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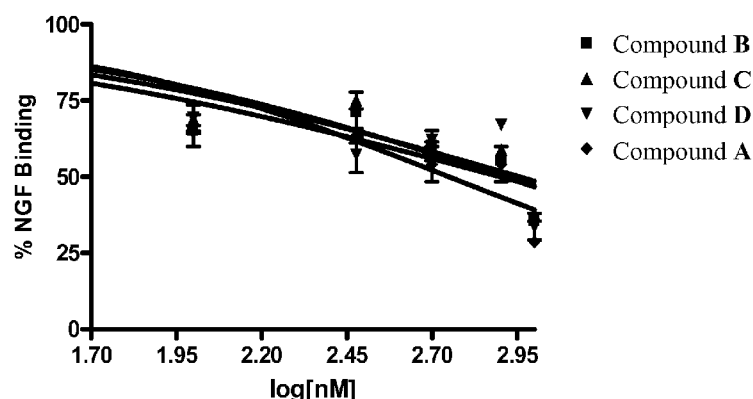


FIG. 2A

(57) Abstract: The invention provides compounds, compositions and methods for preventing and treating tumors of the nervous system, by means of compounds that inhibit or modulate p75 neurotrophic receptors. Compounds of the invention have structures of the form G-H-I, wherein G is a small ring system reminiscent of redox-mediating moieties in metabolism, H is a linker of up to 8 atoms in length, and I is a simple end group such as a lower alkyl or small heteroaryl or heterocyclic ring system.

## **COMPOSITIONS AND METHODS OF TREATMENT FOR TUMORS IN THE NERVOUS SYSTEM**

### **I. CROSS-REFERENCE TO RELATED APPLICATIONS**

1. This application claims benefit to U.S Provisional Application No. 61/353,138, filed on June 9, 2010, and is hereby incorporated herein in its entirety.

### **II. FEDERAL RIGHTS IN THE INVENTION**

2. The development of this invention was assisted by funds from federal grant no. W81XWH-07-1-0366.

### **III. FIELD**

3. Disclosed are compounds, compositions and methods, including for treatment for tumors in the nervous system. The invention relates particularly to compounds and compositions and the use of inhibitors and modulators for p75<sup>NTR</sup> tumor necrosis factor receptors.

### **IV. BACKGROUND**

4. Over 17,000 primary brain tumors are diagnosed each year in the United States. Gliomas, the most common group of primary brain tumor, comprise a heterogeneous group of which the Glioblastoma multiforme (GBM) is by far the most common and deadly, accounting for the majority of deaths from brain tumors of all types, and killing 8,000 young Americans each year. GBMs may arise anywhere in the brain or spinal cord, invading locally and spreading by streaming tentacles of cells that rapidly infiltrate normal brain along compact white matter pathways. GBMs are also the most malignant of all tumors not only because of their rapid infiltrative growth, but also because the blood brain barrier makes them resistant to all forms of conventional treatment.

5. Without treatment, patient survival is less than three months; with surgery, irradiation and chemotherapy, the median survival is 12 months, and 25% of patients may survive to 24 months. The new chemotherapeutic agent, Temodar, has prolonged median survival to 13.9 months. The extent of surgical resection remains the most important factor in outcome, but the propensity for infiltrative growth places virulent GBM cells beyond the reach of resection. Invading GBM cells activate cellular programs to activate motility, increase extracellular matrix degradation and decrease cell division which make them resistant to irradiation (Mariani, 2001; Joy, 2003; Demuth,

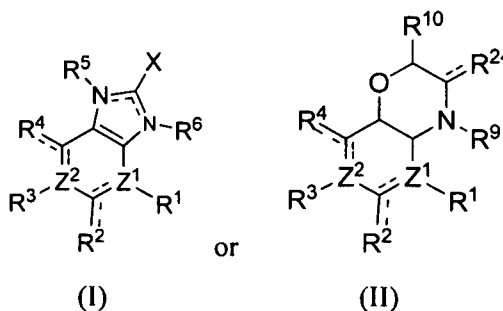
2004; Geise, 2004;). These cells, sequestered within normal brain, are afforded protection by the blood brain barrier (BBB), rendering standard chemotherapeutic treatments ineffective, and affording sources of new tumor growth. Ninety five per cent of GBMs recur within 2.5 centimeters of the resection margin. Recently, several groups have found that the use of anti-angiogenics has changed the pattern of recurrence in patients with gliomas. Patients treated with bevacizumab (Avastin®) develop highly invasive tumors that recur remotely and outside the RT treatment volumes. However to date no truly effective therapy has been reported.

6. There is, therefore, an urgent ongoing need for compositions and methods of treatment to treat or prevent GBM.

## V. SUMMARY

7. Described herein are compounds, compositions and methods for preventing and treating tumors of the nervous system, by means of compounds that inhibit or modulate p75 neurotrophic receptors (p75<sup>NTR</sup>).

8. Disclosed herein is a compound having structure I or II:



wherein:

X can be hydrogen, lower alkyl, haloalkyl or an electron withdrawing group;

R<sup>1</sup> and R<sup>3</sup> can either both present or both absent, and

if R<sup>1</sup> and R<sup>3</sup> are present then each can independently be unsubstituted lower alkyl, alkyl, halide and optionally together form a bridge, R<sup>2</sup> and R<sup>4</sup> can each be double bonded O, and Z<sup>1</sup> and Z<sup>2</sup> can each be an N bearing no double bonds; and  
if R<sup>1</sup> and R<sup>3</sup> are absent then R<sup>2</sup> and R<sup>4</sup> can each be H or be double bonded O, the six-member ring can have 0-3 double bonds, Z<sup>1</sup> and Z<sup>2</sup> can independently be C or N, and the six-member ring if carbocyclic can optionally be substituted;

if  $Z^1$  and  $Z^2$  are C then  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  can independently be present or absent, and if  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are present then each can independently be H, halide, lower alkoxy, lower alkyl, hydroxyl or haloalkyl;

one or both of  $R^5$  or  $R^6$  can be present, can be bonded to a nitrogen atom having two single bonds in the five-member ring, and the other nitrogen atom in the five-member ring can be unsubstituted or substituted and bears a double bond in the ring, if  $R^5$  or  $R^6$  is bonded to a nitrogen that bears a double bond then  $R^5$  or  $R^6$  can be alkyl or halide, and  $R^5$  or  $R^6$  can be of the form  $-\text{linker}-R^7$ , wherein

the linker can comprise in any order  $-\text{C}(=\text{O})-$ ,  $-\text{N}(\text{R}^a)-$ ,  $-\text{O}-$ ,  $-\text{S}-$ , aryl, hetero aryl, heterocyclyl, cycloalkyl and up to ten methylene groups, wherein

$R^a$  can be H or independently unsubstituted  $\text{C}_1\text{-C}_3$ ,

one or more of the methylene groups can optionally be substituted independently by a respective  $R^b$ , wherein each  $R^b$  can be lower alkyl and its identity can be independent of the identity of  $R^a$  and of respective  $R^b$  on other methylene groups in the linker, and

optionally  $R^a$  and a respective  $R^b$  can together form a bridge; and  $R^7$  can be an end group that can be:  $\text{C}_1\text{-C}_8$  alkyl;  $\text{C}_3\text{-C}_8$  cycloalkyl; aryl, heteroaryl,  $\text{C}_3\text{-C}_{10}$  heterocyclic; or a 5-member heteroaryl ring having up to three heteroatoms that can be selected from O, N and S, wherein the heteroaryl ring can optionally bear a substituent  $R^8$ ; and wherein

$R^8$  can be H, an electron withdrawing group, lower hydrocarbon moiety, lower alkoxy, an optionally substituted fused benzo group, or

if  $R^7$  is a triazole, then  $R^8$  can be optionally a six-member heteroaryl ring in which the heteroatoms can be 1 or 2 nitrogen atoms, and  $R^8$  can optionally be substituted at one or more carbon atoms on the ring by an electron withdrawing group, lower hydrocarbon moiety, or lower alkoxy;

$R^9$  can be of the form  $-\text{linker}-R^7$ , wherein

the linker can comprise in any order  $-\text{C}(=\text{O})-$ ,  $-\text{N}(\text{R}^a)-$ ,  $-\text{O}-$ ,  $-\text{S}-$  and up to six methylene groups, wherein

$R^a$  can be H or independently unsubstituted  $\text{C}_1\text{-C}_3$ ,

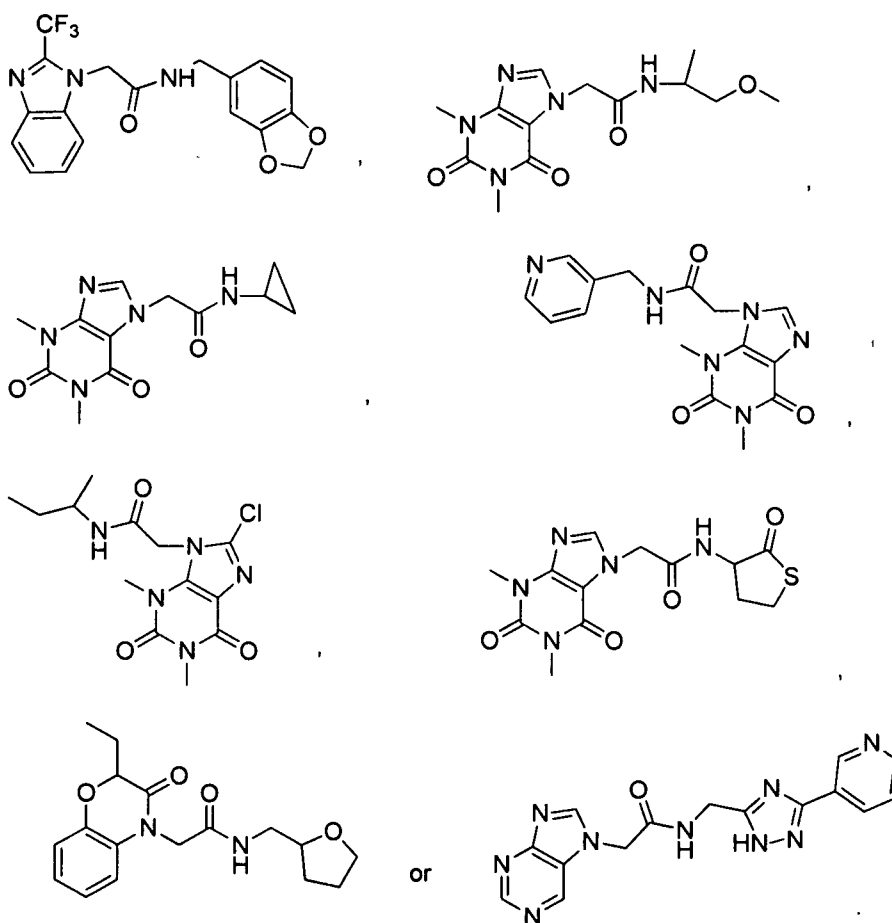
one or more of the methylene groups can optionally be substituted independently by a respective  $R^b$ , wherein each  $R^b$  can be lower alkyl and its identity can be independent of the identity of  $R^a$  and of respective  $R^b$  on other methylene groups in the linker,

optionally  $R^a$  and a respective  $R^b$  can together form a bridge; and

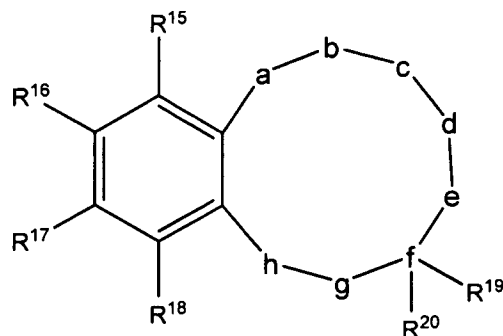
$R^{10}$  can be H or substituted or unsubstituted lower alkyl;

$R^{24}$  can be H or =O; and

with the proviso that structure I or II cannot be:



9. Also disclosed herein is a compound having structure III:



(III)

wherein:

each of R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> and R<sup>18</sup> can independently be H, an electron withdrawing group, lower alkyl, lower alkoxy, OH, or together forms a benzo substituent with a neighboring group from another of R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> and R<sup>18</sup>, except that R<sup>16</sup> is not F when the remainder of the molecule has the formula C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>.

**a** and **b** can be hydrogen atoms bonded to the phenyl ring and **c**, respectively, but not to each other, or together **a** and **b** can form a bond; and **g** and **h** can be hydrogen atoms bonded to the phenyl ring and **f**, respectively, but not to each other, or together **g** and **h** can form a bond; wherein at least one of the pairs **a–b** and **g–h** is a bond;

one of **c** and **d** can be  $\text{--C(=O)--}$  and the other can be  $\text{--N(R}^d\text{)--}$ , wherein  $\text{R}^d$  can be independently H or lower alkyl;

**e can be =CH- or -(CH<sub>2</sub>)<sub>n</sub>-, wherein n can be 1-4; and**

**f** can be a carbon atom, one of R<sup>19</sup> and R<sup>20</sup> can have the form —linker—R<sup>25</sup>, and the other of R<sup>19</sup> and R<sup>20</sup> can be H, an electron withdrawing group, lower alkyl, lower alkoxy, OH, or can be a pi bond to the carbon atom at **e**, wherein:

the linker can comprise in any order  $-C(=O)-$ ,  $-N(R^c)-$ , and up to 10 methylene groups, wherein  $R^c$  can be H or independently lower alkyl and the methylene group can be optionally substituted independently by lower alkyl; and  $R^{25}$  is an end group that can be a lower hydrocarbon moiety.

10. In a third embodiment the invention provides a method of preventing and treating tumors of the nervous system, comprising administering to a subject in need thereof a pharmaceutically effective amount of a composition that inhibits p75<sup>NTR</sup> and prevents the spread of tumors in healthy nervous tissue.

11. In a particular embodiment the invention provides a method of preventing and treating tumors of the nervous system, comprising administering to a subject in need thereof a pharmaceutically effective amount of a composition that inhibits p75<sup>NTR</sup> and prevents the spread of tumors in healthy nervous tissue, wherein the composition comprises a compound or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof having the formula:

**G-H-I**

wherein

12. **G** can be an aryl, heteroaryl, cycloalkyl or heterocyclic residue selected from the group consisting of monocyclic and bicyclic ring systems, wherein **G** can optionally bear one or more substituents selected from electron withdrawing groups, halide, =O, alkyl, alkoxy, lower alkyl, lower alkoxy, and optionally substituted benzo groups;

13. **H** can be a linker having 2 to 12 members in any order of linear sequence, in which  $-C(=O)-$  can be a member,  $-N(R^a)-$  can be a member, and the rest of the members if any can optionally be substituted methylene groups, wherein

$R^a$  can be H or independently unsubstituted lower alkyl;

one or more of the methylene groups if present can be optionally substituted independently by a respective  $R^b$ , wherein each  $R^b$  can be lower alkyl, heteroaryl, or optionally substituted phenyl, and the identity of each  $R^b$  can be independent of the identity of  $R^a$  and of respective  $R^b$  on other methylene groups in the linker; and

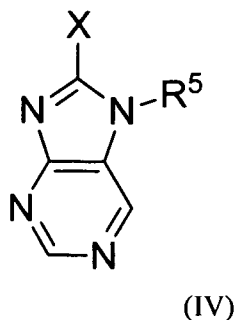
optionally  $R^a$  and a respective  $R^b$  can together form a bridge; and

14. **I** can be an end group that can be: a  $C_1$ - $C_{10}$  hydrocarbon moiety;  $C_3$ - $C_{10}$  aryl,  $C_3$ - $C_{10}$  cycloalkyl,  $C_3$ - $C_9$  heterocyclic; optionally substituted indenyl; optionally substituted phenyl; or a 5- or 6- member heteroaryl ring having up to three heteroatoms selected from O, N and S, wherein the heteroaryl ring can optionally bear a substituent **J**; and wherein

15. **J** can be an electron withdrawing group, lower hydrocarbon moiety, lower alkoxy, optionally substituted phenyl, or can optionally be substituted fused benzo group, or

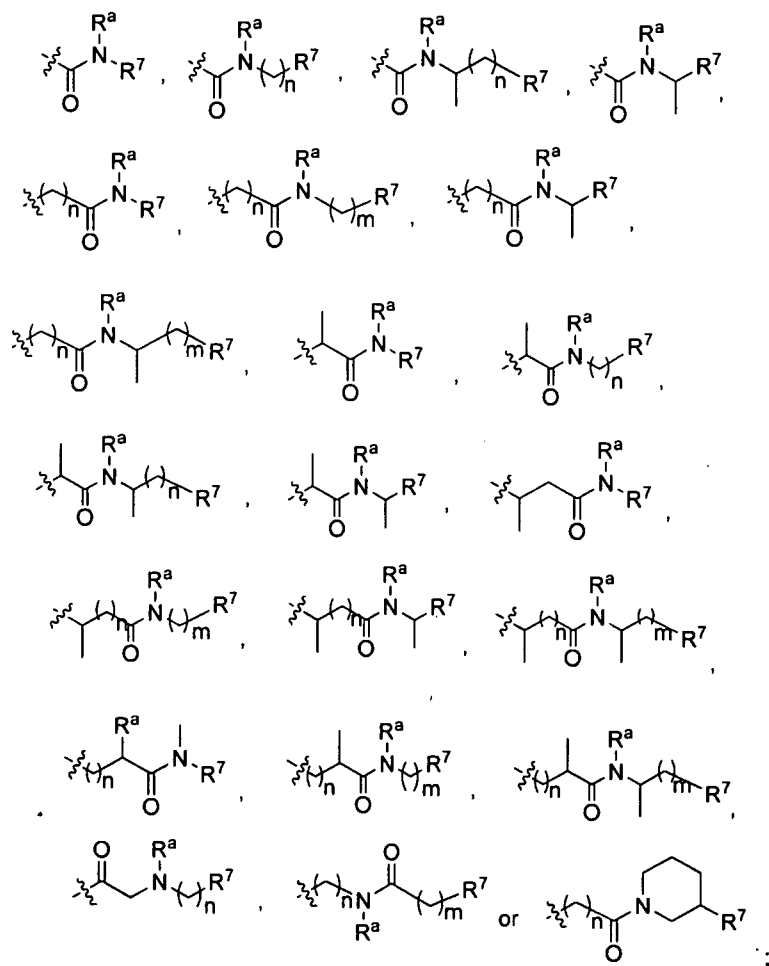
if **I** is a triazole, then **J** can optionally be a six-member heteroaryl ring in which the heteroatoms are 1 or 2 nitrogen atoms, and **J** is optionally substituted at one or more carbon atoms on the ring by an electron withdrawing group, lower hydrocarbon moiety, or lower alkoxy.

16. Also disclosed herein are compound of structure



wherein:

X can be hydrogen, lower alkyl, haloalkyl or an electron withdrawing group;



$R^a$  can be H or independently unsubstituted  $C_1$ - $C_3$ ;

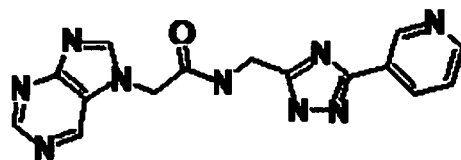
wherein n and m can independently be 1, 2, 3 or 4

$R^7$  can be an end group that can be:  $C_1$ - $C_8$  alkyl;  $C_1$ - $C_6$  alkoxy,  $C_3$ - $C_8$  cycloalkyl; aryl, heteroaryl,  $C_3$ - $C_{10}$  heterocyclic; or a 5-member heteroaryl ring having up to three heteroatoms that are selected from O, N and S, wherein the heteroaryl ring optionally bear a substituent  $R^8$ ; and wherein

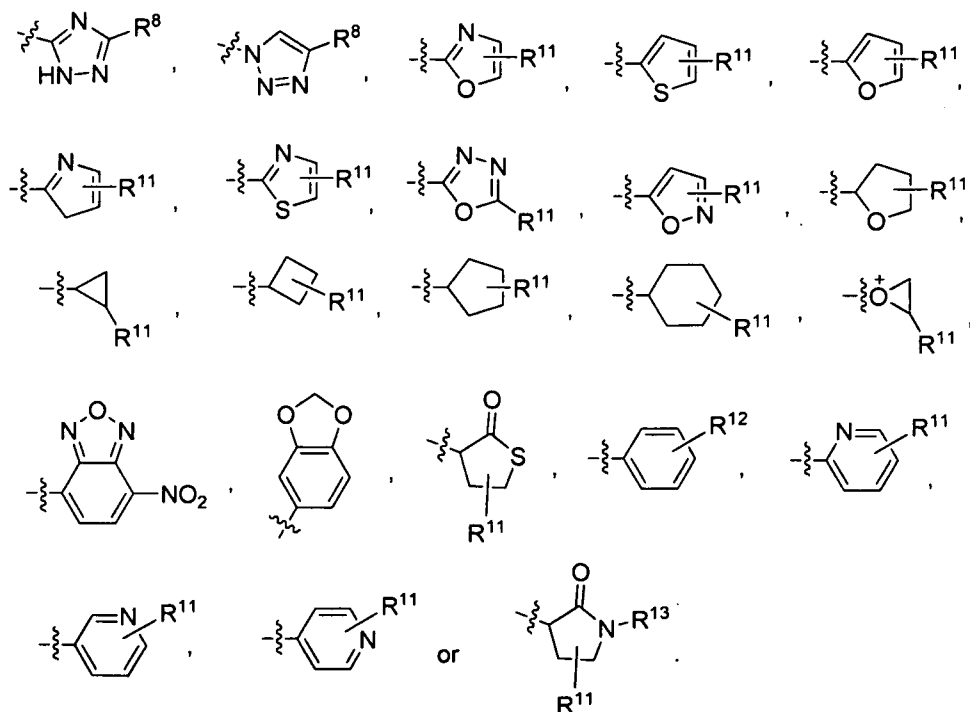
$R^8$  can be H, an electron withdrawing group, lower hydrocarbon moiety, lower alkoxy, an optionally substituted benzo group, substituted fused benzo group, or

if  $R^7$  is a triazole, then  $R^8$  can optionally be a six-member heteroaryl ring in which the heteroatoms is 1 or 2 nitrogen atoms, and  $R^8$  is optionally be substituted at one or more carbon atoms on the ring by an electron withdrawing group, lower hydrocarbon moiety, or lower alkoxy,

with the proviso that structure IV cannot be:

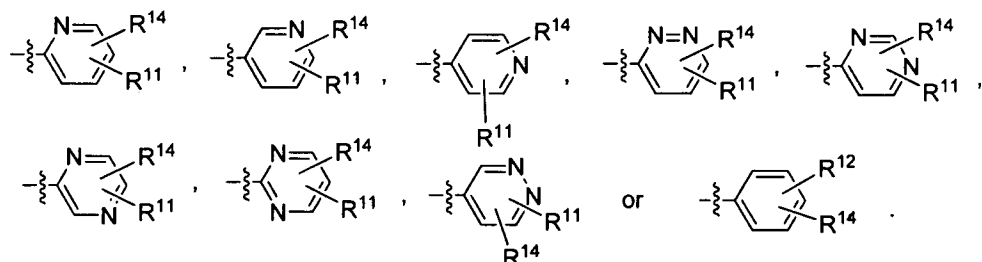


17. In some embodiments  $R^7$  can be  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,

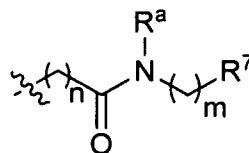


wherein  $R^{11}$  can be H,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halide or hydroxyl;  
 $R^{12}$  can be H,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halide or hydroxyl; and  
 $R^{13}$  can be  $R^8$ .

18. In some embodiments  $R^8$  can be H,  $C_1$ - $C_3$  alkyl,  $C_1$ - $C_3$  alkoxy, halide, hydroxyl,



wherein  $R^{12}$  can be H,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halide or hydroxyl; and  
 $R^{14}$  can be H,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halide or hydroxyl.



19. In some embodiments  $R^5$  can be

## VI. BRIEF DESCRIPTION OF FIGURES

20. Figure 1 shows the structure based assay of inhibitors of  $p75^{NTR}$ /NGF interactions.

21. Figure 2A and 2 B shows a NGF displacement assay for  $p75^{NTR}$ . The assay was performed using the extracellular domain of glycosylated  $p75^{NTR}$ . 96-well plates were incubated in humidity chamber with  $p75^{NTR}$ /Fc protein (R & D Systems) overnight at  $4^\circ\text{C}$  in binding buffer followed by incubation in humidity chamber with blocking buffer for 1 h at room temperature. NGF and different concentrations of compounds A-G were added to wells and incubated for 6 h with shaking at room temperature. Plates were then washed with TBST and incubated in humidity chamber with antibody against NGF overnight at  $4^\circ\text{C}$ . After five washes with TBST, wells were incubated for 2.5 h at room temperature with anti-rabbit IgG horseradish peroxidase (HRP). Following incubation with a substrate at room temperature, optical density was measured at 450 nm and  $IC_{50}$  values were calculated by using the Graphpad.

22. Figure 3 shows a competition assay for  $p75^{NTR}$ . NGF and BDNF binding competition to  $p75^{NTR}$  was performed using the extracellular domain of glycosylated

p75<sup>NTR</sup>. The assay condition is similar to the protocol described above except adding NGF and BDNF together in reactions.

23. Figure 4 shows the effects of compound A on cell growth. Human glioma cells were seeded in 96-well tissue culture plates. At 24 hours after seeding, a solution of the compound or DMSO vehicle control were added to each well (three replicates per concentration), and incubated for 48 hours at 37 °C. Growth inhibition was determined using CellTiter 96<sup>®</sup> AQueous One Solution Cell Proliferation according to manufacturer's instructions (Promega, Inc. Madison, WI), and the absorbance measured at 490 nm on a microplate reader. The 50% growth inhibition (GI<sub>50</sub>) was calculated by using the Graphpad as the compound concentration required reducing cell number by 50% compared with control.

24. Figure 5 shows the results from a tube formation assay on Human Brain Microvascular Endothelial Cells (HBMEC). 5A shows the control of tube formation using DMSO. 5B shows the tube formation after exposure to compound A at 5 µM. 5C shows the total tube length of the control, compound A at 1 µM, compound A at 5 µM and compound A at 10 µM. 5D shows the total number of tubes of the control, compound A at 1 µM, compound A at 5 µM and compound A at 10 µM.

25. Figure 6 shows the results from a tube formation assay on Human Umbilical Vein Epithelial Cells (HUVEC). 6A shows the tube formation of the control. 6B shows the tube formation of after exposure of compound A at 10 µM. 6C shows the polyhedral chambers formed. 6D shows capillary networks formed.

26. Figure 7 shows the results from an *in vitro* rat aortical assay. 7A shows the aorta of a 2 month old rat. 7B shows the aorta of a 2 month old rat after exposure to 10 µM of compound A for 5 days. 7C shows the control of the capillary network formation. 7D shows the capillary network formation of after exposure to 10 µM of compound A for 5 days

27. Figure 8 shows the results from the toxicity study for compounds A-D, E, H and I.

## VII. DETAILED DESCRIPTION OF THE INVENTION

### A. Therapeutic Paradigm

28. As part of the course of invention it is inferred that eliminating the migratory streaming effect will render the GBM surgically treatable. Moreover it is inferred that enabling penetration of the blood brain barrier that serves as a safe harbor for

these malignant cells will render medicinal treatments more efficacious. For instance, cells within the tumor mass, as opposed to invasive cells, have abnormal vascularity with no blood brain barrier, rendering them more susceptible to intravenous treatments, such as chemotherapy.

29. The etiology of brain invasion by GBM cells has been reported by Johnson and Forsythe (2007), who used serial *in vivo* cell selection to identify genotypes important in the development of invasive behavior. It has also been demonstrated that GBMs express p75 Neurotrophic Receptor (p75<sup>NTR</sup>), which is only minimally expressed in low grade astrocytomas. This p75<sup>NTR</sup> is a multi-functional receptor with important roles in neurotrophin signaling, axon outgrowth, and is an important in signaling survival of oligodendroglia and neurons. It is transcriptionally regulated with spatial and temporal precision during nervous system development, injury and regeneration. Very little is known about how p75<sup>NTR</sup> expression is dynamically regulated; p75<sup>NTR</sup> gene expression is directly modulated by the early growth response (Egr) transcriptional activators, Egr1 and Egr3, which bind and transactivate the p75<sup>NTR</sup> promoter *in vitro* and *in vivo*.

30. The low affinity nerve growth factor receptor p75<sup>NTR</sup> belongs to the tumor necrosis factor receptor super-family and has been implicated in induction of apoptosis in various tissues and cell lines. p75<sup>NTR</sup> is a 75-kDa glycoprotein that binds nerve growth factor and has structural and sequential similarity to the tumor necrosis factor receptor (Chao et al., 1986, Radeke et al., 1987). This similarity indicates a role in apoptosis which was demonstrated in neuronal cells (Lee et al., 1994, Frade et al., 1996). Normal prostate and prostatic intraepithelial neoplastic tissue exhibit staining of p75<sup>NTR</sup> in all epithelial cells, while in neoplastic prostate the epithelial cells exhibit a partial loss of p75<sup>NTR</sup> expression (Perez et al., 1997). Western blot analysis of the four naturally occurring human prostate tumor cell lines TSU-pr1, DU-145, PC-3, and LNCaP, derived from metastases, shows that there is a complete loss of p75<sup>NTR</sup> protein expression (Pflug et al., 1992), as later confirmed by Scatchard plot analysis (Pflug et al., 1995). Subsequent transfection and re-expression of the p75<sup>NTR</sup> protein in prostate tumor cells showed a role in the induction of apoptosis (Pflug and Djakiew, 1998). Hence, loss of p75<sup>NTR</sup> expression in prostate tumor cells was proposed as a mechanism by which tumor cells circumvented apoptotic inhibition of tumor cell

growth (Pflug and Djakiew, 1998). However, it is not known whether this loss of expression is due to deletion of part or the entire p75<sup>NTR</sup> gene, or to other factor(s).

31. Loss of expression of p75<sup>NTR</sup> protein is correlated with increased Gleason's score of organ confined pathological prostate tissues (Perez, M., et al. (1997) Prostate 30,274-279), and is completely absent from four prostate epithelial tumor cell lines derived from metastases (Pflug, B. R. et al. (1992) Canc. Res. 52, 5403-5406), indicating an inverse association of p75<sup>NTR</sup> expression with the malignant progression of the prostate. The significance of a loss of expression of p75<sup>NTR</sup> protein during malignant transformation of prostate epithelial cells may be related to observations that this receptor appears to function in the induction of apoptosis (Barrett, G. et al. (1994) Proc. Natl. Acad. Sci USA 91, 6501- 6505; Rabizadeh, S., et al., (1993) Science 261,345-34815). Re-expression of p75<sup>NTR</sup> by stable and transient transfection showed that the p75<sup>NTR</sup> inhibits growth of prostate tumor cells in vitro, at least in part, by induction of apoptosis (Pflug, B. et al., (1998) Mol. Carcinogenesis 23, 106-114). Hence, loss of p75<sup>NTR</sup> expression appears to eliminate a potential apoptotic pathway in prostate cancer cells, thereby facilitating the immortalization of these epithelia during malignant transformation (Perez, M. et al., (1997) Prostate 30,274-279).

32. Considering the characterization of a prostate tumor suppressor gene locus in the vicinity of the p75<sup>NTR</sup> gene, the inverse association of p75<sup>NTR</sup> expression with the malignant progression of the pathologic prostate, and transfection studies showing that p75<sup>NTR</sup> can induce apoptosis in vitro, it was formally investigated whether the p75<sup>NTR</sup> is a new tumor suppressor in the human prostate (Perez, M. et al., (1997) Prostate 30,274-279).

33. Thus, control of p75<sup>NTR</sup> expression is a critical element behind novel therapeutics for nervous system injury and for brain cancer. In its effect p75<sup>NTR</sup> is a divaricate "switch" trans-membrane glycoprotein in neurons, oligodendrocytes and cancer cells; the same molecule can switch on programmed cell death, or conversely promote cell survival. p75<sup>NTR</sup> has also been shown to be essential for malignant invasion of tumor cells into the CNS. Malignant stem cells are known to populate malignant Glioblastoma multiforme tumors, as well as other malignant tumors of the central nervous system (CNS). Malignant stem cells express p75<sup>NTR</sup>, an essential component to migration of the cell into normal brain and other body tissues.

34. Methods and compounds described herein encompass the methodology to employ an agonist/ antagonist to the specific ligand (pro-NGF, NGF or BDNF) receptor, in a manner to alter the receptor molecular conformation, and thereby through consequent intra-cytoplasmic bio-molecular changes to inhibit the cell migratory transformation. The methods and compounds described herein also provides the pharmacological characteristics of compounds that can bind to the p75 receptor for nerve growth factor, thereby eliminating or substantially reducing the ability of the malignant stem cell to migrate into normal tissue. While the primary goal is treatment of Glioblastoma multiforme, alternative embodiments are anticipated for other malignant tumors of the central nervous system.

#### 1. p75<sup>NTR</sup>

35. p75 Neurotrophic Receptor (p75<sup>NTR</sup>), is a trans-membrane glycoprotein member of the tumor necrosis factor super-family, serving as a divaricate switch to either initiate apoptosis constitutively through the intracellular “death domain”, or conversely, through binding of nerve growth factor( NGF) to promote cell survival, growth and development. P75<sup>NTR</sup> binds brain derived neurotrophin factor (BDNF), neurotrophins 3,4,5, as well as proforms of NGF(proNGF). Though binding to all neurotrophins with equal affinity in most cells, p75<sup>NTR</sup> binds to the proform of NGF with a higher affinity than the mature form.

36. Low affinity neurotrophin receptor p75<sup>NTR</sup> mediates glioma invasion in experimental models of glioma (*in vitro* and *in vivo*). It is expressed in both highly invasive glioma cells and in brain tumor stem cells (BTSCs). Cleavage by a gamma secretase is required for glioma invasion. The use of a gamma secretase inhibitor reduces invasion by established glioma lines and brain tumor stem cells that express p75<sup>NTR</sup>.

37. Inhibitors of p75<sup>NTR</sup> (modulators or gamma secretase inhibitors) significantly inhibit glioma invasion and brain tumor stem cells that express p75<sup>NTR</sup>. The combination of a gamma secretase with an anti-angiogenic produce synergistic efficacy (by inhibiting angiogenesis and invasion) without increasing toxicities.

38. The human p75<sup>NTR</sup> gene locus has been mapped closely distal to 17q21 (Huebner, K et al., (1986) Proc. Natl. Acad. Sci. USA 83, 1403-1407). p75<sup>NTR</sup> is a 75 kDa glycoprotein receptor that binds the neurotrophin family of growth factors, including nerve growth factor, brain- derived neurotrophic factor, neurotrophin-3 and

neurotrophin-4/5. Expression of the p75<sup>NTR</sup> protein as studied by immunoblot techniques (Pflug, B. R. et al. (1992) *Canc. Res.* 52, 5403-5406), immunofluorescence (Graham, C., et al. (1992) *J. Urol.* 147, 1444-1447), immunohistochemistry (Pflug, B. et al., (1995) *Endocrinology* 136, 262-268).

39. p75<sup>NTR</sup> is necessary for malignant progression of melanoma and other tumors invading the brain (Walch, 1999), for the migration of other neural crest cells, such as Schwann cells (Anton, 1994), and, in the presence of NGF, for promotion of migration of melanoma cells (Shonukun, 2003). Furthermore, this effect is independent of the neurotrophic receptor tyrosine kinase (trk B) (Marchetti, 1998).

40. *In vitro* tumor models utilize well known cell lines of specific tumor types. Two such malignant Glioblastoma multiforme cell lines commonly used in research are U87, and U251. Johnson et al (2007) stably transfected human glioma cells (U87) with human cDNA of p75<sup>NTR</sup> into immuno-compromised rat brains, and demonstrated that the tumors developed highly invasive edges, which expressed p75<sup>NTR</sup>, while the controls (U87 tumor cells which contained no P75) showed no evidence of invasion and migration; the same effect was demonstrated in other more invasive glioma cell types, such as U251. Forsythe's group also showed that p75<sup>NTR</sup> mutants, which are unable to bind NGF, produce well circumscribed tumors without invasive edges, thus demonstrating that mature neurotrophins are necessary for the formation of the invasive tumor phenotype. P75<sup>NTR</sup> and NGF are thus essential for the malignant invasion of GBM cells.

41. Activation of p75<sup>NTR</sup> with NGF or pro-NGF also causes migration of melanoma cells and increased expression of p75<sup>NTR</sup> correlated with advanced stages and invasive potential of melanoma brain metastasis. The malignant invasiveness is thought to arise from the interaction of p75<sup>NTR</sup> interacts with the actin cytoskeleton; the small GTP-ase RhoA is a downstream effector of p75<sup>NTR</sup>. The capability of p75<sup>NTR</sup> to modulate the activity of RhoA provides a reasonable explanation as to how p75<sup>NTR</sup> regulation might result in changes in cellular architecture of glioma cells.

42. As surgeons have been able to resect the visible tumor mass, the ability to block the interaction between p75<sup>NTR</sup> and NGF, Pro-NGF or BDNF and prevent invasion of GBM cells into normal brain, that is to stop the malignant sequestration of GBM cells, would for the first time impose tractability upon the GBM. Drugs herein were discovered to co-opt the important effects of p75<sup>NTR</sup>. A protein model of

p75<sup>NTR</sup>/NGF was developed to screen a virtual library of 108 million compounds for protein/protein inhibitors. Lead compounds blocking the binding site of mature NGF to p75<sup>NTR</sup> were selected for further investigation and modification.

43. p75 Neurotrophic Receptor (p75<sup>NTR</sup>) is a divaricate “switch” membranous glycoprotein in neurons, oligodendrocytes and cancer cells; the same molecule can switch on programmed cell death, or conversely promote cell survival. It is believed that spinal cord injury from improvised explosive devices, mortars, and similar devices can be mitigated through down-regulation of the protein. CNS tumors are the second most frequent cancer to involve young men and women. P75<sup>NTR</sup> has also been shown to be essential for malignant invasion of tumor cells into the CNS. Current investigations of the glycoprotein p75<sup>NTR</sup> are designed to demonstrate the pathway by which p75<sup>NTR</sup> is switched on and off, and to develop drugs which specifically up-regulate, and contrarily, which down-regulate expression of p75<sup>NTR</sup> in the context of cancer and traumatic CNS injury. The programmatic study of cancer cells as well as cells of the central nervous system has greatly enhanced our insight into the mechanisms of p75<sup>NTR</sup>. Improved understanding of the regulation of p75<sup>NTR</sup> has developed into potential drug therapies for both CNS trauma and cancer.

## **2. Angiogenesis**

44. Angiogenesis is defined as the development of a blood supply to a given area of tissue. The development of a blood supply may be part of normal embryonic development, represent the revascularization of a wound bed, or involve the stimulation of vessel growth by inflammatory or malignant cells. Sometimes angiogenesis is defined as the proliferation of new capillaries from pre-existing blood vessels. New growth of soft tissue requires new vascularization, and the concept of angiogenesis is a key component of tissue growth and in particular, a key point of intervention in pathological tissue growth.

45. Angiogenesis is a fundamental process necessary for embryonic development, subsequent growth, and tissue repair. Angiogenesis is a prerequisite for the development and differentiation of the vascular tree, as well as for a wide variety of fundamental physiological processes including embryogenesis, somatic growth, tissue and organ repair and regeneration, cyclical growth of the corpus luteum and endometrium, and development and differentiation of the nervous system. In the female reproductive system, angiogenesis occurs in the follicle during its

development, in the corpus luteum following ovulation and in the placenta to establish and maintain pregnancy. Angiogenesis additionally occurs as part of the body's repair processes, e.g., in the healing of wounds and fractures.

46. Both controlled and uncontrolled angiogenesis are thought to proceed in a similar manner. Endothelial cells and pericytes, surrounded by a basement membrane, form capillary blood vessels. Angiogenesis begins with the erosion of the basement membrane by enzymes released by endothelial cells and leukocytes. The endothelial cells, which line the lumen of blood vessels, then protrude through the basement membrane. Angiogenic stimulants induce the endothelial cells to migrate through the eroded basement membrane. The migrating cells form a "sprout" off the parent blood vessel, where the endothelial cells undergo mitosis and proliferate. The endothelial sprouts merge with each other to form capillary loops, creating new blood vessels. Creation of the new microvascular system can initiate or exacerbate disease conditions.

