg of compound B is administered as a capsule composition twice daily.

[00171] In another embodiment, about 10 mg of compound B is administered as a capsule composition twice daily.

[00172] In another embodiment, about 20 mg of compound B is administered as a capsule composition twice daily.

[00173] In another embodiment, about 30 mg of compound B is administered as a capsule composition twice daily.

[00174] In another embodiment, about 40 mg of compound B is administered as a capsule composition twice daily.

[00175] In another embodiment, about 50 mg of compound B is administered as a capsule composition twice daily.

[00176] In another embodiment, about 60 mg of compound B is administered as a capsule composition twice daily.

[00177] In another embodiment, about 70 mg of compound B is administered as a capsule composition twice daily.

[00178] In another embodiment, about 80 mg of compound B is administered as a capsule composition twice daily.

[00179] In another embodiment, about 90 mg of compound B is administered as a capsule composition twice daily.

[00180] In another embodiment, about 100 mg of compound B is administered as a capsule composition twice daily.

[00181] In another embodiment, compound A is administered as a capsule consisting of Size 0 capsules filled with 10, 30 or 40 mg of drug substance only. There are no additional excipients other than the capsule gelatin and coloring agents. The composition of the hard gelatin capsule shell and color demarcation are presented in the table below.

### Gelatin Capsule Composition of Compound B

<u>Component</u>	<u>White Opaque Capsule (for 10-mg strength)</u>	<u>Gray/ Orange Capsule (for 30-mg strength)</u>	<u>Gray Opaque Capsule (for 40-mg strength)</u>	<u>Swedish Orange Capsule (for 50-mg strength)</u>
FDA/E171 titanium dioxide	2.9079%  0.4902%  (Body)  (Cap)	2.7074%  (Body)	2.7074%	0.4902%
FDA/E172 black iron dioxide	—	0.3075%  (Body)	0.3075%	—
FDA/E172 red iron dioxide	—	1.4706%  (Cap)	—	1.4706%
Gelatin	qsp 100%	qsp 100%	qsp 100%	qsp 100%

FDA, Food and Drug Administration; qsp, quantity sufficient for preparation.

#### Other Embodiments

**[00182]** In another embodiment, the effective amount of either a compound of formula Ia or IIa that is administered in the method produces at least one therapeutic effect selected from the group consisting of reduction in size of a tumor, reduction in metastasis, complete remission, partial remission, stable disease, increase in overall response rate, or a pathologic complete response.

**[00183]** In another embodiment, the effective amount produces an improved clinical benefit rate (CBR) according to the equation CBR = CR (complete remission) + PR (partial remission) + SD (stable disease)  $\geq$  6 months as compared to other treatments.

**[00184]** In another embodiment, the improvement of clinical benefit rate is about 20 percent or higher.

**[00185]** In another embodiment, the therapeutic effect is an increase in overall response rate.

**[00186]** In another embodiment, the increase in overall response rate is about 10 percent or more or higher.

**[00187]** In another embodiment, a comparable clinical benefit rate (CBR) according to the equation CBR = CR (complete remission) + PR (partial remission) + SD (stable disease)  $\geq$  6 dosing cycles is obtained with compound A or compound B.

**[00188]** In another embodiment, the improvement of clinical benefit rate is at least about 20 percent or higher.

[00189] In another embodiment, a comparable clinical benefit rate (CBR = CR (complete remission) + PR (partial remission) + SD (stable disease) ≥ 6 months) is obtained with treatment with compound B.

[00190] In another embodiment, the improvement of clinical benefit rate is at least about 20 percent or higher.

#### **General Administration**

[00191] In one aspect, the invention provides pharmaceutical compositions comprising an inhibitor of the PI3Ks of formula Ia or IIa and a pharmaceutically acceptable carrier, excipient, or diluent. In certain other specific embodiments, administration is by the oral route. Administration of the compounds of formula Ia or IIa, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, the compound of formula Ia or IIa can be administered in the same or separate vehicles. Administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, specifically in unit dosage forms suitable for simple administration of precise dosages.

[00192] The compositions will include a conventional pharmaceutical carrier or excipient and a compound of formula Ia or IIa as the/an active agent.

[00193] Adjuvants include preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[00194] If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylated hydroxytoluene, etc.

[00195] The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills or

capsules) and the bioavailability of the drug substance. Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

**[00196]** Compositions 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.

**[00197]** One specific route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

**[00198]** Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound 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, cellulose derivatives, starch, alignates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, 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, magnesium stearate and the like (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.

[00199] Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying 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 embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[00200] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like; 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 and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[00201] Suspensions, in addition to the active compounds, may contain suspending 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.

[00202] Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the compounds of the present invention with for example 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 while in a suitable body cavity and release the active component therein.

[00203] Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

[00204] Compressed gases may be used to disperse a compound of this invention in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

[00205] Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

[00206] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state in accordance with the teachings of this invention.

[00207] In the pharmaceutical compositions disclosed herein, the compounds of formula Ia or IIa, or their pharmaceutically acceptable salts or solvates, are administered in an effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. The compounds of formula Ia or IIa can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day, or in the range of 100 mg to 800 mg per day, or in the range of 200 to 700 mg per day, or in the range of 300 to 600 mg per day.

[00208] For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is an example. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to one of ordinary skill in the art. If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described above and the other pharmaceutically active agent(s) within approved dosage ranges. Compounds of formula Ia or

IIa may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

### **Compounds of Formula I and Ia General Synthesis**

**[00209]** Compounds of this invention can be made by the synthetic procedures described in WO2007/044729 and WO 2008/127594.

#### **General Synthesis**

##### **Synthesis of Compounds of Formula I**

**[00210]** The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wis.) or Bache (Torrance, Calif.), or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fisher and Fisher's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rod's Chemistry of Carbon Compounds, Volumes 1-5 and Supplemental (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4<sup>th</sup> Edition) and Larch's Comprehensive Organic Transformations (VICHY Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure. The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

**[00211]** Unless specified to the contrary, the reactions described herein take place at atmospheric pressure and over a temperature range from about -78 °C to about 150 °C, in another embodiment from about 0 °C. to about 125 °C and most specifically at about room (or ambient) temperature, e.g., about 20 °C. Unless otherwise stated (as in the case of a hydrogenation), all reactions are performed under an atmosphere of nitrogen.

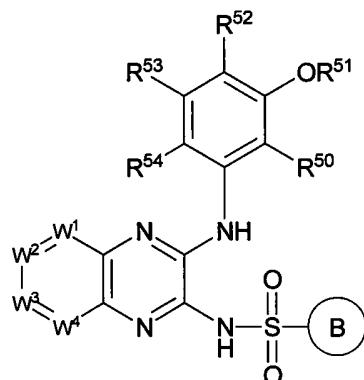
**[00212]** Prodrugs can be prepared by techniques known to one skilled in the art. These techniques generally modify appropriate functional groups in a given compound. These modified functional groups regenerate original functional groups by routine manipulation or *in vivo*. Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T.

Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

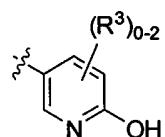
**[00213]** The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms or quaternized nitrogen atoms in their structure. Compounds of formula I that may be prepared through the syntheses described herein may exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention.

**[00214]** Some of the compounds of the invention may exist as tautomers. For example, where a ketone or aldehyde is present, the molecule may exist in the enol form; where an amide is present, the molecule may exist as the imidic acid; and where an enamine is present, the molecule may exist as an imine. All such tautomers are within the scope of the invention, and to the extent that one structure is used to depict a compound, it includes all such tautomeric forms.

**[00215]** Thus, compounds of formula I:

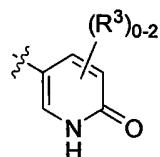


can exist as tautomers. In particular, ring B in the compound of formula I or B can be 2-hydroxy-pyridinyl, also described as its structure.



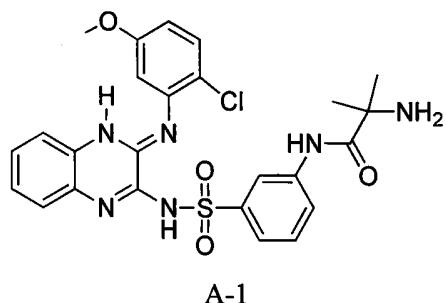
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Both 2-hydroxy-pyridinyl and the above structure 14 include, and are equivalent to, pyridin-2(1*H*)-one and its structure 15.

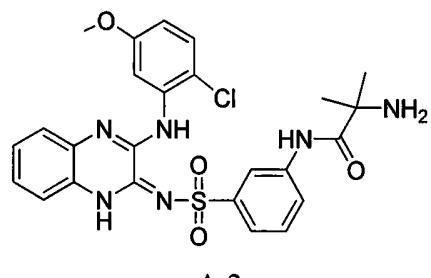


Regardless of which structure or which terminology is used, each tautomer is included within the scope of the invention.

**[00216]** For example, one tautomer of compound A is compound A-1.

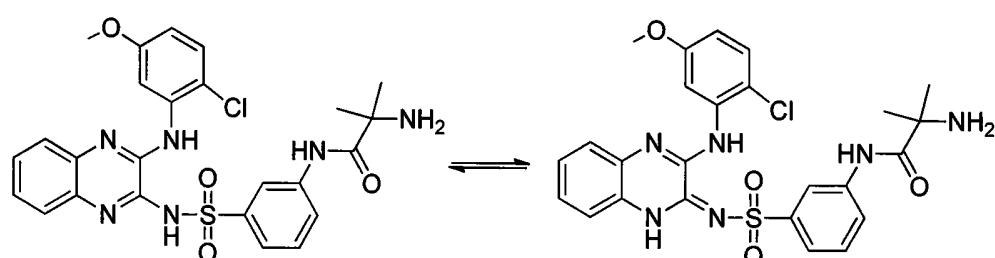


**[00217]** Another tautomer of compound A is compound A-2.



Compound A-2 is named N-(3-{{(2Z)-3-[(2-chloro-5-methoxyphenyl)amino]prop-1-enyl}quinoxalin-2(1H)-ylidene}sulfamoylphenylalanine.

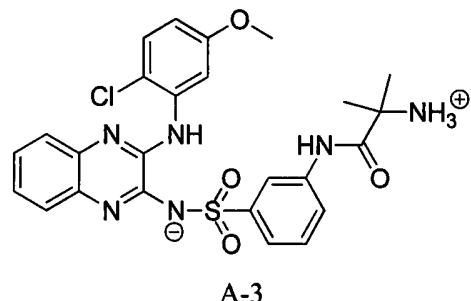
**[00218]** As would be understood by a skilled practitioner, tautomeric forms can interconvert.



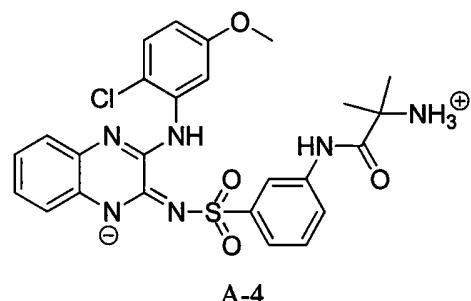
**[00219]** Moreover, intermediates leading to compounds of formula I, as well as compounds of formula I themselves, can be recovered as uncharged or zwitterionic molecules, or cationic salts such as sodium or potassium, depending on the substitutions on the B ring and on reaction conditions. All such zwitterionic forms are within the scope of the

invention, and to the extent that one structure is used to depict a zwitterionic compound, it includes all such zwitterionic forms.

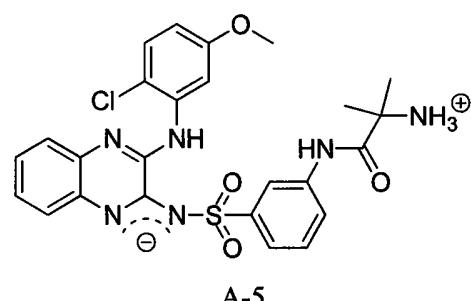
[00220] For example, one zwitterionic form of compound A is compound A-3.



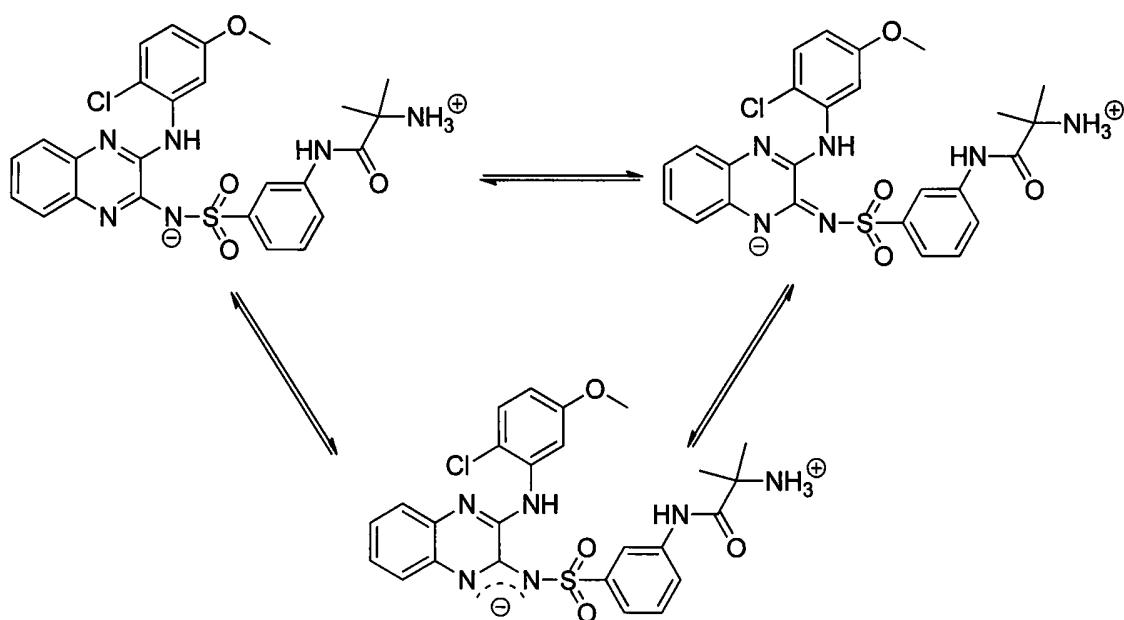
[00221] Another zwitterionic depiction of compound A is compound A-4.



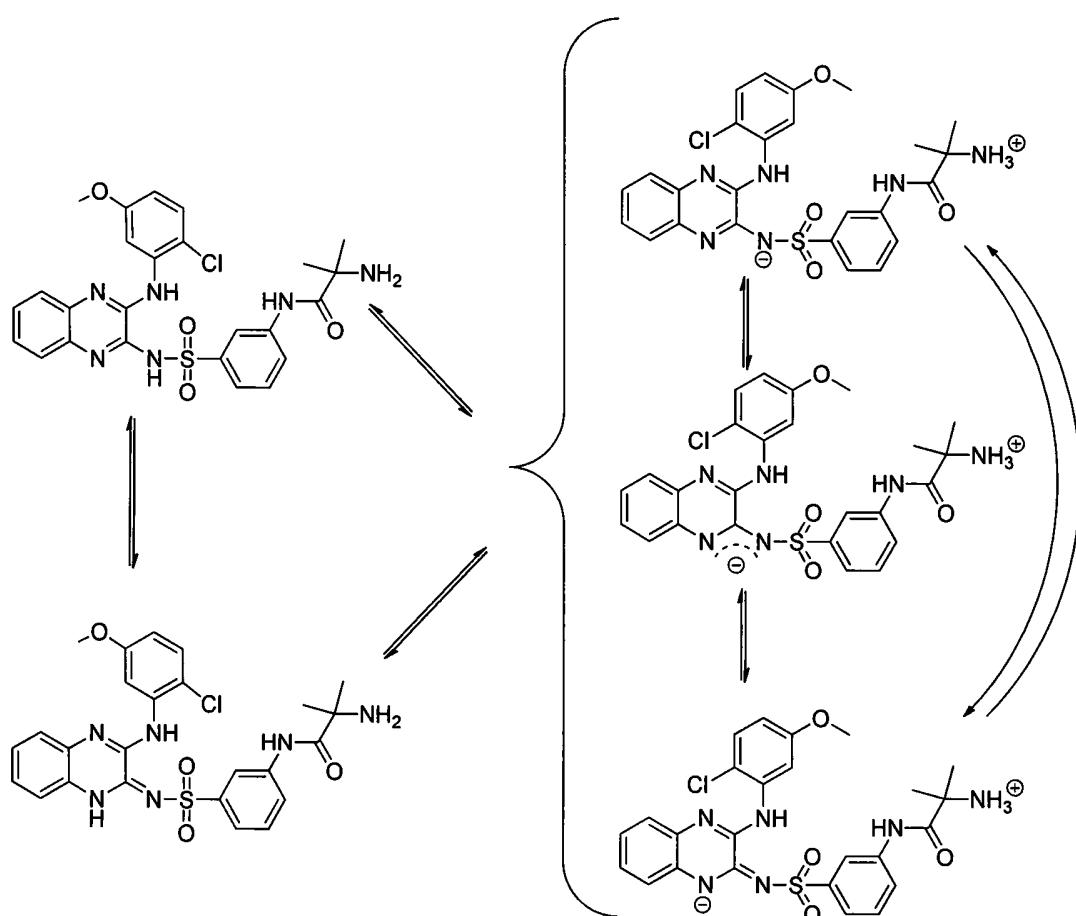
[00222] Another zwitterionic depiction of compound A is compound A-5.



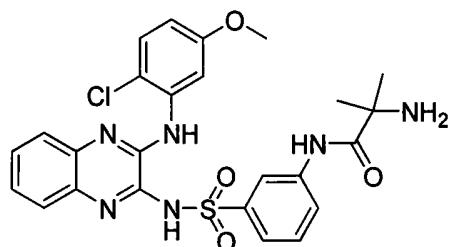
[00223] As would be understood by a skilled practitioner, tautomeric forms can interconvert.



[00224] Moreover, interconversion can also exist between the uncharged tautomeric forms and the zwitterionic forms.



**[00225]** Regardless of which structure or which terminology is used, each tautomer or zwitterion is included within the scope of the invention. Thus, as used herein, the structure



and the associated terms “compound A” and “N-(3-{[(3-{[2-chloro-5-(methoxy)phenyl]amino}quinoxalin-2-yl)amino]sulfonyl}phenyl)-2-methylalaninamide” encompass all possible tautomeric and zwitterionic forms of the compound.

**[00226]** The present invention also includes N-oxide derivatives and protected derivatives of compounds of formula I. For example, when compounds of formula I contain an oxidizable nitrogen atom, the nitrogen atom can be converted to an N-oxide by methods well known in the art. When compounds of formula I contain groups such as hydroxy, carboxy, thiol, or any group containing a nitrogen atom(s), these groups can be protected with a suitable “protecting group” or “protective group.” A comprehensive list of suitable protective groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1991, the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of formula I can be prepared by methods well known in the art.

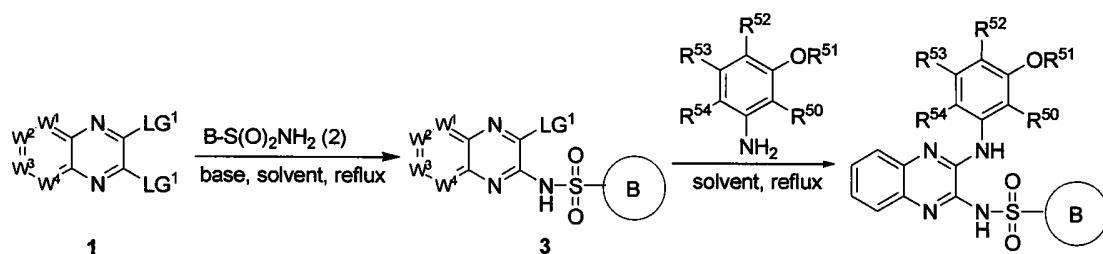
**[00227]** Methods for the preparation and/or separation and isolation of single stereoisomers from racemic mixtures or non-racemic mixtures of stereoisomers are well known in the art. For example, optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. Enantiomers (R- and S-isomers) may be resolved by methods known to one of ordinary skill in the art, for example by: formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallization; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where a desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be required to liberate the desired

enantiomeric form. Alternatively, specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts, or solvents or by converting one enantiomer to the other by asymmetric transformation. For a mixture of enantiomers, enriched in a particular enantiomer, the major component enantiomer may be further enriched (with concomitant loss in yield) by recrystallization.

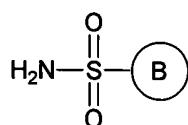
[00228] In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[00229] In the examples that follow, unless otherwise specified, the final form of the compound was assumed to be the uncharged molecule in the absence of analytical techniques that would have determined otherwise. Compounds of formula I can be prepared using methods known to one of ordinary skill in the art or starting from the compound of formula 1 as depicted in Scheme 1 below. Compounds of formula I can be prepared starting from compound 1 by fusion of appropriate reagents at 180 °C in the presence of a base such as K<sub>2</sub>CO<sub>3</sub> and metallic copper. This reaction is known to provide intermediates of formula 1 (see S. H. Dandegaonker and C. K. Mesta, *J. Med. Chem.*, 1965, 8, 884).

### Scheme 1



[00230] Referring again to Scheme 1, an intermediate of formula 3 can be prepared by briefly heating an appropriately substituted quinoxaline (for example, commercially available 2,3-dichloroquinoxaline) and an appropriately substituted sulfonamide of formula 2



O (which are commercially available or can be prepared by one of ordinary skill in the art), a base such as  $K_2CO_3$ , in a solvent, such as DMF or DMSO. Upon completion (about 2 hours), the reaction mixture is then poured into water and followed by 2 N HCl. The product is then extracted into a solvent such as ethyl acetate and washed with water and

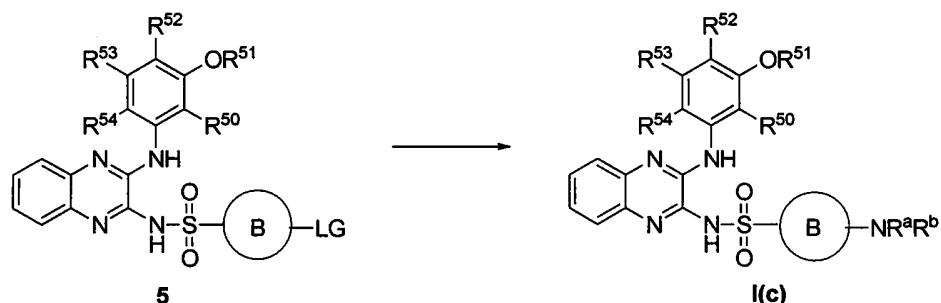
brine. The organic layers are combined and dried over a drying agent such as sodium sulfate, filtered, and concentrated under vacuum to provide a compound of formula 3.

[00231] The intermediate of formula 3 is then treated with an intermediate of formula 4 in a solvent such as DMF or p-xylene at reflux temperature. Upon completion of the reaction (about 16 hours or less), the reaction is allowed to cool, extracted into DCM, washed with 2 N HCl and brine, dried over a drying agent such as sodium sulfate or magnesium sulfate, filtered, and concentrated to give a compound of formula I.

[00232] Alternatively, other methods to prepare quinoxaline derivatives are known to one skilled in the art and include, but are not limited to S. V. Litvinenko, V. I. Savich, D. D. Bobrovnik, *Chem. Heterocycl. Compd.* (Engl. Transl), **1994**, *30*, 340 and W. C. Lumma, R. D. Hartman, *J. Med. Chem.* **1981**, *24*, 93.

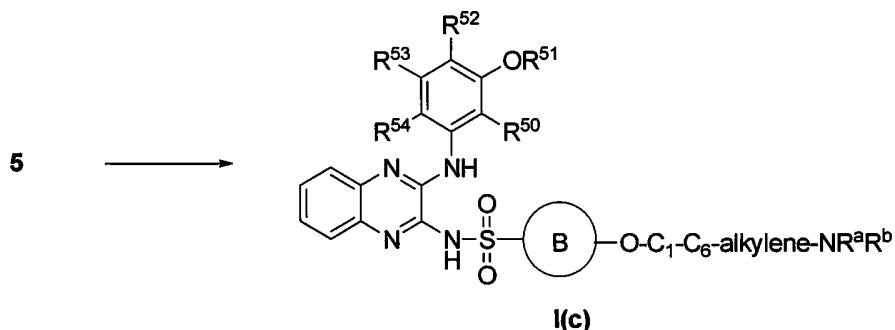
[00233] Compounds of formula I where B is phenyl substituted with  $R^{3a}$  where  $R^{3a}$  is alkylamino or dialkylamino or B is heteroaryl substituted with  $R^3$  where  $R^3$  is amino, alkylamino, or dialkylamino, and all other groups are as defined in the Summary of the Invention can be prepared according to Scheme 2.

## Scheme 2



In Scheme 2, LG is a leaving group such as chloro. Compound **5** is reacted with  $\text{NHR}^a\text{R}^b$  or  $\text{HO-C}_1\text{-C}_6\text{-alkylene-NHR}^a\text{R}^b$  where  $\text{R}^a$  and  $\text{R}^b$  are independently hydrogen or alkyl. The reaction is carried out in the presence of a base, such as  $\text{KHCO}_3$ , in a solvent such as DMF.

[00234] Compounds of formula I where B is phenyl substituted with  $R^{3a}$  where  $R^{3a}$  is aminoalkyloxy, alkylaminoalkyloxy, or dialkylaminoalkyloxy or B is heteroaryl substituted with  $R^3$  where  $R^3$  is aminoalkyloxy, alkylaminoalkyloxy, or dialkylaminoalkyloxy, and all other groups are as defined in the Summary of the Invention can be prepared according to Scheme 3.

**Scheme 3**

**[00235]** The reaction is carried out in the presence of a base such as NaH in a solvent such as DMF.

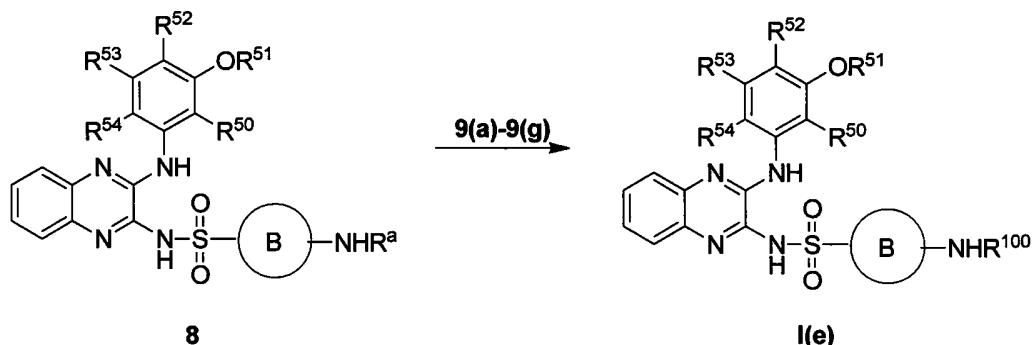
**[00236]** Compounds of formula I where B is phenyl substituted with R<sup>3a</sup> or B is heteroaryl substituted with R<sup>3</sup> where R<sup>3a</sup> and R<sup>3</sup> are

- i. -N(R<sup>7</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>7a</sup>)(R<sup>7b</sup>) where R<sup>7</sup>, R<sup>7a</sup>, and R<sup>7b</sup> are as defined in the Summary of the Invention;
- ii. -NR<sup>9</sup>C(O)R<sup>9a</sup> where R<sup>9</sup> is as defined in the Summary of the Invention;
- iii. -NR<sup>11</sup>C(O)NR<sup>11a</sup>R<sup>11b</sup> where R<sup>11a</sup>, R<sup>11a</sup>, and R<sup>11b</sup> are as defined in the Summary of the Invention;
- iv. -NR<sup>13</sup>C(O)OR<sup>13a</sup> where R<sup>13</sup> and R<sup>13a</sup> are as defined in the Summary of the Invention;
- v. -N(R<sup>18</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>18b</sup>)C(O)R<sup>18a</sup> where R<sup>18</sup>, R<sup>18a</sup>, and R<sup>18b</sup> are as defined in the Summary of the Invention;
- vi. -N(R<sup>20</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-C(O)R<sup>20a</sup> where R<sup>20</sup> and R<sup>20a</sup> as defined in the Summary of the Invention;
- vii. -NR<sup>21</sup>S(O)<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>21b</sup>)R<sup>21a</sup> where R<sup>21</sup>, R<sup>21a</sup>, and R<sup>21b</sup> are as defined in the Summary of the Invention;
- viii. -N(R<sup>22</sup>)C(O)-C<sub>0</sub>-C<sub>6</sub>-alkylene-N(R<sup>22b</sup>)-N(R<sup>22c</sup>)(R<sup>22a</sup>), where R<sup>22</sup>, R<sup>22a</sup> and R<sup>22b</sup> are as defined in the Summary of the Invention;
- ix. -NR<sup>24</sup>C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-OR<sup>24a</sup> where R<sup>24</sup> and R<sup>24a</sup> are as defined in the Summary of the Invention;

and where the alkylene in R<sup>3</sup> and R<sup>3a</sup> are independently optionally substituted as described in the Summary of the Invention can be prepared according to Scheme 4 by reacting with an intermediate of formula 9(a), 9(b), 9(c), 9(d), 9(e), 9(f), or 9(g):

1. 9(a) HOC(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>7a</sup>)(R<sup>7b</sup>) where R<sup>a</sup> is R<sup>7a</sup> or a N-protecting group, such as Boc or Fmoc;
  2. 9(b) HOC(O)R<sup>9a</sup>;
  3. 9(c) HOC(O)NR<sup>11a</sup>R<sup>11b</sup>;
  4. 9(d) HOC(O)OR<sup>13a</sup>;
  5. 9(e) HOC(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>18b</sup>)C(O)R<sup>18a</sup>;
  6. 9(f) HOC(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-C(O)R<sup>20a</sup>;
  7. 9(g) LG-S(O)<sub>2</sub>-C<sub>1</sub>.C<sub>6</sub>-alkylene-N(R<sup>21b</sup>)R<sup>a</sup> where R<sup>a</sup> is R<sup>21a</sup> or a N-protecting group, such as Boc or Fmoc.

### Scheme 4

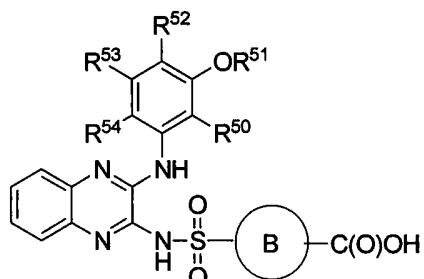


[00237] In Scheme 4, R<sup>100</sup> in Scheme 4 is -C(O)R<sup>9a</sup>, -C(O)NR<sup>11a</sup>R<sup>11b</sup>, -C(O)OR<sup>13a</sup>, -C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>18b</sup>)C(O)R<sup>18a</sup>, -C(O)-C<sub>1</sub>-C<sub>6</sub>-alkylene-C(O)R<sup>20a</sup>, or -S(O)<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub>-alkylene-N(R<sup>21b</sup>)R<sup>a</sup>. The reaction is carried out under standard amide coupling conditions known to one of ordinary skill in the art. In particular, the reaction is carried out in the presence of a coupling agent such as HATU, a base such as DIEA, and in a solvent such as DMF. Where applicable, the N-protecting group is then removed using procedures known to one of ordinary skill in the art, such as treating with acid where PG is Boc.

[00238] Proceeding as described for Scheme 4, compounds of the invention where B is phenyl substituted with R<sup>3a</sup> or B is heteroaryl substituted with R<sup>3</sup> where R<sup>3a</sup> and R<sup>3</sup> are

- i.  $-\text{C}(\text{O})\text{NR}^8\text{R}^{8a};$
  - ii.  $-\text{C}(\text{O})\text{N}(\text{R}^{10})-\text{C}_1\text{-C}_6\text{-alkylene-N}(\text{R}^{10a})\text{R}^{10b};$
  - iii.  $-\text{C}(\text{O})\text{R}^{12}$  where  $\text{R}^{12}$  is an N-substituted heterocycloalkyl;
  - iv.  $-\text{C}(\text{O})\text{N}(\text{R}^{14})\text{N}(\text{R}^{14a})(\text{R}^{14b});$
  - v.  $-\text{C}(\text{O})\text{N}(\text{R}^{16})-\text{C}_1\text{-C}_6\text{-alkylene-C}(\text{O})\text{OR}^{16a};$  or
  - vi.  $-\text{C}(\text{O})\text{N}(\text{R}^{19})-\text{C}_1\text{-C}_6\text{-alkylene-C}(\text{O})\text{R}^{19a};$

can be prepared by exchanging the starting materials as necessary. In particular, the intermediate of formula 11:

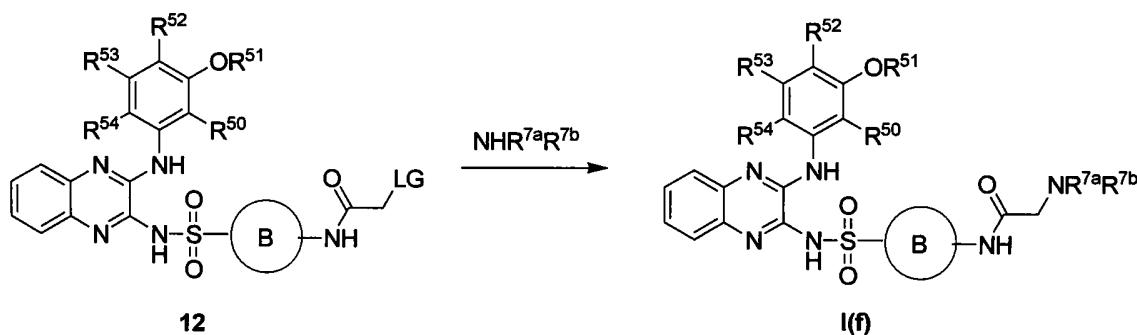


11

is used instead of 8.

**[00239]** Compounds of formula I where B is phenyl substituted with R<sup>3a</sup> or B is heteroaryl substituted with R<sup>3</sup> where R<sup>3a</sup> and R<sup>3</sup> are -NHC(O)CH<sub>2</sub>NR<sup>7a</sup>R<sup>7b</sup> where R<sup>7a</sup> and R<sup>7b</sup> are as defined in the Summary of the Invention can be prepared according to Scheme 5.

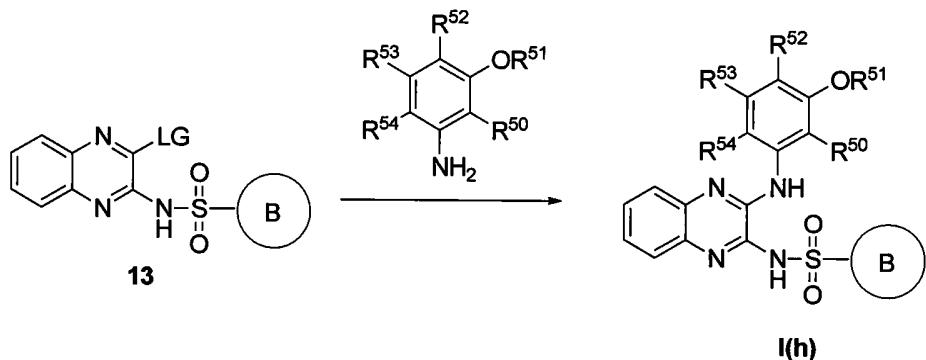
Scheme 5



LG is a leaving group such as bromo or chloro. 12 is reacted with NH(R<sup>7b</sup>)R<sup>7a</sup> in the presence of a base, such as DIEA, in a solvent such as ACN.

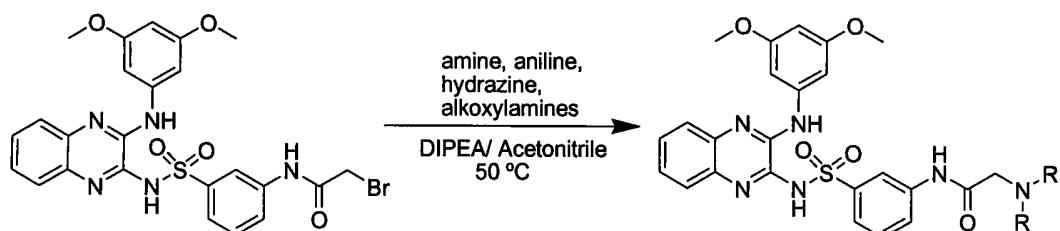
**[00240]** Compounds of formula I can be prepared according to Scheme 6.

Scheme 6



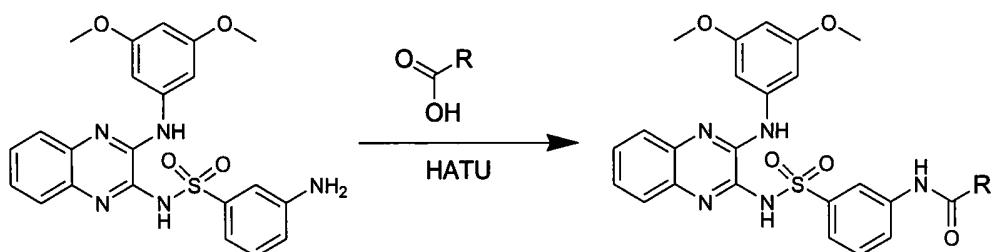
LG in Scheme 6 is a leaving group such as chloro. The reaction can be carried out by irradiating in a solvent such as DMA. Alternatively, the reaction can be carried out in the presence of acetic acid in a solvent such as DMA and by heating.

#### General Alkylation Procedure 1



[00241] Into a 2-dram vial was placed 2-bromo-N-(3-(3,5-dimethoxyphenylamino)quinoxalin-2-yl) sulfamoyl phenyl acetamide (86 mg, 0.15 mmol), prepared using procedures similar to those in Example 171, along with 2 mL of acetonitrile. Eight equivalents (1.2 mmol) of the desired amine, aniline, hydrazine or alkoxylamine were added followed by the addition of Hunig's Base (41  $\mu$ L, 0.25 mmol). The reaction then was stirred at 50 °C for one hour (overnight for aniline reagents). Preparative reverse-phase HPLC was used to isolate the desired product directly from the crude reaction mixture. A Waters Fractionlynx preparative reverse-phase HPLC – equipped with a Waters SunFire Prep C18, OCD 5  $\mu$ M, 30 X 70 mm column and running a 5-100 % gradient with a binary solvent system of 25 mM ammonium acetate in water/acetonitrile – was used to carry out the purification.

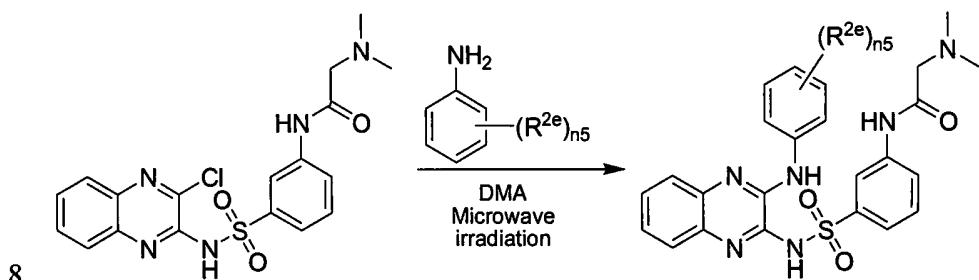
#### General Library Acylation Procedure 1



[00242] Into a 2-dram vial were added 3-amino-N-(3-(3,5-dimethoxyphenylamino)quinoxalin-2-yl)benzenesulfonamide (54 mg, 0.12 mmol), prepared using procedures similar to those described in Example 15, DMA (2 mL) and the desired carboxylic acid (0.17 mmol). DIEA (70  $\mu$ L, 0.4 mmol) followed by HATU (53 mg, 0.14 mmol) were added to the vial and the reaction mixture stirred at 50 °C overnight. Preparative reverse-phase HPLC was used to isolate the desired product directly from the crude reaction mixture. A Waters Fractionlynx preparative reverse-phase HPLC; equipped with a Waters SunFire Prep C18, OCD 5  $\mu$ M, 30 X 70 mm column and running a 5-100 % gradient with a

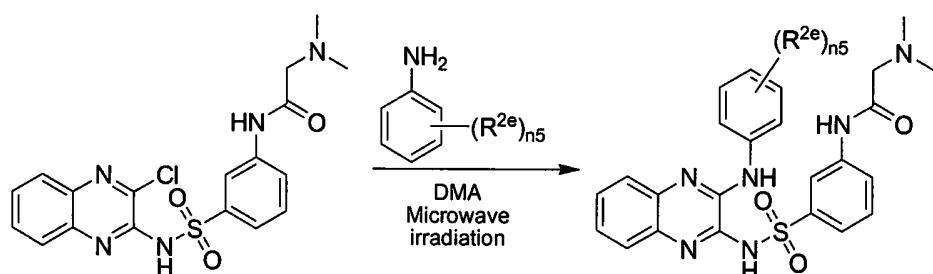
binary solvent system of 25 mM ammonium acetate in water/acetonitrile; was used to carry out the purification.

#### General Amination Procedure 1a



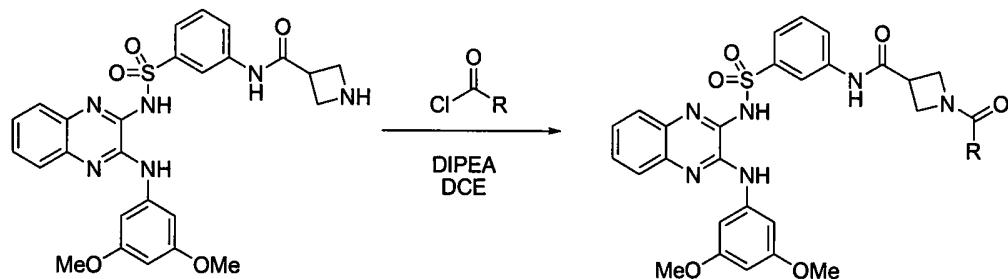
**[00243]** A CEM microwave reaction vessel was charged with *N*-(3-(*N*-(3-chloroquinoxalin-2-yl)sulfamoyl)phenyl)-2-(dimethylamino)acetamide (30 mg, 0.071 mmol), prepared using procedures similar to those described in Example 374, the desired aniline (16 mg, 0.14 mmol, 2 eq), and 0.5 mL of dimethylacetamide. The vessel was sealed and the reaction mixture was heated under microwave radiation for 70 min at 140 °C in a CEM Discover microwave instrument. The solvent was then removed by rotary-evaporation. Purification of the final product was accomplished by preparatory reverse-phase HPLC with the eluents 25 mM aqueous NH<sub>4</sub>OAc/ACN to the desired product.

#### General Amination Procedure 1b



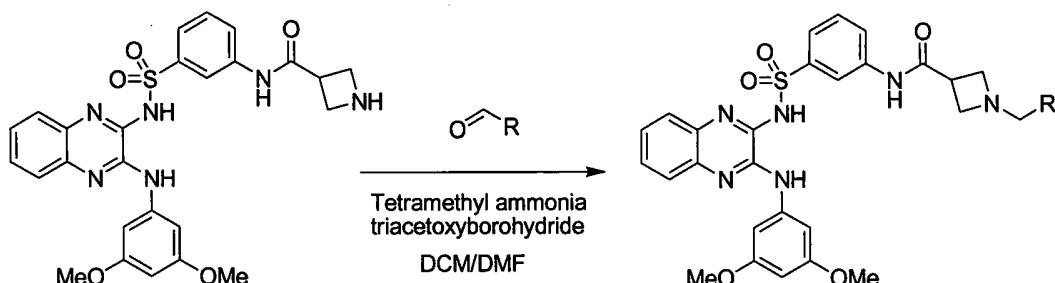
**[00244]** A CEM microwave reaction vessel was charged with *N*-(3-(*N*-(3-chloroquinoxalin-2-yl)sulfamoyl)phenyl)-2-(dimethylamino)acetamide (62 mg, 0.147 mmol), prepared using procedures similar to those in Example 374, the desired aniline (0.567 mmol, 4 eq), and 1.0 mL of toluene. The vessel was sealed and the reaction mixture was heated under microwave radiation for 60 min at 180 °C in a CEM Discover microwave instrument. The solvent was removed on a rotary-evaporator. Purification of the final product was done by preparatory HPLC with NH<sub>4</sub>OAc/ACN as eluent to yield the desired product.

### General Acylation Procedure 2



**[00245]** *N*-(3-(*N*-(3,5-dimethoxy-phenylamino)quinoxalin-2-yl)-sulfamoylphenyl)azetidine-3-carboxamide (125 mg, 0.23 mmol), prepared using procedures similar to those described in Example 372, was dissolved into 5 mL DCE in a 10 mL round-bottom flask. DIEA (1.17 mmol, 5.0 equiv.) was then added with stirring followed by acid chloride (0.47 mmol, 2.0 equiv.). The reaction was then stirred at room temperature for 1 hour or until complete as indicated by LCMS. The solvent was subsequently removed under reduced pressure on a rotary evaporator. The crude material was then re-dissolved in methanol. Purification of the final product was accomplished by preparatory reverse-phase HPLC with the eluents 25 mM aqueous NH<sub>4</sub>OAc/CAN. A Waters Fractionlynx preparative reverse-phase HPLC; equipped with a Waters SunFire Prep C18, OCD 5 μM, 30 X 70 mm column and running a 5-100 % gradient with a binary solvent system of 25 mM ammonium acetate in water/acetonitrile; was used to carry out the purification.

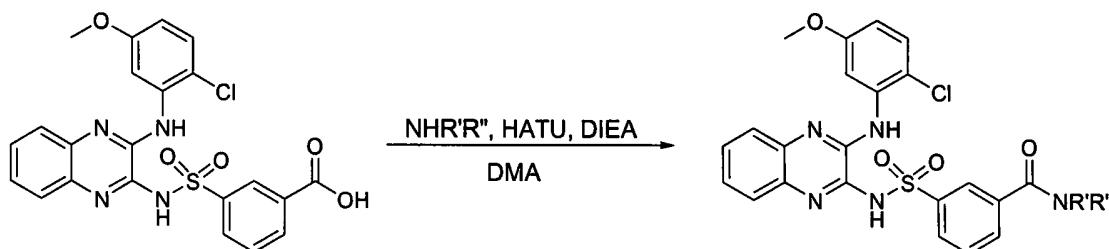
### General Reductive Amination Procedure 1



**[00246]** To a solution of *N*-(3-(*N*-(3,5-dimethoxy-phenylamino)quinoxalin-2-yl)sulfamoylphenyl)azetidine-3-carboxamide (110 mg, 0.19 mmol), prepared using procedures similar to those described in Example 372, in 3 mL of DCE and 200 μL of DMF, aldehyde (0.77 mmol, 4.0 eq.) was added slowly followed by tetramethylammonium triacetoxyborohydride (1.16 mmol, 6.0 eq). The reaction was stirred at room temperature overnight. LC/MS indicated the reaction was completed. The solvent was subsequently removed under reduced pressure on a rotary evaporator. The crude material was then re-dissolved in methanol. Purification of the final product was accomplished by preparatory

reverse-phase HPLC with the eluents 25 mM aqueous NH<sub>4</sub>OAc/CAN. A Waters Fractionlynx preparative reverse-phase HPLC; equipped with a Waters SunFire Prep C18, OCD 5 μM, 30 X 70 mm column and running a 5-100 % gradient with a binary solvent system of 25 mM ammonium acetate in water/acetonitrile; was used to carry out the purification.