47. Medical science has recognized that angiogenesis is an important factor in the initiation and/or proliferation of a large number of diverse disease conditions. Under normal physiological conditions, humans and other animals only undergo angiogenesis in very specific, restricted situations. For example, angiogenesis is normally observed in wound healing, fetal and embryonic development, and in the formation of the corpus luteum, endometrium and placenta. The process of angiogenesis has been found to be altered in a number of disease states, and in many instances, the pathological damage associated with the disease is related to uncontrolled angiogenesis. Since it was first put forward over thirty years ago, the hypothesis that angiogenesis is required for tumor growth and metastasis has gained extensive experimental support (Folkman, J. (1971) *N. Engl. J. Med.* 285, 1182-1186, Hanahan, D. & Folkman, J. (1996) *Cell* 86, 353-364). For example, angiogenesis is a factor in tumor growth, since a tumor must continuously stimulate growth of new capillary blood vessels in order to grow. Angiogenesis is an essential part of the growth of human solid cancer, and abnormal angiogenesis is associated with other diseases such as rheumatoid arthritis, psoriasis, and diabetic retinopathy (Folkman, J. and Klagsbrun, M., *Science* 235:442-447, (1987)). In addition to tumor growth and metastasis, angiogenesis has also been implicated in rheumatoid arthritis, diabetic retinopathy and macular degeneration, indicating that inhibition of angiogenesis

useful for the treatment of these disorders (Carmeliet, P. (2003) Nat. Med. 9, 653-660). Angiogenesis, the formation of new blood vessels, has been implicated in the pathogenesis of several important human diseases, including cancer, diabetic retinopathy, and age-related macular degeneration. Inhibition of angiogenesis is emerging as an effective new strategy for the treatment of angiogenesis-dependent diseases.

### **3. Glioblastoma multiforme (GBM)**

48. As noted above, GBM has completely resisted therapeutic progress for thirty years. The invention employed a new paradigm that appears to be generally applicable to many types of tumors, by focusing on interrupting the cancer's mechanism for invading healthy tissue. The invention developed assays to define specificity, affinity and quantification of binding of the putative tumor receptor blocking agent. And it envisioned applying the blocking agent as a drug to prevent p75<sup>NTR</sup>-induced apoptosis after spinal cord injury, thereby significantly improving outcomes and offering hope to spinal cord injury victims.

### **4. p75<sup>NTR</sup> Inhibitors and Modulators and Angiogenesis Inhibitors and Modulators**

49. The effective inhibitors discovered according to the invention were found to have structural commonalities, and to achieve their effect with surprisingly simple molecular architectures. The discovered inhibitors are for the most part novel structures. Specifically, the inhibitors share a form **G-H-I**, in which **G** is a small heteroaryl or heterocyclic component such as a purine, xanthine derivative, indole, benzopiperidinone, or comparable structure.

50. Monocyclic systems with various heteroatoms in the ring were effective for **G**, but nitrogen-containing bicyclic heteroaryl and bicyclic heterocyclic structures proved to be particularly useful, including some substituted with a benzo group or other bridged substituent to form a tricyclic structure. Without being bound by theory, it appears that planar ring systems of a particular size range, having electron-rich centers (e.g., N atoms or other sources of electron density) and having electron withdrawing groups as ring substituents, are particularly effective. Non-exclusive, illustrative electron rich centers include ring heteroatoms, benzo rings, and the like. Non-exclusive, illustrative, simple electron withdrawing groups include halides, the oxygen of carbonyl groups, and the like.

51. **H** is a linker having typically 1 to 10 members. Non-exclusive illustrative linkers comprised optionally substituted methylene backbone groups, a carbonyl backbone group, and or an amine backbone group. Linkers containing an amide were particularly useful, but linkers having other configurations were also effective. In some cases the effective linkers featured an amide that formed a heterocycle between the nitrogen and another portion of the linker. It appears that the biological function of **H** is largely as a spacer, thus its exact composition may not be critical, though the invention is not limited to applications in which it serves only as a spacer.

52. **I** is a relatively small end group that that is planar or capable of adopting a largely coplanar conformation. Examples of **I** in the invention include a lower hydrocarbon moiety such as sec-butyl, as well as aryl and heteroaryl rings. **G-H-I** is particularly effective when **I** comprises a heteroaryl ring such as a triazole that is further substituted by a pyridyl or pyrimidyl radical, optionally substituted.

53. The compounds of the invention resemble cellular compounds that mediate electron transfer in metabolic pathways. The substituted purines of the invention are reminiscent of the cellular redox reagent NADH. And the benzopiperidinone structures evoke riboflavin, which is a component of the cellular redox coenzyme flavin adenine dinucleotide (FAD); the tricyclic naphthopiperidinones are even more reminiscent of riboflavin and have proved to be particularly useful. The alkyl xanthines of the invention are close chemical cousins of the purines, and also have structural commonalities with the benzopiperidinones. Various xanthines are antagonists of adenosine receptors, and in the brain adenosine acts to suppress neural activity. However the invention is not limited to any particular mechanism for the therapeutic effect of the invention compounds.

## **B. Definitions**

54. Various embodiments of the disclosure will be described in detail with reference to drawings, if any. Reference to various embodiments does not limit the scope of the disclosure, which is limited only by the scope of the claims attached hereto. Additionally, any examples set forth in this specification are not intended to be limiting and merely set forth some of the many possible embodiments for the claimed invention.

**1. A**

55. As used in the specification and the appended claims, the singular forms "a," "an" and "the" or like terms include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.

**2. Abbreviations**

56. Abbreviations, which are well known to one of ordinary skill in the art, may be used (e.g., "h" or "hr" for hour or hours, "g" or "gm" for gram(s), "mL" for milliliters, and "rt" for room temperature, "nm" for nanometers, "M" for molar, and like abbreviations).

**3. About**

57. About modifying, for example, the quantity of an ingredient in a composition, concentrations, volumes, process temperature, process time, yields, flow rates, pressures, and like values, and ranges thereof, employed in describing the embodiments of the disclosure, refers to variation in the numerical quantity that can occur, for example, through typical measuring and handling procedures used for making compounds, compositions, concentrates or use formulations; through inadvertent error in these procedures; through differences in the manufacture, source, or purity of starting materials or ingredients used to carry out the methods; and like considerations. The term "about" also encompasses amounts that differ due to aging of a composition or formulation with a particular initial concentration or mixture, and amounts that differ due to mixing or processing a composition or formulation with a particular initial concentration or mixture. Whether modified by the term "about" the claims appended hereto include equivalents to these quantities.

**4. Cell**

58. The term "cell" or like terms refer to a small usually microscopic mass of protoplasm bounded externally by a semipermeable membrane, optionally including one or more nuclei and various other organelles, capable alone or interacting with other like masses of performing all the fundamental functions of life, and forming the smallest structural unit of living matter capable of functioning independently including synthetic cell constructs, cell model systems, and like artificial cellular systems.

59. A cell can include different cell types, such as a cell associated with a specific disease, a type of cell from a specific origin, a type of cell associated with a spe-

cific target, or a type of cell associated with a specific physiological function. A cell can also be a native cell, an engineered cell, a transformed cell, an immortalized cell, a primary cell, an embryonic stem cell, an adult stem cell, a cancer stem cell, or a stem cell derived cell.

60. Human consists of about 210 known distinct cell types. The numbers of types of cells can almost unlimited, considering how the cells are prepared (e.g., engineered, transformed, immortalized, or freshly isolated from a human body) and where the cells are obtained (e.g., human bodies of different ages or different disease stages, etc).

#### **5. Consisting essentially of**

61. "Consisting essentially of" in embodiments refers, for example, to a surface composition, a method of making or using a surface composition, formulation, or composition on the surface of the biosensor, and articles, devices, or apparatus of the disclosure, and can include the components or steps listed in the claim, plus other components or steps that do not materially affect the basic and novel properties of the compositions, articles, apparatus, and methods of making and use of the disclosure, such as particular reactants, particular additives or ingredients, a particular agents, a particular cell or cell line, a particular surface modifier or condition, a particular ligand candidate, or like structure, material, or process variable selected. Items that may materially affect the basic properties of the components or steps of the disclosure or may impart undesirable characteristics to the present disclosure include, for example, decreased affinity of the cell for the biosensor surface, aberrant affinity of a stimulus for a cell surface receptor or for an intracellular receptor, anomalous or contrary cell activity in response to a ligand candidate or like stimulus, and like characteristics.

#### **6. Components**

62. Disclosed are the components to be used to prepare the disclosed compositions as well as the compositions themselves to be used within the methods disclosed herein. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each various individual and collective combinations and permutation of these molecules may not be explicitly disclosed, each is specifically contemplated and described herein. Thus, if a class of molecules A, B, and C are disclosed as well as a class of molecules D, E, and F and an example of a combination

molecule, A-D is disclosed, then even if each is not individually recited each is individually and collectively contemplated meaning combinations, A-E, A-F, B-D, B-E, B-F, C-D, C-E, and C-F are considered disclosed. Likewise, any subset or combination of these is also disclosed. Thus, for example, the sub-group of A-E, B-F, and C-E would be considered disclosed. This concept applies to all aspects of this application including, but not limited to, steps in methods of making and using the disclosed compositions. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the disclosed methods.

#### **7. Contacting**

63. Contacting or like terms means bringing into proximity such that a molecular interaction can take place, if a molecular interaction is possible between at least two things, such as molecules, cells, markers, at least a compound or composition, or at least two compositions, or any of these with an article(s) or with a machine. For example, contacting refers to bringing at least two compositions, molecules, articles, or things into contact, i.e. such that they are in proximity to mix or touch. For example, having a solution of composition A and cultured cell B and pouring solution of composition A over cultured cell B would be bringing solution of composition A in contact with cell culture B. Contacting a cell with a molecule would be bringing a molecule to the cell to ensure the cell have access to the molecule.

64. It is understood that anything disclosed herein can be brought into contact with anything else. For example, a cell can be brought into contact with a marker or a molecule, a biosensor, and so forth.

#### **8. Compounds and compositions**

65. Compounds and compositions have their standard meaning in the art. It is understood that wherever, a particular designation, such as a molecule, substance, cell, or reagent compositions comprising, consisting of, and consisting essentially of these designations are disclosed. Where appropriate wherever a particular designation is made, it is understood that the compound of that designation is also disclosed.

#### **9. Control**

66. The terms control or "control levels" or "control cells" or like terms are defined as the standard by which a change is measured, for example, the controls are not

subjected to the experiment, but are instead subjected to a defined set of parameters, or the controls are based on pre- or post-treatment levels. They can either be run in parallel with or before or after a test run, or they can be a pre-determined standard. For example, a control can refer to the results from an experiment in which the subjects or objects or reagents etc are treated as in a parallel experiment except for omission of the procedure or agent or variable etc under test and which is used as a standard of comparison in judging experimental effects. Thus, the control can be used to determine the effects related to the procedure or agent or variable etc. For example, if the effect of a test molecule on a cell was in question, one could a) simply record the characteristics of the cell in the presence of the molecule, b) perform a and then also record the effects of adding a control molecule with a known activity or lack of activity, or a control composition (e.g., the assay buffer solution (the vehicle)) and then compare effects of the test molecule to the control. In certain circumstances once a control is performed the control can be used as a standard, in which the control experiment does not have to be performed again and in other circumstances the control experiment should be run in parallel each time a comparison will be made.

## **10. Chemical terms**

### **i. Aryl**

67. The term “aryl” as used herein is a ring radical containing 6 to 18 carbons, or preferably 6 to 12 carbons, comprising at least one aromatic residue therein. Examples of such aryl radicals include phenyl, naphthyl, and ischroman radicals. Moreover, the term “aryl” as used throughout the specification and claims is intended to include both “unsubstituted alkyls” and “substituted alkyls”, the later denotes an aryl ring radical as defined above that is substituted with one or more, preferably 1, 2, or 3 organic or inorganic substituent groups, which include but are not limited to a halogen, alkyl, alkenyl, alkynyl, hydroxyl, cycloalkyl, amino, mono-substituted amino, di-substituted amino, unsubstituted or substituted amido, carbonyl, halogen, sulfhydryl, sulfonyl, sulfonato, sulfamoyl, sulfonamide, azido acyloxy, nitro, cyano, carboxy, carboalkoxy, alkylcarboxamido, substituted alkylcarboxamido, dialkylcarboxamido, substituted dialkylcarboxamido, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy or haloalkoxy, aryl, substituted aryl, heteroaryl, heterocyclic ring, ring wherein the terms are defined herein. The organic substituent groups can comprise from 1 to 12 carbon atoms, or from 1 to 6 carbon atoms, or from 1 to 4 car-

bon atoms. An aryl moiety with 1, 2, or 3 alkyl substituent groups can be referred to as “arylalkyl.” It will be understood by those skilled in the art that the moieties substituted on the “aryl” can themselves be substituted, as described above, if appropriate.

#### **ii. Heteroatom**

68. The term “heteroatom” as used herein refers to an atom of an element other than carbon or hydrogen.

#### **iii. Heteroaryl.**

69. The term “heteroaryl” as used herein is an aryl ring radical as defined above, wherein at least one of the ring carbons, or preferably 1, 2, or 3 carbons of the aryl aromatic ring has been replaced with a heteroatom, which include but are not limited to nitrogen, oxygen, and sulfur atoms. Examples of heteroaryl residues include pyridyl, bipyridyl, furanyl, and thiofuranyl residues. Substituted “heteroaryl” residues can have one or more organic or inorganic substituent groups, or preferably 1, 2, or 3 such groups per ring, as referred to herein-above for aryl groups, bound to the carbon atoms of the heteroaromatic rings. The organic substituent groups can comprise from 1 to 12 carbon atoms, or from 1 to 6 carbon atoms, or from 1 to 4 carbon atoms.

#### **iv. Heterocyclyl**

70. The term “heterocyclyl” or “heterocyclic group” as used herein is a non-aromatic mono- or multi ring radical structure having 3 to 16 members, preferably 4 to 10 members, in which at least one ring structure include 1 to 4 heteroatoms (e.g. O, N, S, P, and the like). Heterocyclyl groups include, for example, pyrrolidine, benzodioxoles, oxolane, thiolane, imidazole, oxazole, piperidine, piperazine, morpholine, lactones, such as thiobutyrolactones, lactams, such as azetidiones, and pyrrolidiones, sultams, sultones, and the like. Moreover, the term “heterocyclyl” as used throughout the specification and claims is intended to include both unsubstituted heterocyclyls and substituted heterocyclyls; the latter denotes a ring radical as defined above that is substituted with one or more, preferably 1, 2, or 3 organic or inorganic substituent groups, which include but are not limited to a halogen, alkyl, alkenyl, alkynyl, hydroxyl, cycloalkyl, amino, mono-substituted amino, di-substituted amino, unsubstituted or substituted amido, carbonyl, halogen, sulfhydryl, sulfonyl, sulfonato, sulfamoyl, sulfonamide, azido acyloxy, nitro, cyano, carboxy, carboalkoxy, alkylcarboxamido, substituted alkylcarboxamido, dialkylcarboxamido, substituted dialkylcarboxamido, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy

or haloalkoxy, aryl, substituted aryl, heteroaryl, heterocyclic ring, ring wherein the terms are defined herein. The organic substituent groups can comprise from 1 to 12 carbon atoms, or from 1 to 6 carbon atoms, or from 1 to 4 carbon atoms. It will be understood by those skilled in the art that the moieties substituted on the "heterocyclyl" can themselves be substituted, as described above, if appropriate.

**v. Carbocyclic**

71. The term "carbocyclic" as used herein refers to a cyclic moiety in which all members forming the ring are carbon atoms.

**vi. Alkyl**

72. The term "alkyl" as used herein refers to a branched or unbranched saturated hydrocarbon moiety, which may optionally be cyclical or contain a cyclical portion. Alkyls comprise a saturated hydrocarbon moiety having from 1 to 24 carbons, 1 to 20 carbons, 1 to 15 carbons, 1 to 12 carbons, 1 to 8 carbons, 1 to 6 carbons, 1 to 4 carbon atoms, or 1 to 3 carbon atoms. It is understood that the term "alkyl" also encompasses linear, branched or cyclic hydrocarbon moieties having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 carbon atoms. Examples of such alkyl radicals include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, *n*-propyl, *iso*-propyl, cyclopropyl, butyl, *n*-butyl, *sec*-butyl, *t*-butyl, cyclobutyl, amyl, *t*-amyl, *n*-pentyl, cyclopentyl, and the like. Lower alkyls comprise a noncyclic, saturated, straight or branched chain hydrocarbon residue having from 1 to 4 carbon atoms, i.e., C<sub>1</sub>-C<sub>4</sub> alkyl.

73. Moreover, the term "alkyl" as used throughout the specification and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls"; the latter denotes an alkyl radical analogous to the above definition, that is further substituted with one, two, or more additional organic or inorganic substituent groups. Suitable substituent groups include but are not limited to H, alkyl, alkenyl, alkynyl, hydroxyl, cycloalkyl, heterocyclyl, amino, mono-substituted amino, di-substituted amino, unsubstituted or substituted amido, carbonyl, halogen, sulfhydryl, sulfonyl, sulfonato, sulfamoyl, sulfonamide, azido, acyloxy, nitro, cyano, carboxy, carboalkoxy, alkylcarboxamido, substituted alkylcarboxamido, dialkylcarboxamido, substituted dialkylcarboxamido, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy, haloalkoxy, heteroaryl, substituted heteroaryl, aryl or substituted aryl. It will be understood by those skilled in the art that an "alkoxy" can be a substituent of a

carbonyl substituted “alkyl” forming an ester. When more than one substituent group is present then they can be the same or different. The organic substituent moieties can comprise from 1 to 12 carbon atoms, or from 1 to 6 carbon atoms, or from 1 to 4 carbon atoms. It will be understood by those skilled in the art that the moieties substituted on the “alkyl” chain can themselves be substituted, as described above, if appropriate.

**vii. Alkenyl**

74. The term “alkenyl” as used herein is an alkyl residue as defined above that also comprises at least one carbon-carbon double bond in the backbone of the hydrocarbon chain. Examples include but are not limited to vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl and the like. The term “alkenyl” includes dienes and trienes of straight and branch chains.

**viii. Alkynyl**

75. The term “alkynyl” as used herein is an alkyl residue as defined above that comprises at least one carbon-carbon triple bond in the backbone of the hydrocarbon chain. Examples include but are not limited ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, 4-pentylnyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and the like. The term “alkynyl” includes di- and tri-ynes.

**ix. Cycloalkyl**

76. The term “cycloalkyl” as used herein is a saturated hydrocarbon structure wherein the structure is closed to form at least one ring. Cycloalkyls typically comprise a cyclic radical containing 3 to 8 ring carbons, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Cycloalkyl radicals can be multicyclic and can contain a total of 3 to 18 carbons, or preferably 4 to 12 carbons, or 5 to 8 carbons. Examples of multicyclic cycloalkyls include decahydronaphthyl, adamantyl, and like radicals.

77. Moreover, the term “cycloalkyl” as used throughout the specification and claims is intended to include both “unsubstituted cycloalkyls” and “substituted cycloalkyls”, the later denotes an cycloalkyl radical analogous to the above definition that is further substituted with one, two, or more additional organic or inorganic substituent groups that can include but are not limited to hydroxyl, cycloalkyl, amino,

mono-substituted amino, di-substituted amino, unsubstituted or substituted amido, carbonyl, halogen, sulfhydryl, sulfonyl, sulfonato, sulfamoyl, sulfonamide, azido, acyloxy, nitro, cyano, carboxy, carboalkoxy, alkylcarboxamido, substituted alkylcarboxamido, dialkylcarboxamido, substituted dialkylcarboxamido, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy, haloalkoxy, heteroaryl, substituted heteroaryl, aryl or substituted aryl. When the cycloalkyl is substituted with more than one substituent group, they can be the same or different. The organic substituent groups can comprise from 1 to 12 carbon atoms, or from 1 to 6 carbon atoms, or from 1 to 4 carbon atoms.

**x. Cycloalkenyl**

78. The term "cycloalkenyl" as used herein is a cycloalkyl radical as defined above that further comprises at least one carbon-carbon double bond. Examples include but are not limited to cyclopropenyl, 1-cyclobutenyl, 2-cyclobutenyl, 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexyl, 2-cyclohexyl, 3-cyclohexyl and the like.

**xi. Lower Hydrocarbon Moiety**

79. The term "hydrocarbon moiety" as used herein refers to hydrocarbons, saturated or unsaturated, linear or branched or cyclic, substituted or unsubstituted, having up to eight carbons.

**xii. Alkoxy**

80. The term "alkoxy" as used herein refers to an alkyl residue, as defined above, bonded directly to an oxygen atom, which is then bonded to another moiety. Examples include methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, *iso*-butoxy and the like. The term "lower alkoxy" as used herein refers to an alkoxy residue having up to eight carbons in the alkyl radical.

**xiii. Amino**

81. The term "amino" as used herein is a moiety comprising a N radical substituted with zero, one or two organic substituent groups, which include but are not limited to alkyls, substituted alkyls, cycloalkyls, aryls, or arylalkyls. If there are two substituent groups they can be different or the same. Examples of amino groups include, -NH<sub>2</sub>, methylamino (-NH-CH<sub>3</sub>); ethylamino (-NHCH<sub>2</sub>CH<sub>3</sub>), hydroxyethylamino (-NH-CH<sub>2</sub>CH<sub>2</sub>OH), dimethylamino, methylethylamino, diethylamino, and the like.

**xiv. Mono-substituted Amino**

82. The term "mono-substituted amino" as used herein is a moiety comprising an NH radical substituted with one organic substituent group, which include but are not limited to alkyls, substituted alkyls, cycloalkyls, aryls, or arylalkyls. Examples of mono-substituted amino groups include methylamino (-NH-CH<sub>3</sub>); ethylamino (-NHCH<sub>2</sub>CH<sub>3</sub>), hydroxyethylamino (-NH-CH<sub>2</sub>CH<sub>2</sub>OH), and the like.

**xv. Di-substituted Amino**

83. The term "di-substituted amino" as used herein is a moiety comprising a nitrogen atom substituted with two organic radicals that can be the same or different, which can be selected from but are not limited to aryl, substituted aryl, alkyl, substituted alkyl or arylalkyl, wherein the terms have the same definitions found throughout. Some examples include dimethylamino, methylethylamino, diethylamino and the like.

**xvi. Acyl**

84. The term "acyl" as used herein is a R-C(O)- residue having an R group containing 1 to 8 carbons. The term "acyl" encompass acyl halide, R-(O)-halogen. Examples include but are not limited to formyl, acetyl, propionyl, butanoyl, *iso*-butanoyl, pentanoyl, hexanoyl, heptanoyl, benzoyl and the like, and natural or unnatural amino acids.

**xvii. Acyloxy**

85. The term "acyloxy" as used herein is an acyl radical as defined above directly attached to an oxygen to form an R-C(O)O- residue. Examples include but are not limited to acetyloxy, propionyloxy, butanoyloxy, *iso*-butanoyloxy, benzoyloxy and the like.

**xviii. Azide**

86. As used herein, the term "azide", "azido" and their variants refer to any moiety or compound comprising the monovalent group --N<sub>3</sub> or the monovalent ion --N<sub>3</sub>.

**xix. Benzo group**

87. The terms "benzo", "benzo group," and "fused benzo group" as used herein refers to a phenyl group that has in common with another moiety two neighboring carbon atoms that are bonded to one another. In particular, these and like terms as used herein refer to the sharing of two neighboring phenyl ring carbons with another cyclic moiety.

**xx. Bond**

88. The term "bond" as used herein has its usual and ordinary meaning in organic chemistry.

**xxi. Together form a bond**

89. The term "together form a bond" as used herein with respect to two labeled indices in a figure means that the indices are in fact absent and that the neighbors shown as connected to either side of those paired indices are in fact bonded to each other. E.g., where the structure shows a phenyl ring connected as [Ph figure]–a–b–c, and it is said herein that "a and b together form a bond," this indicates that a and b are absent, and that c has a covalent bond to the phenyl ring at the ring carbon to which a is shown as being attached.

**xxii. Bridge**

90. The term "bridge" as used herein refers to a cyclic moiety in which two atoms that are part of a covalent sequence of atoms are each bonded to the same substituent such that it defines a bridge between them, and such that together with the covalent sequence of atoms defines a cyclic moiety.

**xxiii. Together form a bridge**

91. The term "together form a bridge" as used herein with respect to respective substituents on two atoms refers to the same phenomenon as defined herein for the term "bridge".

**xxiv. Electron withdrawing group**

92. The term "electron withdrawing" as used herein has its usual and ordinary meaning in organic chemistry, and refers to highly electronegative substituents such as: halides such as fluoride, chloride, and the like; pseudohalides such as cyanide, cyanate, thiocyanate, and the like; nitro and nitroso groups and the like; sulfate groups, tosyl groups and the like; doubly bonded oxygen; and other highly electronegative substituents.

**xxv. Haloalkyl**

93. The term "haloalkyl" as used herein an alkyl residue as defined above, substituted with one or more halogens, preferably fluorine, such as a trifluoromethyl, pentafluoroethyl and the like.

**xxvi. Haloalkoxy**

94. The term “haloalkoxy” as used herein refers to a haloalkyl residue as defined above that is directly attached to an oxygen to form trifluoromethoxy, pentafluoroethoxy and the like.

**xxvii. Halogen or Halo or Halide**

95. The term “halo” or “halogen” or “halide” as used herein refers to a fluoro, chloro, bromo or iodo group.

**xxviii. In any order**

96. The term “in any order” as used herein refers to a linear series having a plurality of members, wherein the members may be arranged in any order relative to one another in the series.

**xxix. Respective**

97. The term “respective” as used herein with respect to substituents and the atoms on which they are substituted and designated by a common index refers to the independent identity of such substituents relative to one another, and indicates that each particular atom or site is treated independently. E.g., for a series of methylene atoms in which each is substituted by  $R^b$ , the term “substituted by a respective  $R^b$ ” indicates that the identity of  $R^b$  is independent and potentially unique for each substituted methylene. In such contexts herein the term “respective” is used for the sake of verbal economy in designating the widest scope of permutation in sequences.

**xxx. Linker**

98. The term “linker” as used herein refers to a covalently bonded sequence of from one to eight atoms, in which one end of the sequence is covalently bonded to a first moiety and the other end of the sequence is covalently bonded to a second moiety; the structures of the first and second moieties may be like or unlike one another. A linker can for example comprise methylene groups, -S-, -O-, -N( $R^a$ )-, aryl, heteroaryl, cycloalkyl, heterocyclyl. The linker can comprise multiple groups of the same type, for example the linker can comprise 1-15 methylene groups.

**xxxi. Moiety**

99. The term “moiety” as used herein refers to part of a molecule (or compound, or analog, etc.). A “functional group” is a specific group of atoms in a molecule. A moiety can be a functional group or can include one or more functional groups.

**xxxii. Ester**

100. The term “ester” as used herein is represented by the formula —C(O)OA, where A can be an alkyl, halogenated alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl group described above.

**xxxiii. Carbonate group**

101. The term “carbonate group” as used herein is represented by the formula -OC(O)OR, where R can be hydrogen, an alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, halogenated alkyl, or heterocycloalkyl group described above.

**xxxiv. Keto group**

102. The term “keto group” as used herein is represented by the formula -C(O)R, where R is an alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, halogenated alkyl, or heterocycloalkyl group described above.

**xxxv. Aldehyde**

103. The term “aldehyde” as used herein is represented by the formula -C(O)H or -R-C(O)H, wherein R can be as defined above alkyl, alkenyl, alkoxy, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl group described above.

**xxxvi. Carboxylic acid**

104. The term “carboxylic acid” as used herein is represented by the formula -C(O)OH.

**xxxvii. Carbonyl group**

105. The term “carbonyl group” as used herein is represented by the formula C=O.

**xxxviii. Ether**

106. The term “ether” as used herein is represented by the formula AOA<sup>1</sup>, where A and A<sup>1</sup> can be, independently, an alkyl, halogenated alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl group described above.

**xxxix. Urethane**

107. The term “urethane” as used herein is represented by the formula -OC(O)NRR', where R and R' can be, independently, hydrogen, an alkyl, alkenyl, al-

kynyl, aryl, aralkyl, cycloalkyl, halogenated alkyl, or heterocycloalkyl group described above.

**xl. Methylene**

108. The term “methylene” as used herein refers to a carbon atom in series  $-C(R)(R')-$  wherein R and R' can be, independently, hydrogen, a lower hydrocarbon moiety, an electron withdrawing group, aryl, aralkyl, alkaryl, halogenated alkyl, alkoxy, heteroaryl or heterocycloalkyl group described above. In particular embodiments R and R' are selected from hydrogen and unsubstituted lower hydrocarbon moieties.

**xli. Respective**

109. The term “respective” as used herein with respect to substituents and the atoms on which they are substituted and designated by a common index refers to the independent identity of such substituents relative to one another, and indicates that each particular atom is treated site is treated independently. E.g., for a series of methylene atoms in which each is substituted by  $R^b$ , the term “substituted by a respective  $R^b$ ” indicates that the identity of  $R^b$  is independent and potentially unique for each substituted methylene. In such contexts herein the term “respective” is used for the sake of verbal economy in designating the widest scope of permutation in sequences.

**xlii. Silyl group**

110. The term “silyl group” as used herein is represented by the formula  $-SiRR'R''$ , where R, R', and R'' can be, independently, hydrogen, an alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, halogenated alkyl, alkoxy, or heterocycloalkyl group described above.

**xliii. Sulfo-oxo group**

111. The term “sulfo-oxo group” as used herein is represented by the formulas  $-S(O)_2R$ ,  $-OS(O)_2R$ , or  $-OS(O)_2OR$ , where R can be hydrogen or as defined above an alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, halogenated alkyl, or heterocycloalkyl group described above.

**11. Clathrate**

112. A compound for use in the invention may form a complex such as a “clathrate”, a drug-host inclusion complex, wherein, in contrast to solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. A compound used herein can also contain two or more organic and/or inorganic components which

can be in stoichiometric or non- stoichiometric amounts. The resulting complexes can be ionised, partially ionised, or non-ionised. For a review of such complexes, see J. Pharm. ScL, 64 (8), 1269-1288, by Haleblan (August 1975).

#### **12. Detect**

113. Detect or like terms refer to an ability of the apparatus and methods of the disclosure to discover or sense a molecule- or a substance-induced response (i.e. cellular) and to distinguish the sensed responses for distinct molecules.

#### **13. Direct action (of a drug candidate molecule)**

114. A “direct action” or like terms is a result (of a drug candidate molecule”) acting independently on a cell.

#### **14. Drug candidate molecule**

115. A drug candidate molecule or like terms is a test molecule which is being tested for its ability to function as a drug or a pharmacophore. This molecule may be considered as a lead molecule.

#### **15. Efficacy**

116. Efficacy or like terms is the capacity to produce a desired size of an effect under ideal or optimal conditions. It is these conditions that distinguish efficacy from the related concept of effectiveness, which relates to change under real-life conditions. Efficacy is the relationship between receptor occupancy and the ability to initiate a response at the molecular, cellular, tissue or system level.

#### **16. Higher and inhibit and like words**

117. The terms higher, increases, elevates, or elevation or like terms or variants of these terms, refer to increases above basal levels, e.g., as compared a control. The terms low, lower, reduces, decreases or reduction or like terms or variation of these terms, refer to decreases below basal levels, e.g., as compared to a control. For example, basal levels are normal in vivo levels prior to, or in the absence of, or addition of a molecule such as an agonist or antagonist to a cell. Inhibit or forms of inhibit or like terms refers to to reducing or suppressing.

#### **17. In the presence of the molecule**

118. “in the presence of the molecule” or like terms refers to the contact or exposure of the cultured cell with the molecule. The contact or exposure can be taken place before, or at the time, the stimulus is brought to contact with the cell.

**18. Known molecule**

119. A known molecule or like terms is a molecule with known pharmacological/biological/physiological/pathophysiological activity whose precise mode of action(s) may be known or unknown. .

**19. Ligand**

120. A ligand or like terms is a substance or a composition or a molecule that is able to bind to and form a complex with a biomolecule to serve a biological purpose. Actual irreversible covalent binding between a ligand and its target molecule is rare in biological systems. Ligand binding to receptors alters the chemical conformation, i.e., the three dimensional shape of the receptor protein. The conformational state of a receptor protein determines the functional state of the receptor. The tendency or strength of binding is called affinity. Ligands include substrates, blockers, inhibitors, activators, and neurotransmitters. Radioligands are radioisotope labeled ligands, while fluorescent ligands are fluorescently tagged ligands; both can be considered as ligands are often used as tracers for receptor biology and biochemistry studies. Ligand and modulator are used interchangeably.

**20. Material**

121. Material is the tangible part of something (chemical, biochemical, biological, or mixed) that goes into the makeup of a physical object.

**21. Mimic**

122. As used herein, "mimic" or like terms refers to performing one or more of the functions of a reference object. For example, a molecule mimic performs one or more of the functions of a molecule.

**22. Modulate**

123. To modulate, or forms thereof, means either increasing, decreasing, or maintaining a cellular activity mediated through a cellular target. It is understood that wherever one of these words is used it is also disclosed that it could be 1%, 5%, 10%, 20%, 50%, 100%, 500%, or 1000% increased from a control, or it could be 1%, 5%, 10%, 20%, 50%, or 100% decreased from a control.

**23. Modulator**

124. A modulator or like terms is a ligand or molecule that controls the activity of a cellular target. It is a signal modulating molecule binding to a cellular target, such as a target protein.

**24. Molecule**

125. As used herein, the terms "molecule" or like terms refers to a biological or biochemical or chemical entity that exists in the form of a chemical molecule or molecule with a definite molecular weight. A molecule or like terms is a chemical, biochemical or biological molecule, regardless of its size.

126. Many molecules are of the type referred to as organic molecules (molecules containing carbon atoms, among others, connected by covalent bonds), although some molecules do not contain carbon (including simple molecular gases such as molecular oxygen and more complex molecules such as some sulfur-based polymers). The general term "molecule" includes numerous descriptive classes or groups of molecules, such as proteins, nucleic acids, carbohydrates, steroids, organic pharmaceuticals, small molecule, receptors, antibodies, and lipids. When appropriate, one or more of these more descriptive terms (many of which, such as "protein," themselves describe overlapping groups of molecules) will be used herein because of application of the method to a subgroup of molecules, without detracting from the intent to have such molecules be representative of both the general class "molecules" and the named subclass, such as proteins. Unless specifically indicated, the word "molecule" would include the specific molecule and salts thereof, such as pharmaceutically acceptable salts.

**25. Molecule mixture**

127. A molecule mixture or like terms is a mixture containing at least two molecules. The two molecules can be, but not limited to, structurally different (i.e., enantiomers), or compositionally different (e.g., protein isoforms, glycoform, or an antibody with different poly(ethylene glycol) (PEG) modifications), or structurally and compositionally different (e.g., unpurified natural extracts, or unpurified synthetic compounds).

**26. Molecule pharmacology**

128. Molecule pharmacology or the like terms refers to the systems cell biology or systems cell pharmacology or mode(s) of action of a molecule acting on a

cell. The molecule pharmacology is often characterized by, but not limited, toxicity, ability to influence specific cellular process(es) (e.g., proliferation, differentiation, reactive oxygen species signaling), or ability to modulate a specific cellular target (e.g., p75NTR with NGF or pro-NGF).

#### **27. Nervous System**

129. The term nervous system has its usual and ordinary meaning in anatomy, and encompasses the entire nervous system, including but not limited to peripheral nerve cells, the central nervous system, and the brain.

#### **28. Optional**

130. “Optional” or “optionally” or like terms means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where the event or circumstance occurs and instances where it does not. For example, the phrase “optionally the composition can comprise a combination” means that the composition may comprise a combination of different molecules or may not include a combination such that the description includes both the combination and the absence of the combination (i.e., individual members of the combination).

#### **29. Or**

131. The word "or" or like terms as used herein means any one member of a particular list and also includes any combination of members of that list.

#### **30. Pharmaceutically effective amount**

132. The term “pharmaceutically effective amount” as used herein refers to an amount of medicinal composition sufficient to provide  $IC_{50}$  p75/NGF biological activity at a concentration below 5000 nM.

#### **31. Positive control**

133. A “positive control” or like terms is a control that shows that the conditions for data collection can lead to data collection.

#### **32. Potency**

134. “Potency” or like terms is a measure of molecule activity expressed in terms of the amount required to produce an effect of given intensity. For example, a highly potent drug evokes a larger response at low concentrations. The potency is proportional to affinity and efficacy. Affinity is the ability of the drug molecule to bind to a receptor.

### 33. Prodrug

135. "Prodrug" or the like terms refers to compounds that when metabolized in vivo, undergo conversion to compounds having the desired pharmacological activity. Prodrugs may be prepared by replacing appropriate functionalities present in pharmacologically active compounds with "pro-moieties" as described, for example, in H. Bundgaard, *Design of Prodrugs* (1985). Examples of prodrugs include ester, ether or amide derivatives of the compounds herein, and their pharmaceutically acceptable salts. For further discussions of prodrugs, see e.g., T. Higuchi and V. Stella "Pro-drugs as Novel Delivery Systems," ACS Symposium Series 14 (1975) and E. B. Roche ed., *Bioreversible Carriers in Drug Design* (1987).

### 34. Publications

136. Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this pertains. The references disclosed are also individually and specifically incorporated by reference herein for the material contained in them that is discussed in the sentence in which the reference is relied upon.

### 35. Receptor

137. A receptor or like terms is a protein molecule embedded in either the plasma membrane or cytoplasm of a cell, to which a mobile signaling (or "signal") molecule may attach. A molecule which binds to a receptor is called a "ligand," and may be a peptide (such as a neurotransmitter), a hormone, a pharmaceutical drug, or a toxin, and when such binding occurs, the receptor goes into a conformational change which ordinarily initiates a cellular response. However, some ligands merely block receptors without inducing any response (e.g. antagonists). Ligand-induced changes in receptors result in physiological changes which constitute the biological activity of the ligands.

### 36. Ranges

138. Ranges can be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antece-

dent “about,” it will be understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as “about” that particular value in addition to the value itself. For example, if the value “10” is disclosed, then “about 10” is also disclosed. It is also understood that when a value is disclosed that “less than or equal to” the value, “greater than or equal to the value” and possible ranges between values are also disclosed, as appropriately understood by the skilled artisan. For example, if the value “10” is disclosed the “less than or equal to 10” as well as “greater than or equal to 10” is also disclosed. It is also understood that the throughout the application, data is provided in a number of different formats, and that this data, represents endpoints and starting points, and ranges for any combination of the data points. For example, if a particular data point “10” and a particular data point 15 are disclosed, it is understood that greater than, greater than or equal to, less than, less than or equal to, and equal to 10 and 15 are considered disclosed as well as between 10 and 15. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

### **37. Response**

139. A response or like terms is any reaction to any stimulation.

### **38. Sample**

140. By sample or like terms is meant an animal, a plant, a fungus, etc.; a natural product, a natural product extract, etc.; a tissue or organ from an animal; a cell (either within a subject, taken directly from a subject, or a cell maintained in culture or from a cultured cell line); a cell lysate (or lysate fraction) or cell extract; or a solution containing one or more molecules derived from a cell or cellular material (e.g. a polypeptide or nucleic acid), which is assayed as described herein. A sample may also be any body fluid or excretion (for example, but not limited to, blood, urine, stool, saliva, tears, bile) that contains cells or cell components.

### **39. Salt(s) and pharmaceutically acceptable salt(s)**

141. The compounds of this invention may be used in the form of salts derived from inorganic or organic acids. Depending on the particular compound, a salt

of the compound may be advantageous due to one or more of the salt's physical properties, such as enhanced pharmaceutical stability in differing temperatures and humidities, or a desirable solubility in water or oil. In some instances, a salt of a compound also may be used as an aid in the isolation, purification, and/or resolution of the compound.

142. Where a salt is intended to be administered to a patient (as opposed to, for example, being used in an in vitro context), the salt preferably is pharmaceutically acceptable. The term "pharmaceutically acceptable salt" refers to a salt prepared by combining a compound of formula I or II with an acid whose anion, or a base whose cation, is generally considered suitable for human consumption. Pharmaceutically acceptable salts are particularly useful as products of the methods of the present invention because of their greater aqueous solubility relative to the parent compound. For use in medicine, the salts of the compounds of this invention are non-toxic "pharmaceutically acceptable salts." Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid.

143. Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention when possible include those derived from inorganic acids, such as hydrochloric, hydrobromic, hydrofluoric, boric, fluoroboric, phosphoric, metaphosphoric, nitric, carbonic, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, trifluoromethanesulfonic, succinic, toluenesulfonic, tartaric, and trifluoroacetic acids. Suitable organic acids generally include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids.

144. Specific examples of suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sufanilate, cyclohexylaminosulfonate, algenic acid,  $\beta$ -

hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, i.e., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts. In another embodiment, base salts are formed from bases which form non-toxic salts, including aluminum, arginine, benzathine, choline, diethylamine, diolamine, glycine, lysine, meglumine, olamine, tromethamine and zinc salts.

145. Organic salts may be made from secondary, tertiary or quaternary amine salts, such as tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl ( $\text{C}_1$ - $\text{C}_6$ ) halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (i.e., dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (i.e., decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), arylalkyl halides (i.e., benzyl and phenethyl bromides), and others.

146. In one embodiment, hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

147. The compounds of the invention and their salts may exist in both unsolvated and solvated forms.

#### **40. Solvate**

148. The compounds herein, and the pharmaceutically acceptable salts thereof, may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. They may also exist in unsolvated and solvated forms. The term "solvate" describes a molecular complex comprising the compound and one or more pharmaceutically acceptable solvent molecules (e.g., EtOH). The term "hydrate" is a solvate in which the solvent is water. Pharmaceutically acceptable solvates include

those in which the solvent may be isotopically substituted (e.g., D<sub>2</sub>O, d<sub>6</sub>-acetone, d<sub>6</sub>-DMSO).

149. A currently accepted classification system for solvates and hydrates of organic compounds is one that distinguishes between isolated site, channel, and metal-ion coordinated solvates and hydrates. See, e.g., K. R. Morris (H. G. Brittain ed.) *Polymorphism in Pharmaceutical Solids* (1995). Isolated site solvates and hydrates are ones in which the solvent (e.g., water) molecules are isolated from direct contact with each other by intervening molecules of the organic compound. In channel solvates, the solvent molecules lie in lattice channels where they are next to other solvent molecules. In metal-ion coordinated solvates, the solvent molecules are bonded to the metal ion.

150. When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and in hygroscopic compounds, the water or solvent content will depend on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

151. The compounds herein, and the pharmaceutically acceptable salts thereof, may also exist as multi- component complexes (other than salts and solvates) in which the compound and at least one other component are present in stoichiometric or non-stoichiometric amounts. Complexes of this type include clathrates (drug-host inclusion complexes) and co-crystals. The latter are typically defined as crystalline complexes of neutral molecular constituents which are bound together through non-covalent interactions, but could also be a complex of a neutral molecule with a salt. Co-crystals may be prepared by melt crystallization, by recrystallization from solvents, or by physically grinding the components together. See, e.g., O. Almarsson and M. J. Zaworotko, *Chem. Commun.*, 17:1889-1896 (2004). For a general review of multi-component complexes, see J. K. Halebian, *J. Pharm. Sci.* 64(8):1269-88 (1975).

#### **41. Stable**

152. When used with respect to pharmaceutical compositions, the term "stable" or like terms is generally understood in the art as meaning less than a certain amount, usually 10%, loss of the active ingredient under specified storage conditions for a stated period of time. The time required for a composition to be considered stable is relative to the use of each product and is dictated by the commercial practicali-

ties of producing the product, holding it for quality control and inspection, shipping it to a wholesaler or direct to a customer where it is held again in storage before its eventual use. Including a safety factor of a few months time, the minimum product life for pharmaceuticals is usually one year, and preferably more than 18 months. As used herein, the term "stable" references these market realities and the ability to store and transport the product at readily attainable environmental conditions such as refrigerated conditions, 2°C to 8°C.

#### **42. Substance**

153. A substance or like terms is any physical object. A material is a substance. Molecules, ligands, markers, cells, proteins, and DNA can be considered substances. A machine or an article would be considered to be made of substances, rather than considered a substance themselves.

#### **43. Subject**

154. As used throughout, by a subject or like terms is meant an individual. Thus, the "subject" can include, for example, domesticated animals, such as cats, dogs, etc., livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), laboratory animals (e.g., mouse, rabbit, rat, guinea pig, etc.) and mammals, non-human mammals, primates, non-human primates, rodents, birds, reptiles, amphibians, fish, and any other animal. In one aspect, the subject is a mammal such as a primate or a human. The subject can be a non-human.

#### **44. Test molecule**

155. A test molecule or like terms is a molecule which is used in a method to gain some information about the test molecule. A test molecule can be an unknown or a known molecule.

#### **45. Treating**

156. Treating or treatment or like terms can be used in at least two ways. First, treating or treatment or like terms can refer to administration or action taken towards a subject. Second, treating or treatment or like terms can refer to mixing any two things together, such as any two or more substances together, such as a molecule and a cell. This mixing will bring the at least two substances together such that a contact between them can take place.

157. When treating or treatment or like terms is used in the context of a subject with a disease, it does not imply a cure or even a reduction of a symptom for example. When the term therapeutic or like terms is used in conjunction with treating or treatment or like terms, it means that the symptoms of the underlying disease are reduced, and/or that one or more of the underlying cellular, physiological, or biochemical causes or mechanisms causing the symptoms are reduced. It is understood that reduced, as used in this context, means relative to the state of the disease, including the molecular state of the disease, not just the physiological state of the disease.

#### **46. Trigger**

158. A trigger or like terms refers to the act of setting off or initiating an event, such as a response.

#### **47. Tumor**

159. The term tumor has its usual and ordinary meaning in oncology.

#### **48. Values**

160. Specific and preferred values disclosed for components, ingredients, additives, cell types, markers, and like aspects, and ranges thereof, are for illustration only; they do not exclude other defined values or other values within defined ranges. The compositions, apparatus, and methods of the disclosure include those having any value or any combination of the values, specific values, more specific values, and preferred values described herein.

161. Thus, the disclosed methods, compositions, articles, and machines, can be combined in a manner to comprise, consist of, or consist essentially of, the various components, steps, molecules, and composition, and the like, discussed herein. They can be used, for example, in methods for characterizing a molecule including a ligand as defined herein; a method of producing an index as defined herein; or a method of drug discovery as defined herein.

#### **49. Unknown molecule**

162. An unknown molecule or like terms is a molecule with unknown biological/pharmacological/physiological/pathophysiological activity, but with known or unknown chemical structure.

#### **50. p75<sup>NTR</sup> inhibitor**

163. A p75<sup>NTR</sup> inhibitor and the like terms is a molecule, compound or composition that binds to p75<sup>NTR</sup>. A p75<sup>NTR</sup> inhibitor can reduce, decrease, or inhibit

other substances from binding to p75<sup>NTR</sup> and/or reduce, decrease, inhibit the activity of p75<sup>NTR</sup>.

**51. Angiogenesis inhibitor**

164. An angiogenesis inhibitor or the like terms is a molecule, compound or composition that reduces, decreases or inhibits angiogenesis.

**52. Optimizing**

165. Optimizing refers to a process of making better or checking to see if it something or some process can be made better.

**53. Therapeutic efficacy**

166. Therapeutic efficacy refers to the degree or extent of results from a treatment of a subject.

**54. Toxicity marker**

167. A toxicity marker is any reagent, molecule, substance etc. that can be used for identifying, diagnosing, prognosing a level of toxicity of a substance, in, for example, an organism or cell or tissue or organ.

**55. Analytical Methods**

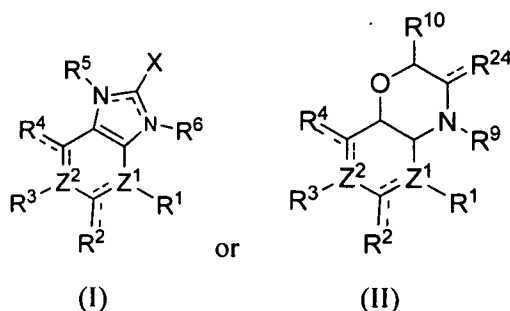
168. An analytical method is, for example, a method which measures a molecule or substance. For example, gas chromatography, gel permeation chromatography, high resolution gas chromatography, high resolution mass spectrometry, or mass spectrometry is analytical methods.

**56. Toxicity**

169. Toxicity is the degree to which a substance, molecule, is able to damage something, such as a cell, a tissue, an organ, or a whole organism, that has been exposed to the substance or molecule. For example, the liver, or cells in the liver, hepatocytes, can be damaged by certain substances.

**C. COMPOUNDS**

170. Disclosed herein is a compound having structure I or II:



wherein:

X can be hydrogen, lower alkyl, haloalkyl or an electron withdrawing group;

R<sup>1</sup> and R<sup>3</sup> can either both present or both absent, and

if R<sup>1</sup> and R<sup>3</sup> are present then each can independently be unsubstituted lower alkyl, alkyl, halide and optionally together form a bridge, R<sup>2</sup> and R<sup>4</sup> can each be double bonded O, and Z<sup>1</sup> and Z<sup>2</sup> can each be an N bearing no double bonds; and

if R<sup>1</sup> and R<sup>3</sup> are absent then R<sup>2</sup> and R<sup>4</sup> can each be H or be double bonded O, the six-member ring can have 0-3 double bonds, Z<sup>1</sup> and Z<sup>2</sup> can independently be C or N, and the six-member ring if carbocyclic can optionally be substituted;

if Z<sup>1</sup> and Z<sup>2</sup> are C then R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> can independently be present or absent, and

if R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are present then each can independently be H, halide, lower alkoxy, lower alkyl, hydroxyl or haloalkyl;

one or both of R<sup>5</sup> or R<sup>6</sup> can be present, can be bonded to a nitrogen atom having two single bonds in the five-member ring, and the other nitrogen atom in the five-member ring can be unsubstituted or substituted and bears a double bond in the ring, if R<sup>5</sup> or R<sup>6</sup> is bonded to a nitrogen that bears a double bond then R<sup>5</sup> or R<sup>6</sup> can be alkyl or halide, and R<sup>5</sup> or R<sup>6</sup> can be of the form -linker-R<sup>7</sup>, wherein

the linker can comprise in any order -C(=O)-, -N(R<sup>a</sup>)-, -O-, -S-, aryl, hetero aryl, heterocyclyl, cycloalkyl and up to ten methylene groups, wherein

R<sup>a</sup> can be H or independently unsubstituted C<sub>1</sub>-C<sub>3</sub>,

one or more of the methylene groups can optionally be substituted independently by a respective R<sup>b</sup>, wherein each R<sup>b</sup> can be lower alkyl and its identity can be independent of the identity

of  $R^a$  and of respective  $R^b$  on other methylene groups in the linker, and

optionally  $R^a$  and a respective  $R^b$  can together form a bridge; and  $R^7$  can be an end group that can be:  $C_1$ - $C_8$  alkyl;  $C_3$ - $C_8$  cycloalkyl; aryl, heteroaryl,  $C_3$ - $C_{10}$  heterocyclic; or a 5-member heteroaryl ring having up to three heteroatoms that can be selected from O, N and S, wherein the heteroaryl ring can optionally bear a substituent  $R^8$ ; and wherein

$R^8$  can be H, an electron withdrawing group, lower hydrocarbon moiety, lower alkoxy, an optionally substituted fused benzo group, or

if  $R^7$  is a triazole, then  $R^8$  can be optionally a six-member heteroaryl ring in which the heteroatoms can be 1 or 2 nitrogen atoms, and  $R^8$  can optionally be substituted at one or more carbon atoms on the ring by an electron withdrawing group, lower hydrocarbon moiety, or lower alkoxy;

$R^9$  can be of the form  $-\text{linker}-R^7$ , wherein

the linker can comprise in any order  $-\text{C}(=\text{O})-$ ,  $-\text{N}(R^a)-$ ,  $-\text{O}-$ ,  $-\text{S}-$  and up to six methylene groups, wherein

$R^a$  can be H or independently unsubstituted  $C_1$ - $C_3$ ,

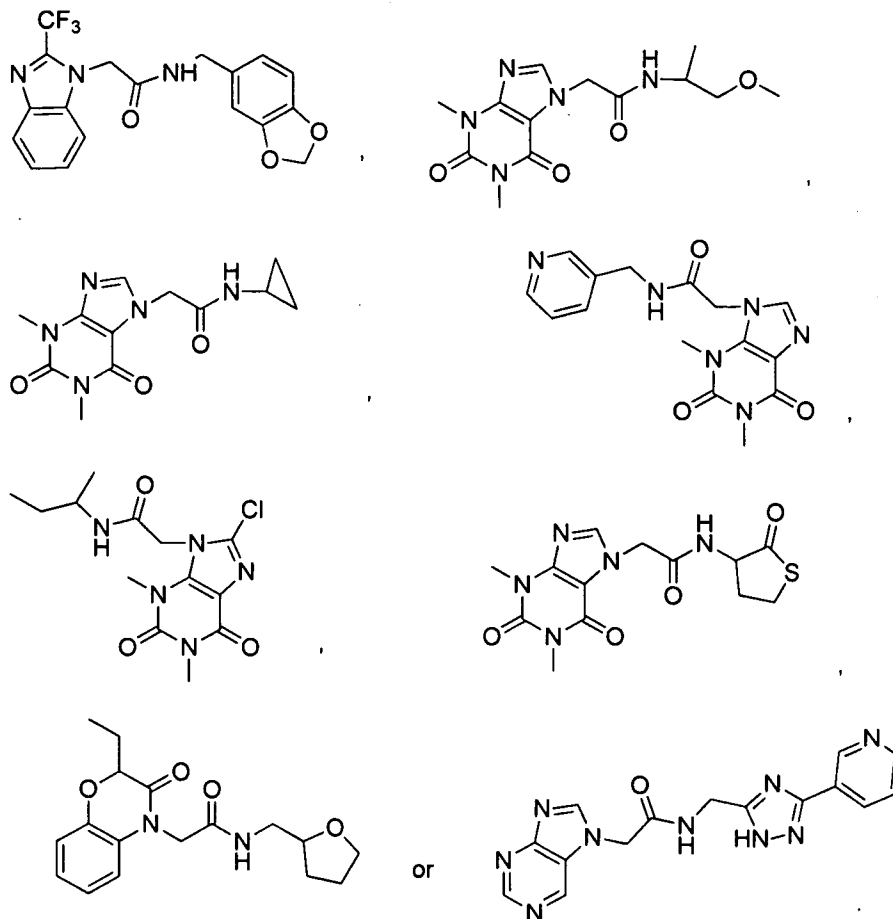
one or more of the methylene groups can optionally be substituted independently by a respective  $R^b$ , wherein each  $R^b$  can be lower alkyl and its identity can be independent of the identity of  $R^a$  and of respective  $R^b$  on other methylene groups in the linker,

optionally  $R^a$  and a respective  $R^b$  can together form a bridge; and

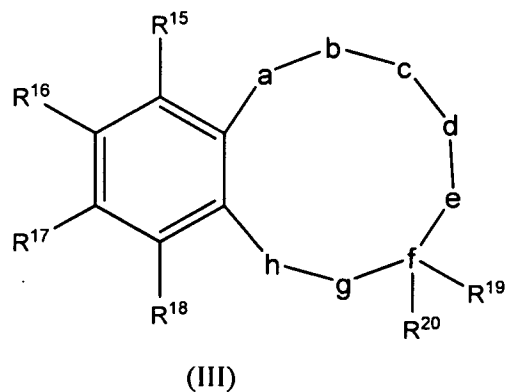
$R^{10}$  can be H or substituted or unsubstituted lower alkyl;

$R^{24}$  can be H or  $=\text{O}$ ; and

with the proviso that structure I or II cannot be:



171. Also disclosed herein is a compound having structure III:



wherein:

each of  $\text{R}^{15}$ ,  $\text{R}^{16}$ ,  $\text{R}^{17}$  and  $\text{R}^{18}$  can independently be H, an electron withdrawing group, lower alkyl, lower alkoxy, OH, or together forms a benzo substituent with a neighboring group

from another of  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$  and  $R^{18}$ , except that  $R^{16}$  is not F when the remainder of the molecule has the formula  $C_{14}H_{16}N_2O_2$ ;

**a** and **b** can be hydrogen atoms bonded to the phenyl ring and **c**, respectively, but not to each other, or together **a** and **b** can form a bond; and **g** and **h** can be hydrogen atoms bonded to the phenyl ring and **f**, respectively, but not to each other, or together **g** and **h** can form a bond; wherein at least one of the pairs **a-b** and **g-h** is a bond;

one of **c** and **d** can be  $-C(=O)-$  and the other can be  $-N(-R^d)-$ , wherein  $R^d$  can be independently H or lower alkyl;

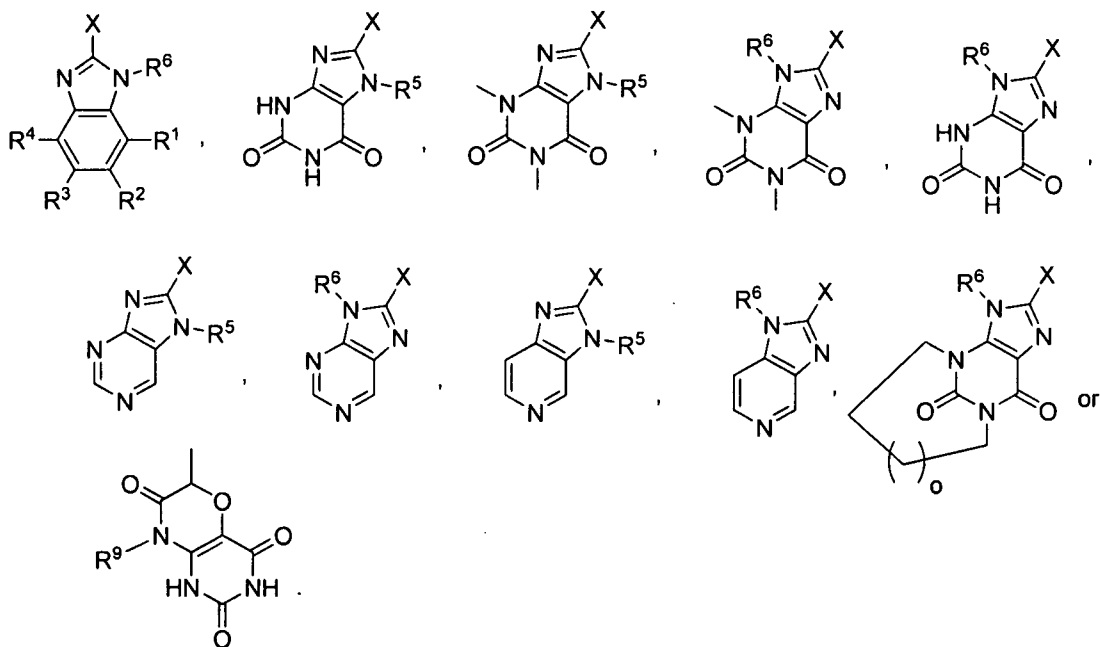
**e** can be  $=CH-$  or  $-(CH_2)_n-$ , wherein  $n$  can be 1-4; and

**f** can be a carbon atom, one of  $R^{19}$  and  $R^{20}$  can have the form  $-\text{linker}-R^{25}$ , and the other of  $R^{19}$  and  $R^{20}$  can be H, an electron withdrawing group, lower alkyl, lower alkoxy, OH, or can be a pi bond to the carbon atom at **e**, wherein:

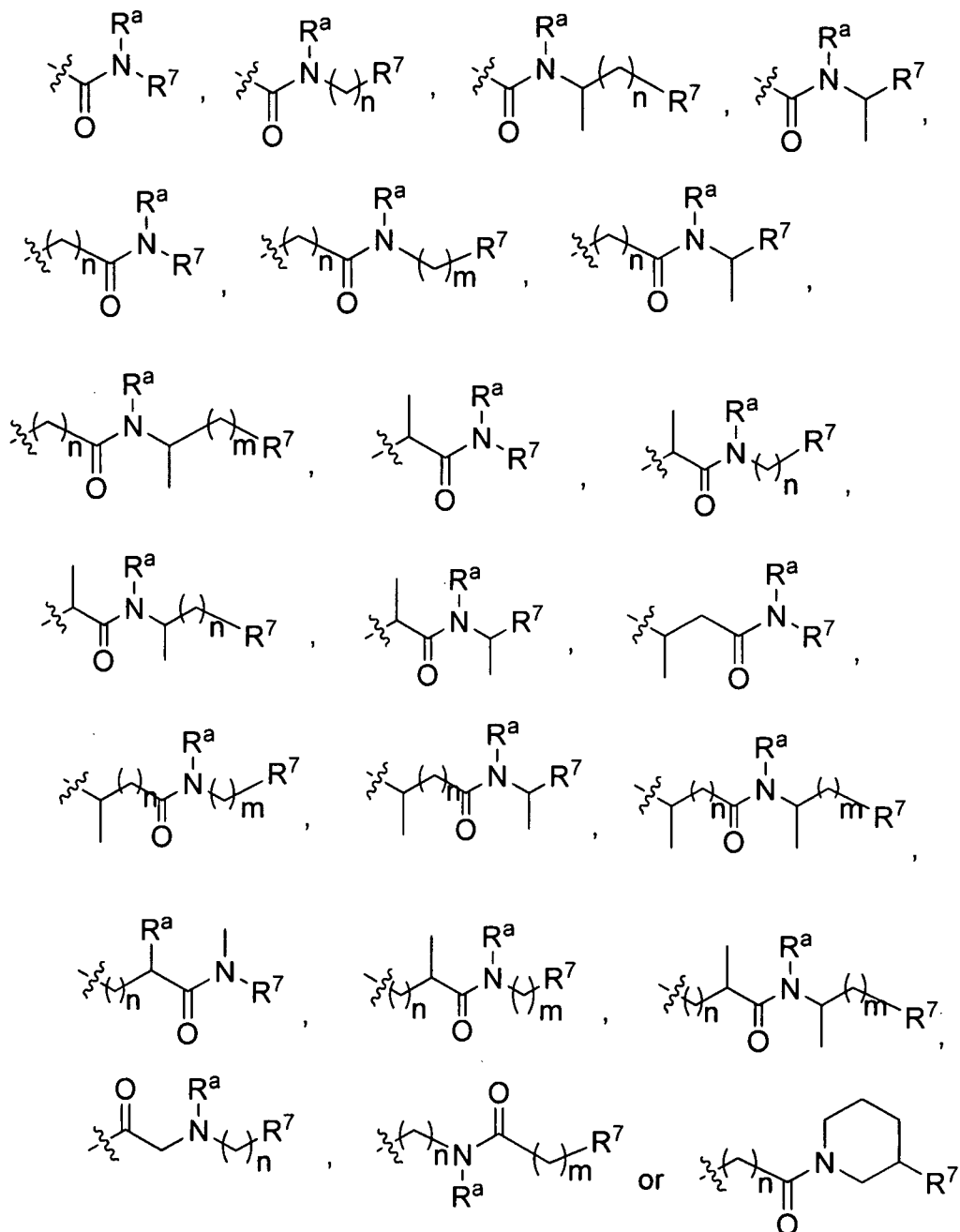
the linker can comprise in any order  $-C(=O)-$ ,  $-N(R^c)-$ , and up to 10 methylene groups, wherein  $R^c$  can be H or independently lower alkyl and the methylene group can be optionally substituted independently by lower alkyl; and

$R^{25}$  is an end group that can be a lower hydrocarbon moiety.

172. In some embodiments structure I or II can be



173. In some embodiments  $R^5$ ,  $R^6$  and  $R^9$  can independently be H,



174. In some embodiments R<sup>a</sup> can be H or C<sub>1</sub>-C<sub>3</sub> alkyl.

175. In some embodiments  $n$  and  $m$  can independently be 1, 2, 3 or 4.

176. In some embodiments  $o$  can be 1, 2 or 3.

177. In some embodiments X can be H, =O, Cl, F or CF<sub>3</sub>.



184. In some embodiments  $R^{11}$  can be H,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halide or hydroxyl.

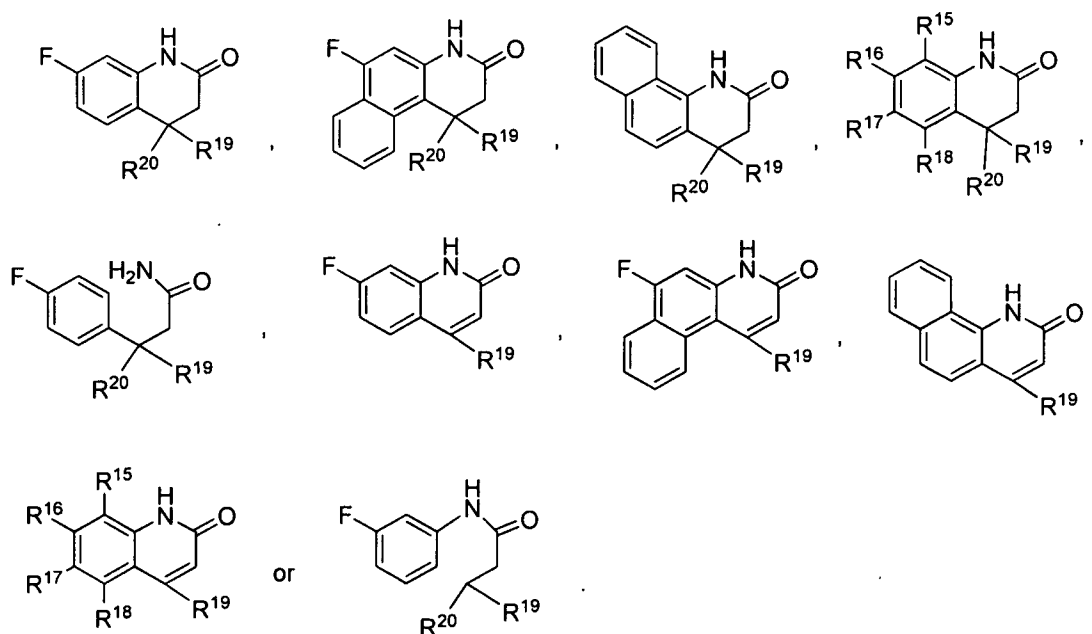
185. In some embodiments  $R^{12}$  can be H,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halide or hydroxyl.

186. In some embodiments  $R^{13}$  can be  $R^8$ .

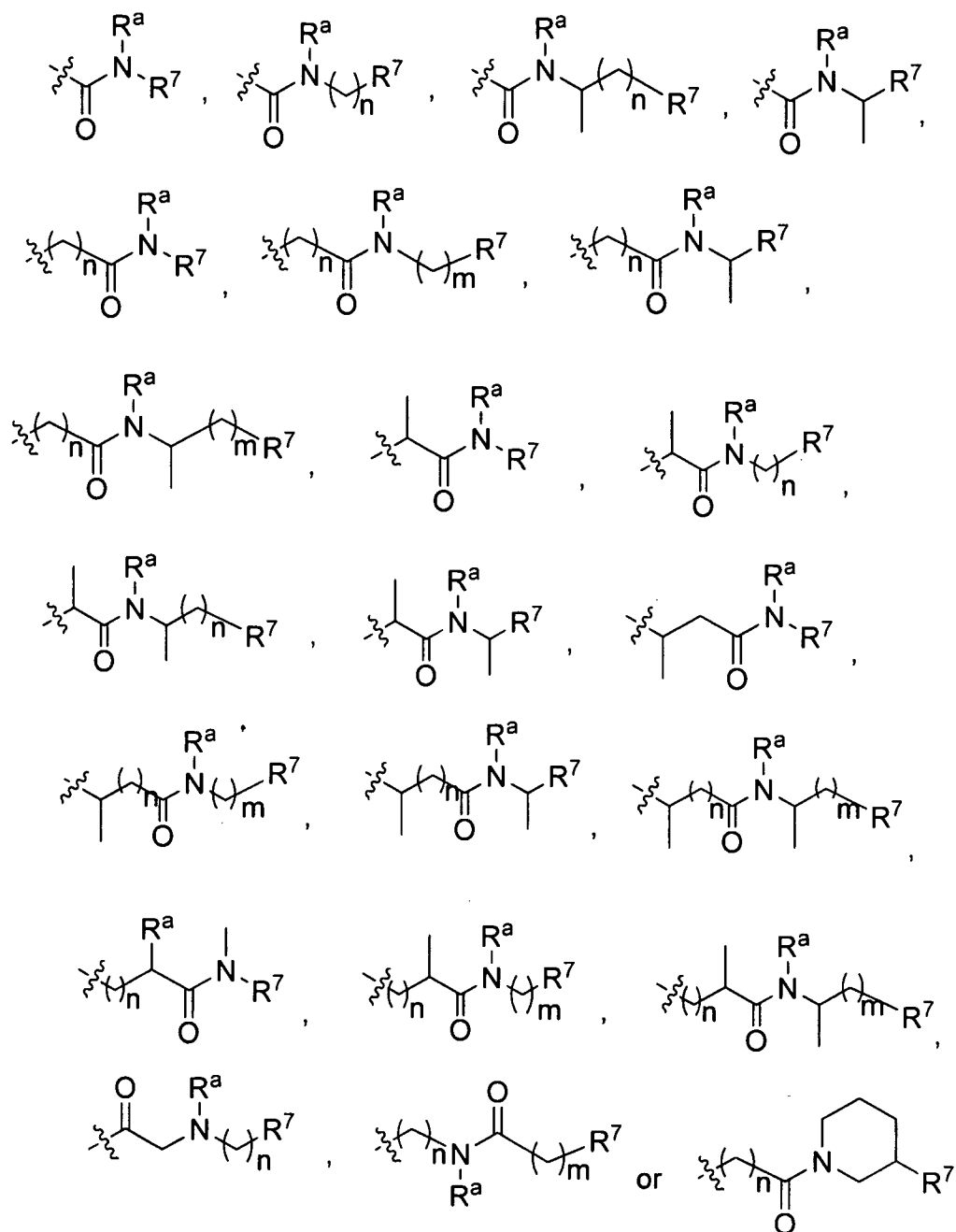
187. In some embodiments  $R^{14}$  can be H,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halide or hydroxyl.

188. In some embodiments  $R^{24}$  can be =O.

189. In some embodiment structure III can be



190. In some embodiments  $R^{19}$  can be H,  $C_1$ - $C_3$  alkyl, halide,



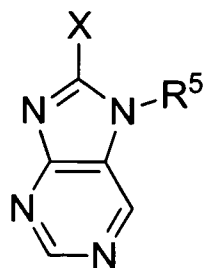
191. In another embodiment  $R^{19}$  can be H,  $C_1$ - $C_3$  alkyl or halide.

192. In some embodiments  $R^{20}$  can be H,  $C_1$ - $C_3$  alkyl or halide.

193. In some embodiments  $R^{19}$  can be R configuration and  $R^{20}$  can be S configuration. In another embodiment  $R^{19}$  can be S configuration and  $R^{20}$  can be R configuration.

194. In some embodiments  $R^7$  can be R configuration and the linker can be S configuration.
195. In some embodiments  $R^7$  can be S configuration and the linker can be R configuration.
196. In some embodiments  $R^1$  and  $R^3$  can each be absent.
197. In some embodiments  $R^1$  and  $R^3$  can each be methyl or together form an  $\alpha,\omega$ -propadiyl,  $\alpha,\omega$ -butadiyl, or  $\alpha,\omega$ -pentadiyl bridge.
198. In some embodiments  $Z^1$  can be C and  $Z^2$  can be N.
199. In some embodiments  $Z^1$  can be N and  $Z^2$  can be C.
200. In some embodiments  $Z^1$  can be C and  $Z^2$  can be C.
201. In some embodiments  $Z^1$  can be N and  $Z^2$  can be N.
202. In some embodiments the linker is  $-\text{CH}_2-\text{C}(=\text{O})-\text{N}(-\text{H})-(\text{CHR}^b)_p-$ , wherein  $p$  is 0-2 and each respective  $R^b$  is independently H or methyl.
203. In some embodiments  $R^a$  and a respective  $R^b$  together can form an alkyl bridge defining a piperidinediyl ring in the linker.
204. In some embodiments pharmaceutical composition can comprise structure I or II.
205. In some embodiments  $R^{16}$  can be F and  $R^{15}$ ,  $R^{17}$  and  $R^{18}$  can each be H.
206. In some embodiments  $R^{15}$  and  $R^{16}$  can together form a benzo group, or  $R^{17}$  and  $R^{18}$  can together form a benzo group.
207. In some embodiments the pair **a** and **b** and the pair **g** and **h**, one of the pairs can be a bond and each member of the other pair can be a hydrogen atom.
208. In some embodiments **e** can be  $-(\text{CH}_2)_n-$  and  $n$  can be 1-4.
209. In some embodiments a double bond can be present between **e** and **f**.
210. In some embodiments **f** can be chiral and can be substituted by H, an electron withdrawing group, lower alkyl, lower alkoxy, or OH.
211. In some embodiments the linker can be  $-(\text{CH}_2)_m-\text{C}(=\text{O})-\text{NH}-$  and  $m$  can be 0-1
212. In some embodiments  $R^{25}$  can be an end group that can be i-propyl, s-butyl, 3-pentyl, or  $\text{C}_3$ - $\text{C}_6$  cycloalkyl.
213. In some embodiments a pharmaceutical composition comprising the compound of structure III.

214. Also disclosed herein are compound of structure

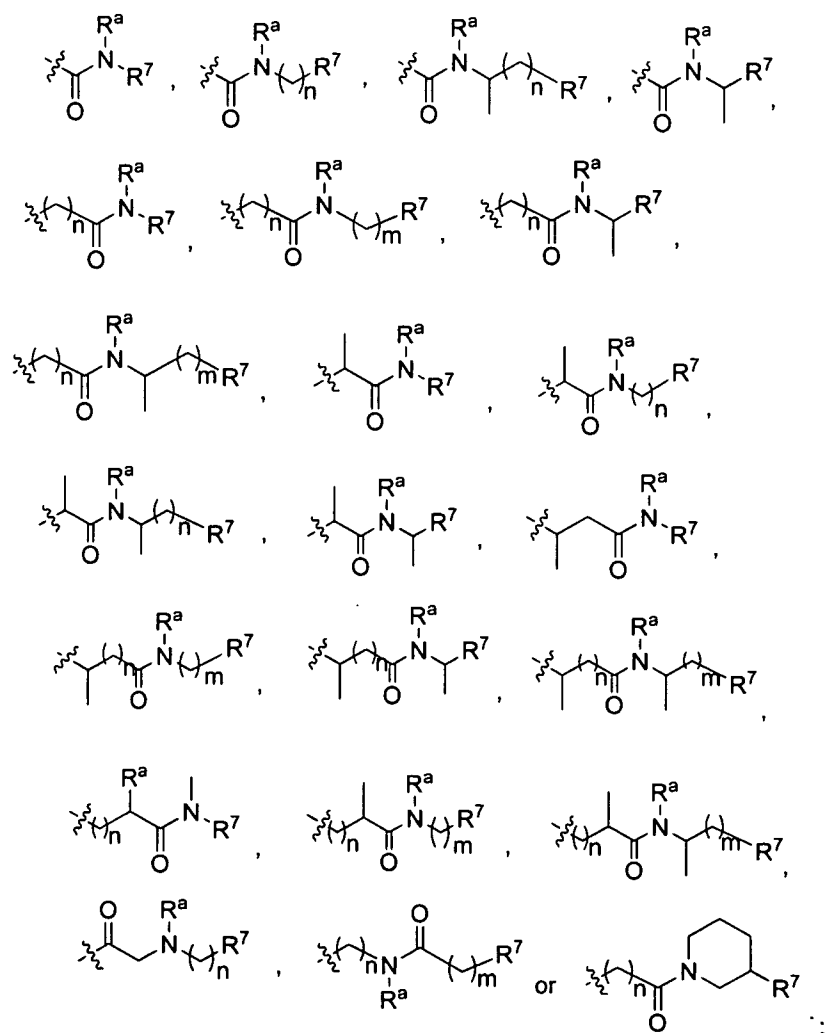


(IV)

wherein:

X can be hydrogen, lower alkyl, haloalkyl or an electron withdrawing group;

R<sup>5</sup> can be



R<sup>a</sup> can be H or independently unsubstituted C<sub>1</sub>-C<sub>3</sub>;

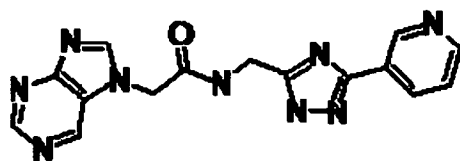
wherein n and m can independently be 1, 2, 3 or 4

R<sup>7</sup> can be an end group that can be: C<sub>1</sub>-C<sub>8</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl; aryl, heteroaryl, C<sub>3</sub>-C<sub>10</sub> heterocyclic; or a 5-member heteroaryl ring having up to three heteroatoms that are selected from O, N and S, wherein the heteroaryl ring optionally bear a substituent R<sup>8</sup>; and wherein

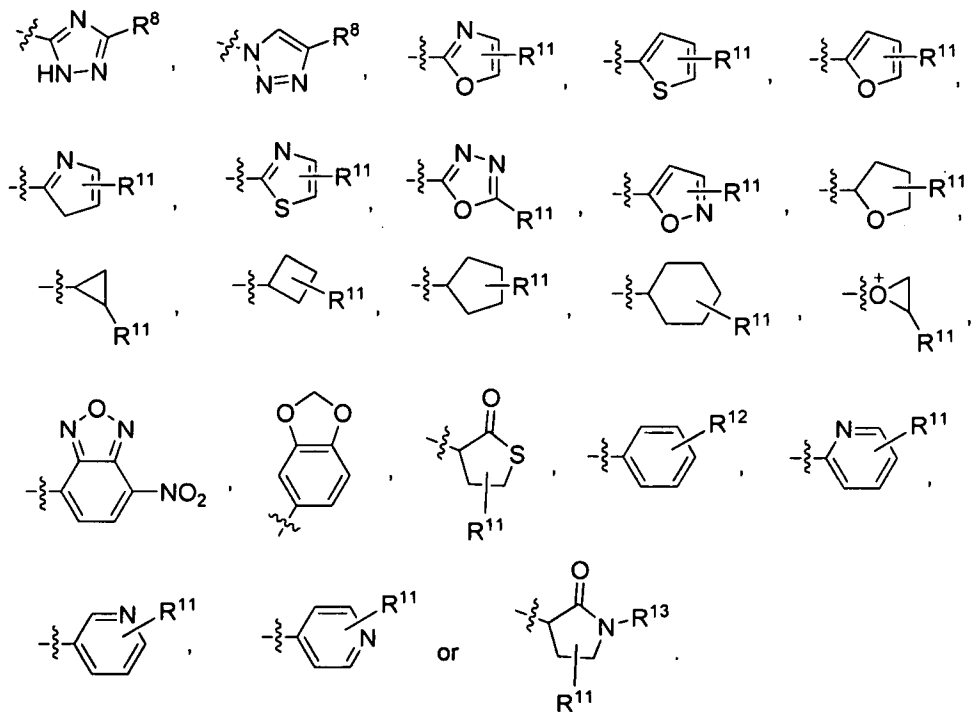
R<sup>8</sup> can be H, an electron withdrawing group, lower hydrocarbon moiety, lower alkoxy, an optionally substituted benzo group, substituted fused benzo group, or

if R<sup>7</sup> is a triazole, then R<sup>8</sup> can optionally be a six-member heteroaryl ring in which the heteroatoms is 1 or 2 nitrogen atoms, and R<sup>8</sup> is optionally be substituted at one or more carbon atoms on the ring by an electron withdrawing group, lower hydrocarbon moiety, or lower alkoxy,

with the proviso that structure IV cannot be:



215. In some embodiments R<sup>7</sup> can be C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy,

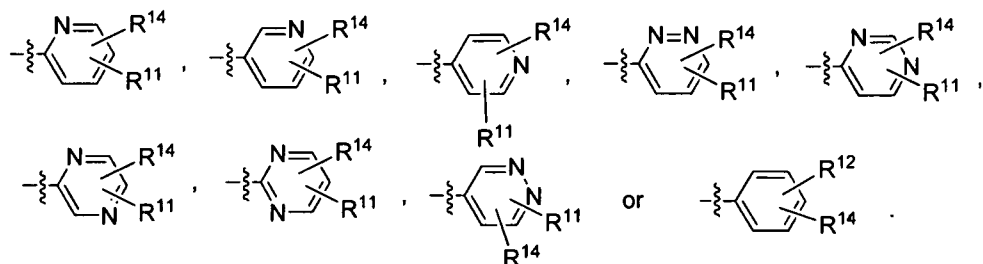


wherein  $R^{11}$  can be H,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halide or hydroxyl;

$R^{12}$  can be H,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halide or hydroxyl; and

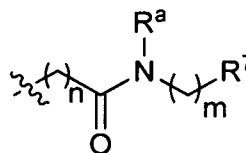
$R^{13}$  can be  $R^8$ .