#### General Amide Formation Procedure 1a



[00247] Into a small 1 dram vial was added 3-(*N*-(3-(2-chloro-5-methoxy-phenylamino)-quinoxalin-2-yl)sulfamoyl)benzoic acid (61 mg, 0.13 mmol, 1.1 equiv), prepared using procedures described for Example 100. The acid was dissolved in DMA (1 mL) and DIEA (42 μL, 0.24 mmol, 2 equiv) was added then added to the solution. The amine reagent (1 mL of 0.12 M solution in DMA) was added to solution with stirring followed by HATU (64 mg, 0.17 mMol, 1.4 equiv). The reaction was stirred overnight at room temperature. Upon completion as indicated by LCMS analysis, 2 mL of methanol was added to the solution. Preparative reverse-phase HPLC was used to isolate the desired product. A Waters Fractionlynx preparative reverse-phase HPLC – equipped with a Waters SunFire Prep C18, OCD 5 μM, 30 X 70 mm column and running a 5-100 % gradient with a binary solvent system of 25 mM ammonium acetate in water/acetonitrile – was used to carry out the purification.

#### General Amide Formation Procedure 1b

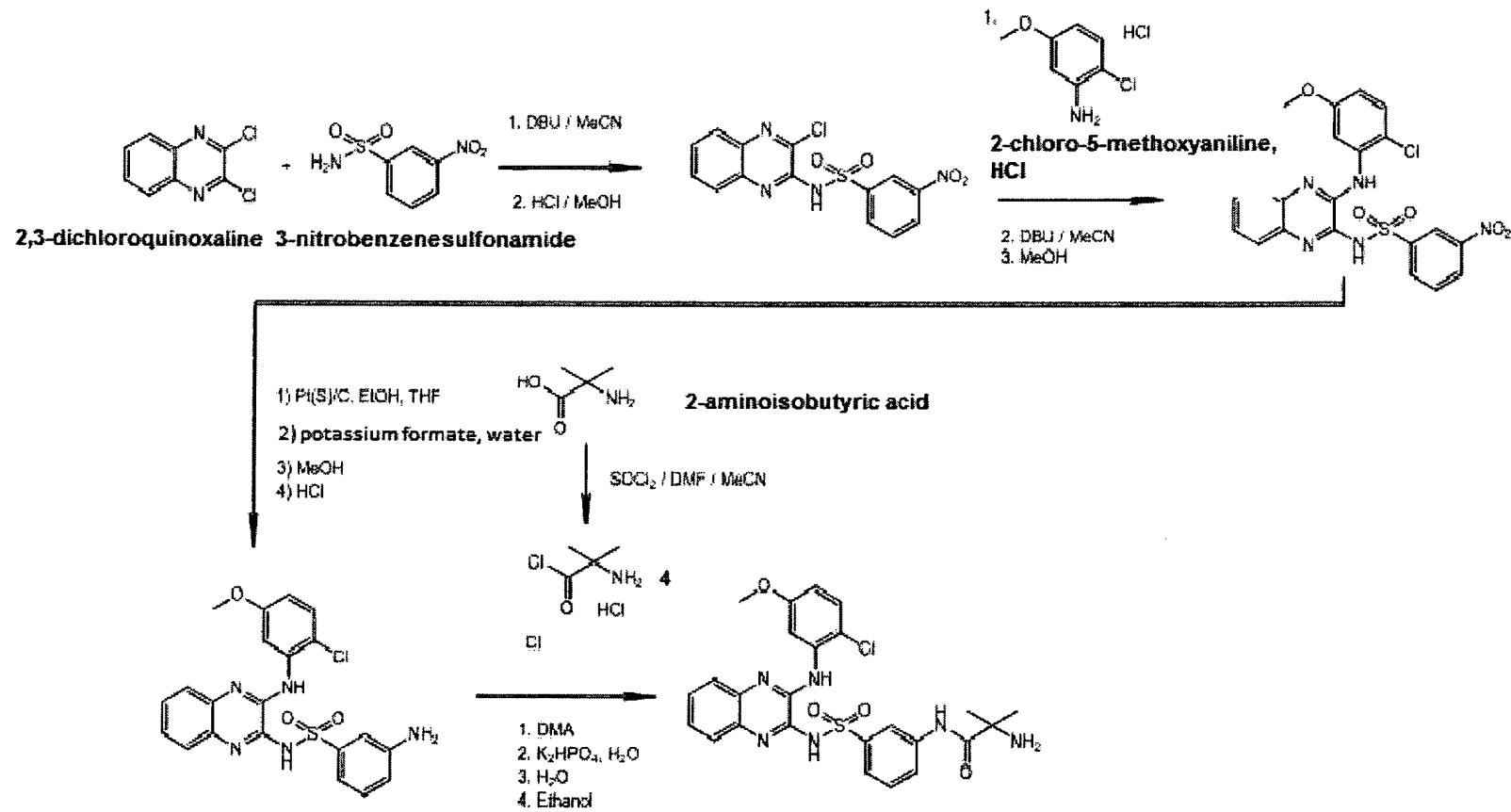
[00248] The procedure outlined in **General Amide Formation Procedure 1a** was used to incorporate a number of amines that contained a second amine group protected as the *tert*-butylcarbamate (i.e. where R', within NHR'R'', contained a Boc-protected amine group). The deprotection was carried out after HPLC purification of the Boc-protected precursor.

[00249] Into a small 1 dram vial was added 3-(*N*-(3-(2-chloro-5-methoxy-phenylamino)-quinoxalin-2-yl)sulfamoyl)benzoic acid (61 mg, 0.13 mmol, 1.1 equiv). The acid was dissolved in 1 mL of DMA and DIEA (42 μL, 0.24 mmol, 2 equiv) was added then added to the solution. The mono-Boc-protected diamine reagent (1 mL of 0.12 M solution in DMA, 1 equiv) was added to solution with stirring followed by HATU (64 mg, 0.17 mmol, 1.4 equiv). The reaction was stirred overnight at room temperature. Upon completion as

indicated by LCMS analysis, 2 mL of methanol was added to the solution. Preparative reverse-phase HPLC was used to isolate the desired product directly from this crude reaction solution. A Waters Fractionlynx preparative reverse-phase HPLC; equipped with a Waters SunFire Prep C18, OCD 5  $\mu$ M, 30 X 70 mm column and running a 5-100 % gradient with a binary solvent system of 25 mM ammonium acetate in water/acetonitrile; was used to carry out the purification. The product fractions were combined and concentrated to dryness under reduced pressure by rotary evaporation. A solution of 4 N HCl in dioxane (2 mL) was added. The solution was then stirred at room temperature until no starting material was detected. The deprotected product precipitated out of solution as an HCl salt and was collected by filtration, washed with ether and dried under vacuum.

#### Synthesis of Compound A

[00250] Crude compound A can be prepared as described below and depicted below in Scheme 7. **Scheme 7. Synthesis of Compound A**



**Synthesis of (N-(3-chloroquinoxalin-2-yl)-3-nitrobenzenesulfonamide):**

[00251] One kg of 2,3 dichloroquinoxaline and one kg of 3-nitrobenzenesulfonamide were mixed in 5 volumes of acetonitrile. The reaction mixture was heated to reflux. 2.3 kg of DBU and 1 volume of acetonitrile were added. After completion of the reaction, the mixture was cooled down at 5 °C. Twelve volumes of methanol and 1.53 kg of HCl were added, and the reaction mixture was filtered. The filter cake was washed with 6 volumes of methanol and dry under vacuum.

**Synthesis of (N-(3-((2-chloro-5-methoxyphenyl)amino)quinoxalin-2-yl)-3-nitrobenzenesulfonamide):**

[00252] A solution was prepared with 0.585 kg of 2-chloro-5-methoxyaniline-HCl, 3.5 volumes of acetonitrile and 0.46 kg of DBU (solution A). Separately, 1 kg of N-(3-chloroquinoxalin-2-yl)-3-nitrobenzenesulfonamide and 5.5 volumes of acetonitrile were combined and heated to reflux. Solution A and 1 volume of acetonitrile was then added to the reaction mixture, and the resulting mixture was heated at reflux. After completion of the reaction, the mixture was cooled down at 20 °C, diluted with 10 volumes of methanol and filtered. The resulting filter cake was washed 3 times with 5 volumes of methanol and then dried under vacuum.

**Synthesis of 3-amino-N-{3-[(2-chloro-5-methoxyphenyl)amino]quinoxalin-2-yl}benzenesulfonamide hydrochloride:**

[00253] To 1 kg of N-{3-[(2-chloro-5-methoxyphenyl)amino]quinoxalin-2-yl}-3-nitrobenzenesulfonamide was added a catalytic amount of platinum sulfide on carbon (Pt(S)C), 6 volumes of THF, 0.16 volume of water, and 2 volumes of ethanol. The resulting reaction mixture was stirred and heated to reflux. An aqueous potassium formate solution (1.4 volume of water + 0.69 kg of potassium formate) was added. The reaction mixture was stirred at reflux until completion of the reaction and then cooled down at 50°C. After the addition of 10 volumes of methanol and one hour of stirring, the catalyst was filtered off and washed with 3.4 volumes of methanol. The filtered solution was cooled down at 20 °C and 0.62 kg of HCl were added. The reaction mixture was stirred at 20 °C, cooled down to 5 °C and filtered. The filter cake was washed with methanol (6 volumes) and dried under vacuum.

**Synthesis of N-[3-(3-[(2-chloro-5-methoxyphenyl)amino]quinoxalin-2-yl}sulfamoyl)phenyl]-2-methylalaninamide (crude):**

[00254] **Synthesis of 2-methylalanyl chloride hydrochloride.** To 0.42 kg of 2-amino-2-methylpropanoic acid, was added 3.7 volumes of acetonitrile, 0.04 volume of dimethylformamide, and 0.62 kg of oxalyl chloride. The reaction mixture was stirred at 20 °C until completion of the reaction. The mixture was then filtered, and the filter cake was washed twice with 1 volume of acetonitrile and dried under vacuum.

[00255] To 1 kg of 3-amino-N-{3-[(2-chloro-5-methoxyphenyl)amino]quinoxalin-2-yl}benzenesulfonamide hydrochloride was added 8 volumes of dimethylformamide and 0.385 kg of 2-methylalanyl chloride hydrochloride at 5°C. After completion of the reaction, the mixture was heated to 50 °C and a solution of K<sub>2</sub>HPO<sub>4</sub> (1.4 kg), water (16.5 volumes) and ethanol (7.1 volumes) was added. The mixture was cooled down to 10 °C, stirred 2 hours at 10 °C, and then filtered. The cake was washed 3 times with 10 volumes of water and dried under vacuum.

**Synthesis of Compound of Formula II**

[00256] Compounds of formula II can be made by the synthetic procedures described below. The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wis.) or Bachem (Torrance, Calif.), or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4<sup>th</sup> Edition), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure. The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography, and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

[00257] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure and over a temperature range from about -78 °C to about 150 °C, more specifically from about 0 °C to about 125 °C and more specifically at about room (or ambient) temperature, e.g., about 20 °C. Unless otherwise stated (as in the case of an hydrogenation), all reactions are performed under an atmosphere of nitrogen.

[00258] Prodrugs can be prepared by techniques known to one skilled in the art. These techniques generally modify appropriate functional groups in a given compound. These modified functional groups regenerate original functional groups by routine manipulation or *in vivo*. Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

[00259] The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms or quaternized nitrogen atoms in their structure. Compounds of formula I that may be prepared through the syntheses described herein may exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention. Some of the compounds of the invention may exist as tautomers. For example, where a ketone or aldehyde is present, the molecule may exist in the enol form; where an amide is present, the molecule may exist as the imidic acid; and where an enamine is present, the molecule may exist as an imine. All such tautomers are within the scope of the invention. In particular, imidazol-5-yl and pyrazol-5-yl each can also exist in their respective tautomeric forms imidazol-4-yl and pyrazol-3-yl. Regardless of which structure or which terminology is used, each tautomer is included within the scope of the Invention.

[00260] The present invention also includes N-oxide derivatives and protected derivatives of compounds of formula II. For example, when compounds of formula I contain an oxidizable nitrogen atom, the nitrogen atom can be converted to an N-oxide by methods well known in the art. When compounds of formula I contain groups such as hydroxy, carboxy, thiol or any group containing a nitrogen atom(s), these groups can be protected with a suitable "protecting group" or "protective group". A comprehensive list of suitable protective groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley &

Sons, Inc. 1991, the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of formula I can be prepared by methods well known in the art.

[00261] Methods for the preparation and/or separation and isolation of single stereoisomers from racemic mixtures or non-racemic mixtures of stereoisomers are well known in the art. For example, optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. Enantiomers (R- and S-isomers) may be resolved by methods known to one of ordinary skill in the art, for example by: formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallization, selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where a desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be required to liberate the desired enantiomeric form. Alternatively, specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts, or solvents, or by converting one enantiomer to the other by asymmetric transformation. For a mixture of enantiomers, enriched in a particular enantiomer, the major component enantiomer may be further enriched (with concomitant loss in yield) by recrystallization.

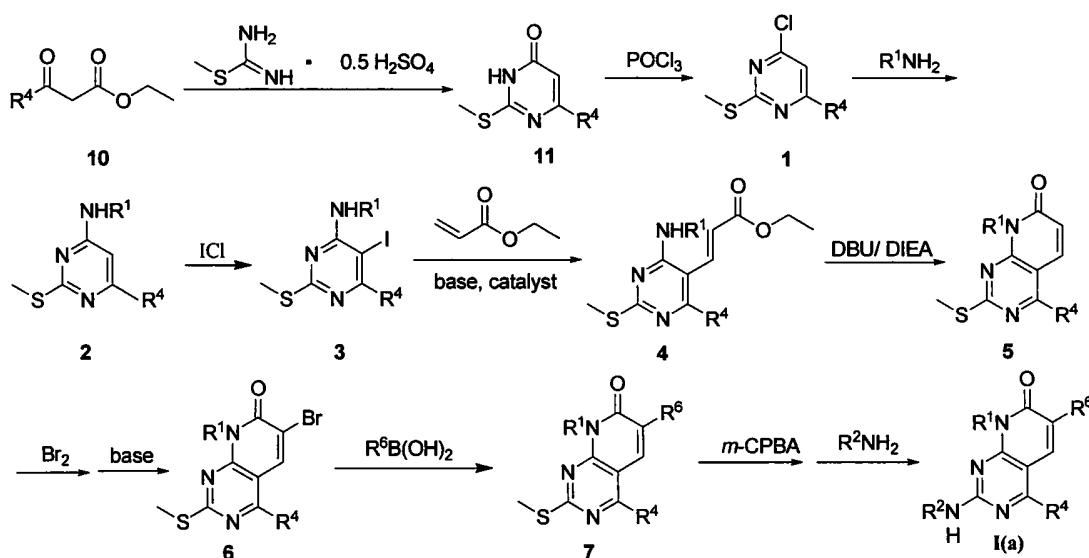
[00262] In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[00263] The chemistry for the preparation of the compounds of this invention is known to those skilled in the art. In fact, there may be more than one process to prepare the compounds of the invention. For specific examples, see M. Barvian et al., J. Med. Chem. 2000, 43, 4606-4616; S. N. VanderWei et al., J. Med. Chem. 2005, 48, 2371-2387; P. L. Toogood et al., J. Med. Chem. 2005, 48, 2388-2406; J. Kasperek et al., Tetrahedron Letters 2003, 44, 4567-4570; and references cited therein. See also U.S. Pre-grant publication US2004/0009993 A1 (M. Angiolini et al.), which is incorporated herein by reference, and references cited therein.

The following examples illustrate but do not limit the invention. All references cited herein are incorporated by reference in their entirety.

[00264] A compound of the invention, wherein R<sup>1</sup> is optionally substituted alkyl, R<sup>2</sup> is hydrogen or optionally substituted alkyl, R<sup>4</sup> is methyl or ethyl, R<sup>6</sup> is phenyl or heteroaryl each of which is optionally substituted with 1, 2, 3, 4, or 5 R<sup>9</sup> groups (as defined in the Summary of the Invention), and R<sup>2</sup> is hydrogen, can be prepared according to Scheme 8.

Scheme 8



[00265] To a solution of commercially available 2-methyl-2-thiopseudourea sulfate in a solvent such as water is added a base such as sodium carbonate and an intermediate of formula **10** at room temperature. The reaction mixture is stirred for overnight or less. After neutralizing, **11** is collected through filtration and followed by drying under vacuum. **11** is then treated with POCl<sub>3</sub> and the reaction is heated to reflux for approximately 2 hours and then concentrated under vacuum to dryness. **1** can be used directly in the next reaction without further purification.

[00266] An intermediate of formula **2** is prepared by reacting an intermediate of formula **1** with a primary amine R<sup>1</sup>NH<sub>2</sub> in a solvent such as water and with heating. **2** is then treated with iodine monochloride in a solvent such as methanol at around 0 °C and allowed to react for approximately overnight or less as needed for the reaction to go to completion to form **3**. After completion the residue is triturated with acetone. The intermediate **3** is then reacted in a solvent, such as DMA, with ethyl acrylate in the presence of a base, such as triethylamine, and in the presence of a catalyst, such as Pd(OAc)<sub>2</sub>, and (+)BINAP. The reaction is heated to approximately 100 °C and allowed to react for approximately overnight or less as needed for

the reaction to go to completion to form **4**. **4** is then optionally purified by column chromatography.

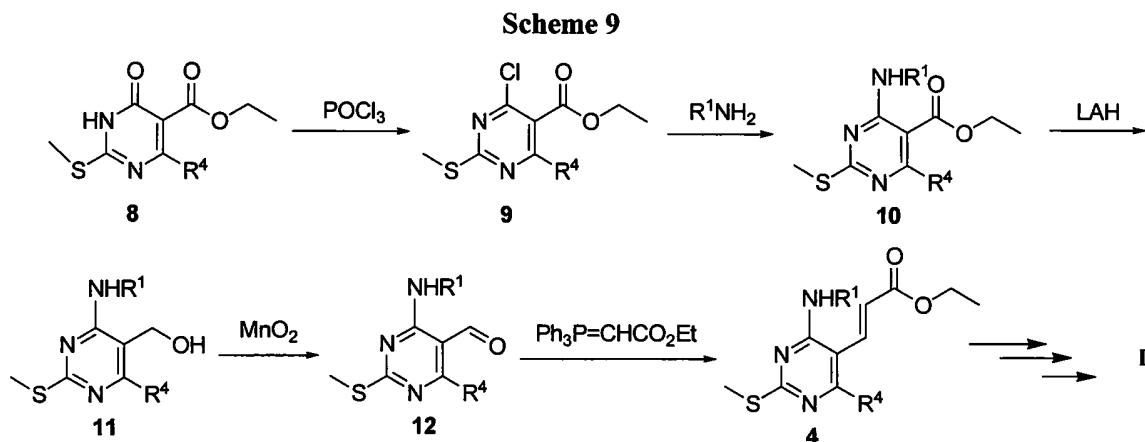
[00267] **5** is prepared by treating **4** with DBU in the presence of a base such as DIPEA at room temperature. The reaction mixture is then heated to reflux and reacted for approximately 15 hours. After evaporation of solvent, the residue is triturated with acetone and collected by filtration to yield **5**.

[00268] **6** is prepared by reacting **5** with a brominating agent such as Br<sub>2</sub> in a solvent such as DCM at room temperature. The reaction mixture is then stirred for approximately overnight. The resulting product is filtered and then suspended in a solvent such as DCM and treated with a base such as triethylamine. The mixture is then washed with water and dried over a drying agent such as Na<sub>2</sub>SO<sub>4</sub> to yield **6**.

[00269] A Suzuki coupling is then performed using **6** and a boronic acid (or ester) of formula R<sup>6</sup>B(OH)<sub>2</sub> in a solvent(s) such as a DME-H<sub>2</sub>O mixture in the presence of a catalyst such as Pd(dpppf) and a base such as triethylamine at room temperature. The reaction mixture is heated to reflux for approximately 4 hours-. After cooling to room temperature, the reaction mixture is partitioned with water and ethyl acetate. After separation, the organic layer is dried over a drying agent such as Na<sub>2</sub>SO<sub>4</sub> to yield **7**.

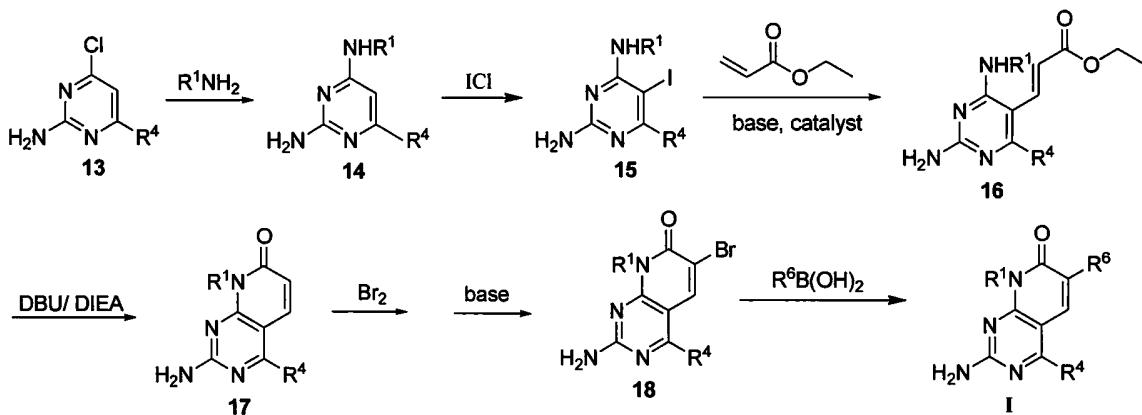
[00270] The methylthio group of **7** is then oxidized with *m*-CPBA in a solvent such as DCM at room temperature with stirring for approximately 4 hour. After removal of the solvent under reduced pressure, the product is treated with an amine of formula R<sup>2</sup>NH<sub>2</sub> in a solvent such as dioxane and stirred at room temperature for approximately overnight to yield a compound of formula I.

[00271] Alternatively, a compound of formula I where R<sup>1</sup> is optionally substituted alkyl, R<sup>4</sup> is methyl or ethyl, R<sup>6</sup> is phenyl or heteroaryl each of which is optionally substituted with 1, 2, 3, 4, or 5 R<sup>9</sup> groups (as defined in the Summary of the Invention), and R<sup>2</sup> is hydrogen can be prepared according to Scheme 9.