216. In some embodiments  $R^8$  can be H,  $C_1$ - $C_3$  alkyl,  $C_1$ - $C_3$  alkoxy, halide, hydroxyl,



wherein  $R^{12}$  can be H,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halide or hydroxyl; and

$R^{14}$  can be H,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halide or hydroxyl.

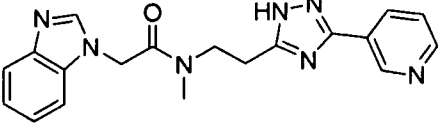
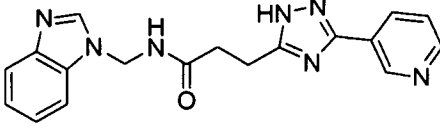
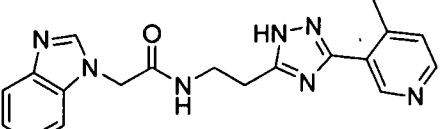
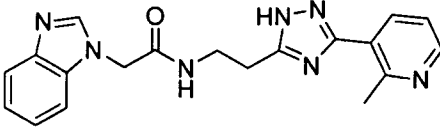
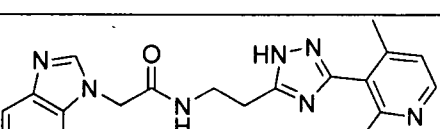
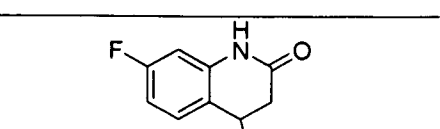
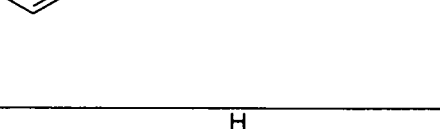
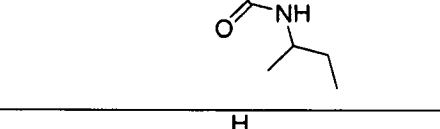
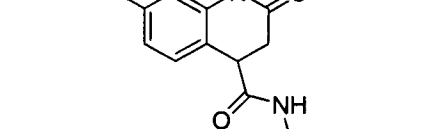
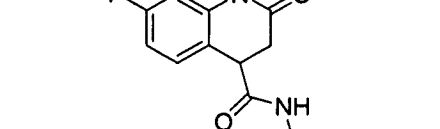
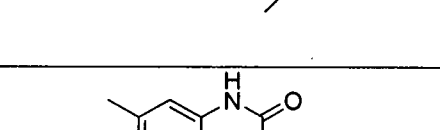
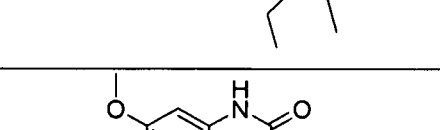
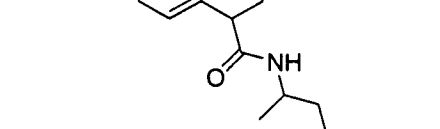
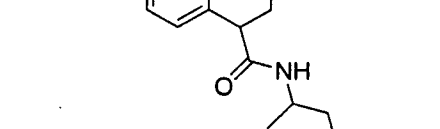
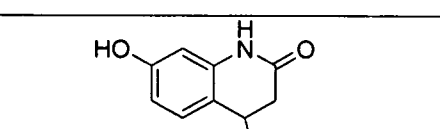
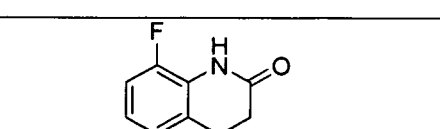
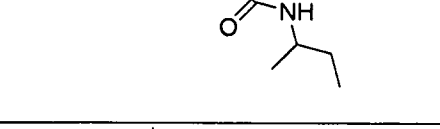
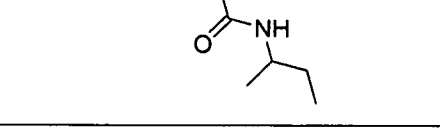
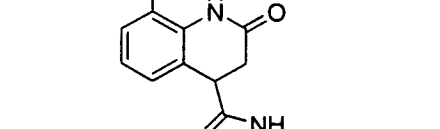
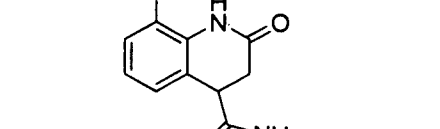


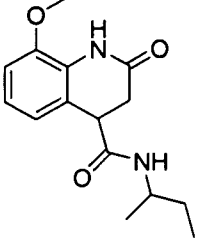
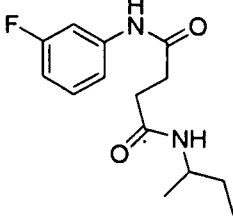
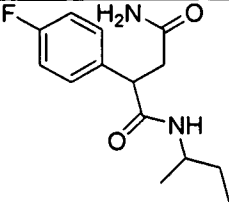
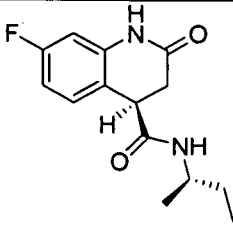
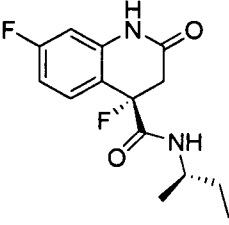
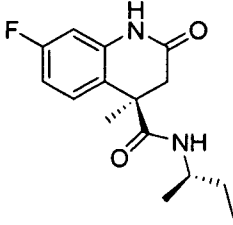
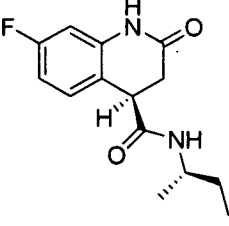
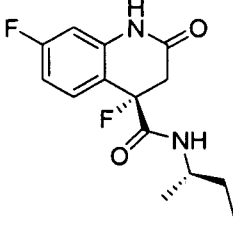
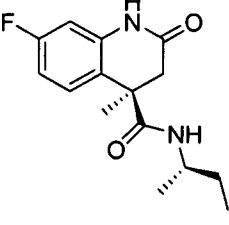
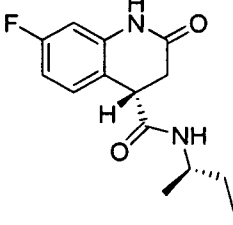
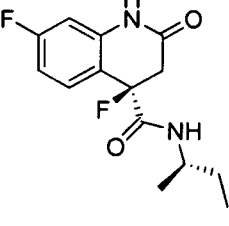
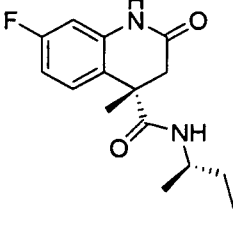
217. In some embodiments  $R^5$  can be

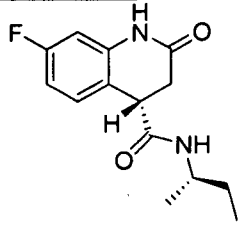
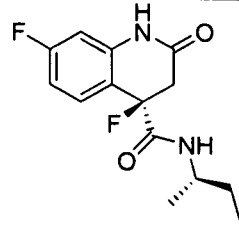
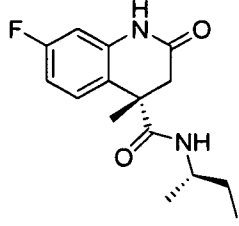
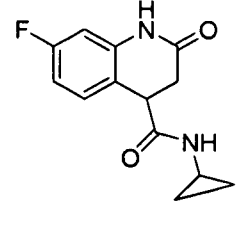
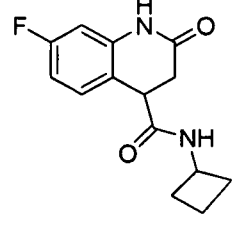
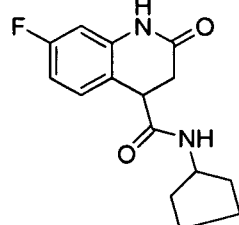
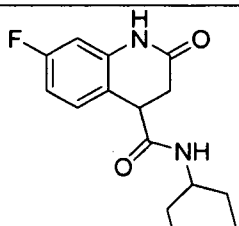
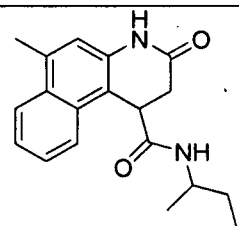
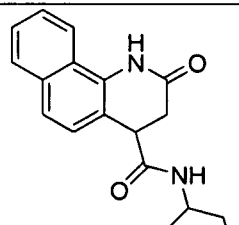
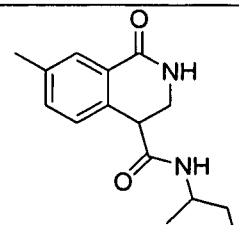
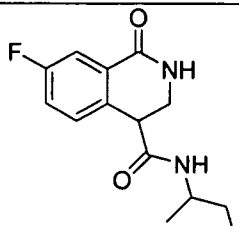
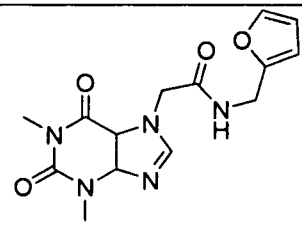
218. Non-limiting examples of compounds disclosed herein are shown in Table 1a.

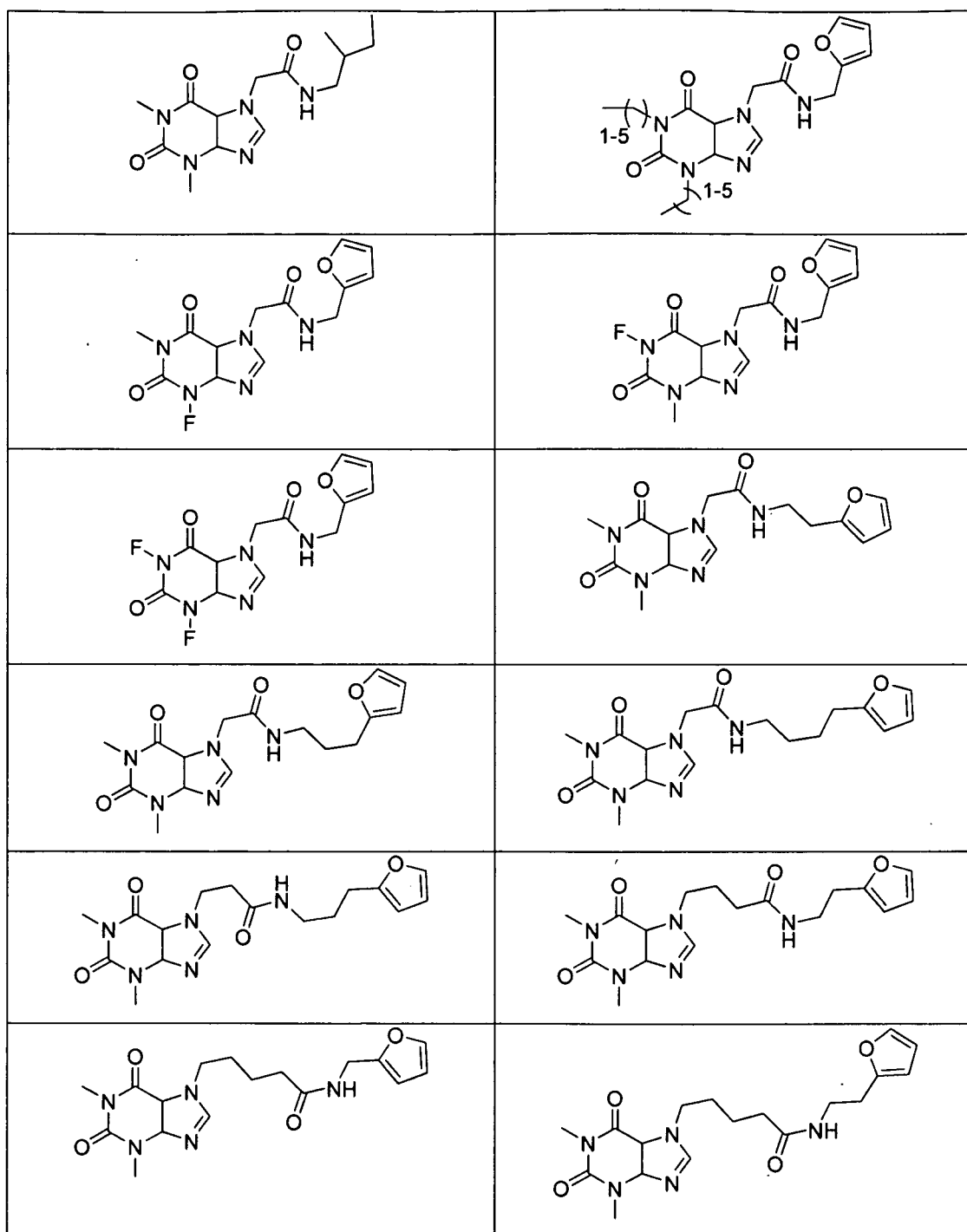
Table 1a.

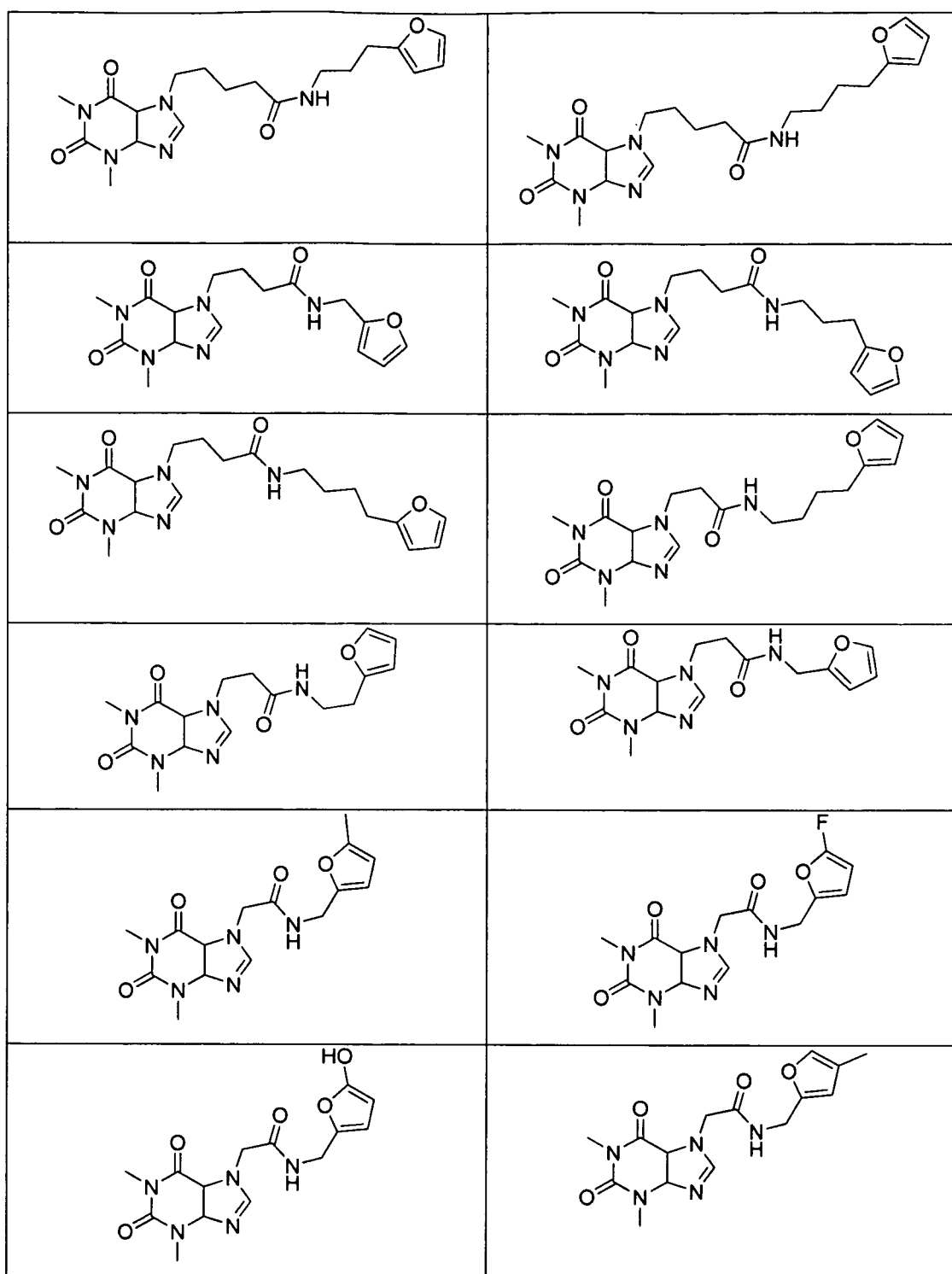
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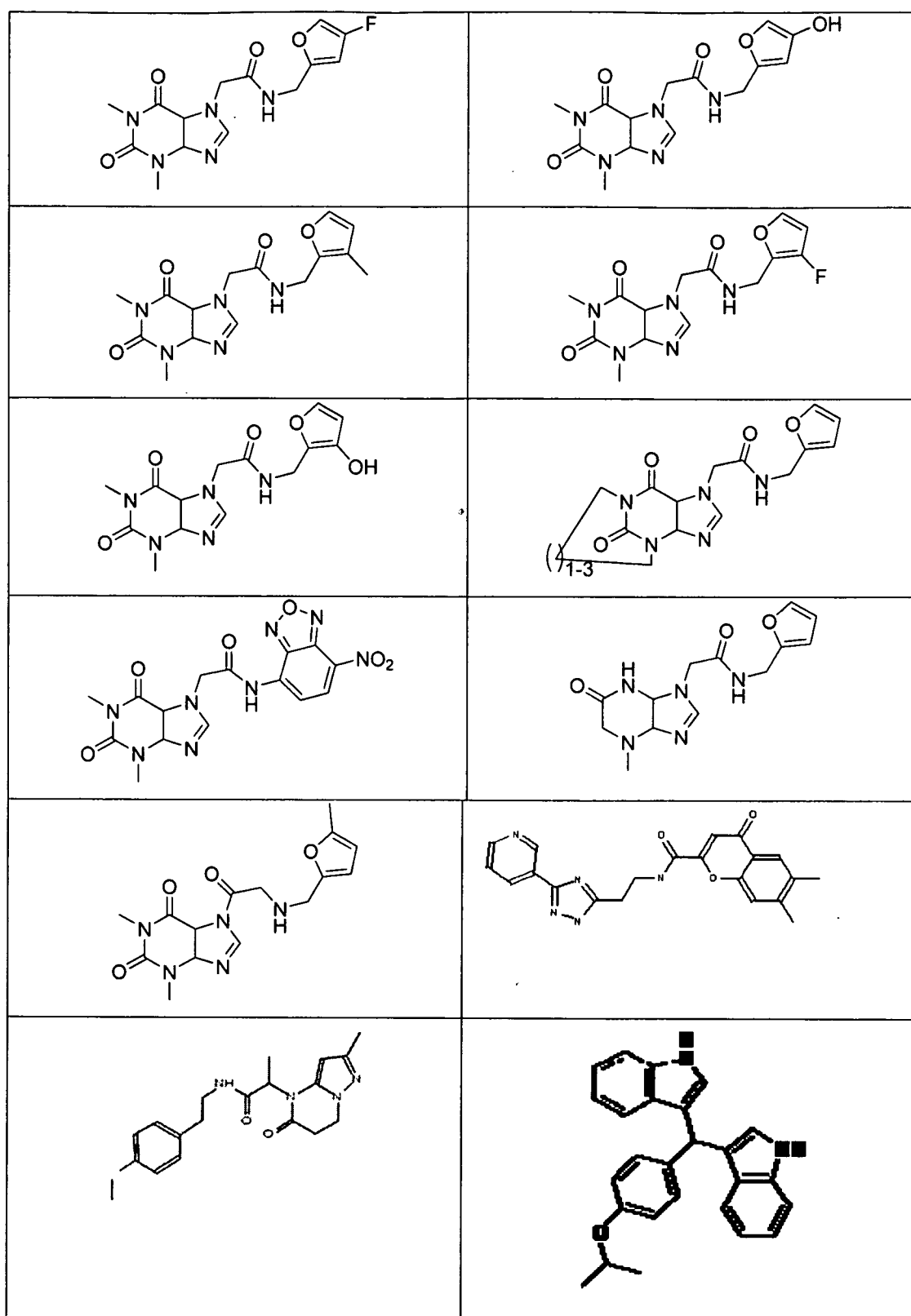
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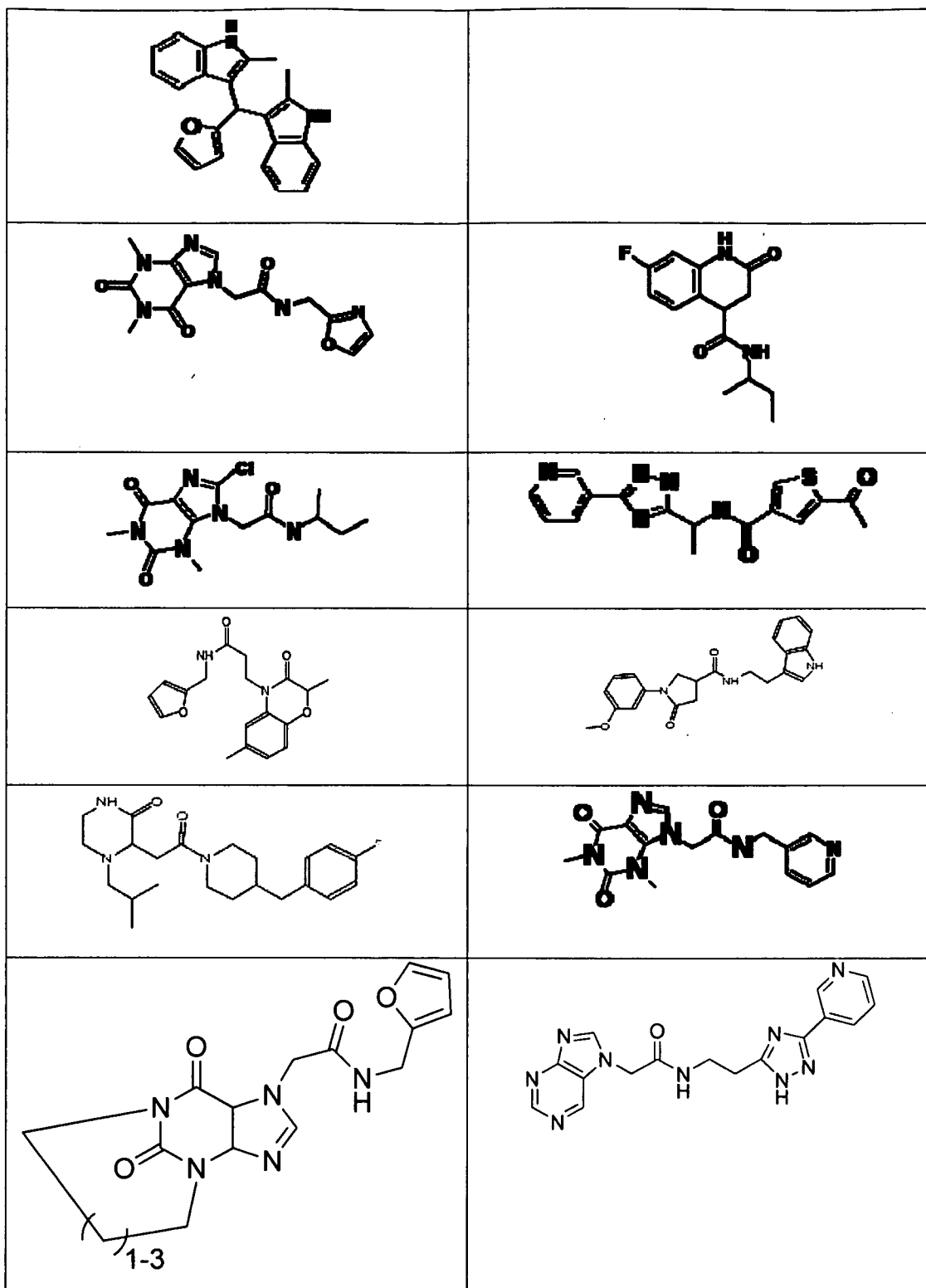
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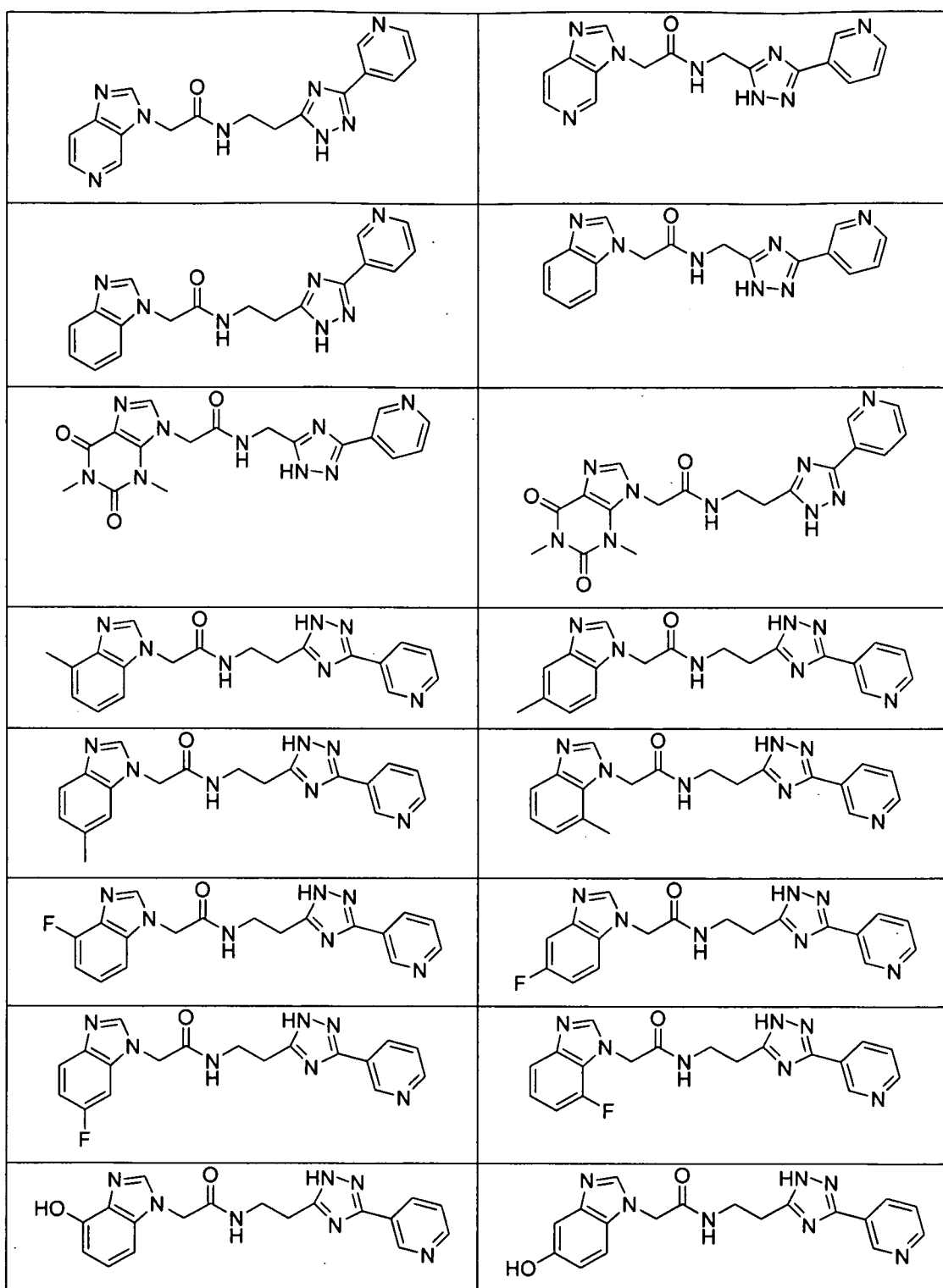
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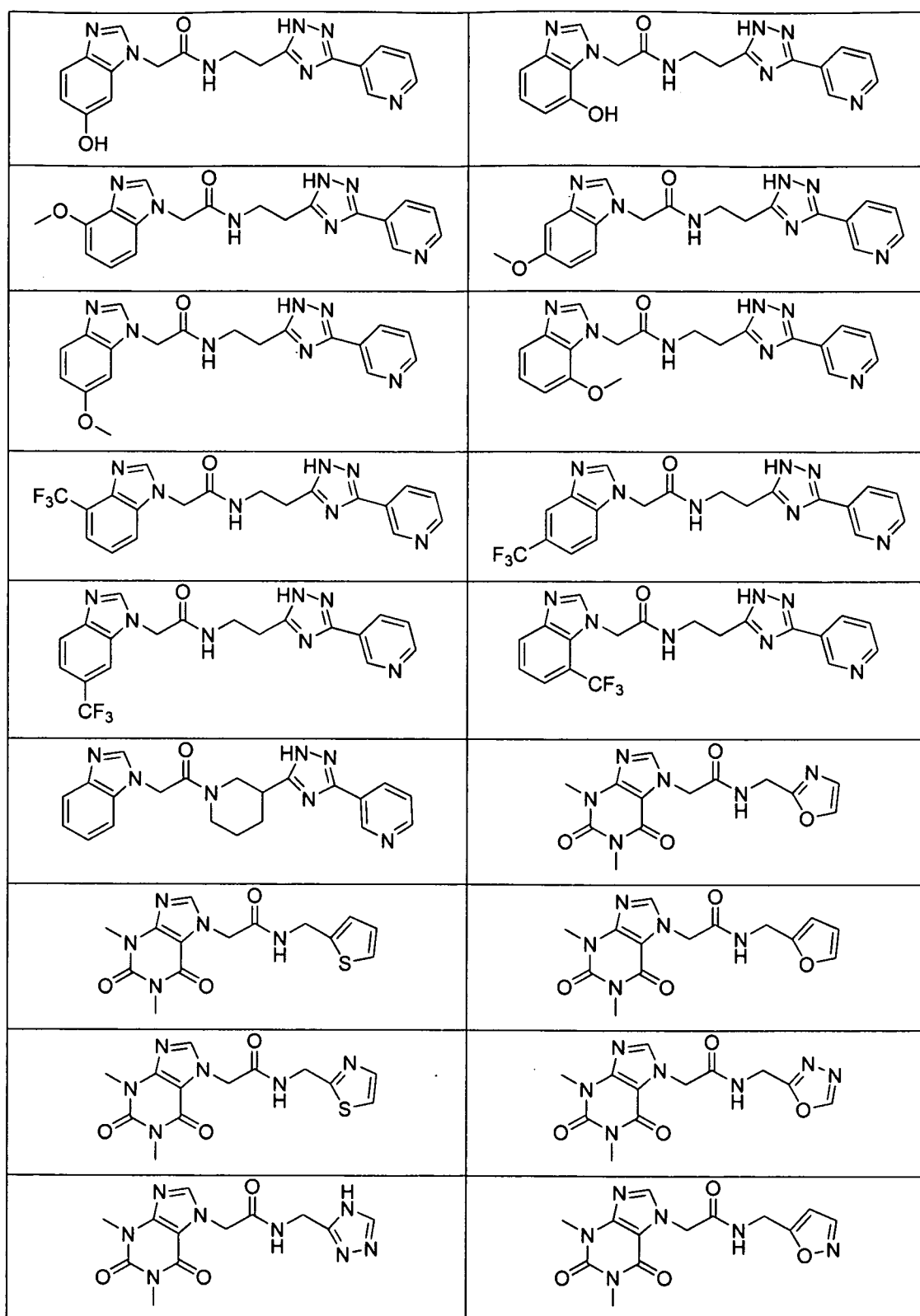


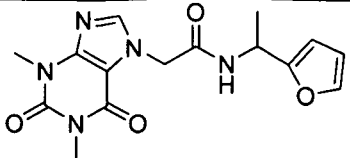
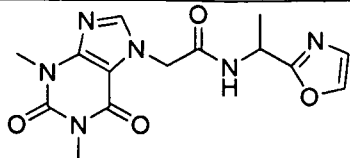
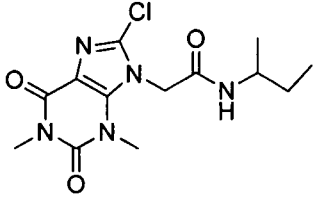
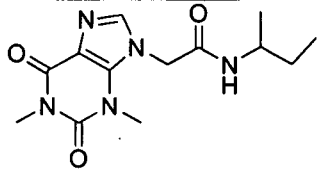
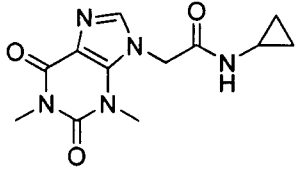
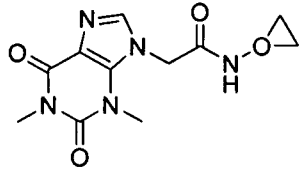
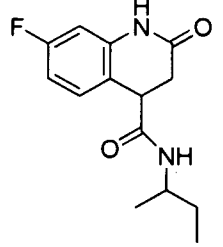
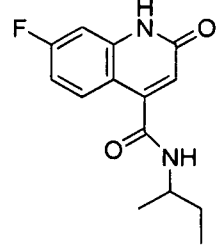
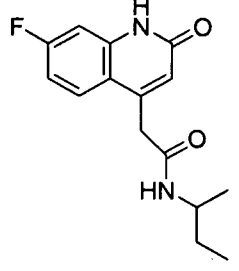
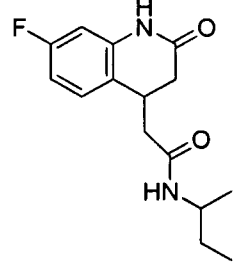
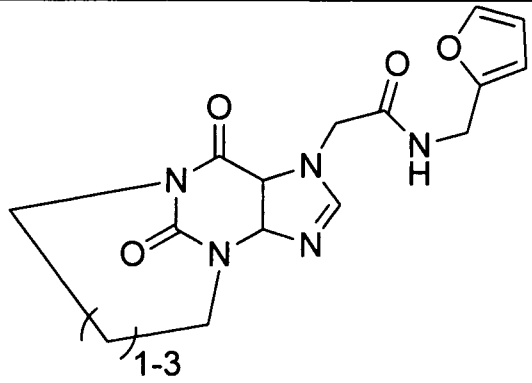










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**D. METHODS**

219. Also disclosed here in are methods of preventing and treating tumors of the nervous system, comprising administering to a subject in need thereof a pharmaceutically effective amount of a composition that inhibits p75 neurotrophic receptors and prevents the spread of tumors in healthy nervous tissue.

220. Also disclosed herein is a method comprising administering to a subject in need of inhibition of a p75 neurotrophic receptors (p75<sup>NTR</sup>) a composition comprising a compound of any one of claims 1-64.

221. In one embodiment the subject can be suffering from or at risk for a disease associated with p75<sup>NTR</sup>. In one aspect of the methods the subject can be diagnosed with a disease associated with p75<sup>NTR</sup>. In another aspect of the methods the disease can be cancer. In another aspect of the methods the cancer can be brain cancer. In another aspect of the methods the brain cancer can be Glioblastoma multiforme. In another aspect of the methods the subject can be monitored for p75<sup>NTR</sup> expression

222. In another embodiment the inhibition of p75<sup>NTR</sup> can inhibit glioma invasion.

223. In another embodiment the composition can further comprise a known p75<sup>NTR</sup> inhibitor.

224. In one embodiment the method can prevent or treat a disease associated with p75<sup>NTR</sup>.

225. Also disclosed here in are methods of preventing and treating tumors of the nervous system, comprising administering to a subject in need thereof a pharmaceutically effective amount of a composition that inhibits angiogenesis.

226. Also disclosed herein is a method comprising administering to a subject in need of inhibition of angiogenesis a composition comprising a compound of any one of structure I, II or III.

227. In one embodiment the subject can be suffering from or at risk for a disease associated with angiogenesis. In one aspect of the methods the subject can be diagnosed with a disease associated with angiogenesis.

228. In another embodiment the composition can further comprise a known angiogenesis inhibitor.

229. In one embodiment the method can prevent or treat a disease associated with angiogenesis.

230. In one embodiment the disease or disorder associated with angiogenesis can be selected from: tumor or cancer growth (neoplasia), skin disorders, neovascularization, inflammatory and arthritic diseases, retinoblastoma, cystoid macular edema (CME), exudative age-related macular degeneration (AMD), diabetic retinopathy, diabetic macular edema, or ocular inflammatory disorders.

231. In another embodiment the disease or disorder associated with angiogenesis can be a tumor or cancer growth (neoplasia). In some aspects the tumor or cancer growth is ocular cancer, rectal cancer, colon cancer, cervical cancer, prostate cancer, breast cancer and bladder cancer, oral cancer, benign and malignant tumors, stomach cancer, liver cancer, pancreatic cancer, lung cancer, corpus uteri, ovary cancer, prostate cancer, testicular cancer, renal cancer, brain/ens cancer, throat cancer, skin melanoma, acute lymphocytic leukemia, acute myelogenous leukemia, Ewing's Sarcoma, Kaposi's Sarcoma, basal cell carcinoma and squamous cell carcinoma, small cell lung cancer, choriocarcinoma, rhabdomyosarcoma, angiosarcoma, hemangioendothelioma, Wilms Tumor, neuroblastoma, mouth/pharynx cancer, esophageal cancer, larynx cancer, lymphoma, neurofibromatosis, tuberous sclerosis, hemangiomas, and lymphangiogenesis.

232. In another embodiment the disease or disorder associated with angiogenesis can be a skin disorder. In some aspects the skin disorder can be psoriasis, acne, rosacea, warts, eczema, hemangiomas, lymphangiogenesis, Sturge-Weber syndrome, venous ulcers of the skin, neurofibromatosis, and tuberous sclerosis.

233. In another embodiment the disease or disorder associated with angiogenesis is neovascularization. In some aspects the neovascularization can be diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma, retrolental fibroplasias, epidemic keratoconjunctivitis, vitamin A deficiency, contact lens overwear, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, Sjogren's, acne rosacea, phlyctenulosis, syphilis, Mycobacteria infections, lipid degeneration, chemical burns, bacterial ulcers, fungal ulcers, herpes simplex infections, herpes zoster infections, protozoan infections, Kaposi's sarcoma, Mooren's ulcer, Terrien's marginal degeneration, marginal keratolysis, trauma, rheumatoid arthritis, systemic lupus, polyarteritis, Wegener's sarcoidosis, scleritis, Stevens-Johnson disease, pemphigoid, radial keratotomy, corneal graft rejection, macular edema, macular degeneration, sickle cell anemia, sarcoid, syphilis,

pseudoxanthoma elasticum, Paget's disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis/vitritis, mycobacterial infections, Lyme disease, systemic lupus erythematosus, retinopathy of prematurity, Eales' disease, Behcet's disease, infections causing a retinitis or choroiditis, presumed ocular histoplasmosis, Best's disease, myopia, optic pits, Stargardt's disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, trauma and post-laser complications, and diseases associated with rubeosis (neovascularization of the ankle).

234. In another embodiment the disease or disorder associated with angiogenesis can be an inflammatory and arthritic disease. In some aspects the inflammatory and arthritic disease can be: rheumatoid arthritis, osteoarthritis, lupus, scleroderma, Crohn's disease, ulcerative colitis, psoriasis, sarcoidosis, Sarcoidosis, skin lesions, hemangiomas, Osier- Weber-Rendu disease, hereditary hemorrhagic telangiectasia, and osteoarthritis.

235. In another embodiment the disease or disorder can affect the dermis, epidermis, endometrium, retina, surgical wound, gastrointestinal tract, umbilical cord, liver, kidney, reproductive system, lymphoid system, central nervous system, breast tissue, urinary tract, circulatory system, bone, muscle, or respiratory tract.