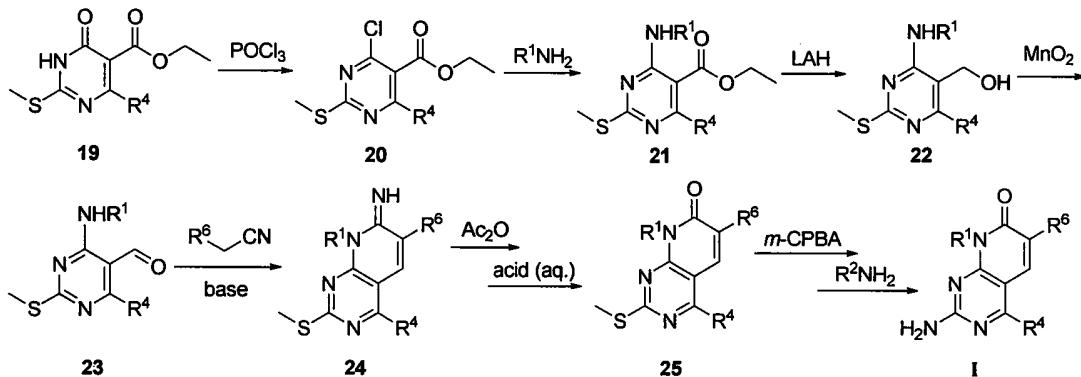
[00272] An intermediate of formula 9 is prepared by reacting an intermediate of formula 8 with neat  $\text{POCl}_3$  and heating. 9 is then treated with a primary amine  $\text{R}^1\text{NH}_2$  in a solvent such as water or THF and triethylamine at 0 °C to form 10. After removal of the solvent under reduced pressure, the intermediate 10 is then reacted with lithium aluminum hydride in a solvent such as THF at 0 °C. After quenching and aqueous workup, solvent removal provided crystalline 11 without further purification. Treatment of 11 with manganese (II) dioxide in a solvent such as methylene chloride or chloroform at room temperature provided aldehyde 12 upon filtration and solvent removal. A Wittig reaction with aldehyde 12 can be employed with (carbethoxymethylene)triphenylphosphorane in refluxing THF to provides the common intermediate 4. 4 can then be used to prepare a compound of formula I using the procedures described in Scheme 1.

[00273] A compound of the invention where R<sup>1</sup> is optionally substituted alkyl, R<sup>4</sup> is methyl or ethyl, R<sup>6</sup> is phenyl or heteroaryl each of which is optionally substituted with 1, 2, 3, 4, or 5 R<sup>9</sup> groups (as defined in the Summary of the Invention), and R<sup>2</sup> is hydrogen can be prepared according to Scheme 10.

**Scheme 10**

**[00274]** An intermediate of formula **14** is prepared by reacting an intermediate of formula **13** with a primary amine  $R^1\text{NH}_2$  in a solvent such as water and with heating. **14** is then treated with iodine monochloride in a solvent such as methanol at around  $0\text{ }^\circ\text{C}$  and allowed to react for approximately overnight or less as needed for the reaction to go to completion to form **15**. After completion the residue is triturated with acetone. The intermediate **15** is then reacted in a solvent, such as DMA, with ethyl acrylate in the presence of a base, such as triethylamine, and in the presence of a catalyst, such as  $\text{Pd}(\text{OAc})_2$ , and (+)BINAP. The reaction is heated to approximately  $100\text{ }^\circ\text{C}$  and allowed to react for approximately overnight or less as needed for the reaction to go to completion to form **16**. **16** is then optionally purified by column chromatography. A compound of formula **I** can then be prepared from **16** by using the same reaction conditions as described in Scheme 1 (starting at the point of the preparation of **5** from **4**).

**[00275]** A compound of the invention where  $R^1$  is optionally substituted alkyl,  $R^4$  is methyl or ethyl,  $R^6$  is phenyl or heteroaryl each of which is optionally substituted with 1, 2, 3, 4, or 5  $R^9$  groups (as defined in the Summary of the Invention), and  $R^2$  is hydrogen can alternatively be prepared according to Scheme 11.

**Scheme 11**

**[00276]** An intermediate of formula 20 is prepared by reacting an intermediate of formula 19 with neat  $\text{POCl}_3$  and heating. 20 is then treated with a primary amine  $\text{R}^1\text{NH}_2$  in a solvent such as water or THF and triethylamine at  $0^\circ\text{C}$  to form 21. After removal of the solvent under reduced pressure, the intermediate 21 is then reacted with lithium aluminum hydride in a solvent such as THF at  $0^\circ\text{C}$ . After quenching and aqueous workup, solvent removal provides crystalline 22 without further purification. Treatment of 22 with manganese (II) dioxide in a solvent such as methylene chloride or chloroform at room temperature provides aldehyde 23 upon filtration and solvent removal. A Knovenegal-type condensation with 23 and an arylacetonitrile in the presence of a base such as potassium carbonate or sodium hydroxide in a protic solvent provides the cyclized imine 24. Acetylation of the imine with acetic anhydride is required prior to hydrolysis, which takes place in the presence of aqueous acid and heating to afford 25. Subsequently, 25 can be oxidized to the corresponding sulfone with *m*-CPBA at room temperature and displaced with ammonium to provide I.

**[00277]** The synthesis of specific compounds is described in WO20070444813 which is hereby incorporated by reference in its entirety.

### Examples

#### Treatment of BCC with Compound A or Compound B

**[00278]** We investigated downstream pathways mediating tazarotene's anti-BCC chemopreventive efficacy to search for novel therapeutic strategies that might be (i) better tolerated and (ii) able to overcome retinoid resistance due to RAR loss. Specifically, we evaluated tazarotene-induced global gene expression changes in our murine BCC cell line ASZ001 {Aszterbaum, 1999 #4; So, 2006 #14} to identify relevant downstream target pathways involved in BCC inhibition that may have potential clinical therapeutic value for BCC prevention and treatment.

## Results

### Tazarotene-induced global gene expression changes in vitro

[00279] To understand better tazarotene's anti-BCC mechanism of action, we investigated downstream target pathways by assessing global gene expression changes induced by tazarotene in a cell line derived from a *Ptch1<sup>+/−</sup>* mouse BCC. We treated log phase cells of the ASZ001 cell line in serum-free conditions for 10 h or 24 h in triplicate with 0 or 10 µM tazarotene, a concentration that inhibits their proliferation by at least 50% after 48 h and does not inhibit the proliferation of the immortalized murine non-tumorigenic keratinocyte cell line C5N nor of a murine medulloblastoma cell line {So, 2006 #14}. We selected these timepoints for analysis based on detectable changes in expression of *Gli1* (a HH target gene) and of *CrabpII* (a RA target gene) {So, 2006 #14} at 10 h of incubation and the first detectable reduction of cell proliferation at 24 h of incubation with 10 µM tazarotene (data not shown). We extracted RNA and converted it to cDNA, which we then hybridized to Mouse Genome 430A 2.0 Array GeneChips (Affymetrix, CA) containing 20,000 probes representing 14,000 transcripts. Each incubation timepoint and treatment group was hybridized at the same time (i.e. hybridized under similar conditions).

[00280] Preprocessing of the raw data from the arrays indicated that for each experimental group (i.e. tazarotene or DMSO treated) the technical replicates looked similar to one another and of good quality (data not shown).

[00281] Figure 1 provides a Principal Component Analysis of the gene expression array data showing that 10 M tazarotene treatment of ASZ001 cells significantly altered the gene expression profiles at both 10 h and 24 h in a manner that was distinct from those profiles altered by DMSO vehicle control-treated ASZ001 (Figure 1A). Heat map representations, using Partek Genomics Suite, of the standardized array data demonstrated that the expression levels of 4292 genes were differentially expressed with 10 tM tazarotene treatment compared to treatment with 0.1% DMSO. Also, replicate samples were comparable to each other for both the tazarotene- or DMSO treated ASZ001 cells (Figure 1B) ( $p < 0.05$  ANOVA test followed by FDR correction). MA-plots of all gene probes: the red dots indicate genes that are the most differentially expressed compared and sit as outliers from the majority of the gene probes (in gray) that are either not-, or only modestly differentially expressed (Figure 1C, left graph – 10 h; right graph -24 h). Analyses of the expression changes in the array data for *Crabp2* and *Gli1* indicated that although they were up- and down-regulated respectively, the changes in expression compared to DMSO control samples

were modest and therefore, these genes were not represented in the DE gene lists since they did not make the stringent cutoff.

[00282] The quantile-normalized array data for treatments with vehicle and tazarotene and for both incubation timepoints were compared by Principal Component Analysis using the Partek Genomics Suite software (Figure 1A), which indicates a high degree of concordance between the replicates and demonstrates that tazarotene treatment significantly perturbed the gene expression profiles of ASZ001 cells at both 10 h and 24 h.

[00283] Overall, similar genes in both 10 h and 24 h groups treated with tazarotene clustered together and were distinct from those in the DMSO-treated control groups. A ‘heat-map’ analysis of the 4292 probes differentially expressed between Tazarotene and DMSO treated cells (FDR *p* value < 0.05) demonstrated that tazarotene treatment up-regulated or down-regulated overlapping differentially expressed (DE) genes at both 10 h and 24 h (Figure 1B). After adjustment for the false discovery rate and comparison to the 10 h or 24 h DMSO control gene sets, using Bioconductor software (worldwideweb.bioconductor.org/index.html), statistically significant lists (*p*<0.05) of DE genes were generated (Gladstone Genomics Core Facility, San Francisco, CA). Tazarotene treatment at 10 h gave 279 DE genes and expressed sequence tags (ESTs) (Figure 1C), which after disregarding replicate probes generated a list of 240 DE genes of which 193 were upregulated and 47 were downregulated (*p*<0.05). Tazarotene treatment at 24 h yielded 649 DE genes, excluding gene/EST replicates, of which 146 were up-regulated and 503 were down-regulated. The greater number of up-regulated than of down-regulated genes at 10 h is consistent with a direct transcriptional activator effect of RARs, which fully dissociate from corepressors/silencing mediators and bind to coactivators in the presence of a retinoid hormone agonist (such as tazarotenic acid) to activate retinoid-target genes {Rochette-Egly, 2009 #15; Xu, 1999 #16}. Indeed, additional known RA target genes such as *Tgm2*, *Dhrs3*, and *Rai3*, were up-regulated after 10 h tazarotene incubation (Figure 2 and data not shown). At 24 h however, more genes were down-regulated than up-regulated as a result of the secondary effects of tazarotene treatment. We designated genes whose expression was altered by 10 h as ‘early’ and those whose expression was not altered at 10 h but were altered at 24 h as ‘late’. To validate the microarray data, we carried out qPCR analyses on the same RNA samples used for Affymetrix analysis or on RNA from ASZ001 cells treated independently. Real-time PCR confirmed the up- or down-regulation of a selection of DE genes from the Bioconductor lists - *Trib3*, *Gadd45a*, *Tgm2*, *FoxM1*, *Dtx4*, *Eif4ebp1* (4EBP1), *Fst*, *Krt14*, *Pcdh7* - albeit at generally greater levels than those indicated from the array data (Figure 2A,

2B; Table 1). To investigate whether tazarotene specifically down-regulates HH signaling, we analyzed the early and late DE gene sets to see whether HH target gene expression was changed by 10 µM tazarotene treatment. We searched the DE gene lists for known direct HH target genes (i.e. genes that contain the consensus Gli binding site) such as *Gli1*, *Ptch1*, *Hhip1*, *Nmyc1*, *Ccnd1*, *Ccnd2*, *Grem1*, *Fst* and *Pthlh* {Katoh, 2009 #17}. Of these genes, *Fst* and *Pthlh* were downregulated at 10 h (Figure 2 and data not shown). *Fst* was also down-regulated at 24 h. Other genes that are strongly associated with HH signaling are *FoxM1*, *Ccnd1*, and *Gas1*. We found that *FoxM1* expression was down-regulated after 24 h of tazarotene treatment and not at 10 h, suggesting it to be an indirect target of tazarotene signaling. *Gas1* was down-regulated at 10 and 24 h while *Ccnd1* was not represented.

[00284] Figure 2 shows the validation of the Affymetrix gene expression data by real-time qPCR. Graphs showing representative values for the amount of fold change compared to the DMSO-treated ASZ001 samples, for a selection of statistically significant DE genes from the microarray Bioconductor gene lists and from qPCR validation. DE genes selected from the 10 h (Figure 2A) and 24 h DE (Figure 2B) gene lists were expressed at comparable up- or downregulated levels although the differential expression was generally greater (compared to DMSO control) in the real-time qPCR assays than in the microarray data. These qPCR data confirm the validity of the microarray datasets.

[00285] However other cyclins – *Ccna2*, *Ccnf*, *Ccne2*, *Ccnb1* and *Ccnb2* – were down-regulated at 24 h (data not shown), suggesting that these late DE genes are indirect targets of tazarotene-mediated signaling and that at least part of tazarotene's anti-BCC efficacy is via blocking of cell cycle progression at the G2/M checkpoint. Consistent with our previous findings (So 2008), the microarray probe representing *Gli1* (1449058\_at) was significantly down-regulated following tazarotene treatment, while the probe representing *Crabp2* (1451191\_at) – a positive control for retinoid receptor-mediated transcriptional activation in our study - was upregulated (FDR corrected *p*-values: 0.008 and 0.024, respectively), however the fold-changes were modest in both cases and therefore did not make the stringent cutoff to be represented in the 10 and 24 h DE gene lists (Figure 1D). Taken together, the microarray expression data suggest that tazarotene does not specifically target the HH signaling pathway.

[00286] DE genes such as *Tgm2*, *Dtx4*, *Eif4ebp1*, *Fst* and *Trib3* were represented more than once in the DE gene lists (i.e. by replicate probes on the microarrays), suggesting that these genes are likely to be 'real' targets of tazarotene-mediated signaling. However, 10 µM tazarotene treatment of ASZ001 and the murine medulloblastoma cell line Med1 (a cell line

that does not respond to 10 µM tazarotene treatment with respect to cell proliferation), and analysis of *Tgm2* expression by qPCR indicated that *Tgm2* was up-regulated in both cell lines irrespective of whether or not tazarotene inhibited cell proliferation (data not shown). This suggested that *Tgm2* upregulation was not related to tazarotene's anti-proliferative effects, but rather to direct effects of retinoid transcriptional activation of target genes involved in other biofunctions related to skin. Therefore, since i) the numbers of DE genes from tazarotene treatment at both 10 h and 24 h were relatively high, and ii) investigating individual DE genes such as *Tgm2* may indicate biological processes that are irrelevant to tazarotene's anti-cancer effects, we used bioinformatic software to identify tazarotene-altered pathways and functions. Bioinformatic analyses of the 10 h and 24 h DE genes using Stratagene's PathwayArchitect™ software indicated that the DE genes with the most connections to other DE genes in their respective lists were associated with VEGF (Table 2); insulin-like growth factor/insulin receptor/phosphatidylinositol 3-kinase/Akt (IGF-IR/PI3K/Akt) signaling (Tables 2, 3), and inflammation (Table 3).

**Table 2**

Gene symbol	Gene Name	# molecules
VEGF	vascular endothelial growth factor	42
ITPR1	inositol 1,4,5-triphosphate receptor, type 1	24
Scd 1	stearoyl-Coenzyme A desaturase 1	23
IGFBP3	insulin-like growth factor binding protein 3	15
HMOX1	heme oxygenase (decycling) <sup>1</sup>	14
ADRB2	adrenergic, beta-2-, receptor, surface	13
SMAD7	SMAD, mothers against DPP homolog 7 (Drosophila)	11
EIF4EBP1	eukaryotic translation initiation factor 4E binding protein 1	10
IL1RN	interleukin 1 receptor antagonist	10
PTHLH	parathyroid hormone-like hormone	9
Vegfa	vascular endothelial growth factor A	8
FST	follistatin	7
CEBPB	CCAAT/enhancer binding protein (C/EBP), beta	7
SREBF1	sterol regulatory element binding transcription factor 1	4
ABCA1	ATP-binding cassette, sub-family A (ABC1), member 1	4

**Table 3**

Gene symbol	Gene name	# molecules
IFNA1	interferon, alpha 1	75
PTGS2	prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	49
ITPR1	inositol 1,4,5-triphosphate receptor, type 1	24
IGFBP3	insulin-like growth factor binding protein 3	15
PIK3R1	phosphoinositide-3-kinase, regulatory subunit 1 (p85)	12
FGF1	fibroblast growth factor 1 (acidic)	10
EIF4EBP1	eukaryotic translation initiation factor 4E binding protein 1	10
BRCA1	breast cancer 1, early onset	11
PTHLH	parathyroid hormone-like hormone	9
PLA2G4A	phospholipase A2, group IVA (cytosolic, calcium-	9
CCNA2	cyclin A2	8
Vegfa	vascular endothelial growth factor A	8
BMP2	bone morphogenetic protein 2	8
CTGF	connective tissue growth factor	8
G NAI 1	guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 1	7
FST	follistatin	7
TIMP2	TIMP metallopeptidase inhibitor 2	6
DCN	decorin	5
RBL1	retinoblastoma-like 1 (p107)	5
MY01B	myosin IB	5
ATM	ataxia telangiectasia mutated (includes complementation groups A, C and D)	5
PA2G4	proliferation-associated 2G4, 38kDa	4
CCN B1	cyclin B1	4
Kitl	kit ligand	4

[00287] Of note, the IGF-IR/PI3K/Akt pathway was represented in the analyses of both 10 h and 24 h DE genes lists. The Ingenuity® software suggested three top networks at 10 h, one of which was also the IGF-IR/PI3K/Akt pathway, indicating that it may be a central downstream functional “node” involved in BCC inhibition by tazarotene (Figure 3)

[00288] Figure 3 provides a bioinformatic analysis using Ingenuity software suggested that a possible downstream pathway that thea number of 10 DE genes had in common was one the PI3K/Akt pathway. The shaded shapes indicate DE genes from the 10 h Bioconductor list, which when ‘networked’ suggested that PI3K/Akt signaling may be a downstream target of tazarotene. ( $p < 0.05$ ). The different shapes assigned to each ‘molecule’ that was represented in the 10 h DE list, indicate the type/function of the protein as classified by the IPA analysis software (Ingenuity, CA).

[00289] The other two ‘top’ networks identified by Ingenuity® Systems IPA software indicated that tazarotene treatment of ASZ001 cells affected cholesterol metabolism and the mitogen activated protein kinase (MAPK) pathway (data not shown). Bioinformatic functional clustering analyses of the late DE genes using Ingenuity® software suggested that many of these were linked to biological processes such as cancer, cell cycling, and DNA recombination and repair ( $p<0.0001$ ) (Table 4).

**Table 4**

Process	Number of genes
Cancer	222
Cell Cycle	150
DNA Replication, Recombination and repair	136

[00290] Also, performing a ‘top canonical pathway’ cluster analysis using the same software suggested that the 24 h DE genes affected by tazarotene treatment were associated with metabolism and cell cycle processes ( $p<0.0001$ ) (Table 3), which are known to be regulated by IGF-IR/PI3K/Akt signaling {Engelman, 2009 #18}. Moreover, the observation that DE genes such as *Trib3*, *Eif4ebp1*, and *Igfbp3* - negative regulators of the IGF-IR/PI3K/Akt pathway - were up-regulated by tazarotene suggests that at least part of tazarotene’s anti-BCC effect is to inhibit the IGF-IR/PI3K/Akt pathway with consequent decrease in cell growth and proliferation.

#### Akt pathway activation in murine BCC

[00291] The IGF-IR/PI3K/Akt pathway is positively associated with cancer development {Engelman, 2009 #18}, and has been shown to enhance Hedgehog pathway signaling by indirectly stabilizing Gli protein {Riobo, 2006 #19}. Activated PI3K/Akt signaling also has been linked specifically in humans to BCCs {Lin, 2007 #20}. To investigate whether BCCs that arise in our murine accelerated model of BCC carcinogenesis (i.e. the tamoxifen-treated *Ptch1<sup>+/−</sup> K14-CreER2 p53<sup>floxed/floxed</sup>* mouse) have activated PI3K/Akt signaling, we assessed expression of phosphorylated (Ser473) (activated) Akt (p-Akt) by immunohistochemistry (Figure 4).

[00292] Figure 4 shows immunohistochemistry with phosphorylated Akt1 (p-Akt) antisera on untreated visible BCC that grew on *Ptch1<sup>+/−</sup>*, basal keratinocyte-deleted p53 mice. p-Akt was detected at low (Figure 4A) or moderate (Figure 4B) levels in approximately 50% of BCCs analyzed (n=8) and in hyperproliferative skin overlying the BCC (Figure 4C). pAkt

was also detected at moderate levels (compared to -actin levels) in the murine BCC cell line ASZ001 (Figure 4D).

[00293] We detected activated Akt at low to moderate levels in 50% (4/8) of visible IR-induced BCCs (n=8) (Figures 4A, 4B) from tamoxifen-treated *Ptch1<sup>+/−</sup> pK14-CreER2 p53<sup>flaxed/flaxed</sup>* mice, as well as in hyperplastic epidermis overlying the tumors (Figure 4C), a finding similar to the moderate levels of p-Akt activity detected in some human BCCs {Lin, 2007 #20}. Similarly, we also detected activated Akt signaling in our ASZ001 BCC cell line (Figure 4D).

#### **Over-expression of AKT1 in ASZ001 cells reduces the in vitro anti-BCC effect of tazarotene**

[00294] Figure 5 shows an over-expression of AKT1 in ASZ001 cells reduces the in vitro anti-BCC effect of tazarotene. ASZ001 cells transfected with HA-tagged AKT1 or myristoylated AKT1 were selected with G418 to generate stable HA-AKT1 expressing cell lines that expressed heterogeneous levels of AKT1 as measured by the HA tag levels (Figure 5A). The higher level of AKT1 expression in the HA-AKT compared to the negative control cell line was confirmed by Western blotting with antibodies against AKT1 (Figure 5B) and 10 µM tazarotene treatment of these cell lines for 48 h showed that the cell lines overexpressing AKT1 were partially resistant to tazarotene (Figure 5C). FACS analysis of the HA-AKT1 cell line after incubation in 10 µM tazarotene or 0.1% DMSO vehicle for 48 h showed that tazarotene enriched the population of HA-AKT1 cells, as measured by HA-tag levels (Figure 5D).

[00295] To test whether tazarotene acts by blocking IGF-IR/PI3K/Akt signaling, constructs containing HA-tagged wildtype AKT1 (HA-AKT1) or constitutively activated (myristoylated) Akt1 (myr-HA-AKT1) were transfected into ASZ001 cells. Stable transfection resulted in a heterogenous population with ~10-12% of the cells expressing detectable levels of HA-AKT1 cells as measured by FACS (Figure 5A). To determine whether altering AKT activity could interfere with the anti-proliferative effects of tazarotene, we treated this mixed population of log-phase ASZ001 cells for 48 hours and measured the amount of cell proliferation and fold-enrichment of the HA-AKT1 overexpressing cells (Figure 5C, 5D). ASZ001 cells expressing myr-HA-AKT1 or HA-AKT1 were less sensitive to tazarotene treatment than were either wildtype ASZ001 cells or the pLNCX' negative control cell line (Figure 5C,  $p<0.05$ ). Also for HA-AKT cells, starting from a baseline of 9%, the proportion of HA-AKT1-expressing cells increased ~2.5 fold to comprise 23% of the

population after 48 hours of tazarotene treatment (Figure 5D,  $p<0.05$ ). These data suggest that elevating Akt activity significantly blunts the anti-proliferative effects of tazarotene in this model.