236. In a particular embodiment the methods provide a method of preventing and treating tumors of the nervous system, comprising administering to a subject in need thereof a pharmaceutically effective amount of a composition that inhibits p75 neurotrophic receptors and prevents the spread of tumors in healthy nervous tissue, wherein the composition comprises a compound or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof having the formula:

### **G-H-I**

wherein

237. **G** can be an aryl, heteroaryl, cycloalkyl or heterocyclic residue selected from the group consisting of monocyclic and bicyclic ring systems, wherein **G** can optionally bear one or more substituents selected from electron withdrawing groups, halide, =O, alkyl, alkoxy, lower alkyl, lower alkoxy, and optionally substituted benzo groups;

238. **H** can be a linker having 2 to 12 members in any order of linear sequence, in which  $-C(=O)-$  can be a member,  $-N(R^a)-$  can be a member, and the rest of the members if any can optionally be substituted methylene groups, wherein  $R^a$  can be H or independently unsubstituted lower alkyl; one or more of the methylene groups if present can be optionally substituted independently by a respective  $R^b$ , wherein each  $R^b$  can be lower alkyl, heteroaryl, or optionally substituted phenyl, and the identity of each  $R^b$  can be independent of the identity of  $R^a$  and of respective  $R^b$  on other methylene groups in the linker; and optionally  $R^a$  and a respective  $R^b$  can together form a bridge; and

239. **I** can be an end group that can be: a  $C_1$ - $C_{10}$  hydrocarbon moiety;  $C_3$ - $C_{10}$  aryl,  $C_3$ - $C_{10}$  cycloalkyl,  $C_3$ - $C_9$  heterocyclic; optionally substituted indenyl; optionally substituted phenyl; or a 5- or 6- member heteroaryl ring having up to three heteroatoms selected from O, N and S, wherein the heteroaryl ring can optionally bear a substituent **J**; and wherein

240. **J** can be an electron withdrawing group, lower hydrocarbon moiety, lower alkoxy, optionally substituted phenyl, or can optionally be substituted fused benzo group, or

241. if **I** is a triazole, then **J** can optionally be a six-member heteroaryl ring in which the heteroatoms are 1 or 2 nitrogen atoms, and **J** is optionally substituted at one or more carbon atoms on the ring by an electron withdrawing group, lower hydrocarbon moiety, or lower alkoxy.

242. In another embodiment the methods provides a method of treating a disease or disorder associated with angiogenesis in a subject, the method comprising the step of administering to the subject an effective amount of a composition comprising a compound or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof having the formula:

### **G-H-I**

wherein

243. **G** can be an aryl, heteroaryl, cycloalkyl or heterocyclic residue selected from the group consisting of monocyclic and bicyclic ring systems, wherein **G** can optionally bear one or more substituents selected from electron withdrawing

groups, halide, =O, alkyl, alkoxy, lower alkyl, lower alkoxy, and optionally substituted benzo groups;

244. H can be a linker having 2 to 12 members in any order of linear sequence, in which  $-C(=O)-$  can be a member,  $-N(R^a)-$  can be a member, and the rest of the members if any can optionally be substituted methylene groups, wherein

$R^a$  can H or independently unsubstituted lower alkyl,

one or more of the methylene groups if present can be optionally substituted independently by a respective  $R^b$ , wherein each  $R^b$  can be lower alkyl, heteroaryl, or optionally substituted phenyl, and the identity of each  $R^b$  can be independent of the identity of  $R^a$  and of respective  $R^b$  on other methylene groups in the linker; and

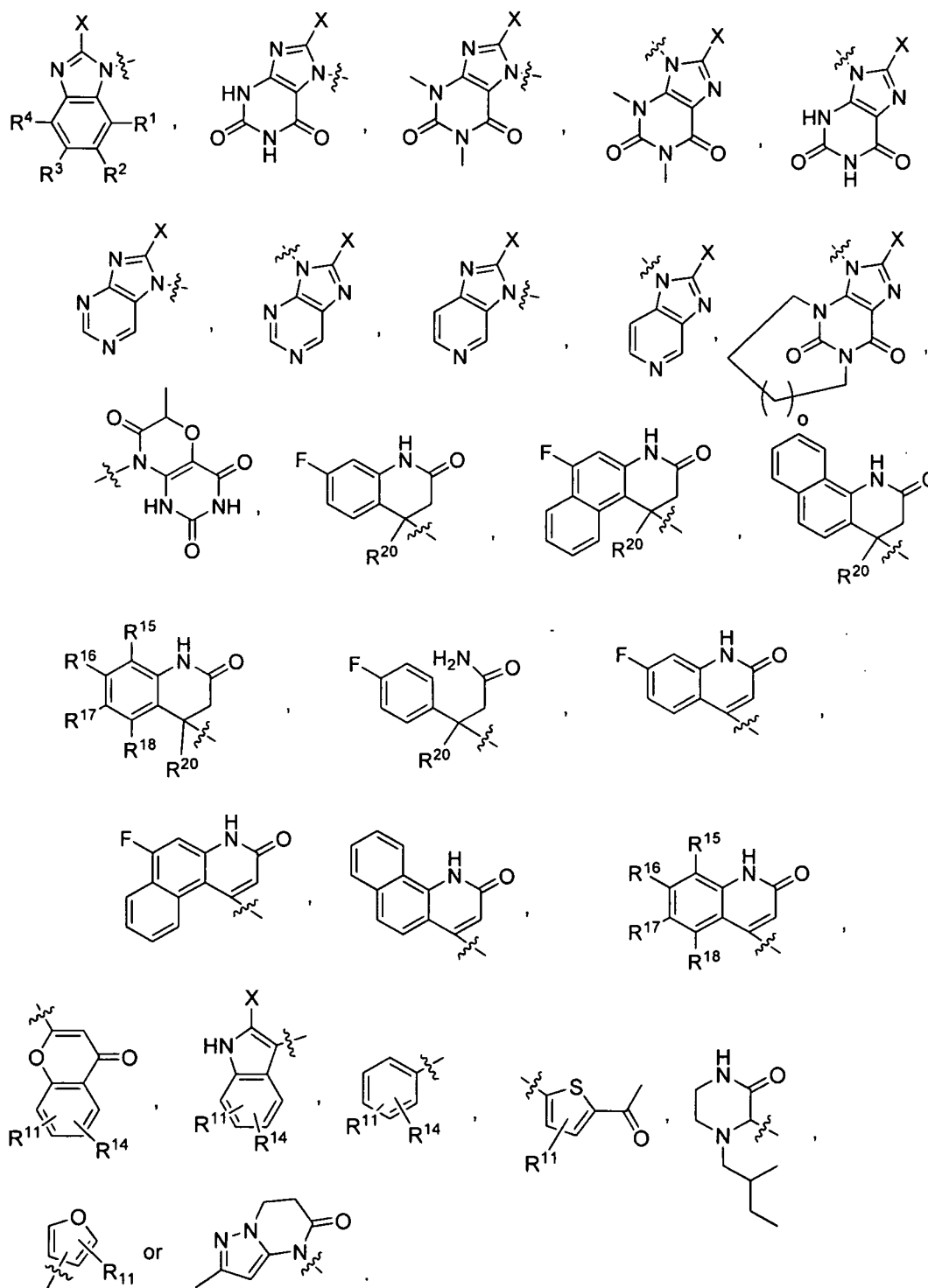
optionally  $R^a$  and a respective  $R^b$  can together form a bridge; and

245. I can be an end group that can be: a  $C_1$ - $C_{10}$  hydrocarbon moiety;  $C_3$ - $C_{10}$  aryl,  $C_3$ - $C_{10}$  cycloalkyl,  $C_3$ - $C_9$  heterocyclic; optionally substituted indenyl; optionally substituted phenyl; or a 5- or 6- member heteroaryl ring having up to three heteroatoms selected from O, N and S, wherein the heteroaryl ring can optionally bear a substituent J; and wherein

246. J can be an electron withdrawing group, lower hydrocarbon moiety, lower alkoxy, optionally substituted phenyl, or can optionally be substituted fused benzo group, or

247. if I is a triazole, then J can optionally be a six-member heteroaryl ring in which the heteroatoms are 1 or 2 nitrogen atoms, and J is optionally substituted at one or more carbon atoms on the ring by an electron withdrawing group, lower hydrocarbon moiety, or lower alkoxy.

248. In some embodiments G can be



249. In some embodiments G can include one to eight methylene groups, each methylene group can be optionally substituted with a lower alkyl, halide,

lower alkoxy, aryl, heteroaryl, cycloalkyl, heterocyclyl; aryl; heteroaryl; cycloalkyl; heterocyclyl; -C(=O)-; -N(R<sup>a</sup>)-; -O-; -S-;

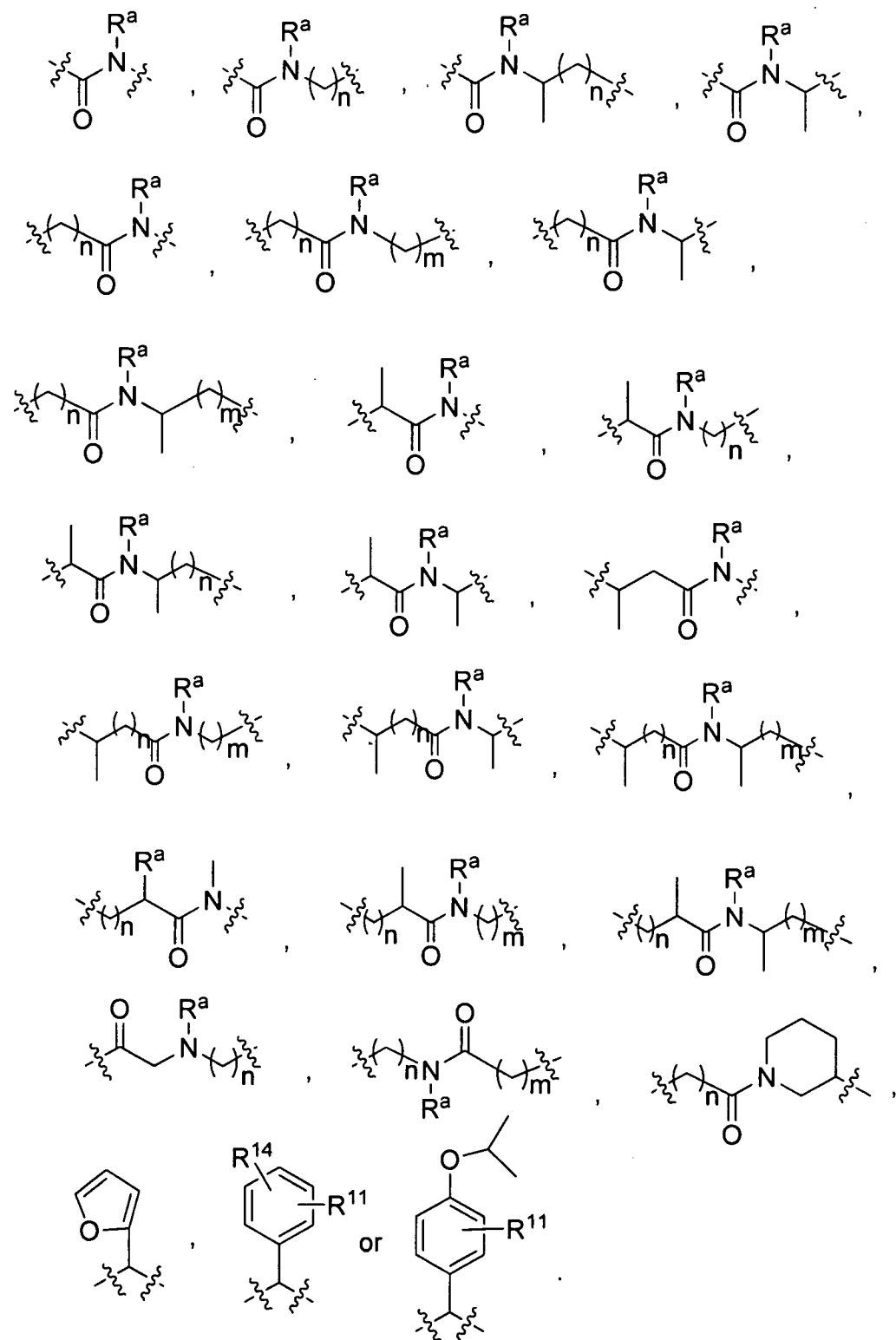
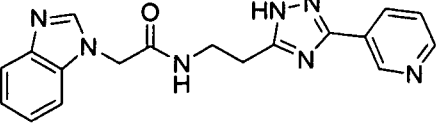
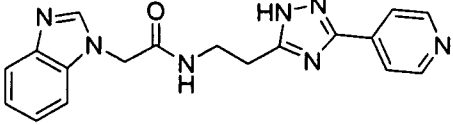
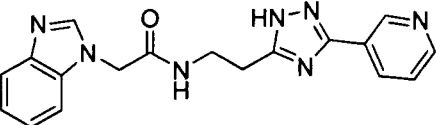
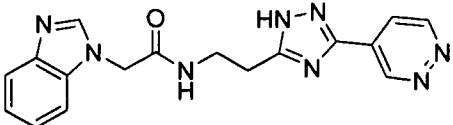
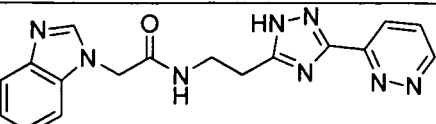
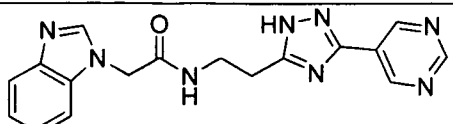
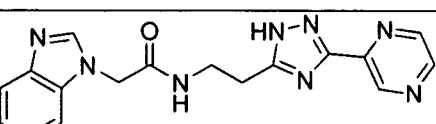
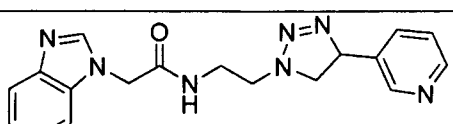
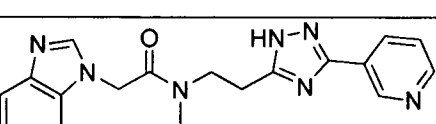
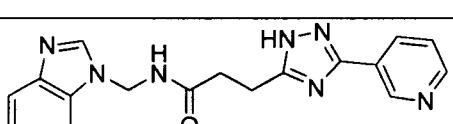
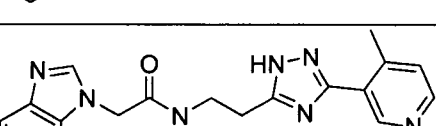
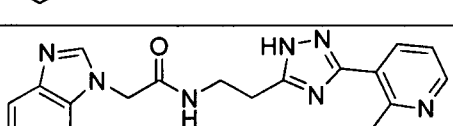
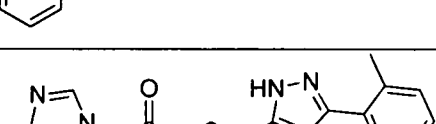
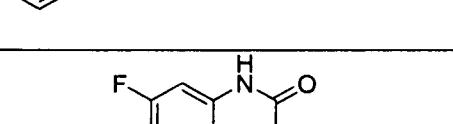
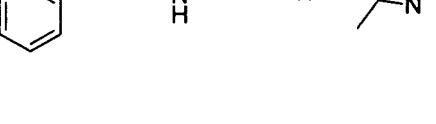
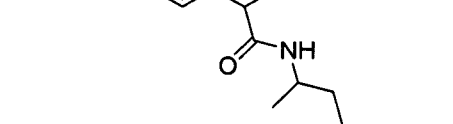
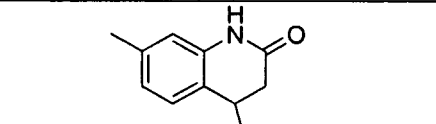
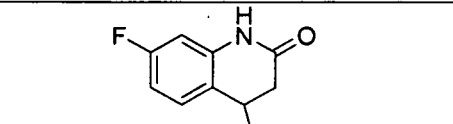
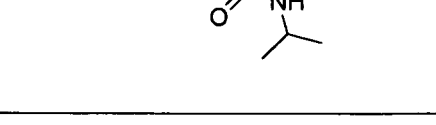
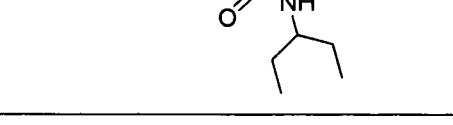
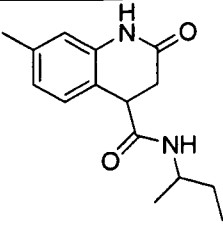
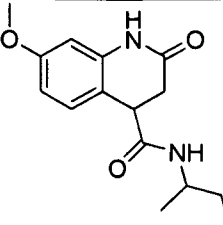
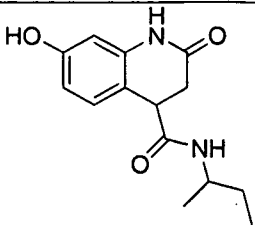
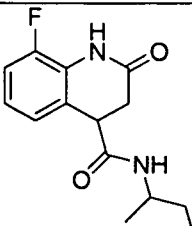
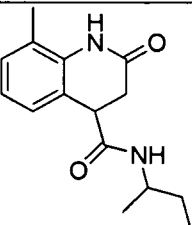
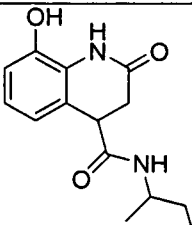
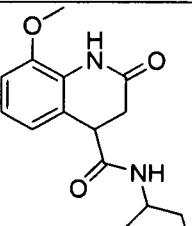
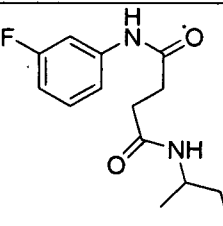
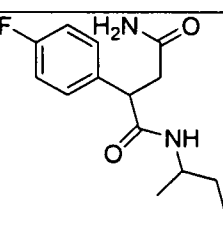
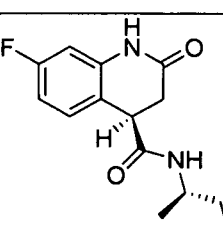
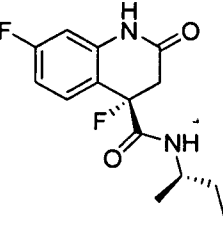
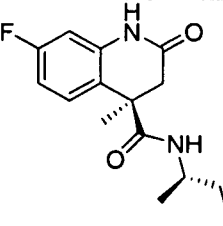
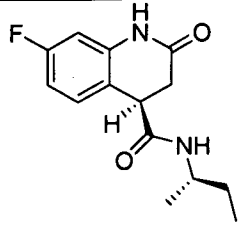
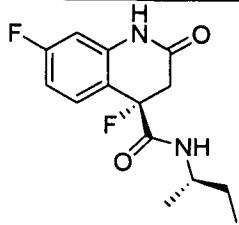
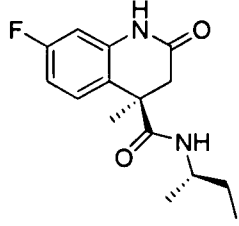
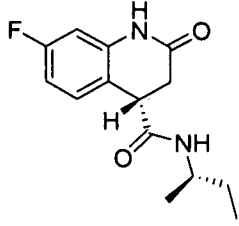
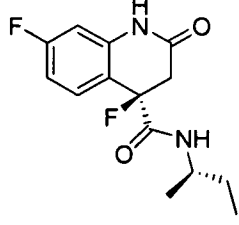
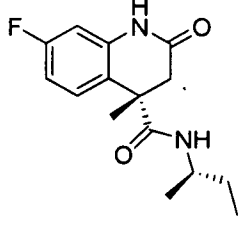
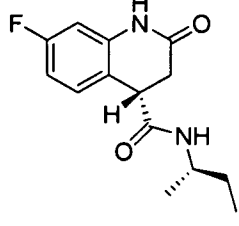
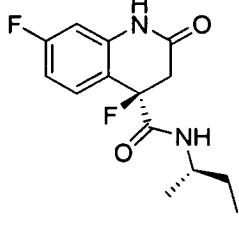
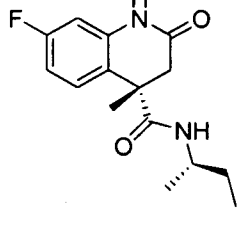
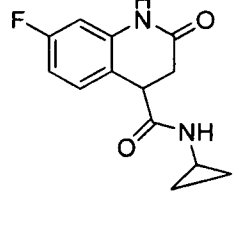
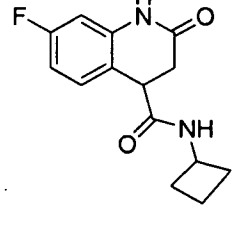
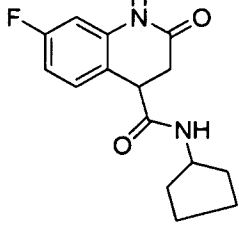


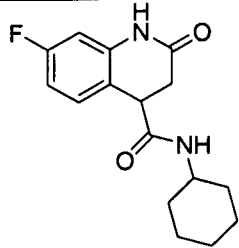
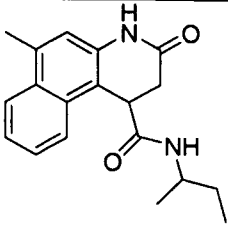
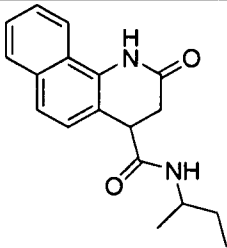
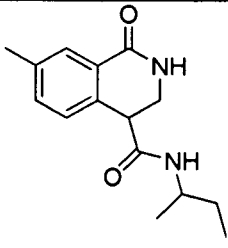
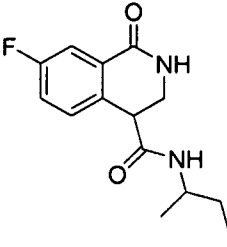
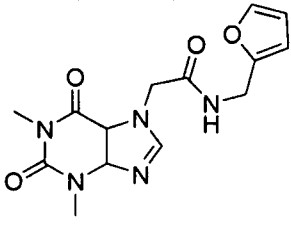
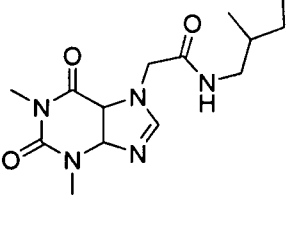
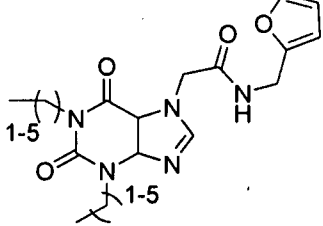
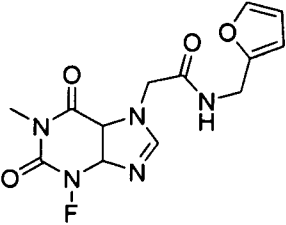
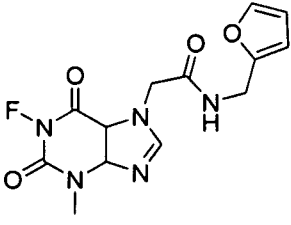
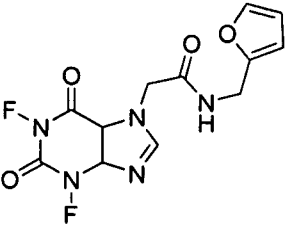
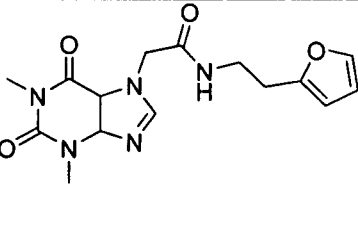


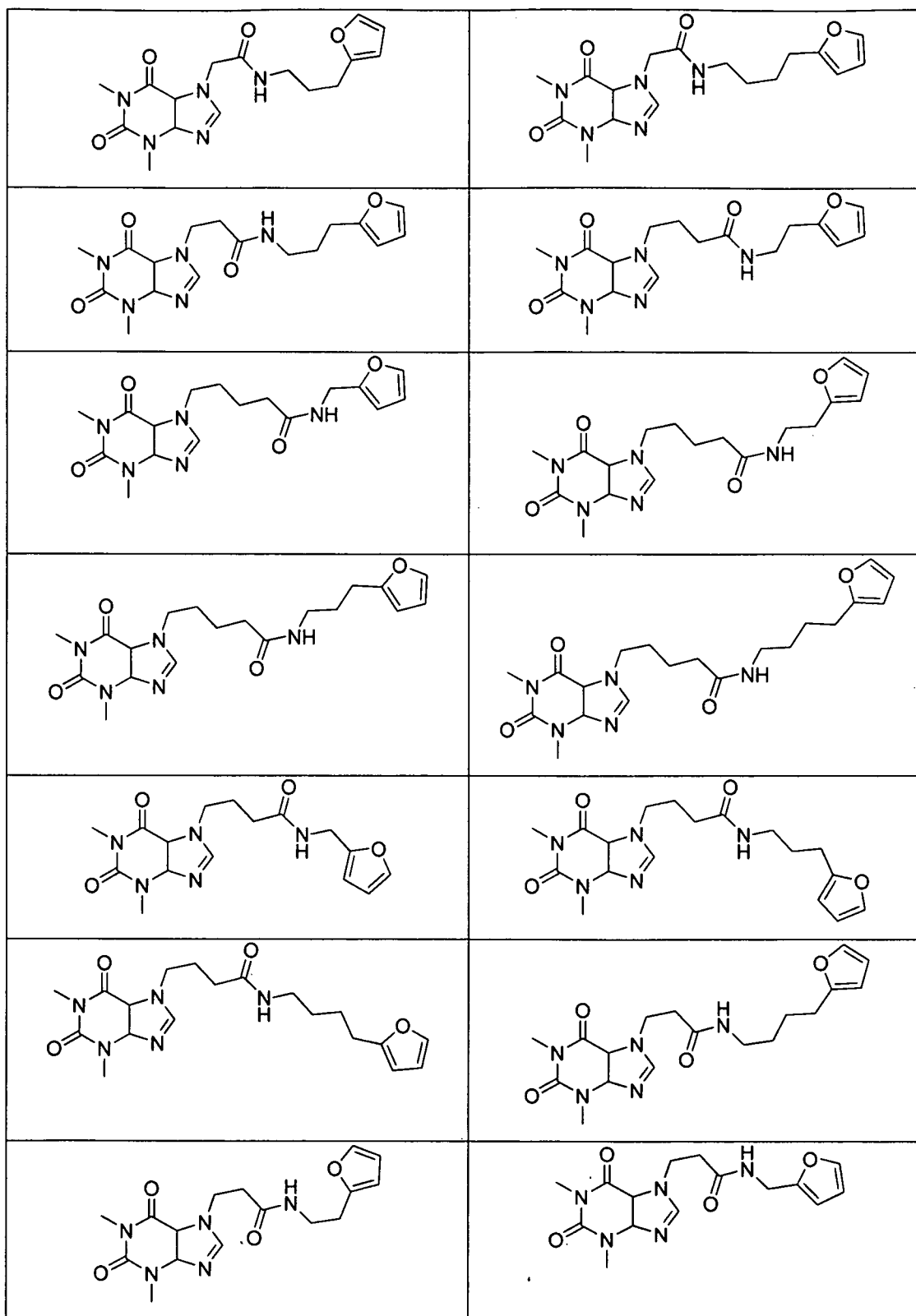
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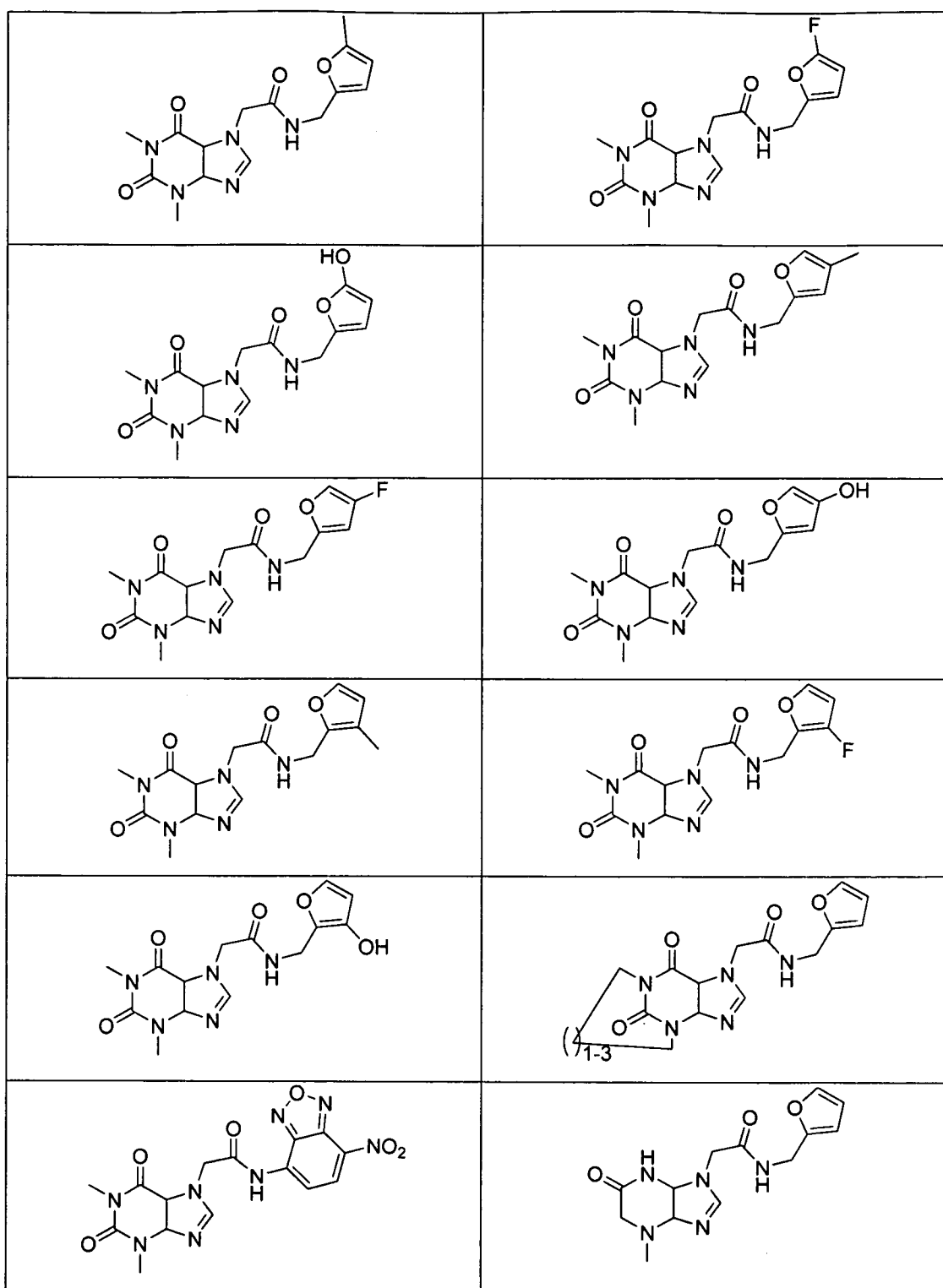
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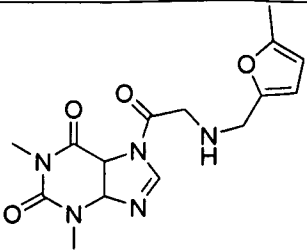
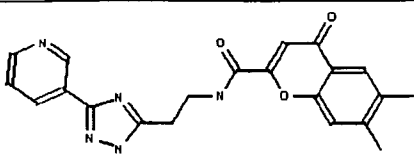
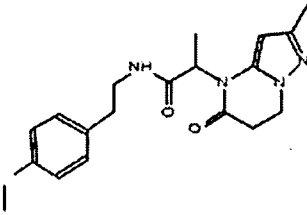
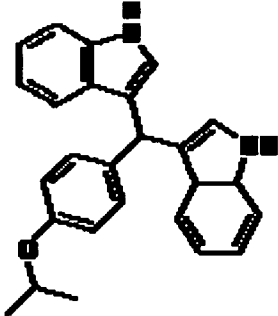
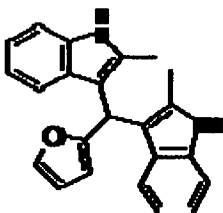
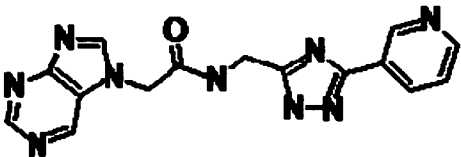
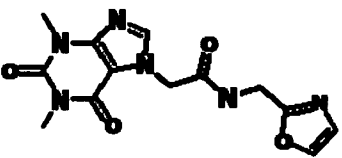
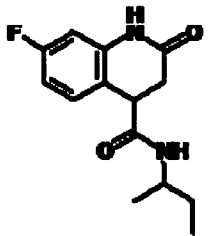
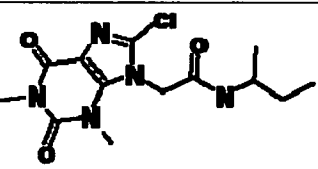
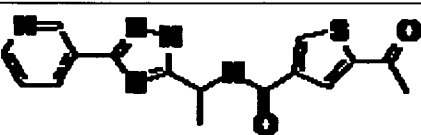
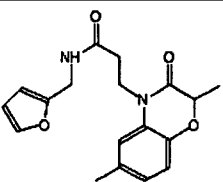
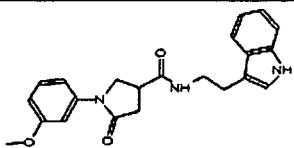
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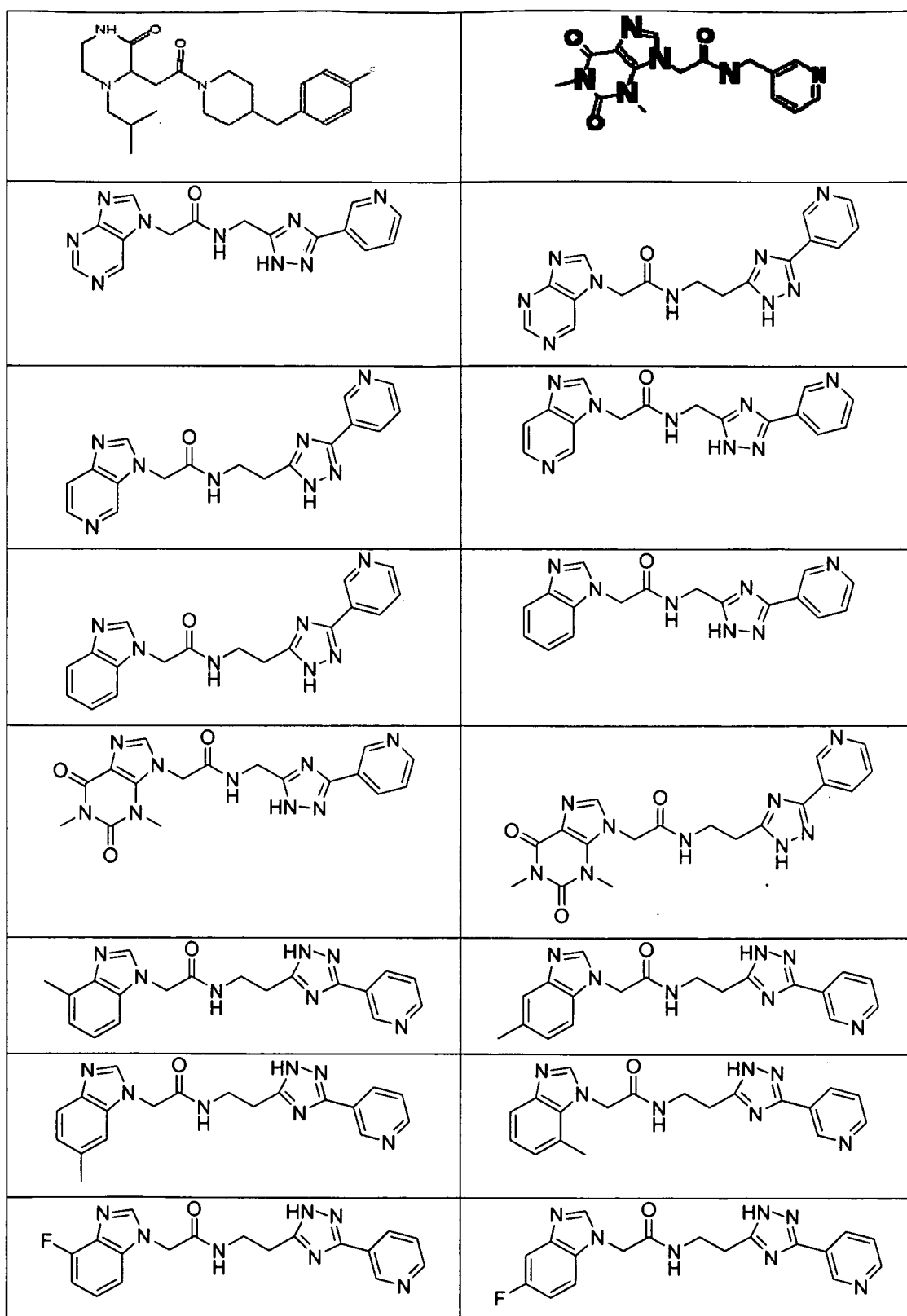
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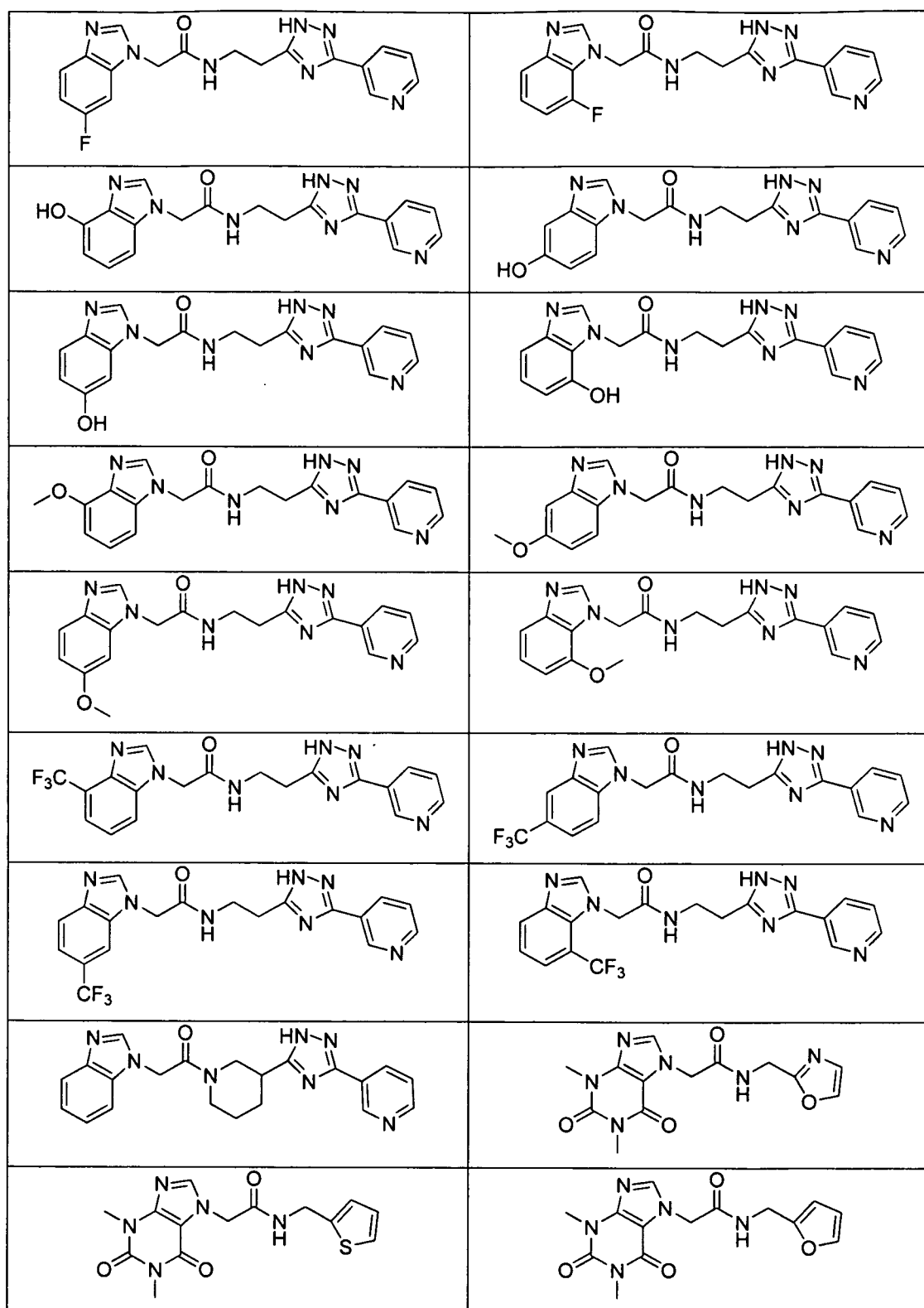
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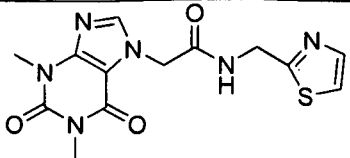
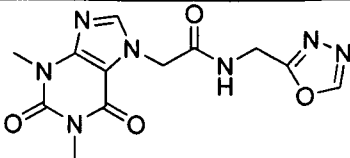
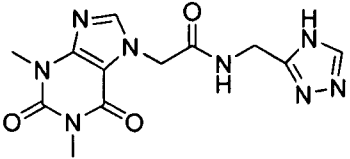
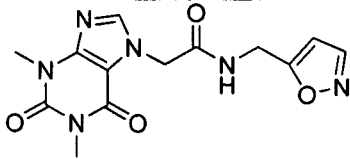
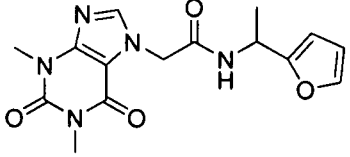
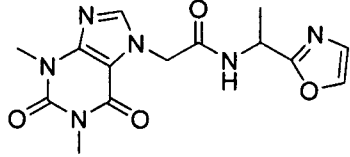
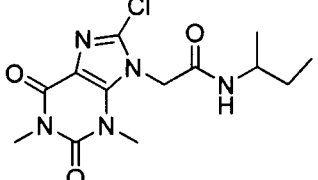
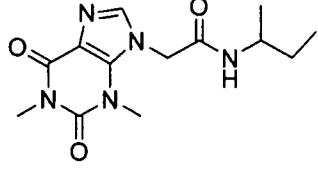
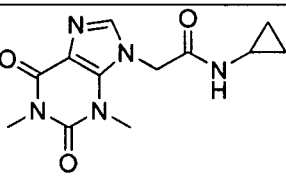
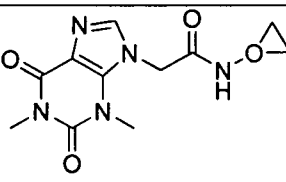
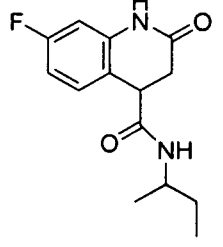
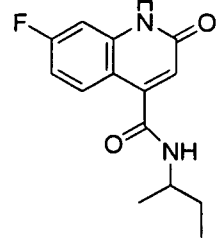
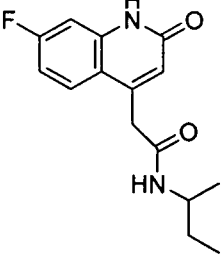
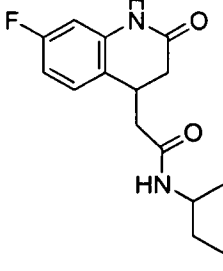


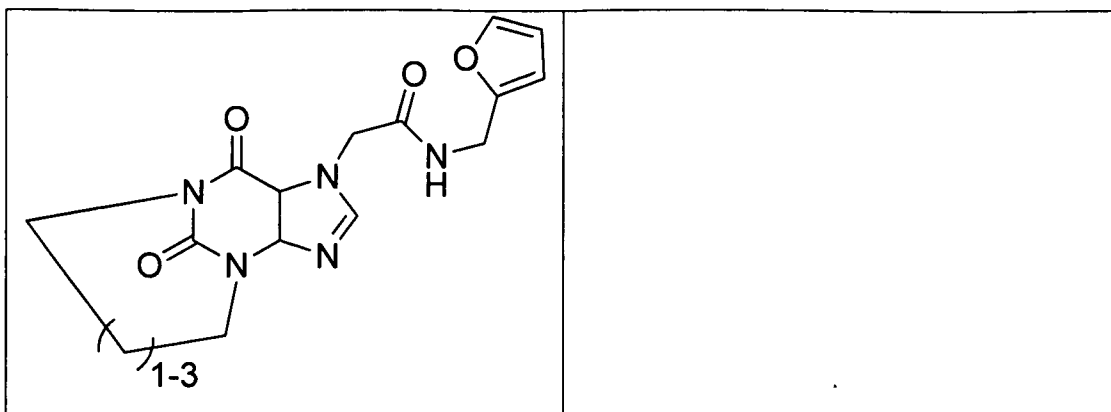


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## E. EXAMPLES

### Example 1 – p75<sup>NTR</sup> Assay

254. The gene coding for p75<sup>NTR</sup> was inserted into the bait vector pEG202 to express a fusion protein with the *E.coli* LexA DNA-binding protein. The genes coding for the proteins (eg. Pro-NGF) which interacts with p75<sup>NTR</sup> is then subcloned in the target plasmid pJG4-5 to form a gene fusion with the bacterial acid blob domain B42. Neither LexA bound upstream of a reporter gene nor B42 alone can activate transcription of a reporter. However, if LEXA and B42 are brought together via fusions with two interacting proteins, reporter gene expression can be detected. Two reporter genes were employed. The first gene lacZ, contained on the reporter plasmid pSH18-38 under the control of 8 LexA operators. The expression of  $\beta$ -galactosidase can easily be monitored on medium containing X-Gal. The second reporter- LEU2 is in the genome of the yeast *S.cerevisiae* host strain EGY48, genetically altered to be under the control of 6 LexA operators. When activated the reporter allows the EGY48 strain to grow on a selective medium without leucine. In addition to leucine, EGY48 is also auxotrophic for histidine, uracil and tryptophan which allows for selection of clones stably transformed with the bait vector EG202, lacZ reporter plasmid pSH18-34 and target plasmid pJG4-5, respectively. The dependence of activation of the reporter genes on the interaction between bait and target can be confirmed in this system due to the nutritional control of the expression of the B42-target protein fusion. It is activated on medium containing galactose as source of carbon and repressed on medium with glucose. When the host EGY48 is transformed with bait, target and reporter plasmids and the interaction between p75 and pro-NGF is confirmed. The experiments are repeated on a medium containing varying concentrations of the drug screening for loss of interaction.

255. The low affinity neurotrophin receptor p75<sup>NTR</sup> is a multifunctional receptor with important roles in neurotrophin signaling, axon outgrowth, and is an important in signalling survival of oligodendroglia and neurons. It is transcriptionally regulated with spatial and temporal precision during nervous system development, injury and regeneration. The p75 gene expression is directly modulated by the early growth response (Egr) transcriptional activators, Egr1 and Egr3, which bind and transactivate the p75 promoter *in vitro* and *in vivo*.

256. Using a protein model of p75<sup>NTR</sup>/NGF 40,000 compounds were virtually screened for protein/protein inhibitors which resulted in the identification of 125 compounds for screening in displacement assays (see Figure 1). 35 of these compounds were purchased or synthesized and tested in a p75/NGF inhibitory assay.

**Example 2 – Development and evaluation of p75<sup>NTR</sup> inhibitors**

257. Development and evaluation of potential p75<sup>NTR</sup> inhibitors can be done as described below.

258. A. Develop and select the optimal p75<sup>NTR</sup> inhibitors (modulators or gamma secretase inhibitors) using *in vitro* high throughput assays. Develop and screen p75<sup>NTR</sup> modulators and gamma secretase inhibitors that inhibit p75<sup>NTR</sup> in glioma invasion and BTSC function. p75<sup>NTR</sup> modulators can be derived from the small molecule libraries and known gamma secretase inhibitors and screened in a high throughput assay. These will be screened for activity *in vitro* for inhibition of p75<sup>NTR</sup> in glioma lines and BTSCs derived from surgical specimens. The best compounds will then be further evaluated in B.

259. B. The toxicity and efficacy of the selected p75<sup>NTR</sup> inhibitors (modulators or gamma secretase inhibitors) will be determined using *in vivo* models of invasive gliomas and BTSCs. The dose will be optimized of the compounds, then their route of administration and their MTD in immunocompromised and immunocompetent rodents will be determined. Fluorescently labeled invasive clones will be used from U87 and U251N, GL261 and p75<sup>NTR</sup> expressing and non-expressing BTSCs. Proliferation, tumor size, invasion/metastases and survival will be assessed using conventional measures and via imaging with our 9.4T animal MRI. The best compounds will then be evaluated for invasive glioma and BTSCs *in vivo* in C.

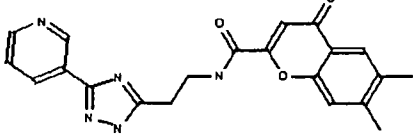
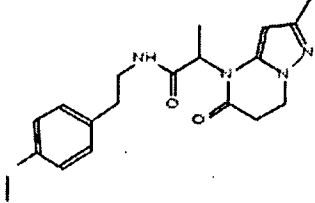
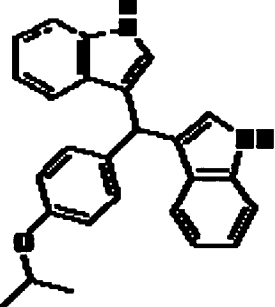
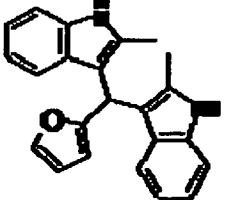
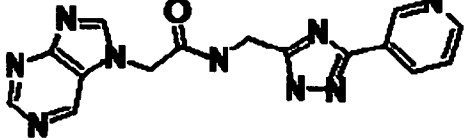
260. C. The toxicity and efficacy of combination therapy (p75<sup>NTR</sup> inhibitor & bevacizumab) will be determined in *in vitro* and *in vivo* models of invasive gliomas and BTSCs. The prevalence of p75<sup>NTR</sup> expression will be determined from clinically available biopsy specimens of remotely invasive tumors in patients taking bevacizumab. The toxicity and efficacy of combination therapy (p75<sup>NTR</sup> inhibitor & bevacizumab) will be determined using approaches described elsewhere herein (and assessing markers of angiogenesis). In particular the combination therapy will be determined that inhibit the invasive phenotype arising when bevacizumab is combined with p75<sup>NTR</sup> inhibitors using invasive glioma clones and BTSCs.

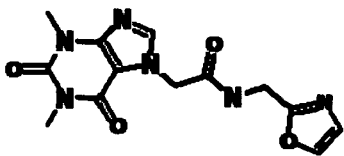
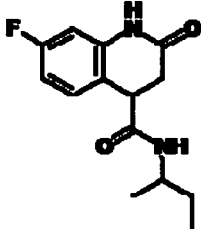
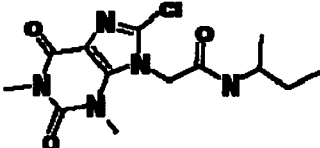
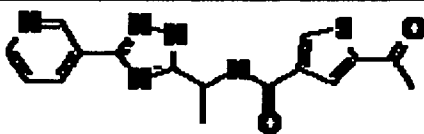
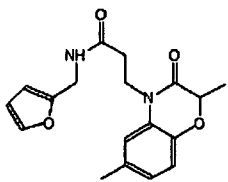
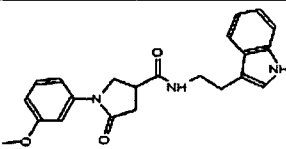
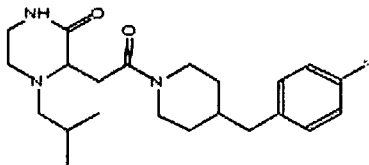
**Example 3 – p75/NGF inhibitors/Screening of small molecule inhibitors of p75<sup>NTR</sup> by ligand displacement assay**

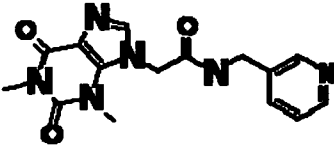
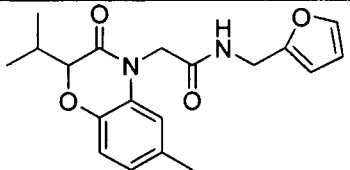
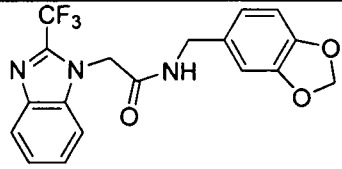
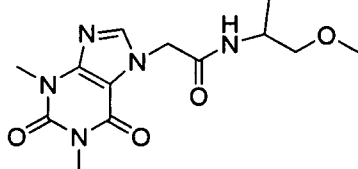
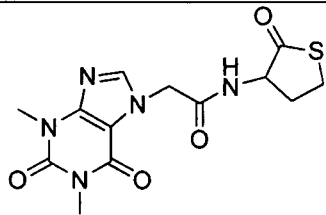
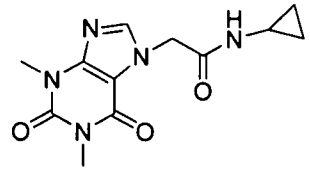
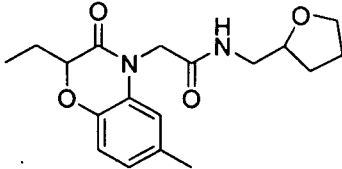
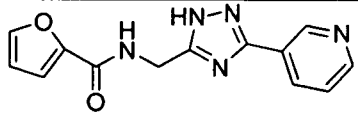
261. Using *in silico* screening of NGF binding pockets in glycosylated p75<sup>NTR</sup> a total of 22 putative p75 inhibitors have been identified and characterized for IC<sub>50</sub>s to inhibit binding in a NGF displacement assay using the extracellular domain of glycosylated p75<sup>NTR</sup>. IC<sub>50</sub>s were in high nanomolar and micromolar ranges (Table 2). The values of IC<sub>50</sub> were calculated using the GraphPad software Prism 4. Four compounds tested (compounds A, B, C, and D) have IC<sub>50</sub> concentrations in the nanomolar range. Compound A has the lowest IC<sub>50</sub> concentration of [562.9 nM] (Figure 2).

262. Compound A's specificity to NGF binding was further examined *in vitro* by testing its ability to disrupt BDNF binding to p75<sup>NTR</sup>. Compound A had no effect to BDNF binding in the nanomolar or micromolar range. The dose response and competition assays for p75 binding was also performed in the presence of NGF and BDNF. Compound A had no effect in inhibiting BDNF binding but its ability to inhibit NGF was attenuated into the micromolar range (Figure 3). Furthermore, compound A sensitized human glioma cells expressing ectopic p75 (U87/p75) at low  $\mu$ M concentration ( $\sim 1 \mu$ M) as compared to cells without p75 (Figure 4 and Table 3). The sensitization was pronounced further in U251 expressing ectopic p75. Taken together, these data indicates that compound A has specificity for NGF binding inhibition to p75.

Table 2.

| IC <sub>50</sub> p75/NGF<br>[nM] | Structure                                                                                              |
|----------------------------------|--------------------------------------------------------------------------------------------------------|
| 1613                             |  <p>Compound E</p>   |
| 74% at 2500 nM                   |  <p>Compound F</p>   |
| 69% at 2500 nM                   |  <p>Compound G</p>  |
| 72% at 2500 nM                   |  <p>Compound H</p> |
| 593.6                            |                    |

|                |                                                                                      |
|----------------|--------------------------------------------------------------------------------------|
|                | Compound A                                                                           |
| 775.3          |    |
|                | Compound B                                                                           |
| 1054           |    |
|                | Compound C                                                                           |
| 952.7          |   |
|                | Compound D                                                                           |
| 69% at 2500 nM |  |
| 75% at 2500 nM |  |
| 63% at 2500 nM |  |
| 52% at 2500 nM |  |

|                |                                                                                                      |
|----------------|------------------------------------------------------------------------------------------------------|
| 91% at 2500 nM |  <p>Compound I</p> |
| 8158 nM        |                    |
| 6990           |                    |
| 7515           |                   |
| 7243           |                  |
| 5777           |                  |
| 6091           |                  |
| 5778           |                  |

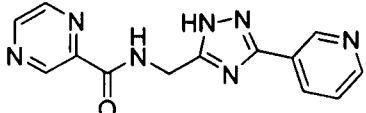
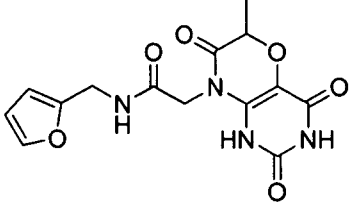
|      |                                                                                    |
|------|------------------------------------------------------------------------------------|
| 5843 |  |
| 5777 |  |

Table 3.

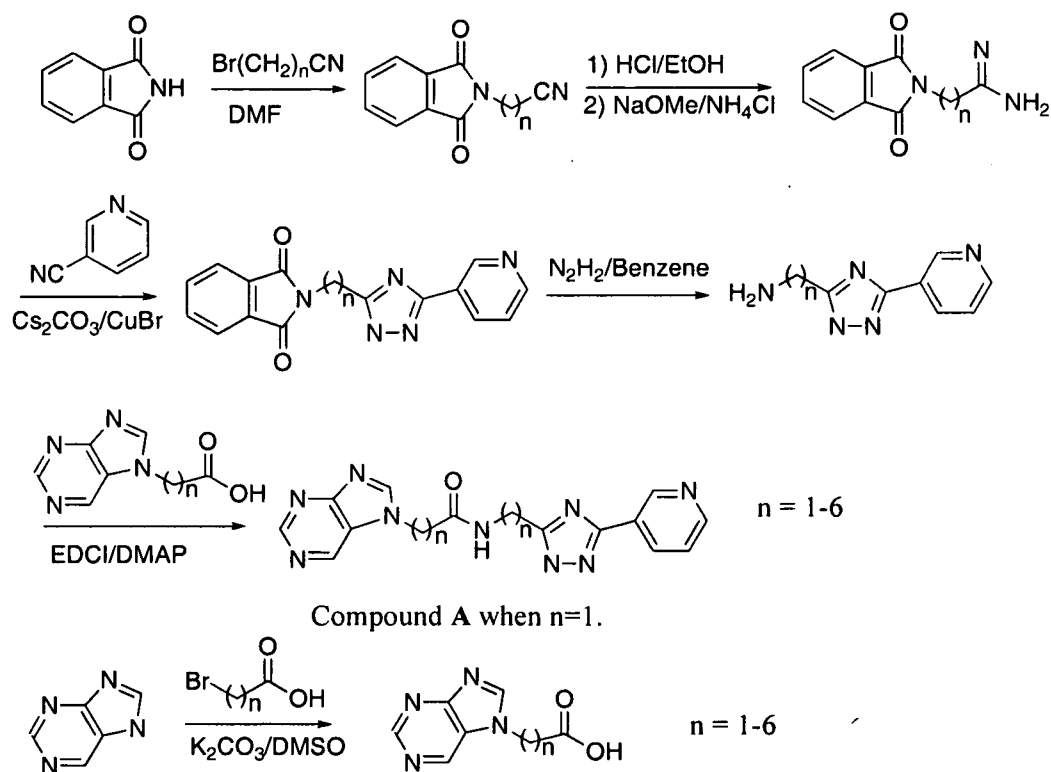
| Cell Line  | Compound A      |        | Compound H      |        |
|------------|-----------------|--------|-----------------|--------|
|            | IC50 [ $\mu$ M] | SEM    | IC50 [ $\mu$ M] | SEM    |
| U87        | 2.946           | 0.3277 | 4.395           | 0.7029 |
| U87 pcDNA  | 4.063           | 0.8439 | 3.286           | 0.0488 |
| U87 p75    | 0.975           | 0.0719 | 2.689           | 0.1788 |
| U251       | 43.890          | 8.1081 | 4.169           | 0.1344 |
| U251 pcDNA | 28.520          | 2.1869 | 3.556           | 0.0836 |
| U251 p75   | 1.725           | 0.0707 | 4.255           | 0.3007 |

**Example 4 – Synthetic schemes of compounds described herein**

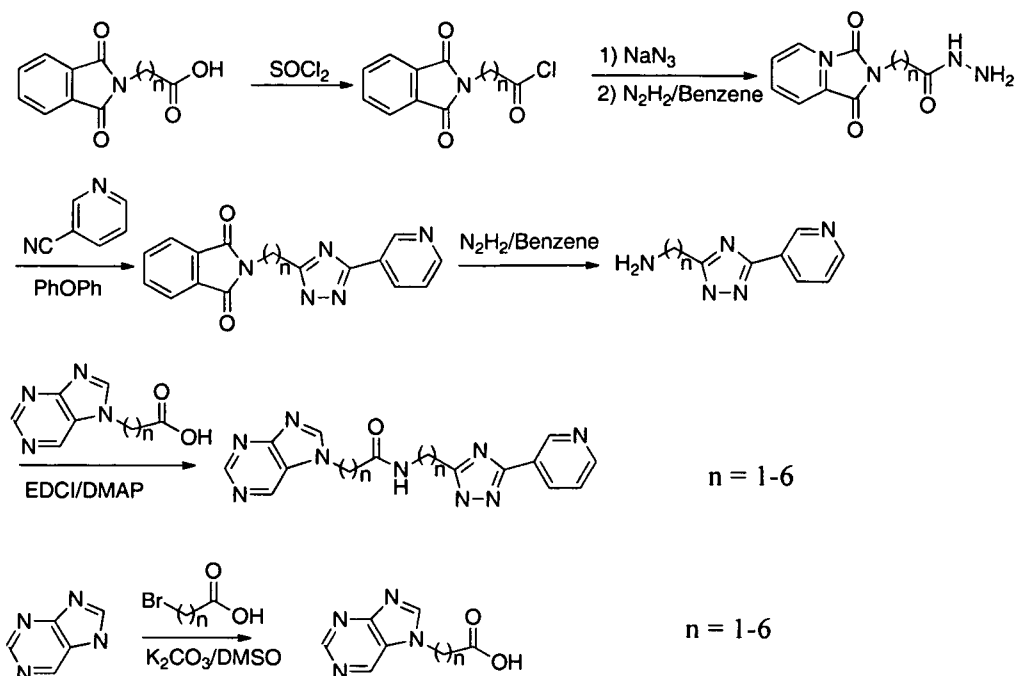
263. The molecules and compound, including those used in methods described herein, can be synthesized using highly versatile synthetic chemistry reactions. Molecules and compounds are typically synthesized using amide chemistry. Amide can be made by reacting carboxylic acid with a primary amine by first activating the carboxylic acid to an acid chloride or an acyl chloride (using  $\text{PCl}_3$ ,  $\text{PCl}_5$ , or similar reactants), the acid chloride then reacts with the primary amine using conditions such as Schotten-Baumann conditions, such as water and diethyl ether. Other synthetic routes include reacting a carboxylic acid with a primary amine using EDCI and DMAP, as shown below. The amide chemistry is especially versatile because there are many

common synthetic methods to form the required carboxylic acid and amine functional groups. Thus, for example, carboxylic acid can be synthesized from alcohols, aldehydes, alkenes, alkyls, ketones, nitriles etc. Also, for example, amines can be synthesized from nitriles, azides, noranesm carbamates, lactams etc. These reactions are all well known and are described by Smith, M., "Organic Synthesis 2<sup>nd</sup> ed," The McGraw-Hill Companies, Inc., New York, NY, 2002 and McMurry, J., "Organic Chemistry 4<sup>th</sup> Ed," Brooks/Cole Publishing Company, Pacific Grove, California, 1995.

264. For example, compound A can be made using the following synthesis:

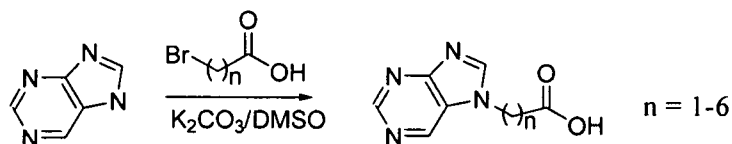


265. Compound A can also be made using the following synthesis:



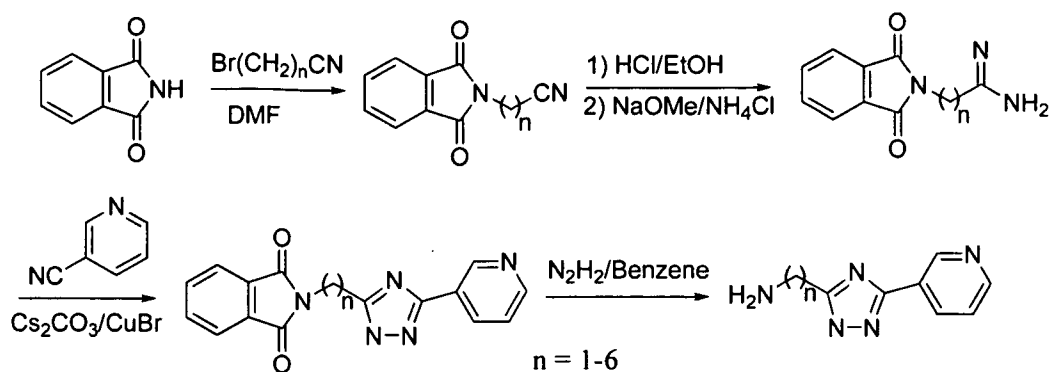
266. The synthetic techniques for these reactions are described in J. Organomet. Chem. 620 (1-2), 95-105, 2001; J. A. C. S. 110 (7), 2192-2201, 1988; and J. A. C. S. 131 (42), 15080-15081, 2009.

267. Versatile synthetic chemistry routes are also available to synthesize the carboxylic acid derivatives needed to make the compounds.



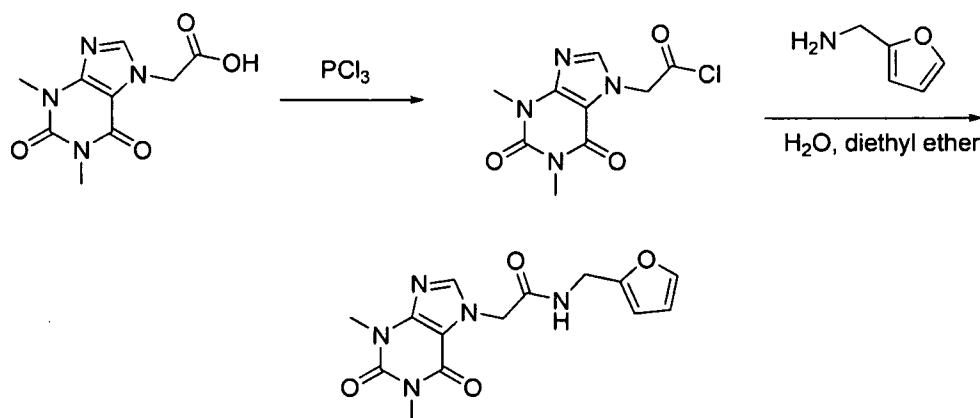
268. Similar reactions can be done to with other amine functionalized cyclic moieties.

269. Versatile synthetic chemistry routes are also available to synthesize the amine derivatives needed to make the compounds.

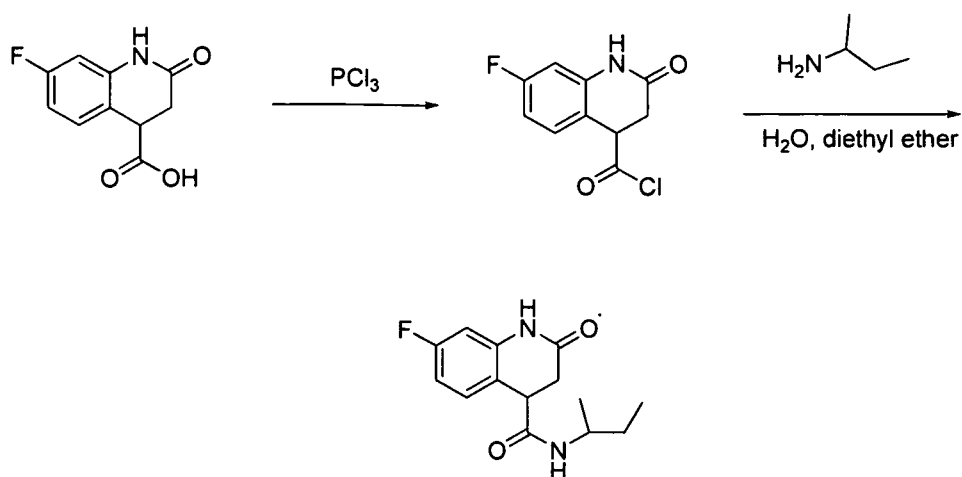


270. Similar reactions can be done to with other 1,2,4 triazole derivatives.

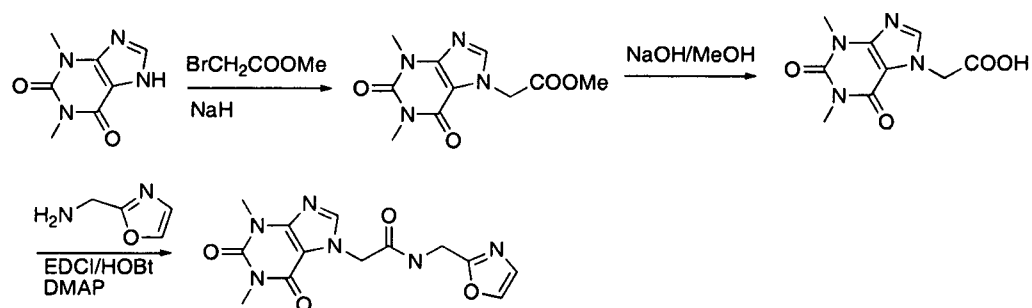
271. Other compounds can be made using commercially available carboxylic acids such as theophylline-7-acetic acid, available from Purum, and amines, such as furfurylamine. The amide formation can, for example, be made using a Schotten-Baumann reaction as seen below.



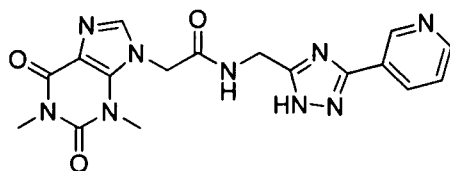
272. Another commercially available can also be used in a similar fashion, 7-fluoro-2-oxo-1, 2, 3, 4-tetrahydro-4-quinoline carboxylic acid, available from Aldrich., can be reacted with 2-aminobutane, available from Aldrich using the Shotten-Baumann reaction.



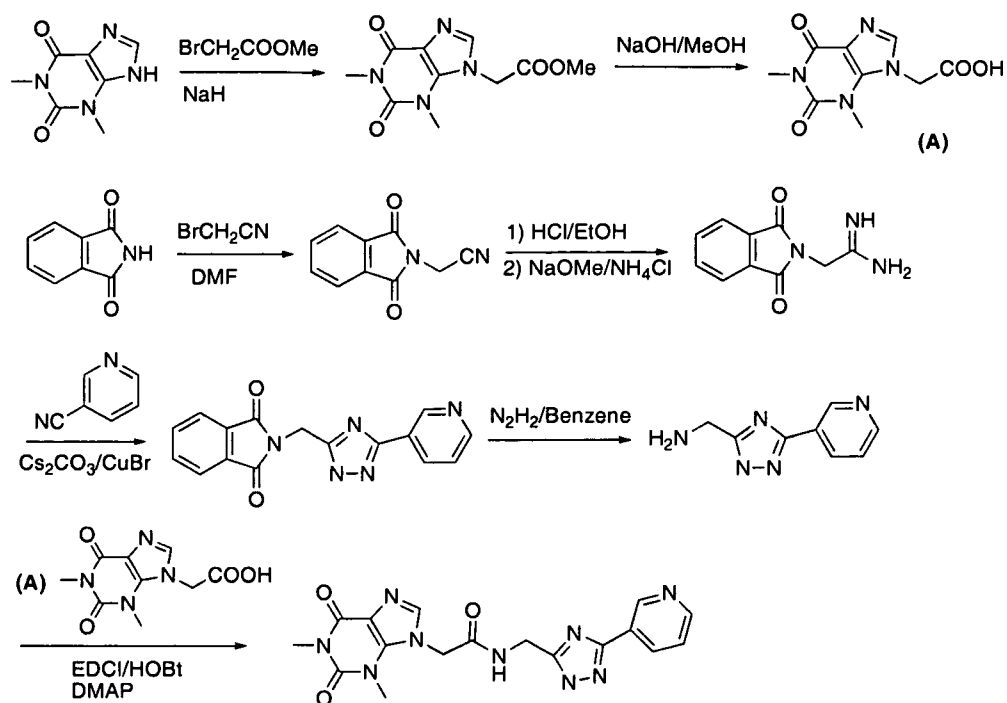
273. For example, compound **B** can be made using the following synthesis:



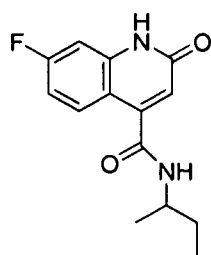
274. For example, compound



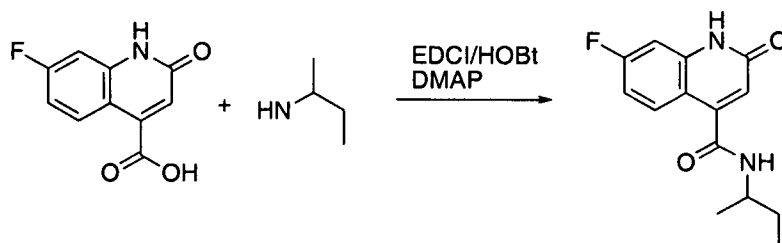
can be made using the following synthesis:



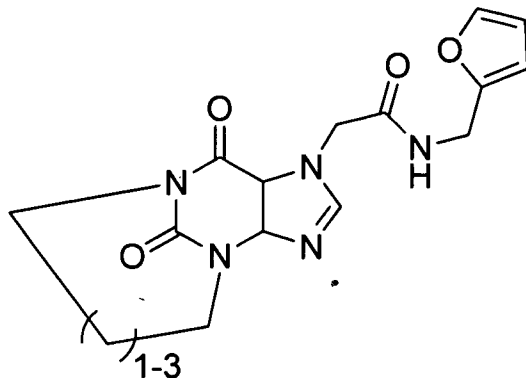
275. For example, compound



can be made using the following synthesis:

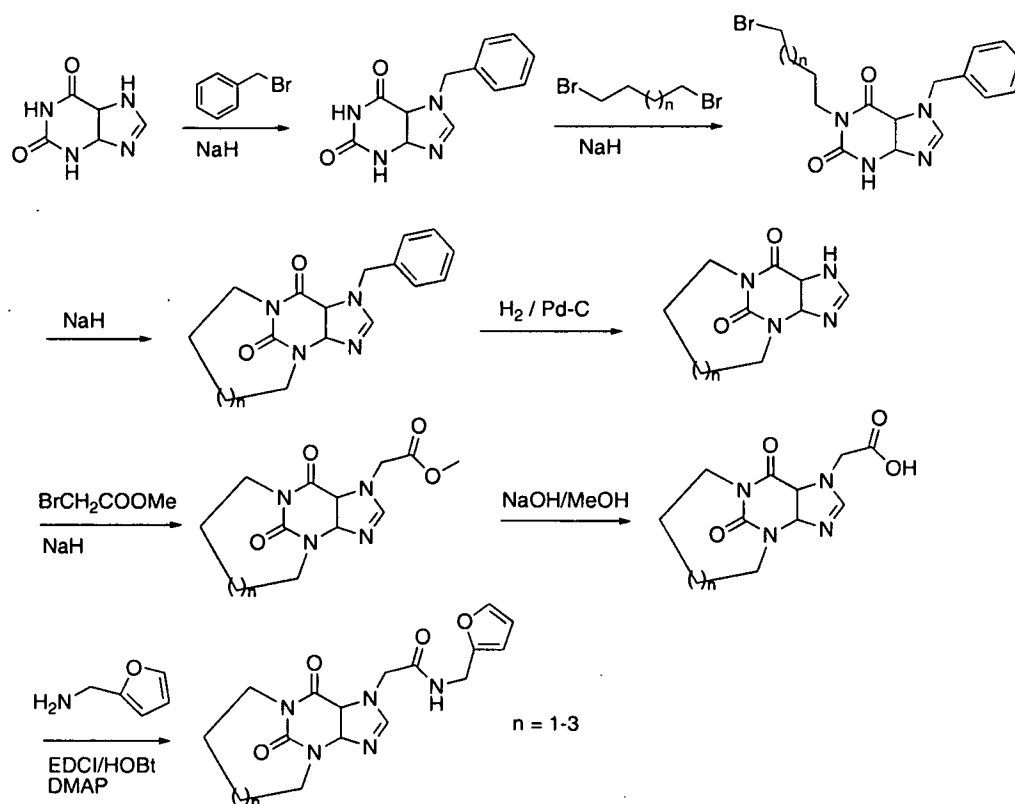


276. For example, compound



can be made using the following synthe-

sis:



#### Example 5 – Tube formation assay

277. Inhibiting angiogenesis is a potential therapeutic target in MGs. Thus, compound A were also assessed *in vitro* and *in vivo* co-cultures of microvascular endothelial cells and invasive gliomas (U87p75+, U87R) for vascular branch-

ing/tubulogenesis using 2-D/3-D cultures and corneal assays. These compounds had inhibitory effects on Human Brain Microvascular Endothelial Cell (HBMEC) proliferation with  $IC_{50}$ 's at low  $\mu$ M concentration and inhibited tube formation. Inhibitory effects are not due to toxicity to the endothelial cells.

278. Matrigel was added to 24 well plates, and incubated for 30 min at 37 degrees. HBMEC cells at a concentration of  $5 \times 10^4$ /ml mixed with SD compounds (0, 1.0, 5.0 and 10.0  $\mu$ M) was added to the wells and incubated for 24 h. Photographs were taken at 4x magnification and analyzed with ImagePro Plus. Tube lengths were measured (see Fig. 5A-D), and counted the number of tubes per field at 4x magnification. Tube formation assay, each concentration was performed in duplicate and the measurements were made in at least 4 separate fields per well.

279. Similar procedures were performed on Human Umbilical Vein Epithelial Cells (HUVEC) (see Fig. 6 A-D).

280. An *in-vitro* rat aortical assay was also performed. Segments of the aorta for a 2 months old rat were tested. Compound A was administered at 10  $\mu$ M for 5 days. Microscopic pictures of the aorta can be seen in Fig. 7A and 7B. The capillary network was also studied using microscopy (see Fig. 7C and 7D).

#### **Example 6 – Toxicity study**

281. Compounds A-D, E, H and I inhibited the cell growth without killing the cells. The compounds were administered to BTIC at 5 $\mu$ M for 72 hrs. The number of surviving cells was compared to a DMSO control. Approximately 85-100% of the cells survived after being exposed to compounds A-D, E and I (see Fig. 8).

282. Experimental procedure: 40,000 brain tumor initiating cells (BTIC) were resuspended in 70  $\mu$ l of a collagen based matrix containing 10  $\mu$ g/ml of laminin, fibronectin and chondroitin sulfate proteoglycan and any appropriate drug treatments. The cell/matrix mix was placed in a transwell filter unit and incubated for 1 hr at 37  $^{\circ}$ C to solidify the matrix. The transwell unit was then placed in 1 ml of serum containing media (with any appropriate drug) and 100  $\mu$ l of serum-free media (with drug) was placed above the cell/matrix mix to create a chemotactic gradient. The cells were allowed to invade through the matrix and filter for 6 hrs at 37  $^{\circ}$ C and the number of invading cells was quantified by staining the formalin fixed filters with DAPI and examination under a fluorescent microscope.

283. Having described and illustrated specific exemplary embodiments of the invention, it is to be understood that the invention is not limited to those precise embodiments. Various adaptations, modifications, and permutations will occur to persons of ordinary skill in the art without departing from the scope or the spirit of the invention as defined in the appended claims, and are contemplated within the invention.

#### **Example 7 – Analysis of p75 antagonist**

284. An *In vitro* (ELISA) binding displacement assay was performed to determine the specificity of compound A. Compound A's inhibitory activity in pro-NGF, BDNF and NGF binding to p75 was examined. The data indicates that compound A has little activity against pro-NGF and BDNF. Compound A's specificity in NGF binding was consistent. To confirm this specificity a competition assay for NGF and BDNF binding was performed *in vitro* and in cultured cells.