#### **Pharmacologic PI3K inhibitors inhibit BCC proliferation in vitro**

[00296] We investigated whether pharmacologic PI3K inhibitors could themselves inhibit BCC proliferation in vitro. Specifically we assayed inhibition by treating log phase ASZ001 cells with LY294002 (Eli-Lilly), compound A (Exelixis), and compound B (Exelixis). LY294002 is a first generation pan class I PI3K inhibitor that inhibits PI3K activity via competitive inhibition of an ATP binding site on the p85 subunit of PI3K. LY294002 not only binds to class I PI3Ks and other PI3K-related kinases, inhibiting PI3K-dependent production of the second messenger PIP3, but also to novel targets unrelated to the PI3K family {Gharbi, 2007 #21}. Compound A is a potent, orally bioavailable, specific inhibitor of class I PI3K kinases  $\alpha$ ,  $\beta$ ,  $\delta$ , and  $\gamma$ . It too binds the ATP-binding pocket of the catalytic domain of Class I PI3Ks and inhibits their activities with IC50 values at nanomolar concentrations in biochemical assays {Foster, 2007 #22}. Similarly, compound B is a bioavailable, highly selective, potent inhibitor of all four Class I PI3K isoforms with IC50 values at nanomolar concentrations in biochemical assays. However, in contrast to compound A, compound B also inhibits mTOR and DNA-PK with IC50 values in the nanomolar range {Patnaik, 2007 #23}. As well as inhibiting PI3K phosphorylation and consequent PI3K-dependent production of the second messenger PIP3, compound B also inhibits nutrient stimulated mTOR-dependent signaling in cellular assays by inhibiting mTOR-dependent phosphorylation of key PI3K pathway components including AKT, the AKT substrates PRAS40 and GSK3 $\beta$ , p70S6K, and the p70S6K substrate S6, and 4E-BP1. In various cancer models compound B-treated tumors regressed with a decrease in proliferation and angiogenesis, and an increase in apoptosis {Patnaik, 2007 #23}. We found that all three pharmacologic inhibitors reduced ASZ001 cell proliferation in a dose-dependent manner (Figure 6).

[00297] Figure 6 shows the potential of compound A and compound B as therapies for treating BCC. In vitro, PI3K inhibitors compound B and compound A, as well as LY294002 inhibited ASZ001 cell proliferation in a dose-dependent manner at micromolar concentrations. Compound A was the most effective inhibitor at 5 and 10  $\mu$ M.

[00298] Compound A and compound B appeared to be more effective than LY294002 in their inhibition of ASZ001, significantly reducing proliferation with an IC50 dose at

approximately 5  $\mu$ M and with a more pronounced inhibition at 10  $\mu$ M ( $p<0.0001$ , two way ANOVA test). The IGF-IR inhibitor AG1024 (Sigma Aldrich, CO) also inhibited ASZ001 cell proliferation at 10  $\mu$ M (data not shown). These data are similar to those we observed for tazarotene treatment of ASZ001 cells {So, 2006 #14} and are consistent with the idea that much of tazarotene's anti-BCC efficacy is mediated via inhibition of this pathway.

### **Pharmacologic PI3K inhibitors and chemoprevention of murine BCC in vivo**

[00299] Having confirmed that inhibition of PI3K/Akt signaling can reduce BCC cell proliferation *in vitro*, we investigated the chemopreventive efficacy of PI3K inhibitors *in vivo* in our *Ptch1<sup>+/−</sup> K14-CreER2 p53<sup>flaxed/flaxed</sup>* mice, a model in which topical tazarotene retains its anti-BCC carcinogenesis effect (Epstein lab, unpublished data). This mouse allows tamoxifen-controlled, Cre recombinase-mediated conditional deletion of *p53* limited to Keratin 14 (K14)-expressing basal epithelia. *p53* mutations are very common in sporadic human BCCs {Reifenberger, 2005 #24; Ling, 2001 #25}, and after exposure to ionizing radiation (Cesium<sup>237</sup> or X-rays), these mice develop far greater numbers of microscopic and visible BCCs than do *Ptch1<sup>+/−</sup> p53* wildtype mice and do so at an accelerated rate (visible BCCs develop from age 5 months vs. from age 9 months) {Wang, 2011 #26}. We investigated the *in vivo* anti-BCC efficacy of compound A and compound B, the PI3K inhibitors that inhibited ASZ001 cell line proliferation *in vitro* (Figure 6), as well as the efficacy of an additional PI3K inhibitor, GDC0941 (Genentech), a highly selective pan class I PI3K inhibitor that also has favorable pharmacokinetic and toxicological properties for therapeutic use *in vivo* {Folkes, 2008 #27}. For each drug we administered orally a single dose regimen of drug, which we selected based on data from preclinical testing in mice in which no obvious skin toxicity was observed (*personal communication*, Genentech and Exelixis). Initially, we confirmed the systemic tolerability of each drug in tamoxifen-treated *Ptch1<sup>+/−</sup> K14-CreER2 p53<sup>flaxed/flaxed</sup>* mice starting at approximately age 6 weeks. Mouse weights and appearances did not change significantly during 4-6 weeks of ingestion (data not shown). We then administered the drugs for approximately 8 weeks to tamoxifen-treated *Ptch1<sup>+/−</sup> K14-CreER2 p53<sup>flaxed/flaxed</sup>* mice starting at age 9 weeks (after one dose of 4 Gy X-ray irradiation at age 8 weeks), after which a dorsal skin biopsy was taken and processed for microscopic BCC analysis. As a positive control for this study, we treated three *Ptch1<sup>+/−</sup> K14-CreER2 p53<sup>flaxed/flaxed</sup>* mice topically with tazarotene and confirmed its efficacy in reducing BCC number and size (data not shown). Of the three PI3K inhibitors used in this study, we

found that only compound B inhibited both microscopic BCC number ( $p<0.001$ ) and size ( $p<0.05$ ) significantly (Figure 7A, 7B).

[00300] Figure 7 depicts the in vivo treatment with PI3K inhibitors: Microscopic and visible BCC assessment at age 21 and 28 weeks respectively, after 8 weeks of drug treatment. For microscopic BCC assessment, dorsal skin biopsies of mice given oral formulations of PI3K inhibitors compound A, compound B, or GDC0941 were analysed to determine the microscopic BCC number (Figure 7A) and size (Figure 7B). Although different control vehicles were used, there were not significantly different from each other in terms of microscopic BCC numbers and size (data not shown), therefore the vehicle groups were combined. For visible BCC assessment, mice were given oral formulations of PI3K inhibitors compound A, compound B, or GDC0941 from age 9 weeks to 21 weeks, and monitored thereafter to assess the time of visible BCC appearance. A Kaplan Meier graph showed that only compound B-treated mice had a delay in the first visible BCC appearance (Figure 7C). Mice were assessed at age 28 weeks to determine the visible BCC number (Figure 7D) and size (Figure 7E). Again, although different control vehicles were used, there were not significantly different from each other in terms of BCC numbers and size (data not shown), therefore the vehicle groups were combined. Only compound B treatment reduced visible BCC number and volume by statistically significant amounts at the doses tested. There was a delay in the appearance of visible BCCs in mice dosed with compound B compared to the vehicle group however this was not statistically significant (Figure 7E). There was no delay in the appearance of the first BCCs with compound A and GDC0941.

[00301] Next, we assessed whether the PI3K inhibitors had a sustained effect on BCC growth after cessation of drug dosing. We monitored mice for the appearance of their first visible BCC (Figure 7C). Similar to tamoxifen-treated *Ptch1<sup>+/+</sup> K14-CreER2 p53<sup>flaxed/flaxed</sup>* mice {Wang, 2011 #26}, the vehicle control-treated mice developed visible BCCs from age 20 weeks, and by age 28 weeks almost all mice had a significant burden of macroscopic BCCs (Figure 7C). Under these test conditions, there was no obvious delay in the appearance of the first visible BCC in mice treated with compound A or GDC0941. In contrast, compound B treatment appeared to delay the appearance of the first visible BCC, although the difference in the age of onset was not statistically significant (Figure 7C). Treatment with compound B significantly reduced the visible BCC number ( $p<0.05$ ) (Figure 7D). All three PI3K inhibitors appeared to reduce visible BCC size (Figure 7E). Compound B treatment produced the largest reduction ( $p<0.05$ ), while GDC0941- and compound A-treated mice also

had tumors at least 50% reduction in size but this reduction did not attain statistical significance in this study.

[00302] Overall, these data suggest that pharmacologic inhibition of PI3K/Akt/mTOR signaling can significantly inhibit the development of both microscopic and visible murine BCCs and that at the single dose of each tested, compound B was significantly more effective than the other inhibitors tested.

## Discussion

[00303] We have demonstrated previously the remarkable efficacy of tazarotene against murine BCC, effects that likely are mediated via RAR $\gamma$ -mediated transcriptional activation of RA-target genes {So, 2004 #4; So, 2008 #5}. In this study we have identified downstream mechanisms of tazarotene's anti-BCC effects by analyzing changes in global gene expression induced by 10 and 24 hour treatment of the murine BCC cell line ASZ001 with 10  $\mu$ M tazarotene, a concentration that inhibits cell proliferation by at least 50% after 48 h. Specifically, we found that (i) analysis of gene expression changes *in vitro* indicate that inhibition of the PI3K-Akt signaling pathway is a central 'node' downstream of retinoid treatment, (ii) this pathway is activated in visible BCCs in our murine BCC model and in the ASZ001 murine BCC cell line, a finding consistent with reports identifying p-AKT in human BCCs, (iii) hyperactivation of the PI3K-Akt pathway in ASZ001 by stable transfection of wildtype AKT1 significantly inhibits tazarotene's anti-proliferative effects on this cell line, and (iv) inhibition of PI3K-Akt signaling by small molecule inhibitors of class I PI3K can inhibit both ASZ001 cell proliferation *in vitro* and, crucially, BCC carcinogenesis *in vivo*. Accordingly, PI3K inhibitors, by acting downstream of retinoid receptors, might overcome resistance to ATRA therapy in those BCCs whose resistance is due to loss of RAR expression. Of note, others have suggested that inhibition of PI3K/Akt signaling can reverse resistance to retinoids and other drugs by enhancing apoptosis {Martelli, 2003 #28; Neri, 2003 #29}. By contrast we find that inhibition of this pathway can inhibit tumor growth independent of additional pharmacologic interventions.

[00304] Hyperactivation of IGF-IR/PI3K/Akt/mTOR signaling is an important contributor to tumorigenesis {Engelman, 2009 #18}. Cellular level interactions between HH and IGF-IR/PI3K/Akt signaling in cancers have been identified, generally through candidate pathway measurements rather than via an unbiased approach such as we used. The first such hints came from the finding that loss of Igf2 expression renders *Ptch1*<sup>+/−</sup> mice completely refractory to their expected development of medulloblastomas and rhabdomyosarcomas

{Hahn, 2000 #30} and that, contrarily, over-expression of Igf2 or of Akt enhances Shh-induced murine medulloblastoma formation {Rao, 2004 #31}. Subsequent studies have confirmed such enhancement but have disagreed as to whether the major impact of Igf2 is during early {Tanori, 2010 #32} or late {Corcoran, 2008 #33; Rao, 2004 #31} medulloblastoma development. One possible mechanistic explanation is that both pathways converge to co-regulate downstream targets. Thus HH signaling enhances N-myc expression and PI3K/Akt signaling inhibits GSK3 activity, thereby reducing N-myc phosphorylation and its proteolytic destruction {Kenney, 2004 #34}. N-myc is over-expressed not only in HH driven medulloblastomas but also in human BCCs {Freier, 2006 #35}. Although it is possible that the two pathways simply enhance tumorigenesis independently, some data have indicated direct interactions between the two pathways. Thus HH signaling can enhance Igf2 transcription in some, albeit not all, contexts and PI3K/Akt/mTOR signaling, again by reducing GSK3-mediated phosphorylation and degradation, can stabilize Gli protein and thereby enhance HH signaling {Riobo, 2006 #36; Stecca, 2007 #37; Mizuarai, 2009 #38; Singh, 2009 #39}. More recently, analysis of the effects of the new small molecule HH signaling pathway inhibitors has suggested that medulloblastomas may retain their sensitivity to inhibitors of PI3K/Akt inhibitors even after they develop resistance to HH signaling pathway inhibitors {Buonamici, 2010 #40; Dijkgraaf, 2011 #41}, findings which do not support the suggestion that, at least in these tumors, excess HH signaling is the cause of the enhanced PI3K/Akt signaling.

[00305] Contrary to our finding that the retinoid tazarotene *inhibits* HH-driven BCC carcinogenesis via its inhibition of IGF-IR/PI3K/Akt/mTOR signaling, in some contexts ATRA (which like tazarotene, inhibits murine BCC carcinogenesis) *activates* PI3K/Akt signaling to induce a differentiation program {Bastien, 2006 #42; Doi, 2010 #43; Lopez-Carballo, 2002 #44; MA Antonyak et al J Biol Chem 277:14712, 2002}. In acute promyelocytic leukemia, in which ATRA treatment results in differentiation, PI3K/Akt signaling also is upregulated by ATRA in his instance thereby promoting cellular survival rather than differentiation {Billottet, 2009 #45}. However, in mouse F9 embryonal carcinoma cells ATRA induced an early activation of the PI3K/Akt pathway (via RAR $\gamma$ :RXR signaling) to initiate F9 cell differentiation into primitive endoderm-like cells, which was followed by an inhibition of Akt activity that resulted in cell growth arrest {Bastien, 2006 #42}. This suggests a biphasic model of ATRA action on the PI3K/Akt pathway in which ATRA can regulate PI3K/Akt signaling positively as well as negatively, thereby inducing initial differentiation and later cellular growth arrest. Therefore, the relationship between retinoid

and PI3K/Akt signaling pathways appears to be complex and cell-type specific but at least in BCCs inhibition of PI3K/Akt signaling appears to inhibit tumor development. Indeed the reports of cures of some human BCCs with topical tazarotene lend weight to that assumption. Thus our study not only points to enhanced PI3K/Akt signaling as a target for anti-BCC strategies but also suggests that results of topical tazarotene may already have been a “proof of principle” of this idea.

[00306] We have found that, of the PI3K inhibitors assessed, the one with the greatest *in vivo* anti-BCC efficacy was compound B, the only one tested that inhibits not only PI3K but also mTOR. Although we do not know whether the drugs used inhibited PI3K equivalently at the single doses tested *in vivo*, our finding that inhibition of multiple sites in the PI3K/Akt/mTOR pathway appears to have better anti-tumor efficacy than does inhibition of a single site is not a new one {Fan, 2007 #46; Fan, 2010 #47}. Thus, specifically we found that a 2 month dosing regimen of the dual PI3K/mTOR inhibitor compound B started before and during microscopic BCC development could reduce their development by at least 50% and could reduce the development of clinically relevant, visible BCCs by approximately 60% even after the cessation of treatment. This degree of inhibition by COMPOUND B is somewhat less than we found in our previous trials of topical tazarotene , which inhibited microscopic BCC development by at least 70% in *Ptch1<sup>+/−</sup>* mice and in *Ptch1<sup>+/−</sup>* with basal keratinocyte deleted p53 {So, 2008 #5;So, 2004 #4}, (unpublished data), but in those studies the retinoid was applied for at least 5 rather than 2 months, a more difficult undertaking for a drug requiring daily gavage. Compound A and GDC0941 also appeared to reduce visible BCC growth. These observations suggest that class I PI3Ks promote the growth of clinically significant BCCs and that their inhibition would be detrimental to the growth and maintenance of the established BCC.

[00307] In summary, these data suggest (i) that the PI3K/Akt/mTOR pathway is a positive effector pathway of BCC carcinogenesis that is inhibited by tazarotene and (ii) that targeting this pathway directly may inhibit BCC carcinogenesis in tumors that are resistant to tazarotene. Also, our data suggest that short-term treatment was effective at preventing BCC carcinogenesis even after its cessation. Therefore it might be possible for BCC treatment to use PI3K inhibitors for a relatively short duration, and thereby avoiding potential toxic side effects (e.g. interference with glucose metabolism and the immune response) that occur with chronic use of these agents.

## Materials and Methods

### Global gene changes with tazarotene

[00308] BCC cell line treatment and RNA extraction: We cultured ASZ001 cells in complete medium (154-CF medium containing 0.05 mM CaCl<sub>2</sub>, 2% chelexed fetal bovine serum), as described previously {So, 2006 #14}. At 80% confluence, the media was removed, and cells were incubated in serum-free media (154-CF medium containing 0.05 mM CaCl<sub>2</sub> and 1x Penicillin/Streptomycin) for 2 h. Working concentrations of tazarotene and DMSO were prepared as follows: for tazarotene, the powder was dissolved in 100% DMSO at a stock concentration of 10 mM and diluted to 10 µM working concentration in 154-CF medium containing 0.05 mM Ca<sup>2+</sup> and 1X penicillin/streptomycin. As a control, DMSO was diluted to 0.1% working concentration. Cells were then incubated with 10 µM tazarotene or 0.1% DMSO for 10 and 24 h in a 5% CO<sub>2</sub> incubator. Four replicates were done for each treatment. After the incubation, the media was removed and cells were washed briefly in phosphate-buffered saline (PBS) and then harvested in 1 ml of Trizol for RNA extraction (Invitrogen, CA), which we stored at -80 °C until processing according to the manufacturer's instructions. Total RNA was re-purified using RNeasy RNA isolation columns (Qiagen, CA) and its 'integrity' was confirmed using the RNA Bioanalyzer (Ambion/Applied Biosystems, CA). Two micrograms of total RNA was used for cRNA amplification using the MessageAmp™ II-Biotin Kit (Ambion/Applied Biosystems, CA), according to the manufacturers' instructions. Briefly, reverse transcription of total RNA was carried out using an oligo(dT) primer bearing a T7 promoter using ArrayScript™, a reverse transcriptase (RT) engineered to produce high yields of first-strand cDNA. Second-strand synthesis using the cDNA was carried out and purified for use as a template for in vitro transcription in a reaction containing biotin-modified UTP and T7 RNA Polymerase (Ambion/Applied Biosystems, CA). Biotin-labeled amplified RNA (aRNA) was then purified for gene expression analysis on Mouse Genome 430A 2.0 Array GeneChips (Affymetrix, CA), which was carried out by the Gladstone Genomic Core Facility (San Francisco, CA). Assessment of hybridization quality was also performed by the Gladstone Genomic Core Facility (San Francisco, CA), using the Bioconductor software *affyPLM*, which fitted a specified robust linear model to the probe level data. Preprocessing of the data was performed using an Bioconductor Robust Multiarray Analysis (RMA) algorithm to correct for background; the data was normalized using the quantile method {Bolstad, 2003 #48} to generate lists of statistical significant, differentially expressed (DE) genes (comparing tazarotene and DMSO vehicle control groups). After correcting for the false discovery rate, Partek Genomics Suite

was used for Principal Component analysis and hierarchical clustering, and DE genes that were significantly differentially expressed were further analyzed using bioinformatic software DAVID, Ingenuity, and Stratagene.

#### **Immunohistochemistry (IHC)**

[00309] IHC for phosphorylated-Akt1 (p-Akt1<sup>Ser473</sup>) was carried out on 4 µM paraffin wax sections taken from visible BCCs, using rabbit anti-Akt1 (#4058, 1:200 dilution; Cell Signaling Technologies, MA). Briefly, sections were immersed in xylene and then rehydrated from 100% ethanol to 100% water and then PBS. Antigen retrieval was carried out using DeCloaker Solution (Biocare, CA) for 20 min at 98 °C and cooled sections were pre-blocked with 5% goat serum/PBS for 1 h, then incubated with antibodies to p-Akt1<sup>Ser473</sup> overnight at 4 °C. Sections were washed and endogenous biotin, biotin receptors, or avidin binding sites present in tissues were blocked using the Biotin-Avidin System kit (Vector Laboratories, Burlingame, CA). Antigen detection was carried out using the VECTASTAIN® Elite ABC with the peroxidase-based detection system ((Vector Laboratories, Burlingame, CA). After signal development, slides were washed in water, dehydrated through a series of ethanols and xylene, and then mounted by microscopy.

#### **Quantitative RT-PCR (qPCR)**

[00310] To validate the Affymetrix GeneChip array experiments, a number of target genes that were differentially expressed were confirmed by Taqman Real-time PCR. ASZ001 cells were treated, total RNA was isolated and purified as described above, and cDNA was synthesized by Reverse Transcription (RT; Applied Biosystems). Taqman real-time RT-PCR was carried out using validated gene expression primer-probe assays according to manufacturers' instructions (Applied Biosystems, CA). The prevalidated Taqman probe:primer sets used were:

*18S rRNA - Hs\_99999901\_s1, Gadd45a - Mm00432802\_m1, Trib3 - Mm00454876\_m1  
Dtx4 - Mm00549843\_m1 Tgm2 - Mm00436980\_m1, FoxM1 - Mm00514924\_m1  
Eif4ebp1 - Mm01962435\_g1, Fst - Mm00514982\_m1, Krt14 - Mm00516876\_m1  
Pcdh7 - Mm00479679\_m1*

#### **Western Blotting**

[00311] Cell pellets were lysed, electrophoresed and Western blotting was carried out according to manufacturer's instructions. Blots were probed with antibodies against Akt1

(mouse monoclonal anti-Akt1#2967, Cell Signaling Technologies),  $\beta$ -actin loading control (ab8227; abcam, Cambridge, MA) or mouse monoclonal anti- $\beta$ -tubulin (#T4026; Sigma Aldrich, MO). The secondary antibodies used were HRP-linked anti-mouse IgG (#7076, Cell Signaling Technologies, MA).

#### **Generation of stably-transfected MyrHA-Akt1 and HA-Akt1 cell lines.**

[00312] One million log phase ASZ001 cells were transfected with pLNCX-Myr-HA-AKT1 and pLNCX-HA-AKT1 - Addgene # 903 and #901 respectively - generated by the Sellers lab {Ramaswamy, 1999 #49} and obtained from Addgene using the Amaxa Nucleoporation system (Amaxa-Lonza, MD) {So, 2006 #14}. These plasmids contain the human AKT1 sequence. As a negative control, plasmid # 903 was digested with restriction enzymes to remove the anti-hemagglutinin (HA) tag and most of the AKT1 open reading frame, generating pLNCX'. One million cells were resuspended in transfection reagent and electroporated using program T29. Cells were then mixed with 154-CF complete media and replated. Media was removed after 24 h to remove the dead cells and living cells were allowed to recover for 1-2 days, and when they grew to 70% confluency, the cells were passaged and replated at a lower density. After 4 days, ASZ001 cells containing the pLNCX-Myr-HA-AKT1, pLNCX-HA-AKT1 or pLNCX' were selected using G418 (Life Technologies, Carlsbad CA) at 1 mg/ml (a dose that killed non-transfected ASZ001 cells) to generate myr-HA-AKT1, HA-AKT1 and pLNCX' cell lines, respectively. After at least 1 month of G418 selection, cells were expanded for cell proliferation experiments.