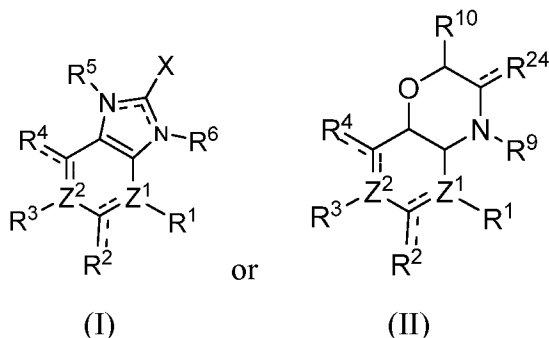
285. Cell proliferation assays were performed in two glioma cell lines ectopically expressing p75 to determine the specificity and cytotoxicity of compound A. Cells with vector alone and compound H served as controls. Both U87/p75 and U250/p75 were significantly sensitive to compound A while compound H conferred non-specificity and appeared to be cytotoxic overall, see Table 4.

Table 4.

| Cell Line | Compound A            |         | Compound H            |        |
|-----------|-----------------------|---------|-----------------------|--------|
|           | IC <sub>50</sub> [μM] | SEM     | IC <sub>50</sub> [mM] | SEM    |
| U87       | 44.4400               | 7.2381  | 3.9530                | 0.2497 |
| U87pcDNA  | 40.1000               | 1.1540  | 8.5900                | 0.2228 |
| U87 p75   | 2.8220                | 0.6372  | 6.3430                | 0.7445 |
| U251      | 62.8700               | 7.2997  | 3.5550                | 0.3930 |
| U251pcDNA | 47.3100               | 11.6062 | 4.0140                | 0.1621 |
| U251 p75  | 6.0530                | 1.7693  | 4.4960                | 0.2819 |

We claim:

1. A compound having structure I or II:



wherein:

X is hydrogen, lower alkyl, haloalkyl or an electron withdrawing group;

R<sup>1</sup> and R<sup>3</sup> are either both present or both absent, and

if R<sup>1</sup> and R<sup>3</sup> are present then each independently is unsubstituted lower alkyl, alkyl, halide and optionally together form a bridge, R<sup>2</sup> and R<sup>4</sup> are each double bonded O, and Z<sup>1</sup> and Z<sup>2</sup> are each an N bearing no double bonds; and

if R<sup>1</sup> and R<sup>3</sup> are absent then R<sup>2</sup> and R<sup>4</sup> are each H or be double bonded O, the six-member ring have 0-3 double bonds, Z<sup>1</sup> and Z<sup>2</sup> is independently C or N, and the six-member ring is carbocyclic is optionally be substituted;

if Z<sup>1</sup> and Z<sup>2</sup> are C then R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently present or absent, and if R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are present then each is independently H, halide, lower alkoxy, lower alkyl, hydroxyl or haloalkyl;

one or both of R<sup>5</sup> or R<sup>6</sup> is present, can be bonded to a nitrogen atom having two single bonds in the five-member ring, and the other nitrogen atom in the five-member ring is unsubstituted or substituted and bears a double bond in the ring, if R<sup>5</sup> or R<sup>6</sup> is bonded to a nitrogen that bears a double bond then R<sup>5</sup> or R<sup>6</sup> is alkyl or halide, and R<sup>5</sup> or R<sup>6</sup> is of the form -linker-R<sup>7</sup>, wherein

the linker comprise in any order -C(=O)-, -N(R<sup>a</sup>)-, -O-, -S-, aryl, hetero aryl, heterocyclyl, cycloalkyl and up to ten methylene groups, wherein

R<sup>a</sup> is H or independently unsubstituted C<sub>1</sub>-C<sub>3</sub>,

one or more of the methylene groups is optionally substituted independently by a respective R<sup>b</sup>, wherein each R<sup>b</sup> is lower alkyl and its identity is independent of the identity of R<sup>a</sup> and of respective R<sup>b</sup> on other methylene groups in the linker, and

optionally  $R^a$  and a respective  $R^b$  together form a bridge; and

$R^7$  is an end group that can be:  $C_1$ - $C_8$  alkyl;  $C_3$ - $C_8$  cycloalkyl; aryl, heteroaryl,  $C_3$ - $C_{10}$  heterocyclic; or a 5-member heteroaryl ring having up to three heteroatoms that are selected from O, N and S, wherein the heteroaryl ring optionally bear a substituent  $R^8$ ; and wherein

$R^8$  is H, an electron withdrawing group, lower hydrocarbon moiety, lower alkoxy, an optionally substituted fused benzo group, or

if  $R^7$  is a triazole, then  $R^8$  is optionally a six-member heteroaryl ring in which the heteroatoms is 1 or 2 nitrogen atoms, and  $R^8$  is optionally be substituted at one or more carbon atoms on the ring by an electron withdrawing group, lower hydrocarbon moiety, or lower alkoxy;

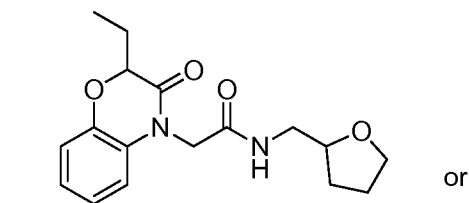
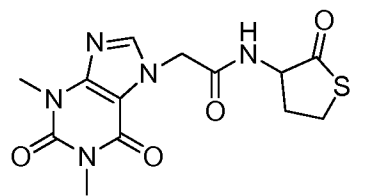
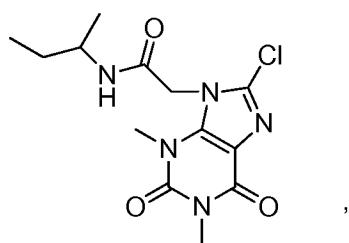
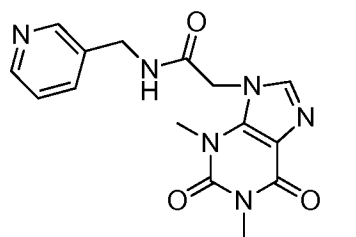
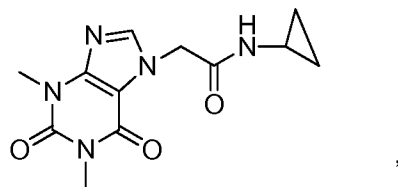
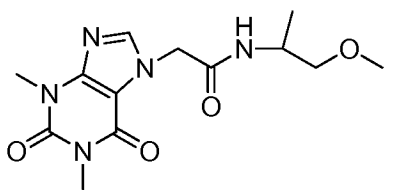
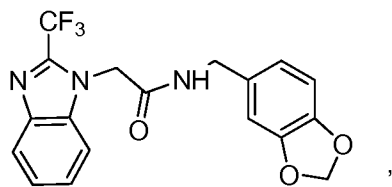
$R^9$  is of the form  $-\text{linker}-R^7$ , wherein the linker comprise in any order  $-\text{C}(=\text{O})-$ ,  $-\text{N}(R^a)-$ ,  $-\text{O}-$ ,  $-\text{S}-$  and up to six methylene groups, wherein

$R^a$  is H or independently unsubstituted  $C_1$ - $C_3$ , one or more of the methylene groups is optionally be substituted independently by a respective  $R^b$ , wherein each  $R^b$  is lower alkyl and its identity is independent of the identity of  $R^a$  and of respective  $R^b$  on other methylene groups in the linker, optionally  $R^a$  and a respective  $R^b$  together form a bridge; and

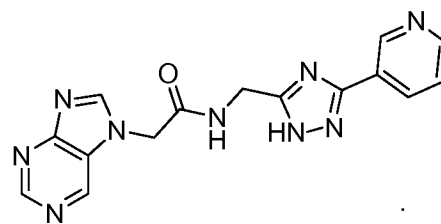
$R^{10}$  is H or substituted or unsubstituted lower alkyl;

$R^{24}$  is H or  $=\text{O}$ ; and

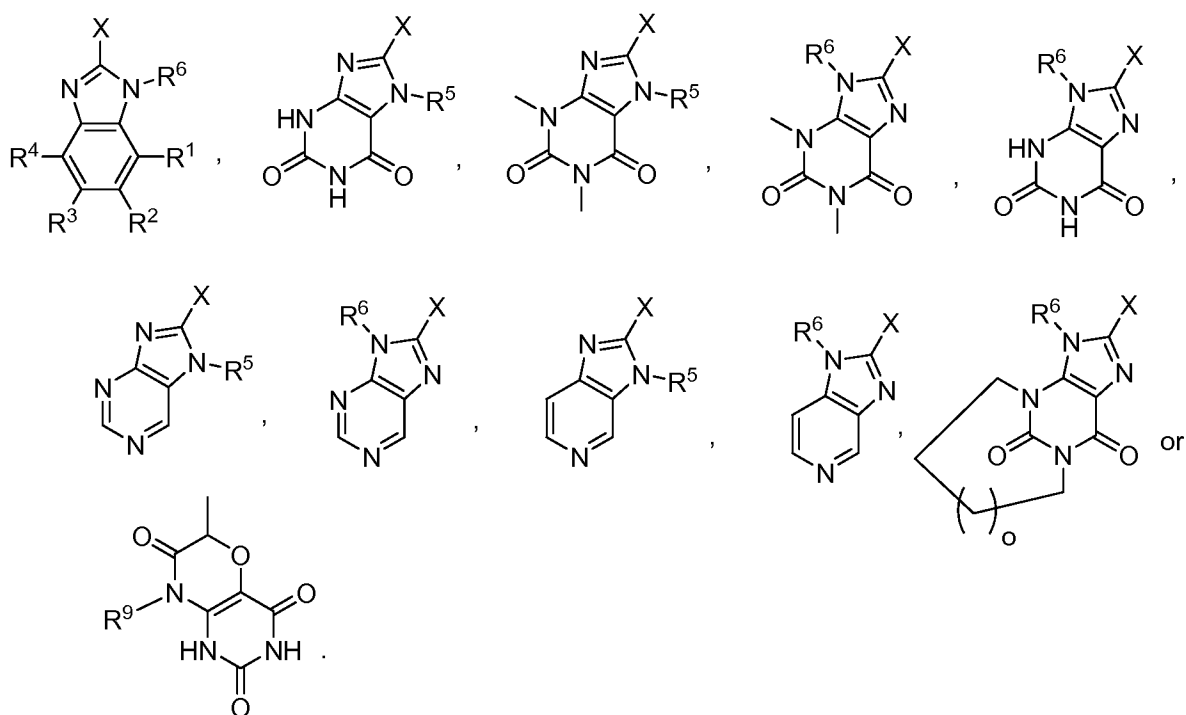
with the proviso that structure I or II cannot be:



or



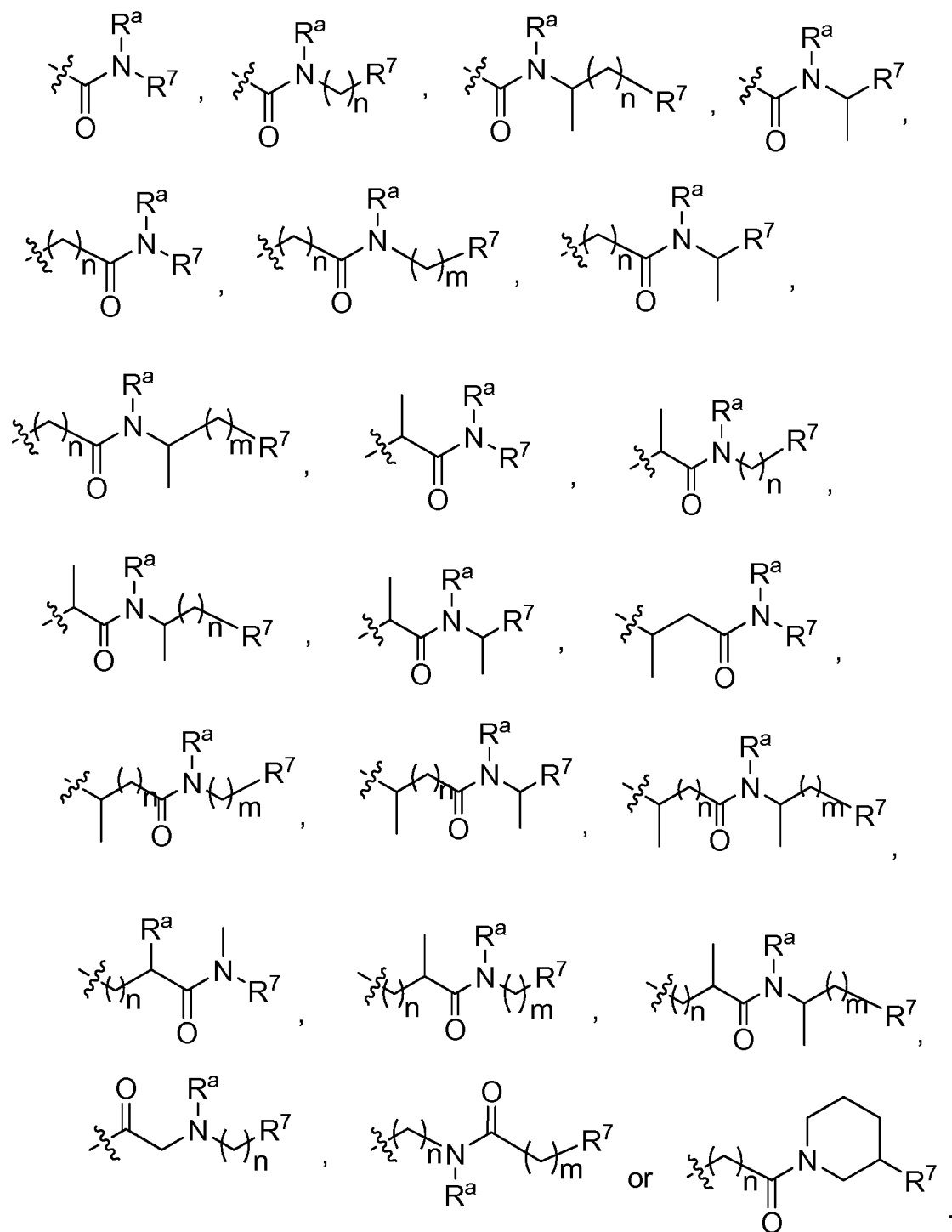
2. Then compound according to claim 1, wherein structure I or II is:



3. The compound according to claim 2, wherein o is 1, 2 or 3.
4. The compound according to claim 1, wherein X is H, -CF<sub>3</sub> or Cl.
5. The compound according to claim 1, wherein R<sup>1</sup> and R<sup>3</sup> are each absent.
6. The compound according to claim 1, wherein R<sup>1</sup> and R<sup>3</sup> are each methyl or together form an  $\alpha,\omega$ -propadiyl,  $\alpha,\omega$ -butadiyl, or  $\alpha,\omega$ -pentadiyl bridge.
7. The compound according to claim 1, wherein R<sup>1</sup> and R<sup>3</sup> independently are H, C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, F, Cl, hydroxyl or CF<sub>3</sub>.
8. The compound according to claim 1, wherein R<sup>1</sup> and R<sup>3</sup> independently are H or CH<sub>3</sub>.
9. The compound according to claim 1, wherein R<sup>2</sup> and R<sup>4</sup> independently are H, =O, C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, F, Cl, hydroxyl or CF<sub>3</sub>.
10. The compound according to claim 1, wherein R<sup>2</sup> and R<sup>4</sup> independently H or =O.

11. The compound according to claim 1, wherein  $Z^1$  is C and  $Z^2$  is N.
12. The compound according to claim 1, wherein  $Z^1$  is N and  $Z^2$  is C.
13. The compound according to claim 1, wherein  $Z^1$  is C and  $Z^2$  is C.
14. The compound according to claim 1, wherein  $Z^1$  is N and  $Z^2$  is N.
15. The compound according to claim 1, wherein the linker is  $-\text{CH}_2-\text{C}(=\text{O})-\text{N}(-\text{H})-(\text{CHR}^b)_p-$ , wherein p is 0-2 and each respective  $\text{R}^b$  is independently H or methyl.
16. The compound according to claim 1, wherein  $\text{R}^a$  and a respective  $\text{R}^b$  together form an alkyl bridge defining a piperidinediyl ring in the linker.

17. The compound according to claim 1, wherein  $R^5$ ,  $R^6$  and  $R^9$  independently are H,

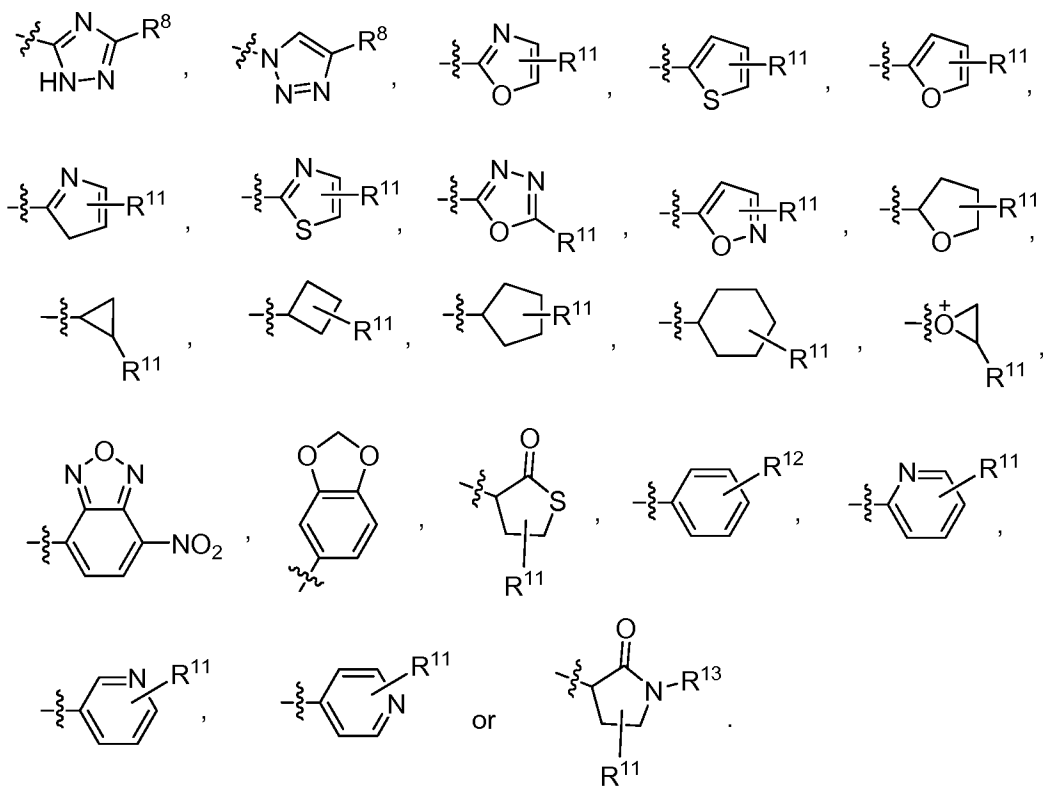


18. The compound according to claim 17, wherein n and m independently are 1, 2, 3 or 4.

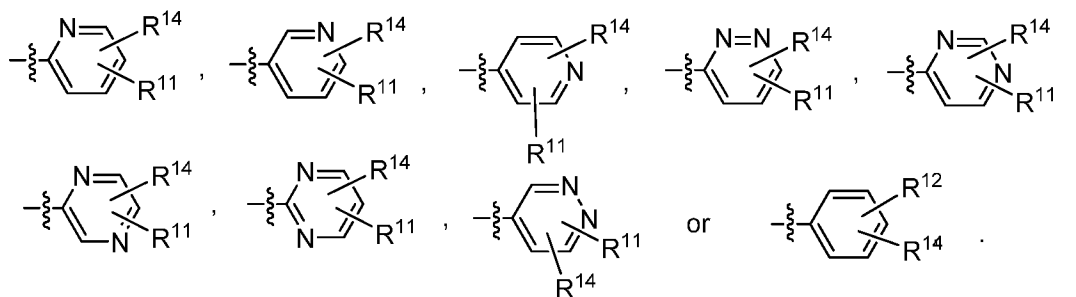
19. The compound according to claim 1, wherein  $R^7$  is:  $C_3$ - $C_5$  sec-alkyl; pyridinyl; 1,3-oxazol-2-yl; or is 1,2,4-triazol-3-Q-5-yl wherein Q is a pyridinyl, pyrazinyl, pyrimidinyl, or pyridazinyl group, any carbon of Q is bonded to the linker provided that Q has only one such bond, and if present the pyridinyl group is optionally substituted by 1 or 2 methyl groups.

20. The compound according to claim 17, wherein  $R^a$  is H or  $C_1$ - $C_3$  alkyl.

21. The compound according to claim 1, wherein  $R^7$  is  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,



22. The compound according to claim 21, wherein  $R^8$  is H, C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, halide, hydroxyl,



23. The compound according to claim 21 or 22, wherein  $R^{11}$  is H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halide or hydroxyl.

24. The compound according to claim 21, wherein  $R^{13}$  is  $R^8$ .

25. The compound according to claim 22, wherein  $R^{14}$  is H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halide or hydroxyl.

26. The compound according to claim 1, wherein  $R^{24}$  is =O.

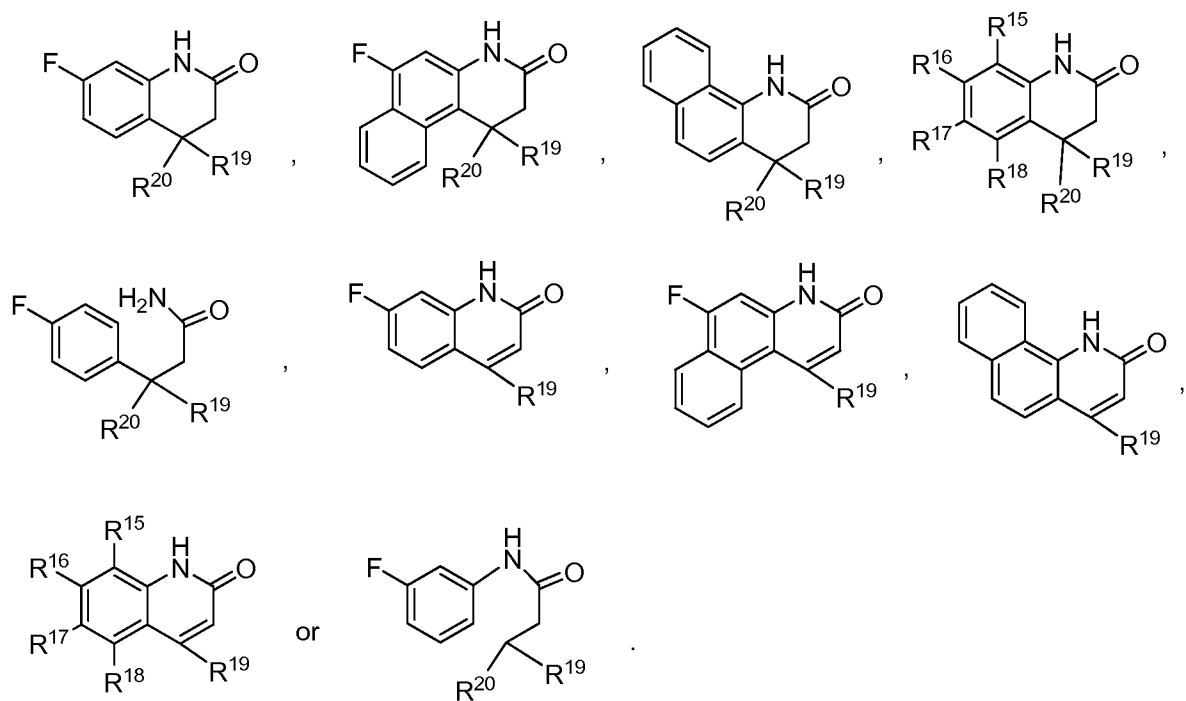
27. The compound according to claim 1, wherein  $R^{10}$  is H, halide, C<sub>1</sub>-C<sub>3</sub> alkyl or branched C<sub>3</sub>-C<sub>6</sub> alkyl.

28. The compound according to claim 22, wherein  $R^{12}$  is H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halide or hydroxyl.

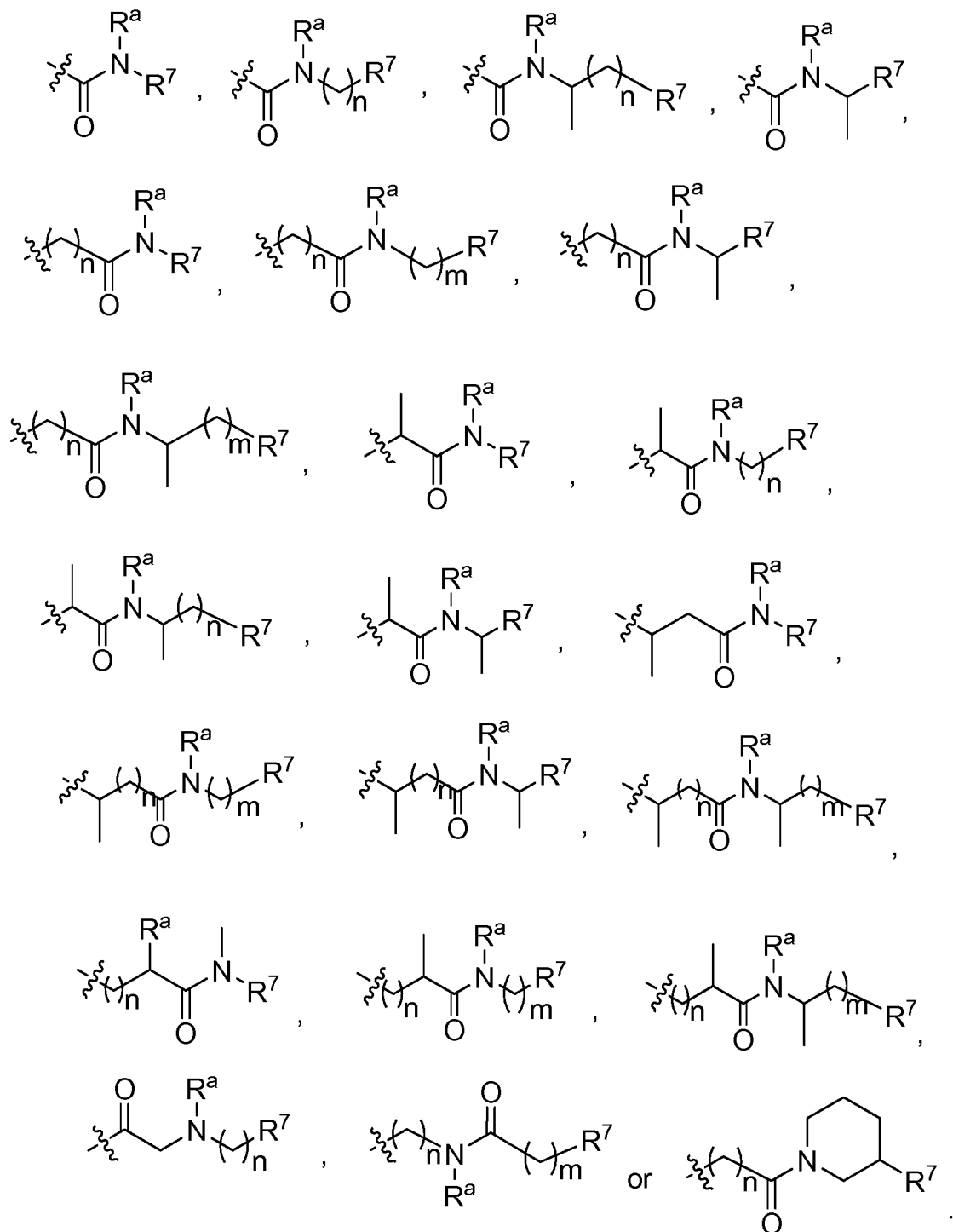
29. A pharmaceutical composition comprising the compound according to claim 1.



31. The compound according to claim 30, wherein structure III is:



32. The compound according to claim 30, wherein  $R^{19}$  is H,  $C_1$ - $C_3$  alkyl, halide,



33. The compound according to claim 30, wherein  $R^{20}$  is H,  $C_1$ - $C_3$  alkyl or halide.

34. The compound according to claim 30, wherein  $R^{19}$  is in R configuration and  $R^{20}$  is in S configuration.

35. The compound according to claim 30, wherein R<sup>19</sup> is in S configuration and R<sup>20</sup> is in R configuration.

36. The compound according to claim 30, wherein R<sup>7</sup> is in R configuration and the linker can be S configuration.

37. The compound according to claim 30, wherein R<sup>7</sup> is in S configuration and the linker is in R configuration.

38. The compound according to claim 30, wherein R<sup>16</sup> is F and R<sup>15</sup>, R<sup>17</sup> and R<sup>18</sup> are each H.

39. The compound according to claim 30, wherein R<sup>15</sup> and R<sup>16</sup> together forms a benzo group, or R<sup>17</sup> and R<sup>18</sup> together forms a benzo group.

40. The compound according to claim 30, wherein the pair **a** and **b** and the pair **g** and **h**, one the of the pairs is a bond and each member of the other pair is a hydrogen atom.

41. The compound of claim 30, wherein **e** is  $-(CH_2)_n-$  and n is 1-4.

42. The compound of claim 30, wherein a double bond is present between **e** and **f**.

43. The compound of claim 30, wherein **f** is chiral and can be substituted by H, an electron withdrawing group, lower alkyl, lower alkoxy, or OH.

44. The compound of claim 30, wherein R<sup>7</sup> is an end group that is i-propyl, s-butyl, 3-pentyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl.

45. A pharmaceutical composition comprising the compound of claim 29.

46. A method of preventing and treating tumors of the nervous system, comprising administering to a subject in need thereof a pharmaceutically effective amount of a composition that inhibits p75 neurotrophic receptors and prevents the spread of tumors in healthy nervous tissue.

47. The method according to claim 46, wherein the composition comprises a compound or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof having the formula:

### G-H-I

wherein

**G** is aryl, heteroaryl, cycloalkyl or heterocyclic residue selected from the group consisting of monocyclic and bicyclic ring systems, wherein **G** optionally bear one or more

substituents selected from electron withdrawing groups, halide, =O, alkyl, alkoxy, lower alkyl, lower alkoxy, and optionally substituted benzo groups;

**H** is a linker having 2 to 12 members in any order of linear sequence, in which –C(=O)– is a member, –N(R<sup>a</sup>)– is a member, and the rest of the members if any is optionally substituted methylene groups, wherein

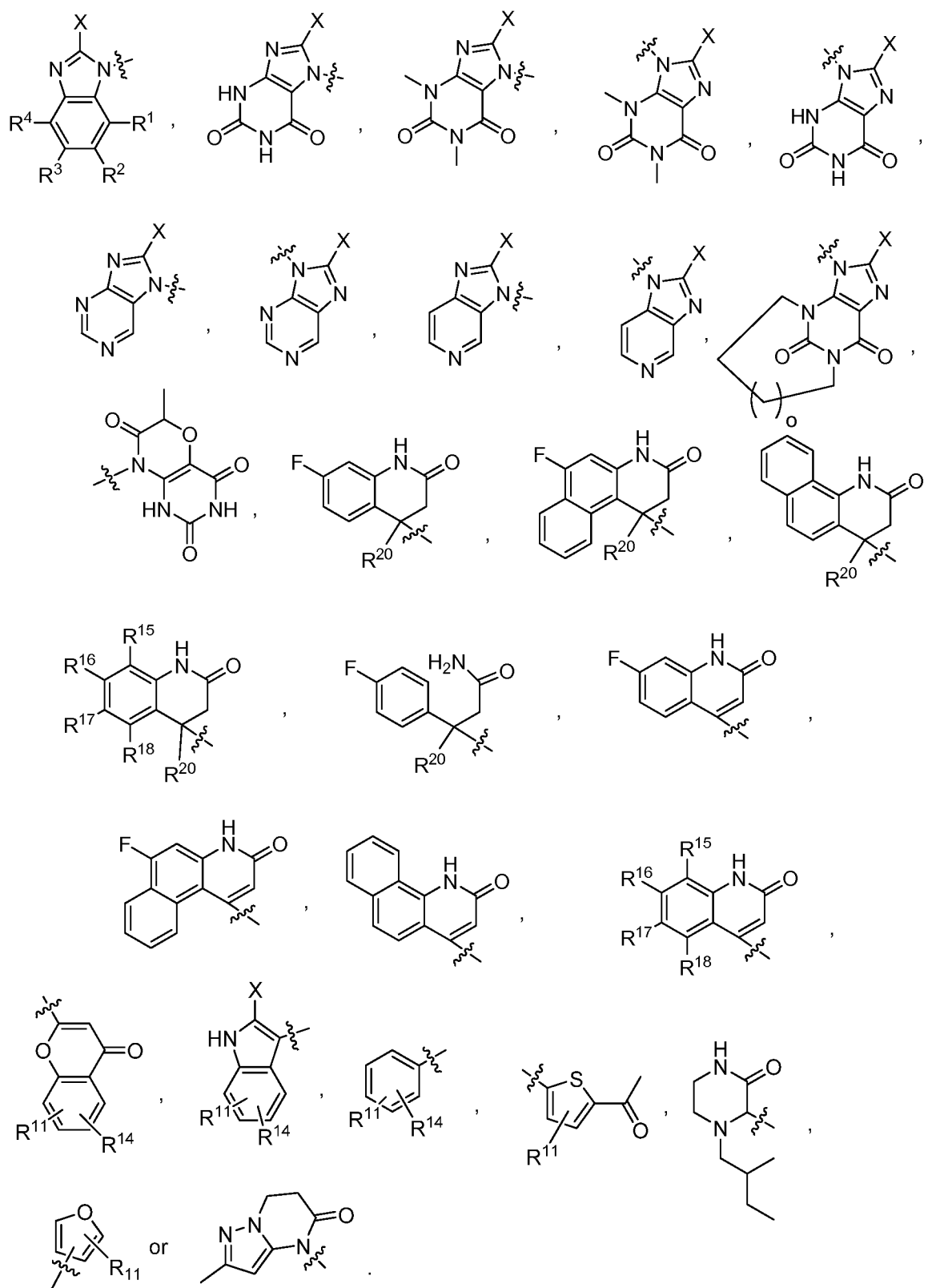
R<sup>a</sup> is H or independently unsubstituted lower alkyl;  
one or more of the methylene groups if present is optionally substituted independently by a respective R<sup>b</sup>, wherein each R<sup>b</sup> is lower alkyl, heteroaryl, or optionally substituted phenyl, and the identity of each R<sup>b</sup> is independent of the identity of R<sup>a</sup> and of respective R<sup>b</sup> on other methylene groups in the linker; and

optionally R<sup>a</sup> and a respective R<sup>b</sup> together forms a bridge; and

**I** is an end group that is: a C<sub>1</sub>-C<sub>10</sub> hydrocarbon moiety; C<sub>3</sub>-C<sub>10</sub> aryl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>3</sub>-C<sub>9</sub> heterocyclic; optionally substituted indenyl; optionally substituted phenyl; or a 5- or 6- member heteroaryl ring having up to three heteroatoms selected from O, N and S, wherein the heteroaryl ring optionally bears a substituent **J**; and wherein

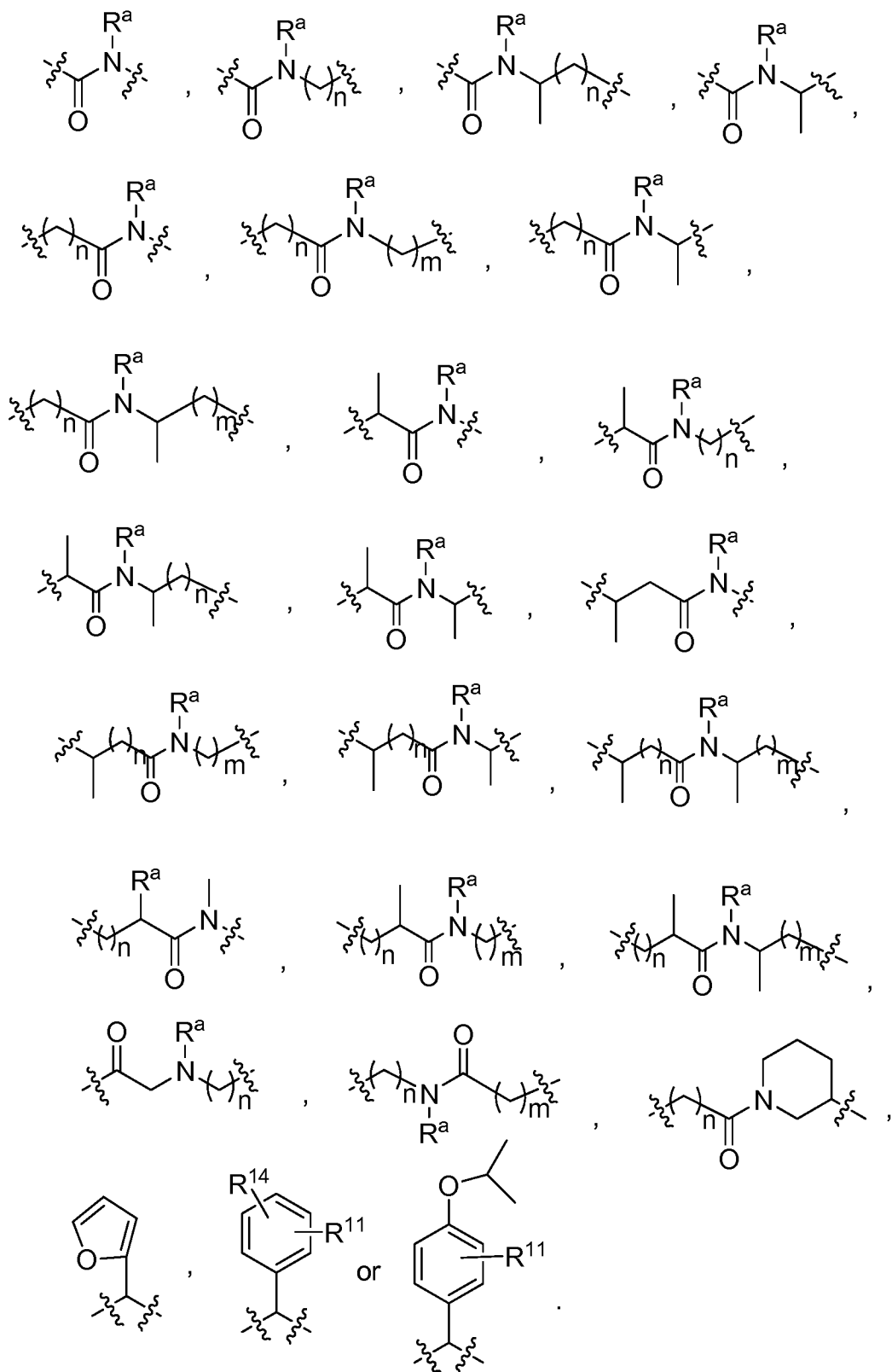
**J** is an electron withdrawing group, lower hydrocarbon moiety, lower alkoxy, optionally substituted phenyl, or is optionally substituted fused benzo group, or if **I** is a triazole, then **J** optionally is a six-member heteroaryl ring in which the heteroatoms are 1 or 2 nitrogen atoms, and **J** is optionally substituted at one or more carbon atoms on the ring by an electron withdrawing group, lower hydrocarbon moiety, or lower alkoxy.

48. The method according to claim 47, wherein **G** is purinyl, xanthinyl, 5-azabenzimidazolyl, benzimidazolyl, indolyl, thiophenyl, piperidin-2-onyl, morpholin-2-onyl, benzopyran-4-onyl, piperazin-2-onyl, and 1,4,8-triaza-4,5,6,7-tetrahydro-5-oxo-indenyl, and wherein **G** is optionally substituted by one or more groups selected from oxo, lower alkyl, lower alkoxy, electron withdrawing groups, and benzo substituents,



49. The method according to claim 47, wherein **H** includes one to eight methylene groups, each methylene group can be optionally substituted with a lower alkyl, halide,

lower alkoxy, aryl, heteroaryl, cycloalkyl, heterocyclyl; aryl; heteroaryl; cycloalkyl; hetero-  
cyclyl; -C(=O)-; -N(R<sup>a</sup>)-; -O-; -S-;





53. The method of claim 47, wherein **G** is benzopiperidin-2-onyl, and the carbon that is ortho on the phenyl ring to the amide has quaternary substitution and bears a substituent that is a lower alkyl, lower alkoxy, or electron withdrawing substituent.