#### **Cell Proliferation Assays**

[00313] For tazarotene treatment, approximately 5000 ASZ001, myr-HA-Akt1, HA-Akt1 and pLNCX' cells were plated in 96 well plates for 2 days and serum-starved for 2 h prior to drug application. Tazarotene at 10  $\mu$ M and 0.1% DMSO were prepared as described above and cells were incubated in tazarotene or DMSO. After 48 h, 10  $\mu$ l of Wst-1 Cell Proliferation Assay Reagent (Roche, IN) was added to each well and mixed with the media for 1 minute, then incubated for 2 h at 37 °C in a CO<sub>2</sub> incubator. Plates were read on a spectrophotometer at a wavelength of 450 nm, according to manufacturer's instructions (Biorad, CA). For in vitro treatment with PI3K inhibitors the latter were dissolved in 100% DMSO to give a stock concentration of 30 mM (compound A) and 100 mM (compound B and LY942002) respectively, which were further diluted with DMSO to generate working concentrations. Cells were treated and assayed as described for tazarotene.

### FACS analysis

[00314] One million cells were trypsinized, washed in PBS and fixed in 2% paraformaldehyde at room temperature for 10 min and then permeabilized with 0.1% Triton-X100 for 10 min. Cells were labeled with mouse monoclonal HA-tag antibodies conjugated with AlexaFluor 488 (#2350, 1:100 dilution; Cell Signal Technology, MA) in 2% FBS for 60 min on ice, and analyzed using the FACSCalibur flow cytometer. FACS data was processed and analyzed with CellQuest Pro software (BD Biosciences, CA).

### In vivo pharmacologic PI3K inhibitor drug efficacy testing.

[00315] *Mice.* All mouse studies were carried out in accordance to IACUC guidelines. *Ptch1<sup>+/+</sup> K14-CreER<sup>T2</sup> p53<sup>f/f</sup>* mice were injected i.p. with tamoxifen (0.1 mg/day) for 3 consecutive days at age 1.5 months (to generate *Ptch1<sup>+/+</sup> K14-CreER2 p53<sup>flaxed/flaxed</sup>* mice that have deleted *p53* sequences in the basal keratinocytes) and irradiated with 4 Gray (Gy) of X-rays at age 8 weeks. A dorsal skin biopsy at age 3 months was taken to confirm the lack of microscopic BCC at ‘baseline’. Drug/vehicle treatments were given by oral gavage at age 13 weeks, 5 days/week until age 21 weeks when a dorsal skin biopsy (1 cm x 1 cm) was carried out. All skin biopsies were fixed in 2% glutaraldehyde/0.2% formaldehyde, washed in PBS and stained for β-galactosidase activity as described previously {So, 2004 #4}. Mice were then monitored for the first visible BCC, and visible BCC burden was assessed at age 28 weeks. Mice that died or were euthanized for unrelated causes were censored in the study.

[00316] *In vivo drug treatments.* Small molecule PI3K inhibitors GDC0941 (gift from Genentech-Roche), compound A or compound B (gifts from Exelixis) or their respective vehicle (control) were given orally once or twice daily, respectively, 5x/week for 2 months. GDC0941, compound A and compound B were given in amounts of 50 mg/Kg daily, 100 mg/Kg and 30 mg/Kg/twice a day, respectively.

[00317] *Microscopic BCC assessment.* The 5 month skin biopsy sections were scanned digitally and total microscopic BCC number and cross-sectional size for each mouse biopsy was assessed using image analysis software (Aperio, CA). The data was then standardized to plot the BCC number and size for a 1 cm skin surface length of skin.

[00318] *Visible BCC assessment.* Mice were monitored from age 5 months to assess the time when the first tumor was observed. Also, the number and approximate total volume (the sum of the length x width x height of each tumor) of visible BCCs for each mouse was measured at age 7 months.

[00319] *Graphs and Statistics.* Graphs were plotted using the Prism<sup>TM</sup> software. Statistical significance between the drug groups and vehicle control was assessed using the Student T test comparing the vehicle-treated group to the drug-treated group. A two way ANOVA test was used to detect statistical significance between the different doses of drug on the ASZ001 cells.

## References

1. Rigel, D.S. (2008). Cutaneous ultraviolet exposure and its relationship to the development of skin cancer. *J Am Acad Dermatol* 58, S129-132.
2. Gorlin, R.J. (2004). Nevoid basal cell carcinoma (Gorlin) syndrome. *Genet Med* 6, 530-539.
3. Epstein, E.H. (2008). Basal cell carcinomas: attack of the hedgehog. *Nat Rev Cancer* 8, 743-754.
4. Aszterbaum, M., Epstein, J., Oro, A., Douglas, V., LeBoit, P.E., Scott, M.P., and Epstein, E.H., Jr. (1999). Ultraviolet and ionizing radiation enhance the growth of BCCs and trichoblastomas in patched heterozygous knockout mice. *Nat Med* 5, 1285-1291.
5. Mancuso, M., Pazzaglia, S., Tanori, M., Hahn, H., Merola, P., Rebessi, S., Atkinson, M.J., Di Majo, V., Covelli, V., and Saran, A. (2004). Basal cell carcinoma and its development: insights from radiation-induced tumors in Ptch1-deficient mice. *Cancer Res* 64, 934-941.
6. Schmuth, M., Watson, R.E., Deplewski, D., Dubrac, S., Zouboulis, C.C., and Griffiths, C.E. (2007). Nuclear hormone receptors in human skin. *Horm Metab Res* 39, 96-105.
7. Wright, T.I., Spencer, J.M., and Flowers, F.P. (2006). Chemoprevention of nonmelanoma skin cancer. *J Am Acad Dermatol* 54, 933-946; quiz 947-950.
8. Nagpal, S., and Chandraratna, R.A. (2000). Recent developments in receptor-selective retinoids. *Curr Pharm Des* 6, 919-931.
9. So, P.L., Lee, K., Hebert, J., Walker, P., Lu, Y., Hwang, J., Kopelovich, L., Athar, M., Bickers, D., Aszterbaum, M., and Epstein, E.H., Jr. (2004). Topical tazarotene chemoprevention reduces Basal cell carcinoma number and size in Ptch1<sup>+/−</sup> mice exposed to ultraviolet or ionizing radiation. *Cancer Res* 64, 4385-4389.

10. So, P.L., Fujimoto, M.A., and Epstein, E.H., Jr. (2008). Pharmacologic retinoid signaling and physiologic retinoic acid receptor signaling inhibit basal cell carcinoma tumorigenesis. *Mol Cancer Ther* 7, 1275-1284.
11. Peris, K., Farnoli, M.C., and Chimenti, S. (1999). Preliminary observations on the use of topical tazarotene to treat basal-cell carcinoma. *N Engl J Med* 341, 1767-1768.
12. Bianchi, L., Orlandi, A., Campione, E., Angeloni, C., Costanzo, A., Spagnoli, L.G., and Chimenti, S. (2004). Topical treatment of basal cell carcinoma with tazarotene: a clinicopathological study on a large series of cases. *Br J Dermatol* 151, 148-156.
13. Orlandi, A., Bianchi, L., Costanzo, A., Campione, E., Giusto Spagnoli, L., and Chimenti, S. (2004). Evidence of increased apoptosis and reduced proliferation in basal cell carcinomas treated with tazarotene. *J Invest Dermatol* 122, 1037-1041.
14. So, P.L., Langston, A.W., Daniallinia, N., Hebert, J.L., Fujimoto, M.A., Khaimskiy, Y., Aszterbaum, M., and Epstein, E.H., Jr. (2006). Long-term establishment, characterization and manipulation of cell lines from mouse basal cell carcinoma tumors. *Exp Dermatol* 15, 742-750.
15. Rochette-Egly, C., and Germain, P. (2009). Dynamic and combinatorial control of gene expression by nuclear retinoic acid receptors (RARs). *Nucl Recept Signal* 7, e005.
16. Xu, L., Glass, C.K., and Rosenfeld, M.G. (1999). Coactivator and corepressor complexes in nuclear receptor function. *Curr Opin Genet Dev* 9, 140-147.
17. Katoh, Y., and Katoh, M. (2009). Hedgehog target genes: mechanisms of carcinogenesis induced by aberrant hedgehog signaling activation. *Curr Mol Med* 9, 873-886.
18. Engelman, J.A. (2009). Targeting PI3K signalling in cancer: opportunities, challenges and limitations. *Nat Rev Cancer* 9, 550-562.
19. Riobo, N.A., Lu, K., and Emerson, C.P., Jr. (2006). Hedgehog signal transduction: signal integration and cross talk in development and cancer. *Cell Cycle* 5, 1612-1615.
20. Lin, N., Moroi, Y., Uchi, H., Fukiwake, N., Dainichi, T., Takeuchi, S., Takahara, M., Tu, Y., Furue, M., and Urabe, K. (2007). Significance of the expression of phosphorylated-STAT3, -Akt, and -ERK1/2 in several tumors of the epidermis. *J Dermatol Sci* 48, 71-73.
21. Gharbi, S.I., Zvelebil, M.J., Shuttleworth, S.J., Hancox, T., Saghir, N., Timms, J.F., and Waterfield, M.D. (2007). Exploring the specificity of the PI3K family inhibitor LY294002. *Biochem J* 404, 15-21.

22. Foster, P.G., and Exelixis (2007). Potentiating the Antitumor Effects of Chemotherapy With the Selective PI3K Inhibitor COMPOUND A. In *AACR-NCI-EORTC International Conference, Molecular Targets and Cancer Therapeutics. Discovery, Biology, and Clinical Applications.*
23. Patnaik, A., LoRusso, P., Tabernero, J., Laird, D., Aggarwal, K., and Papadopoulos, K. (2007). Biomarker development for XL-765, a potent and selective oral dual inhibitor of PI3K and mTOR currently being administered to patients in a Phase I clinical trial. Presented at: 19th EORTC-NCI-AACR symposium on molecular targets and cancer therapeutics. San Francisco, CA, USA.
24. Reifenberger, J., Wolter, M., Knobbe, C.B., Kohler, B., Schoniche, A., Scharwachter, C., Kumar, K., Blaschke, B., Ruzicka, T., and Reifenberger, G. (2005). Somatic mutations in the PTCH, SMOH, SUFUH and TP53 genes in sporadic basal cell carcinomas. *Br J Dermatol* **152**, 43-51.
25. Ling, G., Ahmadian, A., Persson, A., Unden, A.B., Afink, G., Williams, C., Uhlen, M., Toftgard, R., Lundeberg, J., and Ponten, F. (2001). PATCHED and p53 gene alterations in sporadic and hereditary basal cell cancer. *Oncogene* **20**, 7770-7778.
26. Wang, G.Y., Wang, J., Mancianti, M.L., and Epstein, E.H., Jr. (2011). Basal cell carcinomas arise from hair follicle stem cells in Ptch1(+-) mice. *Cancer Cell* **19**, 114-124.
27. Folkes, A.J., Ahmadi, K., Alderton, W.K., Alix, S., Baker, S.J., Box, G., Chuckowree, I.S., Clarke, P.A., Depledge, P., Eccles, S.A., Friedman, L.S., Hayes, A., Hancox, T.C., Kugendradas, A., Lensun, L., Moore, P., Olivero, A.G., Pang, J., Patel, S., Pergl-Wilson, G.H., Raynaud, F.I., Robson, A., Saghir, N., Salphati, L., Sohal, S., Ultsch, M.H., Valenti, M., Wallweber, H.J., Wan, N.C., Wiesmann, C., Workman, P., Zhyvoloup, A., Zvelebil, M.J., and Shuttleworth, S.J. (2008). The identification of 2-(1H-indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin -4-yl-thieno[3,2-d]pyrimidine (GDC-0941) as a potent, selective, orally bioavailable inhibitor of class I PI3 kinase for the treatment of cancer. *J Med Chem* **51**, 5522-5532.
28. Martelli, A.M., Tazzari, P.L., Tabellini, G., Bortul, R., Billi, A.M., Manzoli, L., Ruggeri, A., Conte, R., and Cocco, L. (2003). A new selective AKT pharmacological inhibitor reduces resistance to chemotherapeutic drugs, TRAIL, all-trans-retinoic acid, and ionizing radiation of human leukemia cells. *Leukemia* **17**, 1794-1805.
29. Neri, L.M., Borgatti, P., Tazzari, P.L., Bortul, R., Cappellini, A., Tabellini, G., Bellacosa, A., Capitani, S., and Martelli, A.M. (2003). The phosphoinositide 3-

- kinase/AKT1 pathway involvement in drug and all-trans-retinoic acid resistance of leukemia cells. *Mol Cancer Res* 1, 234-246.
30. Hahn, H., Wojnowski, L., Specht, K., Kappler, R., Calzada-Wack, J., Potter, D., Zimmer, A., Muller, U., Samson, E., and Quintanilla-Martinez, L. (2000). Patched target Igf2 is indispensable for the formation of medulloblastoma and rhabdomyosarcoma. *J Biol Chem* 275, 28341-28344.
31. Rao, G., Pedone, C.A., Del Valle, L., Reiss, K., Holland, E.C., and Fults, D.W. (2004). Sonic hedgehog and insulin-like growth factor signaling synergize to induce medulloblastoma formation from nestin-expressing neural progenitors in mice. *Oncogene* 23, 6156-6162.
32. Tanori, M., Santone, M., Mancuso, M., Pasquali, E., Leonardi, S., Di Majo, V., Rebessi, S., Saran, A., and Pazzaglia, S. (2010). Developmental and oncogenic effects of insulin-like growth factor-I in Ptc1<sup>+-</sup> mouse cerebellum. *Mol Cancer* 9, 53.
33. Corcoran, R.B., Bachar Raveh, T., Barakat, M.T., Lee, E.Y., and Scott, M.P. (2008). Insulin-like growth factor 2 is required for progression to advanced medulloblastoma in patched1 heterozygous mice. *Cancer Res* 68, 8788-8795.
34. Kenney, A.M., Widlund, H.R., and Rowitch, D.H. (2004). Hedgehog and PI-3 kinase signaling converge on Nmyc1 to promote cell cycle progression in cerebellar neuronal precursors. *Development* 131, 217-228.
35. Freier, K., Flechtenmacher, C., Devens, F., Hartschuh, W., Hofele, C., Lichter, P., and Joos, S. (2006). Recurrent NMYC copy number gain and high protein expression in basal cell carcinoma. *Oncol Rep* 15, 1141-1145.
36. Riobo, N.A., Lu, K., Ai, X., Haines, G.M., and Emerson, C.P., Jr. (2006). Phosphoinositide 3-kinase and Akt are essential for Sonic Hedgehog signaling. *Proc Natl Acad Sci U S A* 103, 4505-4510.
37. Stecca, B., Mas, C., Clement, V., Zbinden, M., Correa, R., Piguet, V., Beermann, F., and Ruiz, I.A.A. (2007). Melanomas require HEDGEHOG-GLI signaling regulated by interactions between GLI1 and the RAS-MEK/AKT pathways. *Proc Natl Acad Sci U S A* 104, 5895-5900.
38. Mizuarai, S., Kawagishi, A., and Kotani, H. (2009). Inhibition of p70S6K2 down-regulates Hedgehog/GLI pathway in non-small cell lung cancer cell lines. *Mol Cancer* 8, 44.
39. Singh, R.R., Cho-Vega, J.H., Davuluri, Y., Ma, S., Kasbidi, F., Milito, C., Lennon, P.A., Drakos, E., Medeiros, L.J., Luthra, R., and Vega, F. (2009). Sonic hedgehog

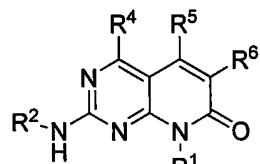
- signaling pathway is activated in ALK-positive anaplastic large cell lymphoma. *Cancer Res* 69, 2550-2558.
40. Buonamici, S., Williams, J., Morrissey, M., Wang, A., Guo, R., Vattay, A., Hsiao, K., Yuan, J., Green, J., Ospina, B., Yu, Q., Ostrom, L., Fordjour, P., Anderson, D.L., Monahan, J.E., Kelleher, J.F., Peukert, S., Pan, S., Wu, X., Maira, S.M., Garcia-Echeverria, C., Briggs, K.J., Watkins, D.N., Yao, Y.M., Lengauer, C., Warmuth, M., Sellers, W.R., and Dorsch, M. (2010). Interfering with resistance to smoothened antagonists by inhibition of the PI3K pathway in medulloblastoma. *Sci Transl Med* 2, 51ra70.
41. Dijkgraaf, G.J., Alicke, B., Weinmann, L., Januario, T., West, K., Modrusan, Z., Burdick, D., Goldsmith, R., Robarge, K., Sutherlin, D., Scales, S.J., Gould, S.E., Yauch, R.L., and de Sauvage, F.J. (2011). Small molecule inhibition of GDC-0449 refractory smoothened mutants and downstream mechanisms of drug resistance. *Cancer Res* 71, 435-444.
42. Bastien, J., Plassat, J.L., Payrastre, B., and Rochette-Egly, C. (2006). The phosphoinositide 3-kinase/Akt pathway is essential for the retinoic acid-induced differentiation of F9 cells. *Oncogene* 25, 2040-2047.
43. Doi, T., Sugimoto, K., Ruttenstock, E., Dingemann, J., and Puri, P. (2010). Prenatal retinoic acid upregulates pulmonary gene expression of PI3K and AKT in nitrofen-induced pulmonary hypoplasia. *Pediatr Surg Int* 26, 1011-1015.
44. Lopez-Carballo, G., Moreno, L., Masia, S., Perez, P., and Barettono, D. (2002). Activation of the phosphatidylinositol 3-kinase/Akt signaling pathway by retinoic acid is required for neural differentiation of SH-SY5Y human neuroblastoma cells. *J Biol Chem* 277, 25297-25304.
45. Billottet, C., Banerjee, L., Vanhaesebroeck, B., and Khwaja, A. (2009). Inhibition of class I phosphoinositide 3-kinase activity impairs proliferation and triggers apoptosis in acute promyelocytic leukemia without affecting atra-induced differentiation. *Cancer Res* 69, 1027-1036.
46. Fan, Q.W., Cheng, C.K., Nicolaides, T.P., Hackett, C.S., Knight, Z.A., Shokat, K.M., and Weiss, W.A. (2007). A dual phosphoinositide-3-kinase alpha/mTOR inhibitor cooperates with blockade of epidermal growth factor receptor in PTEN-mutant glioma. *Cancer Res* 67, 7960-7965.

47. Fan, Q.W., and Weiss, W.A. (2010). Targeting the RTK-PI3K-mTOR axis in malignant glioma: overcoming resistance. *Curr Top Microbiol Immunol* **347**, 279-296.
48. Bolstad, B.M., Irizarry, R.A., Astrand, M., and Speed, T.P. (2003). A comparison of normalization methods for high density oligonucleotide array data based on variance and bias. *Bioinformatics* **19**, 185-193.
49. Ramaswamy, S., Nakamura, N., Vazquez, F., Batt, D.B., Perera, S., Roberts, T.M., and Sellers, W.R. (1999). Regulation of G1 progression by the PTEN tumor suppressor protein is linked to inhibition of the phosphatidylinositol 3-kinase/Akt pathway. *Proc Natl Acad Sci U S A* **96**, 2110-2115.

[00320] The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled. All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.

What is claimed is:

1. A method for treating basal cell carcinoma (BCC) in a patient in need of such treatment, comprising administering a therapeutically effective amount of a compound of formula IIa:



IIa

or a pharmaceutically acceptable salt thereof, wherein:

- R<sup>1</sup> is alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl;
- R<sup>2</sup> is hydrogen or alkyl;
- R<sup>4</sup> is alkyl;
- R<sup>5</sup> is hydrogen;
- R<sup>6</sup> is phenyl, acyl, or heteroaryl wherein the phenyl and heteroaryl are is optionally substituted with 1, 2, 3, 4, or 5 R<sup>9</sup> groups; and
- each R<sup>9</sup>, when present, is independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, amino, alkylamino, dialkylamino, alkoxyalkyl, carboxyalkyl, alkoxycarbonyl, aminoalkyl, cycloalkyl, aryl, arylalkyl, aryloxy, heterocycloalkyl, or heteroaryl and where the cycloalkyl, aryl, heterocycloalkyl, and heteroaryl, each either alone or as part of another group within R<sup>9</sup>, are independently optionally substituted with 1, 2, 3, or 4 groups selected from halo, alkyl, haloalkyl, hydroxy, alkoxy, haloalkoxy, amino, alkylamino, and dialkylamino.

2. The method of claim 1, wherein R<sup>1</sup> is alkyl, cycloalkyl, heterocycloalkylalkyl, or arylalkyl; R<sup>2</sup> is hydrogen or alkyl; R<sup>4</sup> is alkyl; R<sup>5</sup> is hydrogen; R<sup>6</sup> is phenyl or heteroaryl wherein the phenyl and heteroaryl are is optionally substituted with one, two, or three R<sup>9</sup> groups.
3. The method of claims 1 or 2, wherein R<sup>4</sup> is methyl in the compound of formula IIa.

4. The method of any of claims 1 to 3, wherein R<sup>2</sup> is hydrogen in the compound of formula IIa and R<sup>4</sup> is methyl, R<sup>1</sup> is optionally substituted alkyl, cycloalkyl, or heterocycloalkyl, and R<sup>6</sup> is heteroaryl optionally substituted with 1, 2, or 3 R<sup>9</sup> groups.

5. The method of claim 1-4, wherein the compound of formula IIa is

2-amino-8-ethyl-4-methyl-6-(1 <i>H</i> -pyrazol-5-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-cyclopentyl-4-methyl-6-(1 <i>H</i> -pyrazol-3-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-4-methyl-8-(1-methylethyl)-6-(1 <i>H</i> -pyrazol-3-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-4-methyl-8-(phenylmethyl)-6-(1 <i>H</i> -pyrazol-3-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-4-methyl-6-(4-methyl-3-thienyl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-4-methyl-6-(2-thienyl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-4-methyl-6-(3-thienyl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-6-furan-3-yl-4-methylpyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-4-methyl-6-phenylpyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-6-isoxazol-4-yl-4-methylpyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-6-furan-2-yl-4-methylpyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
5-(2-amino-8-ethyl-4-methyl-7-oxo-7,8-dihydropyrido[2,3- <i>d</i> ]pyrimidin-6-yl)thiophene-2-carbonitrile;
2-amino-8-ethyl-4-methyl-6-pyrimidin-5-ylpyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-6-(1 <i>H</i> -imidazol-5-yl)-4-methylpyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-4-methyl-6-(1 <i>H</i> -1,2,3-triazol-5-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-4-methyl-6-(1 <i>H</i> -pyrazol-4-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-4-methyl-6-(1,3-thiazol-2-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-4-methyl-6-(1 <i>H</i> -tetrazol-5-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-8-ethyl-4-methyl-6-(1-methyl-1 <i>H</i> -pyrrol-2-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one;
2-amino-4,8-diethyl-6-(1 <i>H</i> -pyrazol-5-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one; or
2-amino-8-cyclopentyl-4-methyl-6-(1,3-thiazol-5-yl)pyrido[2,3- <i>d</i> ]pyrimidin-7(8 <i>H</i> )-one; or a pharmaceutically acceptable salt thereof.

6. The method of any of claims 1 to 5, wherein the compound of formula IIa is 2-amino-8-ethyl-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one or a pharmaceutically acceptable salt thereof.
7. The method of any of claims 1 to 6, wherein the BCC is hormone receptor-positive (ER+ and/or PGR+), HER2-negative (HER2-) BCC which is refractory to a nonsteroidal aromatase inhibitor
8. The method of any of claims 1 to 5, wherein BCC is resistant to tazarotene.

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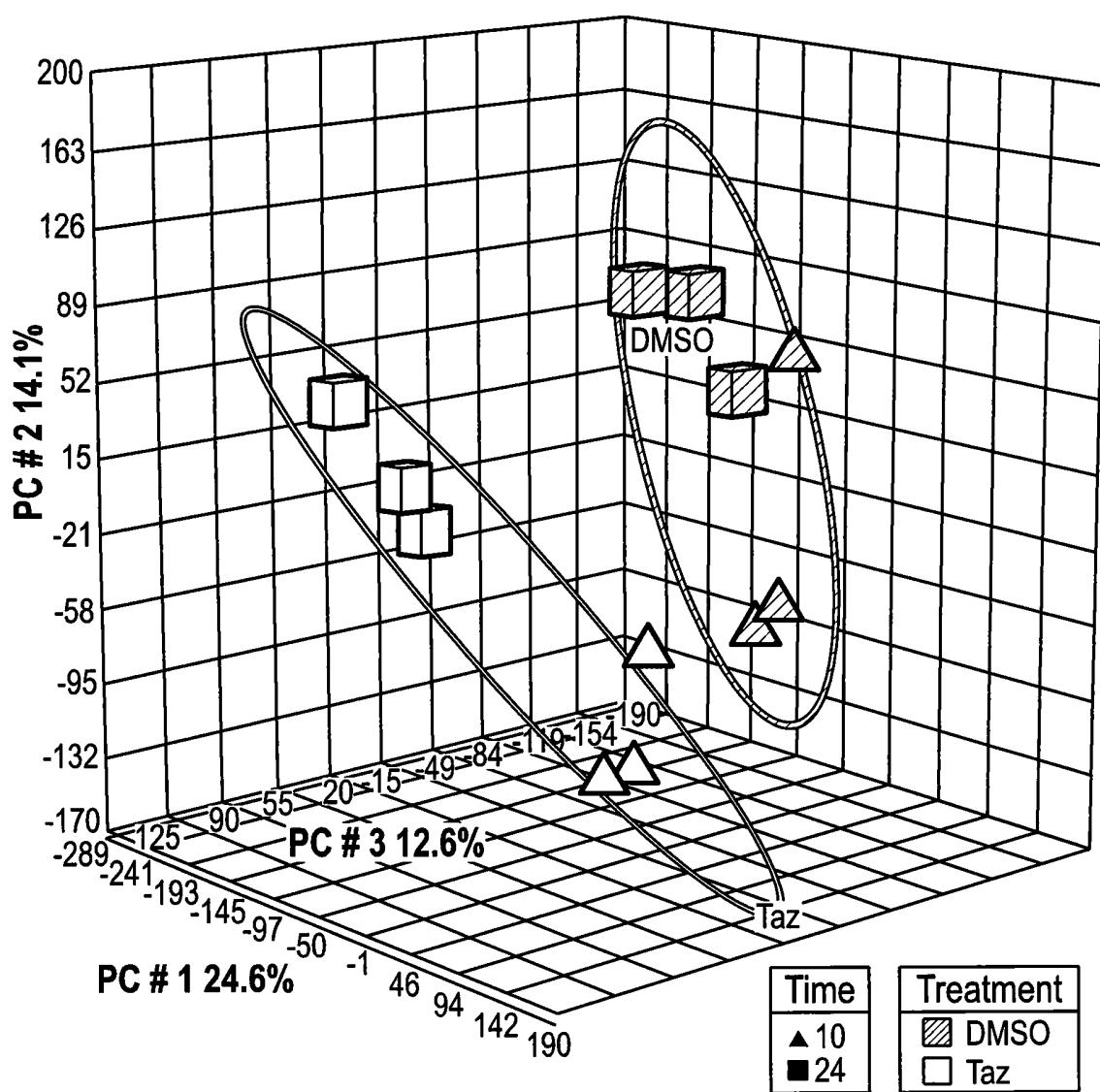


FIG. 1A

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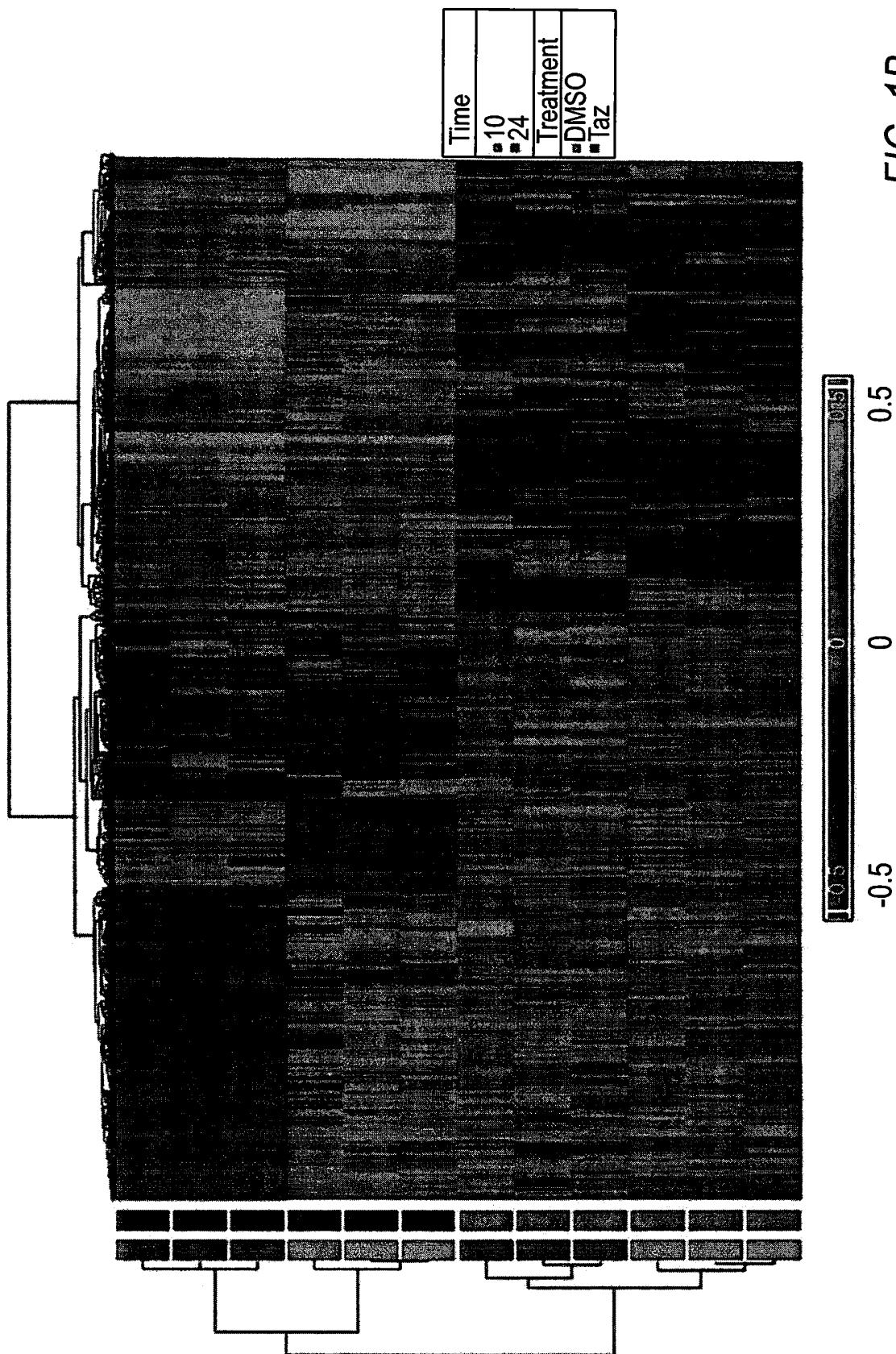


FIG. 1B

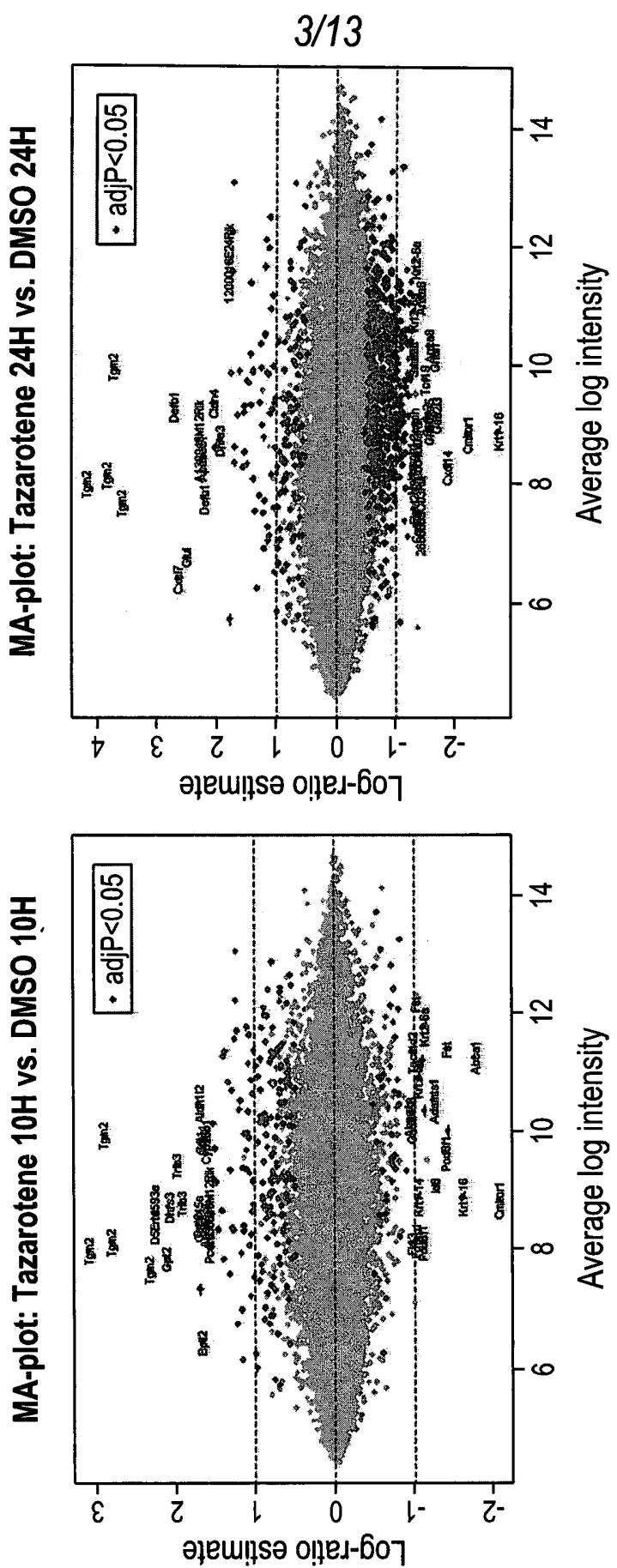


FIG. 1C

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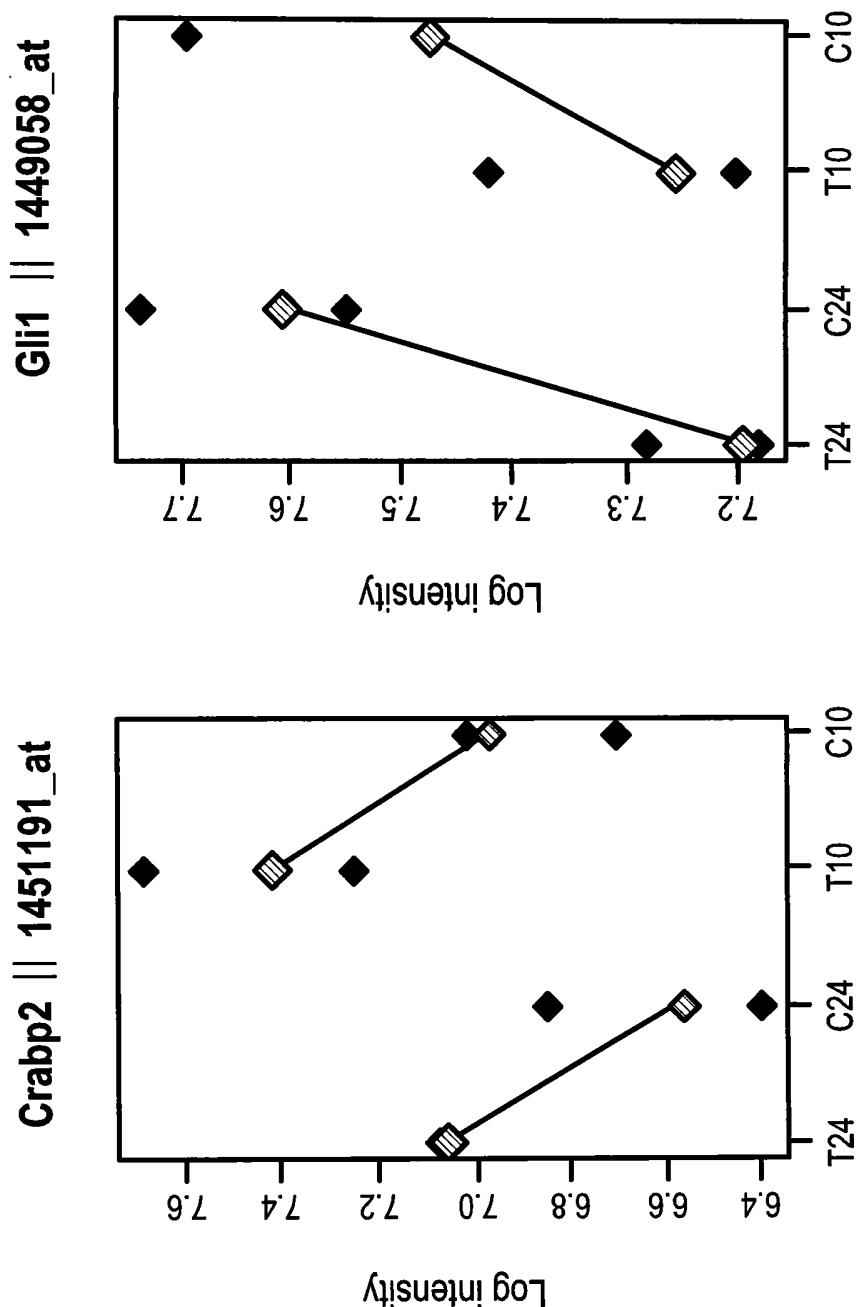


FIG. 1D

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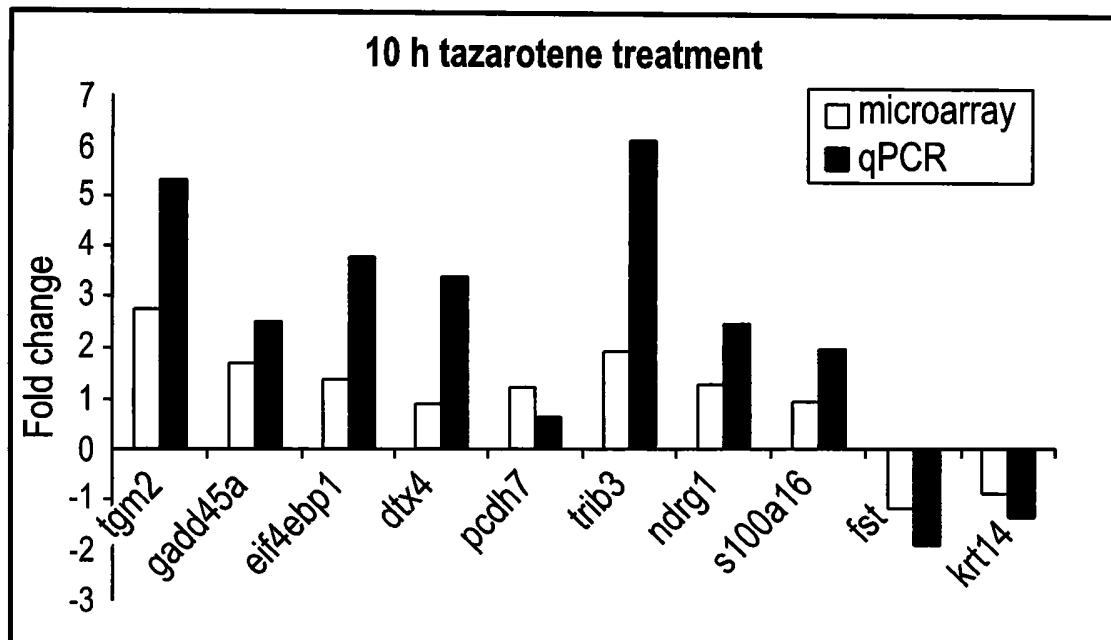


FIG. 2A

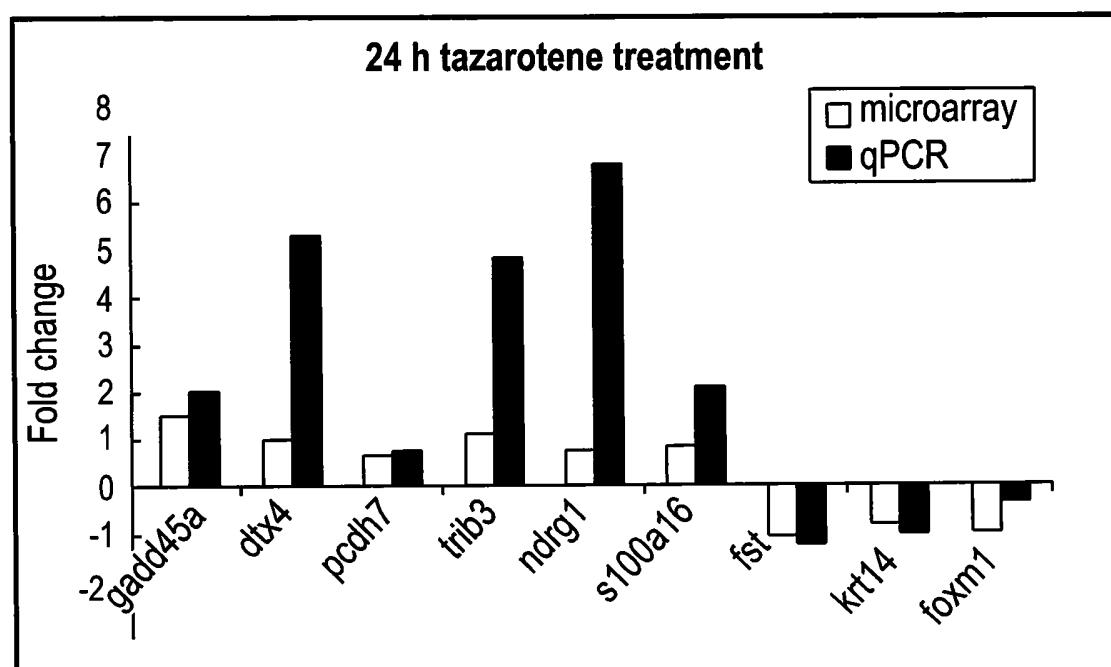


FIG. 2B

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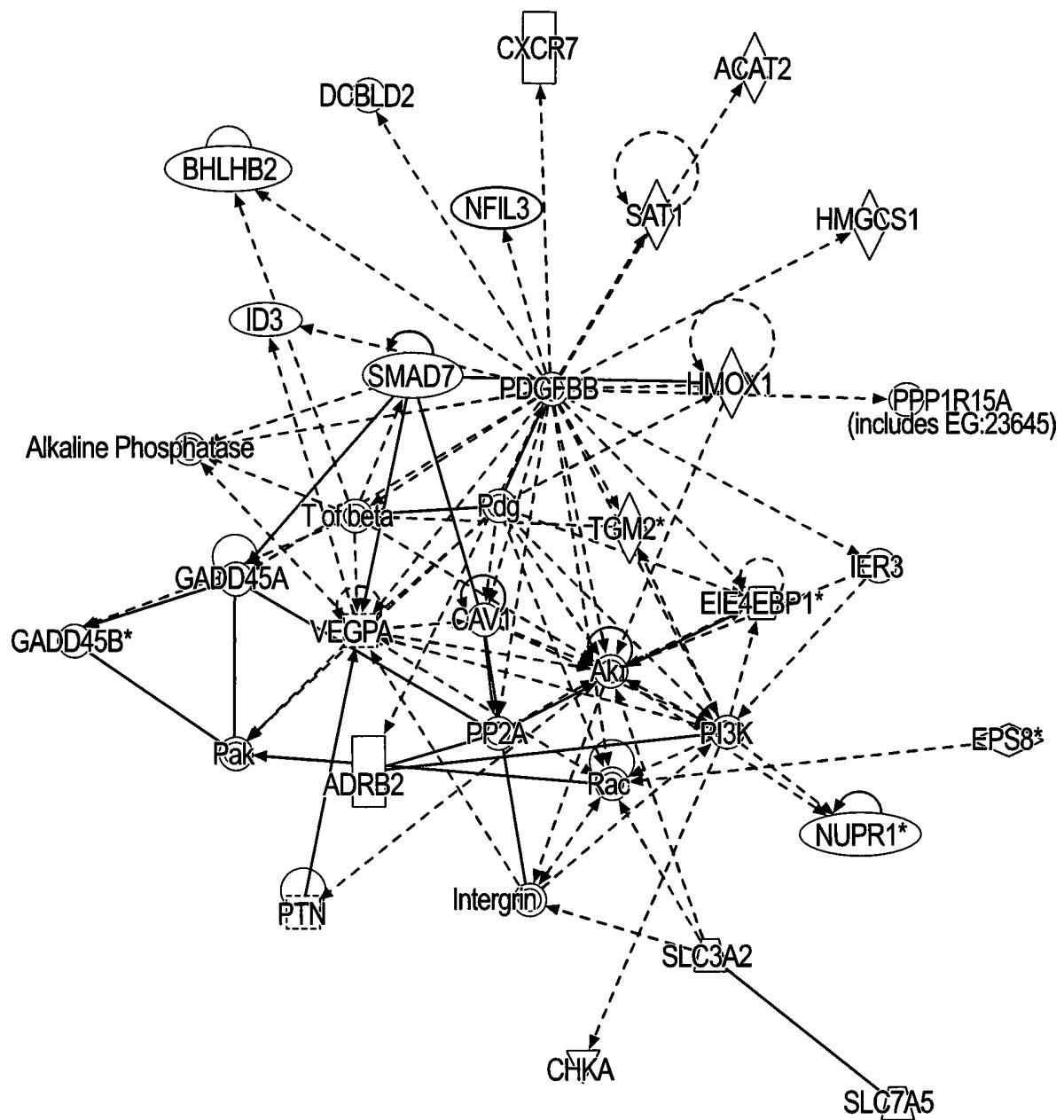


FIG. 3

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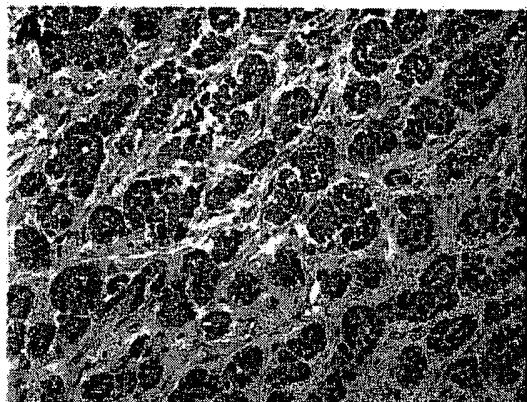


FIG. 4A



FIG. 4B

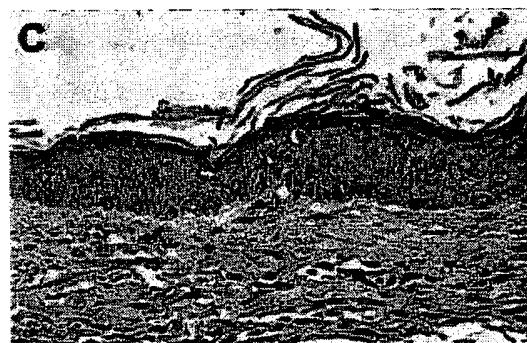


FIG. 4C

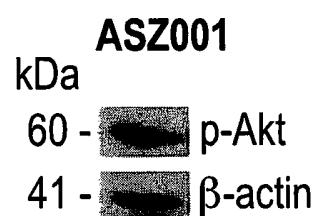


FIG. 4D

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FIG. 5A

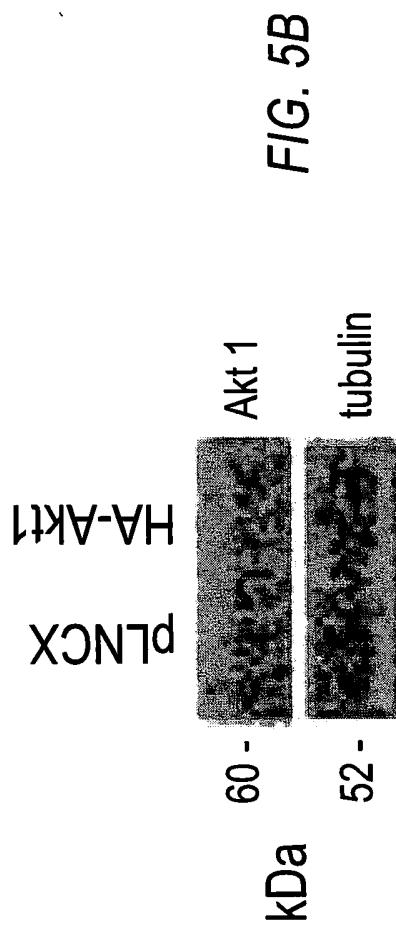


FIG. 5B

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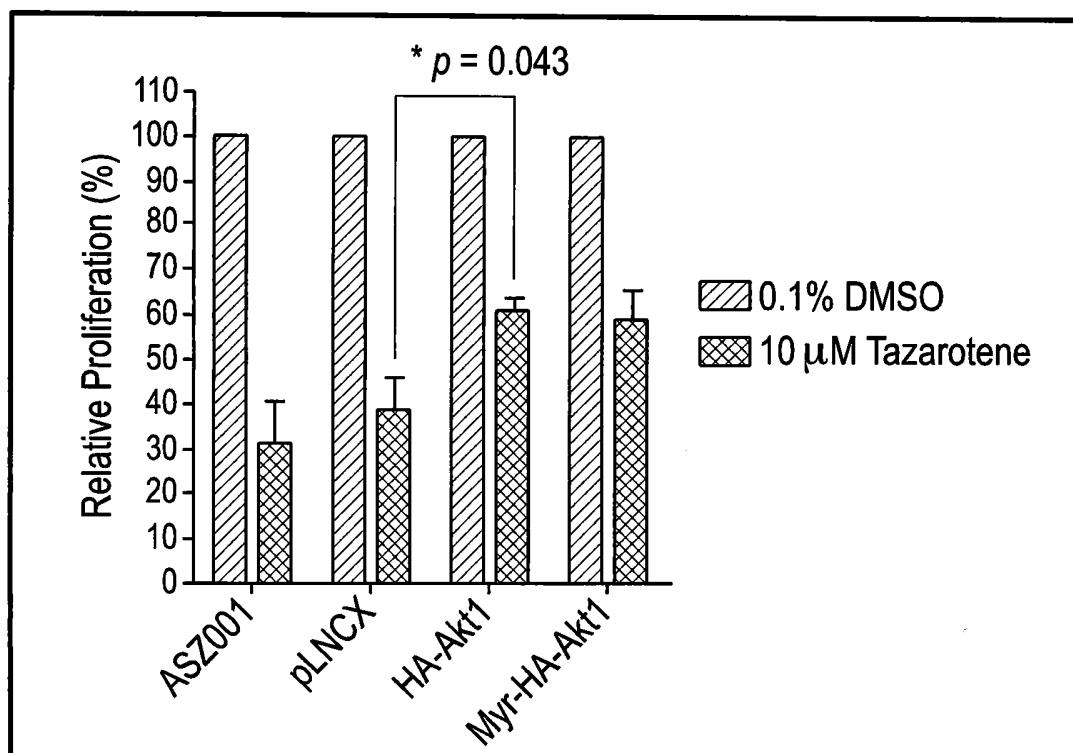


FIG. 5C

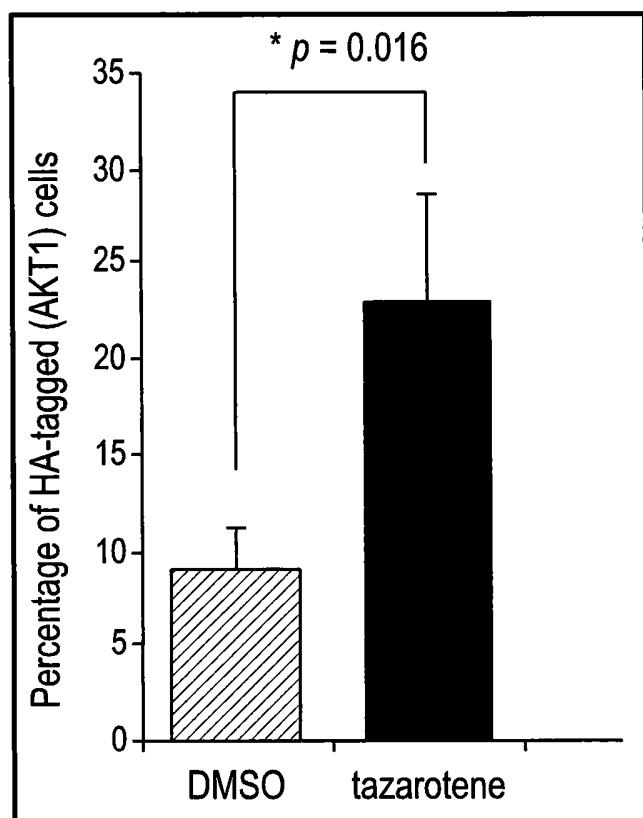
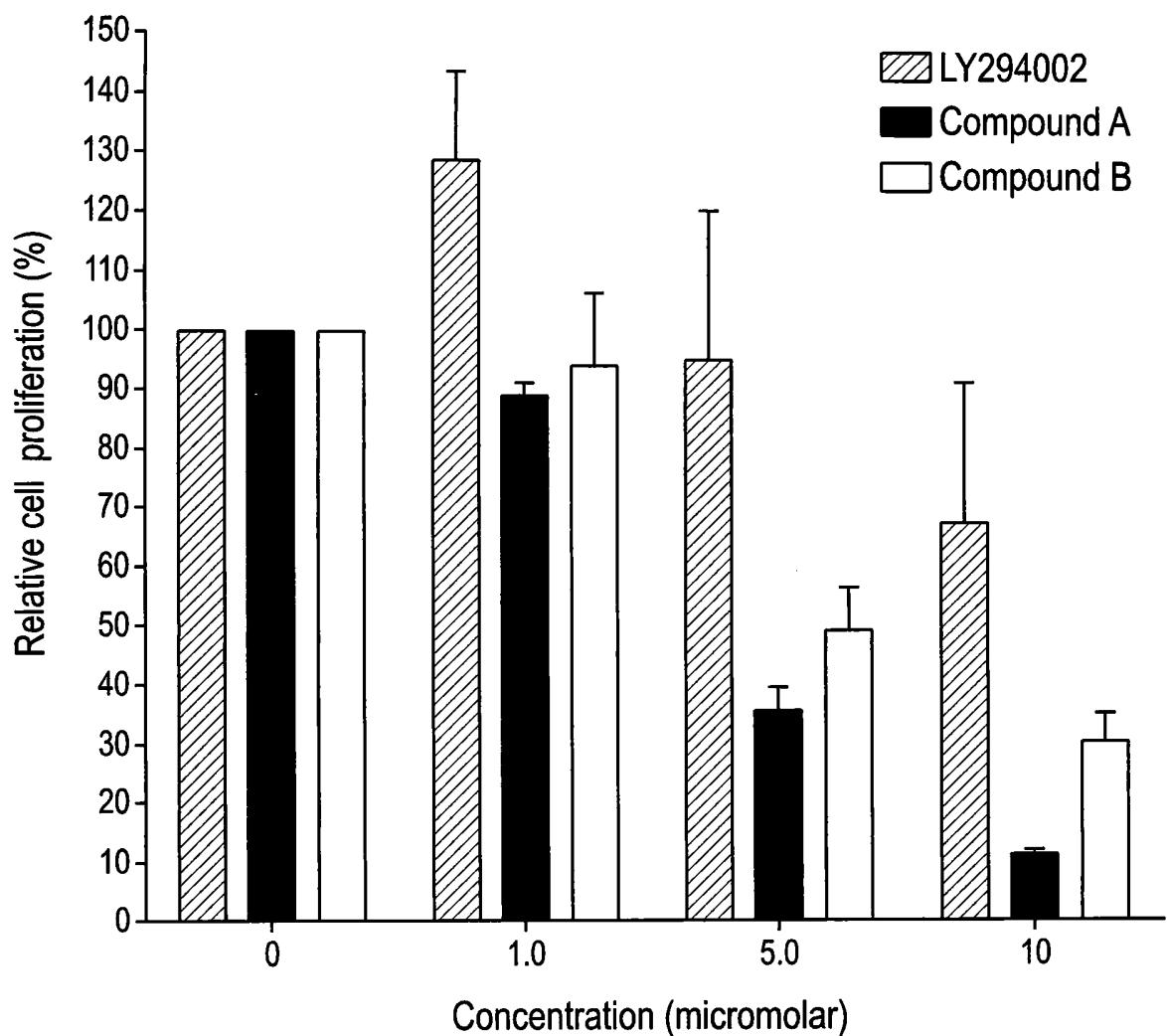


FIG. 5D

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**PI3K inhibitors on ASZ001****FIG. 6**

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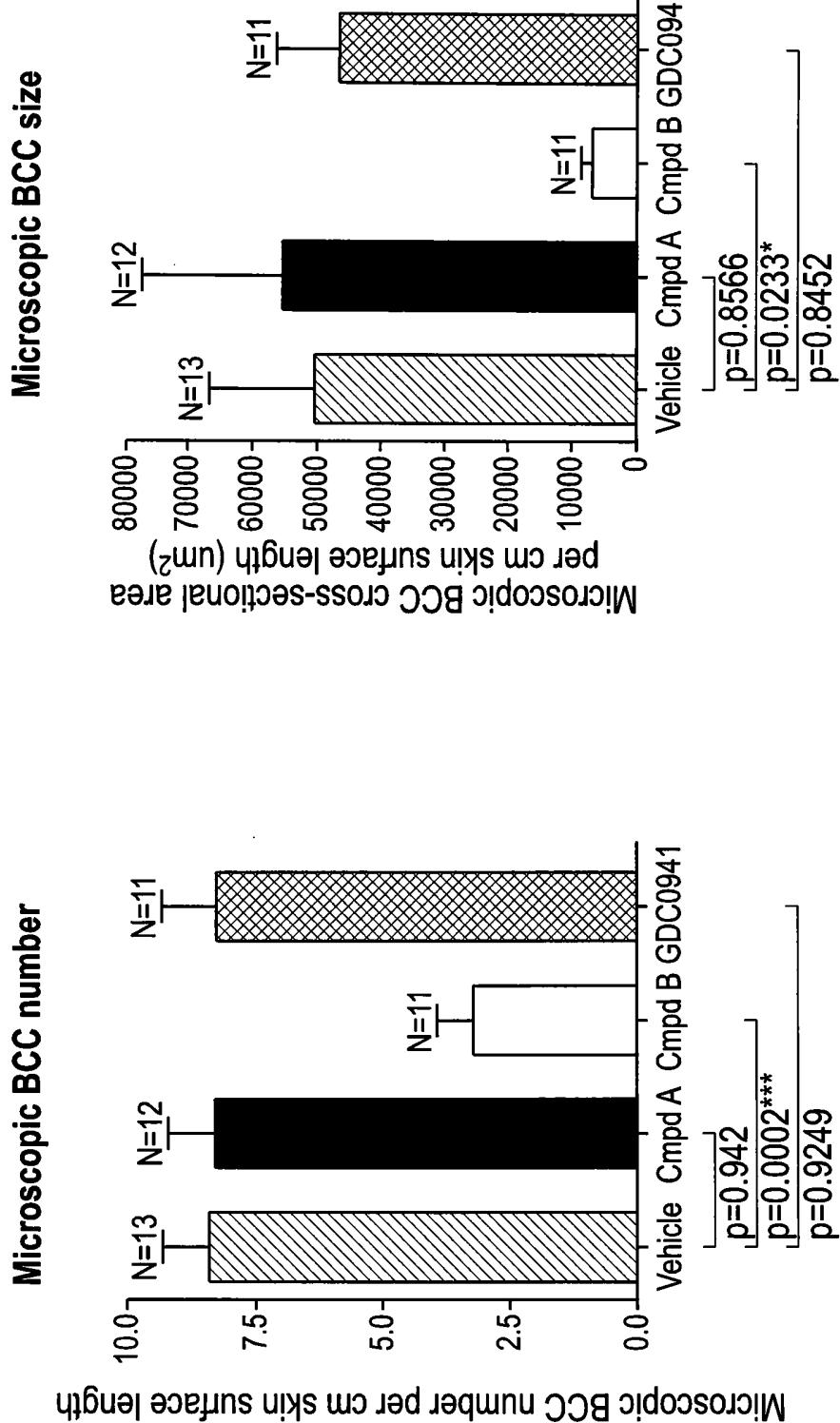


FIG. 7A

FIG. 7A

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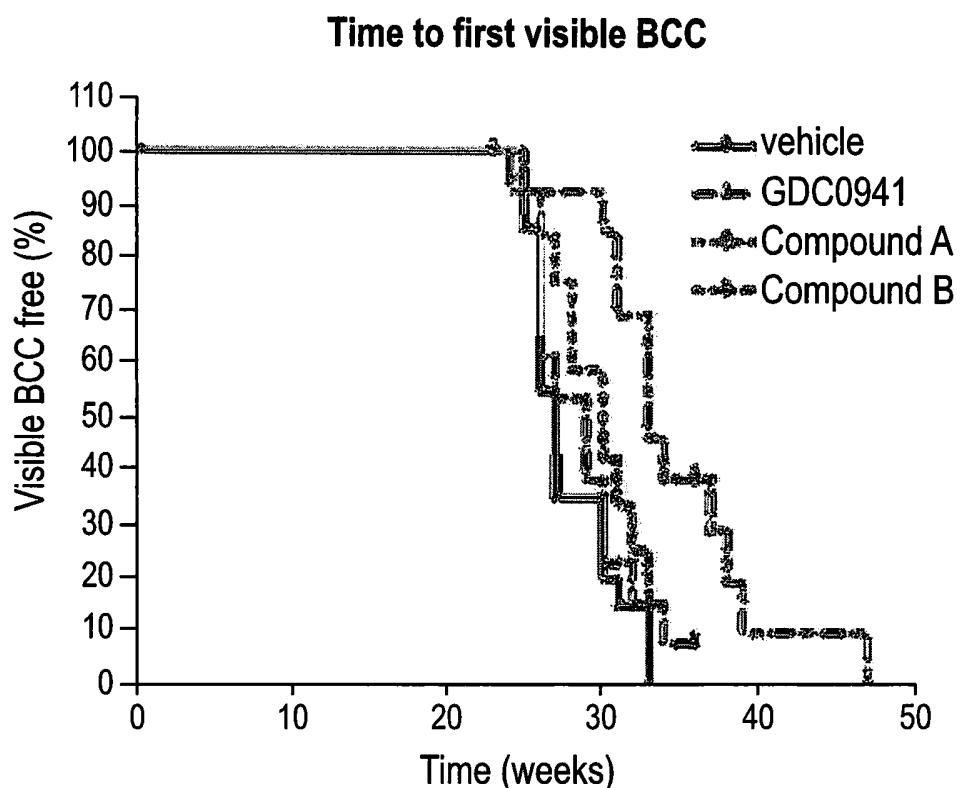


FIG. 7C

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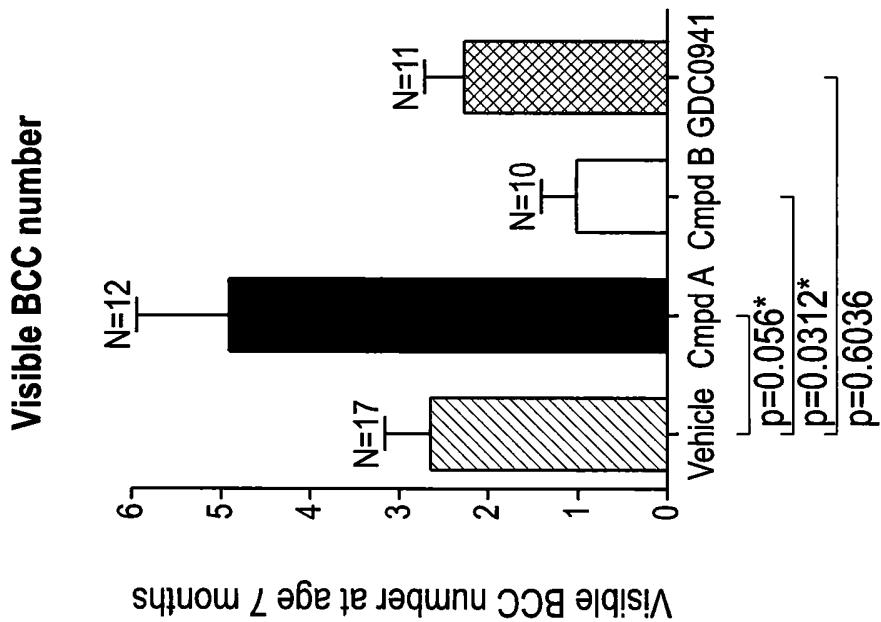
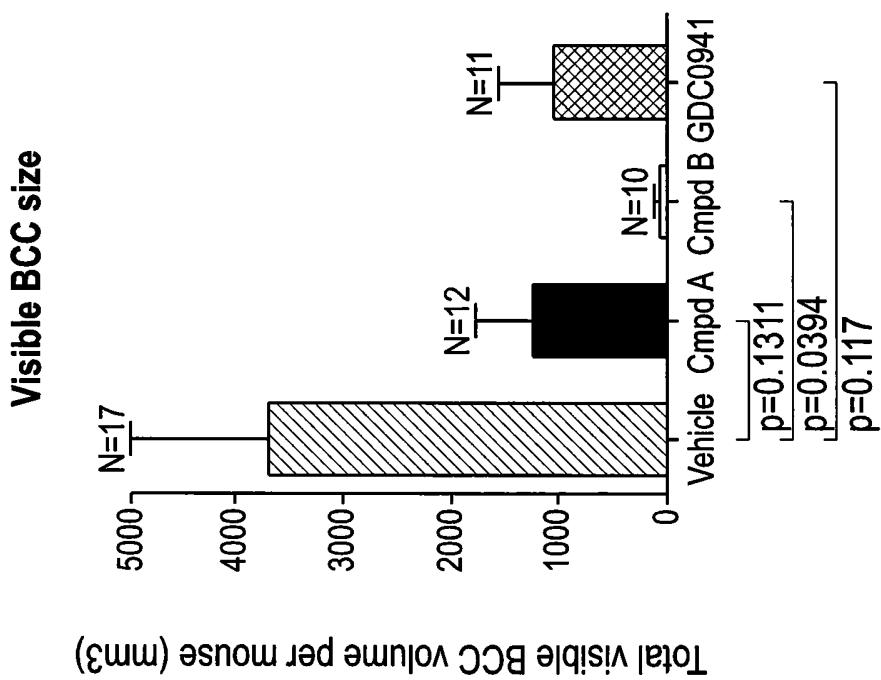


FIG. 7E

FIG. 7D

# INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/059976

**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. A61K31/519 A61P35/00  
 ADD.

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
**A61K**

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

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

EPO-Internal, WPI Data, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/044813 A1 (EXELIXIS INC [US]; BAIK TAE-GON [US]; BUHR CHRIS A [US]; LARA KATHERIN) 19 April 2007 (2007-04-19) cited in the application claims 1,44 page 20, paragraph 0082 ----- US 2010/209420 A1 (LAMB PETER [US] ET AL) 19 August 2010 (2010-08-19) claims 1,17 column 8, paragraph 0102 ----- WO 2008/127712 A1 (EXELIXIS INC [US]; BUHR CHRIS A [US]; WANG LONGCHENG [US]) 23 October 2008 (2008-10-23) claim 1 page 15, line 10 -----	1-6 1-6 1-4

Further documents are listed in the continuation of Box C.

See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

3 December 2012

10/12/2012

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Authorized officer

Baurand, Petra

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/059976

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 2007044813	A1	19-04-2007		AU 2006302078 A1 CA 2623770 A1 CN 101395155 A EA 200800760 A1 EP 1940839 A1 EP 2322523 A1 GE P20115304 B JP 2009511504 A KR 20080056195 A NZ 566903 A US 2009270430 A1 US 2011237608 A1 WO 2007044813 A1		19-04-2007 19-04-2007 25-03-2009 29-08-2008 09-07-2008 18-05-2011 10-10-2011 19-03-2009 20-06-2008 30-09-2011 29-10-2009 29-09-2011 19-04-2007
US 2010209420	A1	19-08-2010		AU 2008236562 A1 CA 2683641 A1 CN 101715345 A CN 102727498 A CO 6251254 A2 CR 11100 A DO P2009000243 A EA 200970932 A1 EC SP099724 A EP 2139484 A1 JP 2010523670 A KR 20100016354 A MA 31358 B1 NZ 580110 A US 2010209420 A1 WO 2008124161 A1 ZA 200906764 A		16-10-2008 16-10-2008 26-05-2010 17-10-2012 21-02-2011 19-01-2010 31-10-2010 30-04-2010 31-03-2010 06-01-2010 15-07-2010 12-02-2010 03-05-2010 29-06-2012 19-08-2010 16-10-2008 25-08-2010
WO 2008127712	A1	23-10-2008		AU 2008239596 A1 CA 2683820 A1 CN 101711249 A CO 6241119 A2 CR 11098 A DO P2009000242 A EA 200970936 A1 EC SP099722 A EP 2142544 A1 JP 2010523681 A KR 20090130104 A MA 31336 B1 NZ 579945 A SV 2009003389 A US 2010209340 A1 WO 2008127712 A1 ZA 200906648 A		23-10-2008 23-10-2008 19-05-2010 20-01-2011 27-01-2010 30-04-2010 26-02-2010 28-12-2009 13-01-2010 15-07-2010 17-12-2009 01-04-2010 25-05-2012 27-04-2010 19-08-2010 23-10-2008 28-04-2010