54. The method of claim 47, wherein for **H**,  $R^b$  is: methyl; furanyl; thiophene-2-yl, p-isopropoxyphenyl; or together with  $R^a$  forms a bridge defining a 1,4-piperidinediyl moiety.

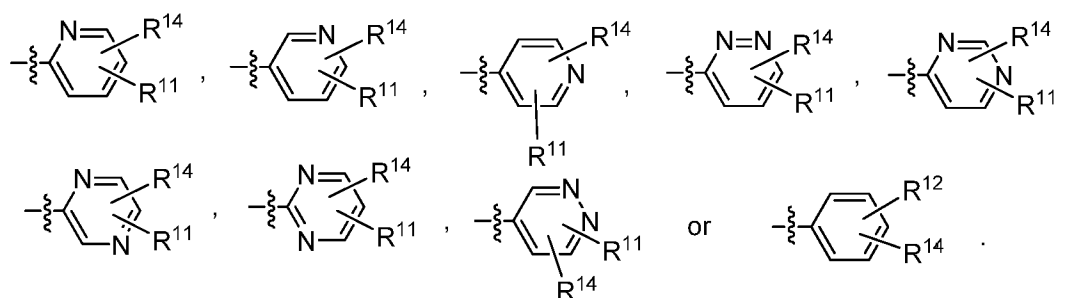
55. The method of claim 47, wherein **I** is: 1,2- or 1,3- oxazolyl; thiazolyl; oxadiazolyl; thiadiazolyl; 1,2,4-triazolyl; pyridinyl; s-butyl; i-propyl; cyclopropyl; epoxidyl; glycidyl; 3-pentyl; phenyl; indolyl; furanyl; N-(3-methoxyphenyl)-pyrrolidin-2-on-4-yl; or 3-(aza- or diaza-benzenyl)-1,2,4-triazol-5-yl, or benzimidazolyl.

56. The method according to claim 47 or 49, wherein  $R^a$  is H or  $C_1$ - $C_3$  alkyl.

57. The method according to claim 48, wherein  $R^{20}$  is H,  $C_1$ - $C_3$  alkyl or halide.

58. The method according to claim 49, wherein  $R^{13}$  is  $R^8$ .

59. The method according to claim 58, wherein  $R^8$  is H,  $C_1$ - $C_3$  alkyl,  $C_1$ - $C_3$  alkoxy, halide, hydroxyl,



60. The method according to claim 49-51 or 59, wherein  $R^{11}$  is H,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halide or hydroxyl.

61. The method according to claim 49, 51 or 59 wherein  $R^{14}$  is H,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halide or hydroxyl.

62. The method of claim 50, 51 or 59, wherein  $R^{12}$  is H,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halide or hydroxyl.

63. The method of claim 48, wherein X is H,  $-CF_3$  or Cl

64. The method of claim 46, wherein the composition comprises any compound from structures I, II or III.

65. A method comprising administering to a subject in need of inhibition of a p75 neurotrophic receptors (p75<sup>NTR</sup>) a composition comprising a compound of any one of claims 1-64.

66. The method of claim 65, wherein the subject is suffering from or at risk for a disease associated with p75 neurotrophic receptors.

67. The method of claim 66, wherein the disease is brain cancer.

68. The method of claim 67, wherein the brain cancer is Glioblastoma multiforme.

69. The method of claim 65, wherein the inhibition of p75<sup>NTR</sup> inhibits glioma invasion.

70. The method of claim 65, wherein the subject is monitored for p75<sup>NTR</sup> expression.

71. The method of claim 65, wherein the composition further comprises a known p75<sup>NTR</sup> inhibitor.

72. The method of claim 65, wherein the subject has been diagnosed with a disease associated with p75<sup>NTR</sup>.

73. The method of claim 65 or 66, wherein the method prevents or treats a disease associated with p75<sup>NTR</sup>.

74. A method of treating a disease or disorder associated with angiogenesis in a subject, the method comprising the step of administering to the subject an effective amount of a composition comprises a compound or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof having the formula:

### **G-H-I**

wherein

**G** is aryl, heteroaryl, cycloalkyl or heterocyclic residue selected from the group consisting of monocyclic and bicyclic ring systems, wherein **G** optionally bear one or more substituents selected from electron withdrawing groups, halide, =O, alkyl, alkoxy, lower alkyl, lower alkoxy, and optionally substituted benzo groups;

**H** is a linker having 2 to 12 members in any order of linear sequence, in which –C(=O)– is a member, –N(R<sup>a</sup>)– is a member, and the rest of the members if any is optionally substituted methylene groups, wherein

R<sup>a</sup> is H or independently unsubstituted lower alkyl,

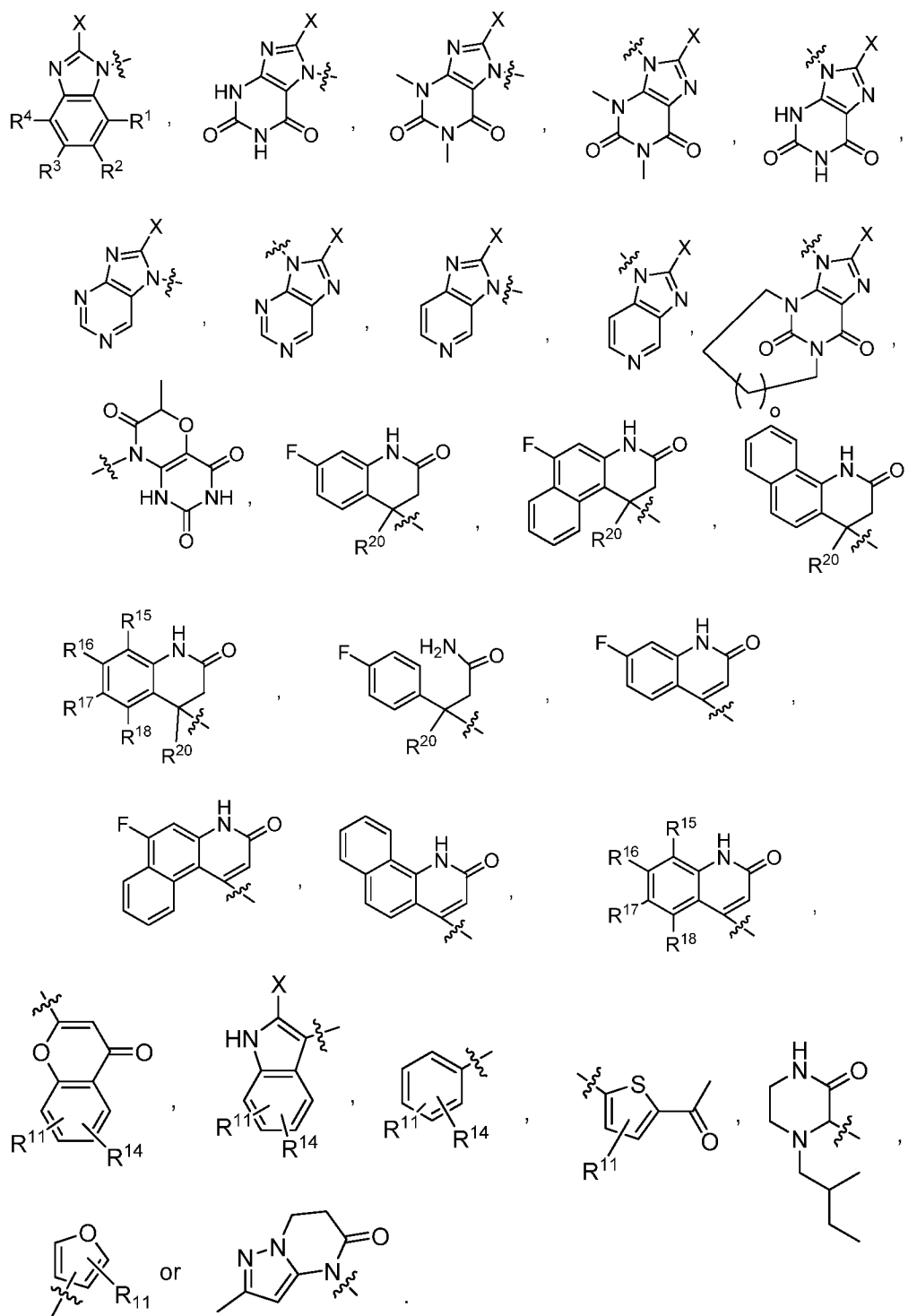
one or more of the methylene groups if present is optionally substituted independently by a respective R<sup>b</sup>, wherein each R<sup>b</sup> is lower alkyl, heteroaryl, or optionally substituted phenyl, and the identity of each R<sup>b</sup> is independent of the identity of R<sup>a</sup> and of respective R<sup>b</sup> on other methylene groups in the linker; and

optionally R<sup>a</sup> and a respective R<sup>b</sup> together forms a bridge; and

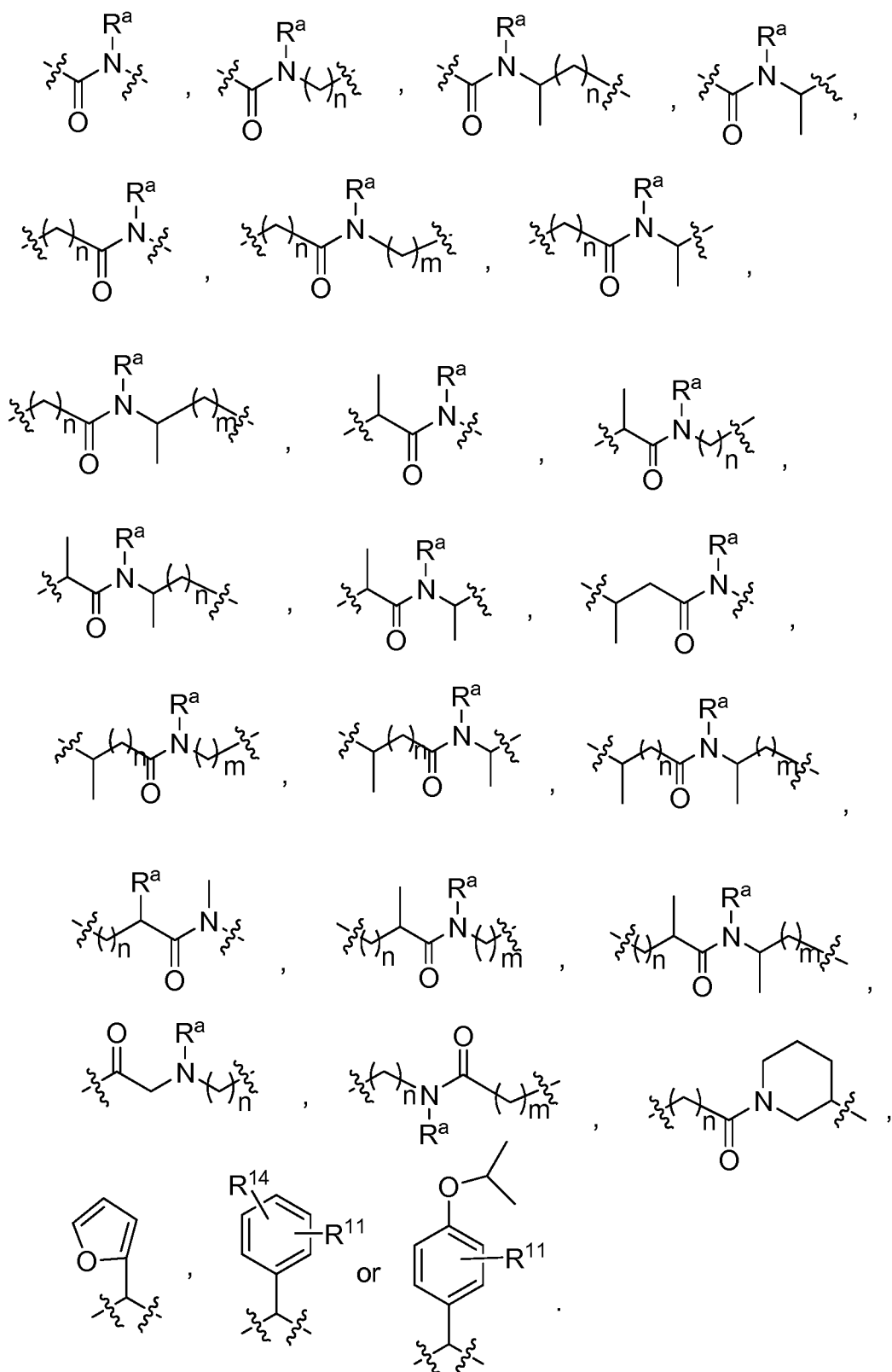
**I** is an end group that is: a C<sub>1</sub>-C<sub>10</sub> hydrocarbon moiety; C<sub>3</sub>-C<sub>10</sub> aryl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>3</sub>-C<sub>9</sub> heterocyclic; optionally substituted indenyl; optionally substituted phenyl; or a 5- or 6- member heteroaryl ring having up to three heteroatoms selected from O, N and S, wherein the heteroaryl ring optionally bears a substituent **J**; and wherein

**J** is an electron withdrawing group, lower hydrocarbon moiety, lower alkoxy, optionally substituted phenyl, or is optionally substituted fused benzo group, or if **I** is a triazole, then **J** optionally is a six-member heteroaryl ring in which the heteroatoms are 1 or 2 nitrogen atoms, and **J** is optionally substituted at one or more carbon atoms on the ring by an electron withdrawing group, lower hydrocarbon moiety, or lower alkoxy.

75. The method according to claim 74, wherein **G** is purinyl, xanthinyl, 5-azabenzimidazolyl, benzimidazolyl, indolyl, thiophenyl, piperidin-2-onyl, morpholin-2-onyl, benzopyran-4-onyl, piperazin-2-onyl, and 1,4,8-triaza-4,5,6,7-tetrahydro-5-oxo-indenyl, and wherein **G** is optionally substituted by one or more groups selected from oxo, lower alkyl, lower alkoxy, electron withdrawing groups, and benzo substituents,



76. The method according to claim 74, wherein **H** includes one to eight methylene groups, each methylene group can be optionally substituted with a lower alkyl, halide, lower alkoxy, aryl, heteroaryl, cycloalkyl, heterocyclyl; aryl; heteroaryl; cycloalkyl; heterocyclyl; -C(=O)-; -N(R<sup>a</sup>)-; -O-; -S-;



77. The method according to claim 74, wherein **I** is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, 2- or 1,3- oxazolyl; thiazolyl; oxadiazolyl; thiadiazolyl; 1,2,4-triazolyl; pyridinyl; s-butyl; i-propyl; cyclopropyl; epoxidyl; glycidyl; 3-pentyl; phenyl; indolyl; furanyl; N-(3-



81. The method of claim 74, wherein for **H**, R<sup>b</sup> is: methyl; furanyl; thiophene-2-yl, p-isopropoxyphenyl; or together with R<sup>a</sup> forms a bridge defining a 1,4-piperidinediyl moiety.

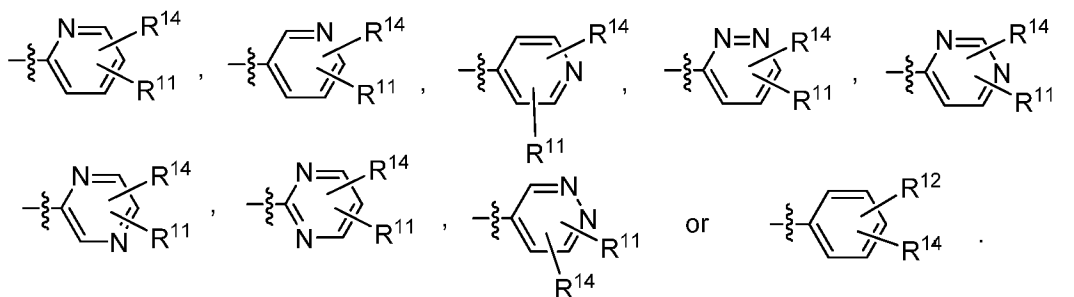
82. The method of claim 74, wherein **I** is: 1,2- or 1,3- oxazolyl; thiazolyl; oxadiazolyl; thiadiazolyl; 1,2,4-triazolyl; pyridinyl; s-butyl; i-propyl; cyclopropyl; epoxidyl; glycidyl; 3-pentyl; phenyl; indolyl; furanyl; N-(3-methoxyphenyl)-pyrrolidin-2-on-4-yl; or 3-(aza- or diaza-benzenyl)-1,2,4-triazol-5-yl, or benzimidazolyl.

83. The method according to claim 74 or 76, wherein R<sup>a</sup> is H or C<sub>1</sub>-C<sub>3</sub> alkyl.

84. The method according to claim 75, wherein R<sup>20</sup> is H, C<sub>1</sub>-C<sub>3</sub> alkyl or halide.

85. The method according to claim 76, wherein R<sup>13</sup> is R<sup>8</sup>.

86. The method according to claim 85, wherein R<sup>8</sup> is H, C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, halide, hydroxyl,



87. The method according to claim 76-78 or 86, wherein R<sup>11</sup> is H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halide or hydroxyl.

88. The method according to claim 76, 78 or 86 wherein R<sup>14</sup> is H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halide or hydroxyl.

89. The method of claim 77, 78 or 86, wherein R<sup>12</sup> is H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halide or hydroxyl.

90. The method of claim 75, wherein X is H, -CF<sub>3</sub> or Cl

91. The method of any one of claims 74-90, wherein the disease or disorder associated with angiogenesis is selected from: tumor or cancer growth (neoplasia), skin disorders, neovascularization, inflammatory and arthritic diseases, retinoblastoma, cystoid macular edema (CME), exudative age-related macular degeneration (AMD), diabetic retinopathy, diabetic macular edema, or ocular inflammatory disorders.

92. The method of claim 91, wherein the disease or disorder associated with angiogenesis is tumor or cancer growth (neoplasia).

93. The method of claim 92, wherein the disease or disorder is ocular cancer, rectal cancer, colon cancer, cervical cancer, prostate cancer, breast cancer and bladder cancer, oral cancer, benign and malignant tumors, stomach cancer, liver cancer, pancreatic cancer, lung cancer, corpus uteri, ovary cancer, prostate cancer, testicular cancer, renal cancer, brain/ens cancer, throat cancer, skin melanoma, acute lymphocytic leukemia, acute myelogenous leukemia, Ewing's Sarcoma, Kaposi's Sarcoma, basal cell carcinoma and squamous cell carcinoma, small cell lung cancer, choriocarcinoma, rhabdomyosarcoma, angiosarcoma, hemangioendothelioma, Wilms Tumor, neuroblastoma, mouth/pharynx cancer, esophageal cancer, larynx cancer, lymphoma, neurofibromatosis, tuberous sclerosis, hemangiomas, and lymphangiogenesis .

94. The method of claim 91, wherein the disease or disorder associated with angiogenesis is a skin disorder.

95. The method of claim 94, wherein the disease or disorder is psoriasis, acne, rosacea, warts, eczema, hemangiomas, lymphangiogenesis, Sturge-Weber syndrome, venous ulcers of the skin, neurofibromatosis, and tuberous sclerosis.

96. The method of claim 91, wherein the disease or disorder associated with angiogenesis is neovascularization.

97. The method of claim 96, wherein the disease or disorder is diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma, retrolental fibroplasias, epidemic keratoconjunctivitis, vitamin A deficiency, contact lens overwear, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, Sjogren's, acne rosacea, phlyctenulosis, syphilis, Mycobacteria infections, lipid degeneration, chemical burns, bacterial ulcers, fungal ulcers, herpes simplex infections, herpes zoster infections, protozoan infections, Kaposi's sarcoma, Mooren's ulcer, Terrien's marginal degeneration, marginal keratolysis, trauma, rheumatoid arthritis, systemic lupus, polyarteritis, Wegener's sarcoidosis, scleritis, Stevens- Johnson disease, pemphigoid, radial keratotomy, corneal graft rejection, macular edema, macular degeneration, sickle cell anemia, sarcoid, syphilis, pseudoxanthoma elasticum, Paget's disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis/vitritis, mycobacterial infections, Lyme disease, systemic lupus erythematosus, retinopathy of prematurity, Eales' disease, Behcet's disease, infections causing a retinitis or choroiditis, presumed ocular histoplasmosis, Best's disease, myopia, optic pits, Stargardt's disease, pars planitis, chronic

retinal detachment, hyperviscosity syndromes, toxoplasmosis, trauma and post-laser complications, and diseases associated with rubeosis (neovascularization of the ankle).

98. The method of claim 91, wherein the disease or disorder associated with angiogenesis is inflammatory and arthritic disease.

99. The method of claim 98, wherein the disease or disorder is: rheumatoid arthritis, osteoarthritis, lupus, scleroderma, Crohn's disease, ulcerative colitis, psoriasis, sarcoidosis, Sarcoidosis, skin lesions, hemangiomas, Osier- Weber-Rendu disease, hereditary hemorrhagic telangiectasia, and osteoarthritis.

100. The method of claim 91, wherein the disease or disorder affects the dermis, epidermis, endometrium, retina, surgical wound, gastrointestinal tract, umbilical cord, liver, kidney, reproductive system, lymphoid system, central nervous system, breast tissue, urinary tract, circulatory system, bone, muscle, or respiratory tract.

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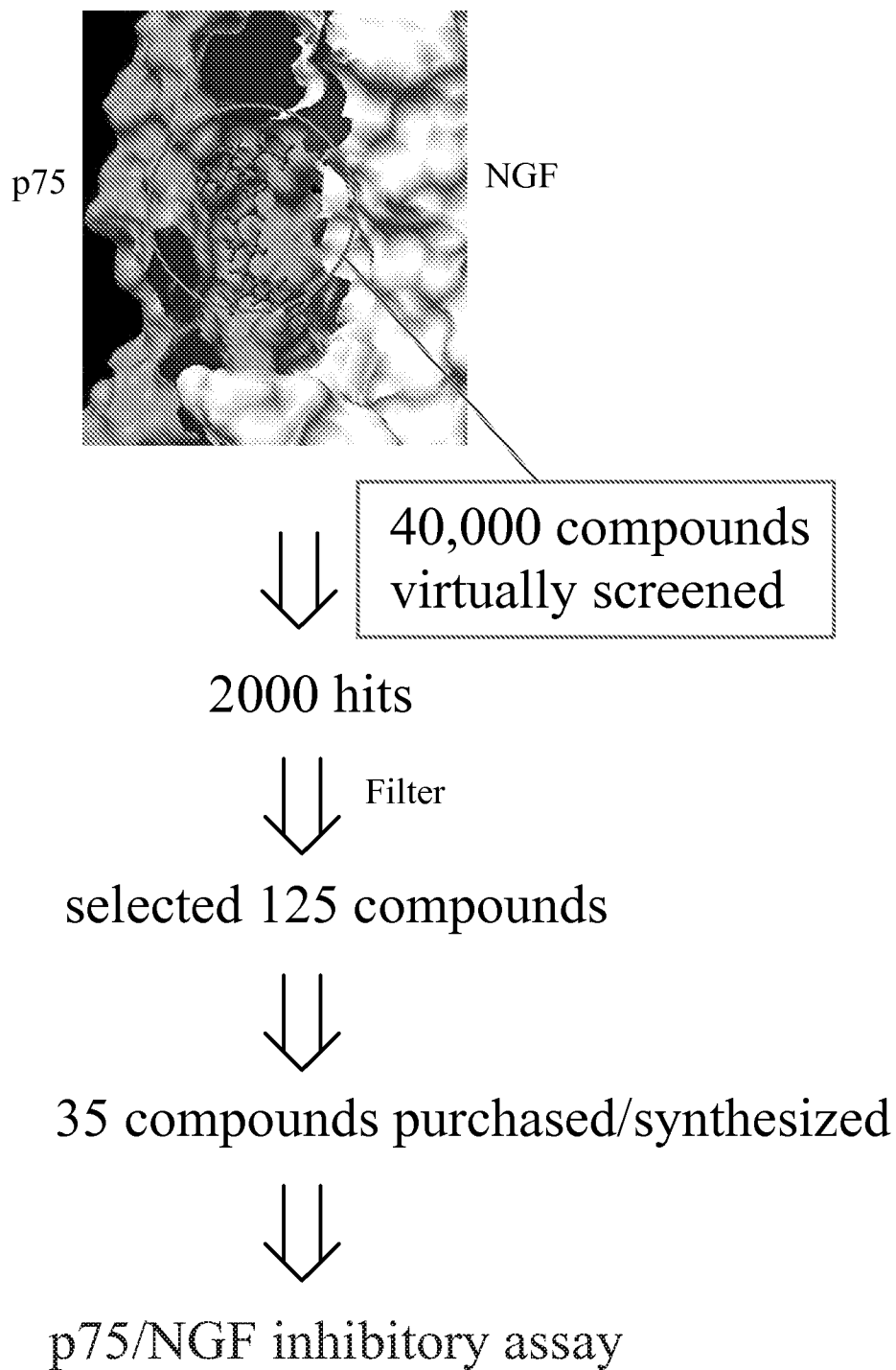


FIG. 1

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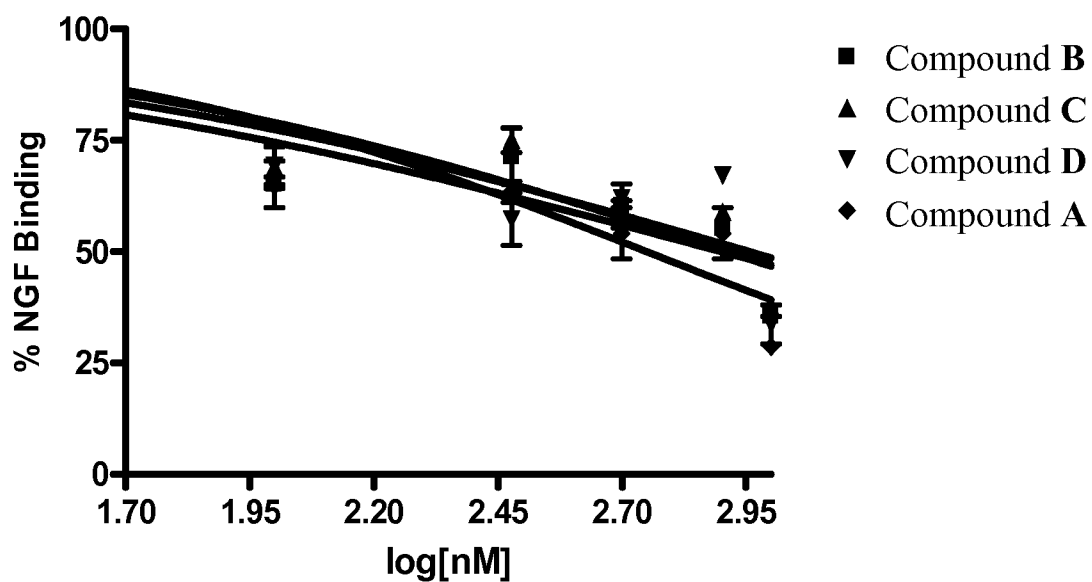


FIG. 2A

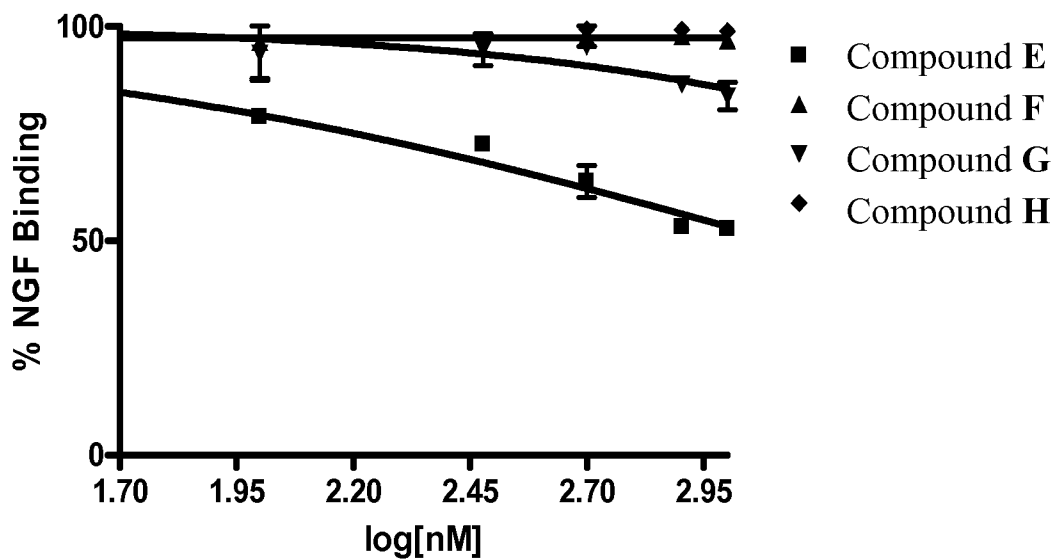


FIG. 2B

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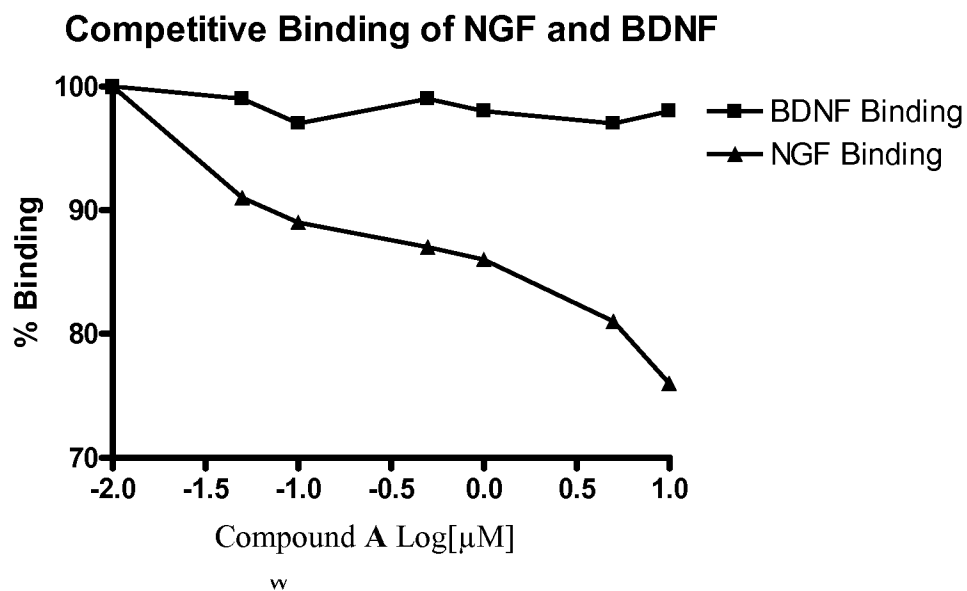


FIG. 3

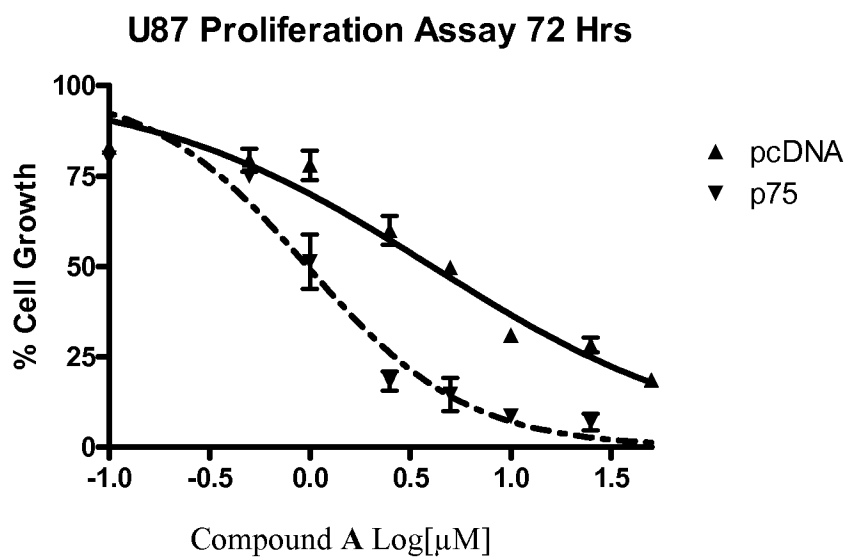
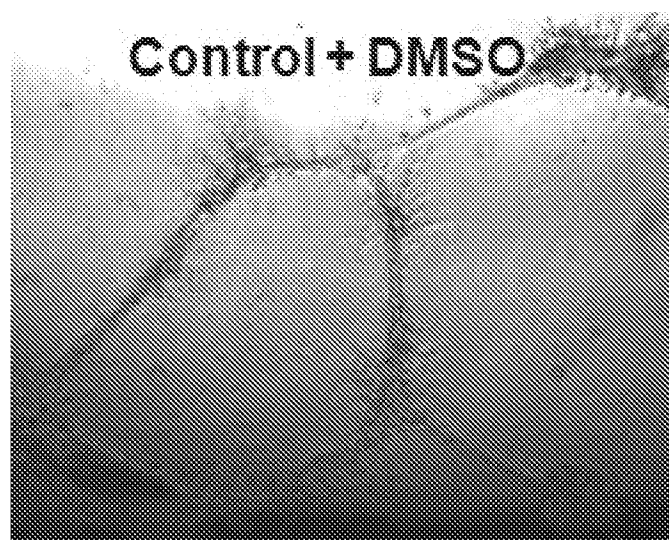
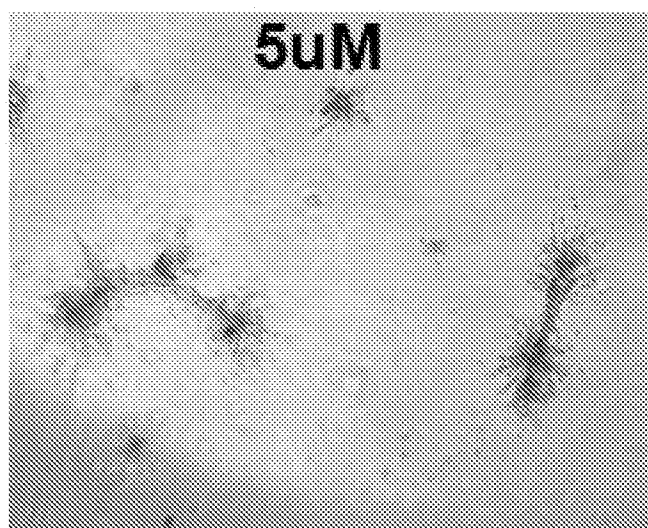


FIG. 4

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**FIG. 5A**



**FIG. 5B**

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Total tube length in field compound A

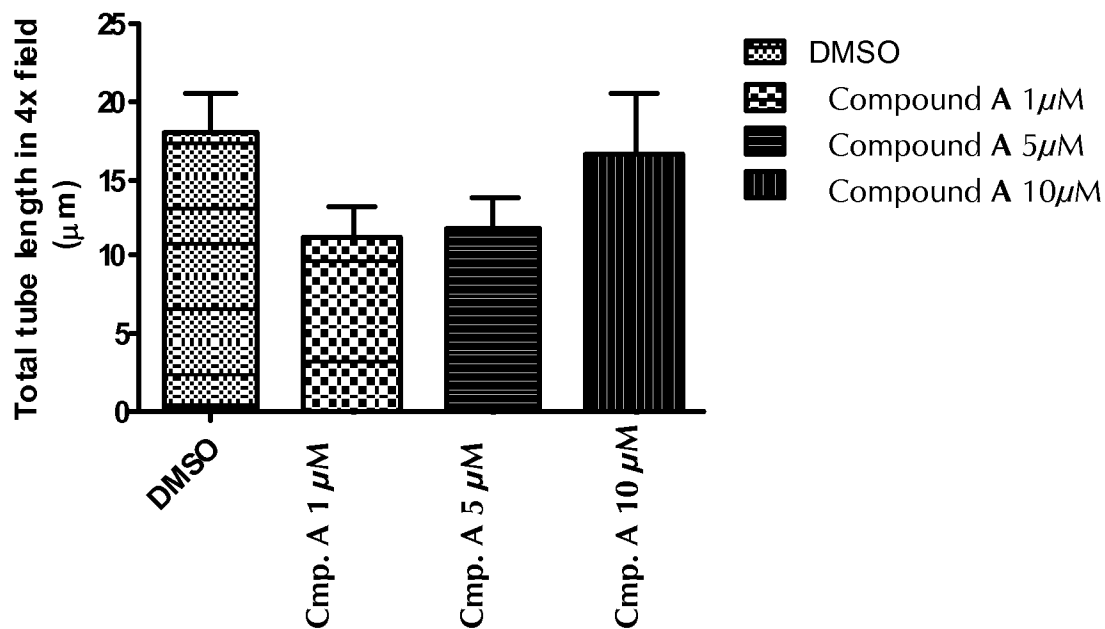


FIG. 5C

Number of tubes in field Compound A

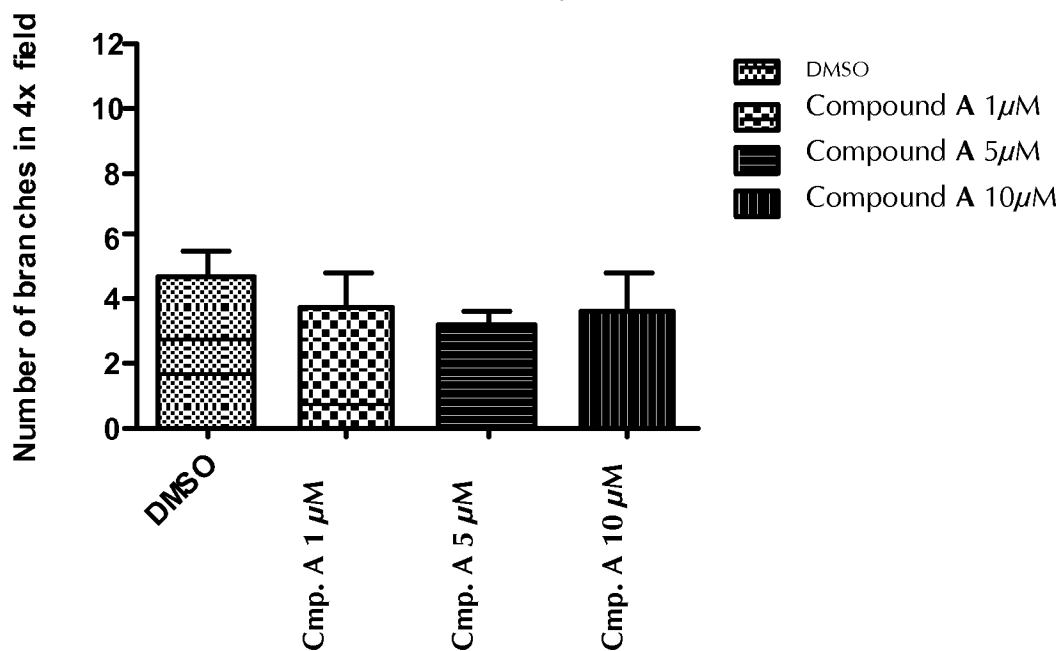
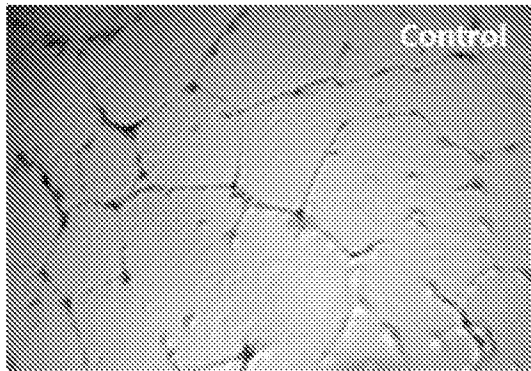
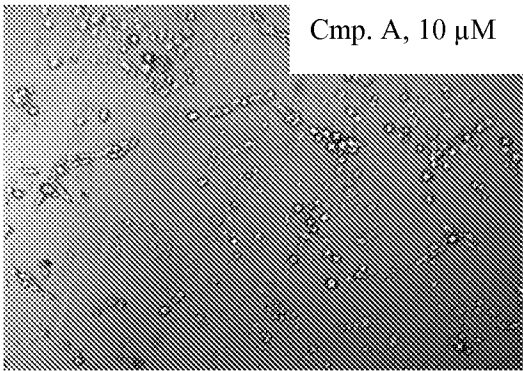


FIG. 5D

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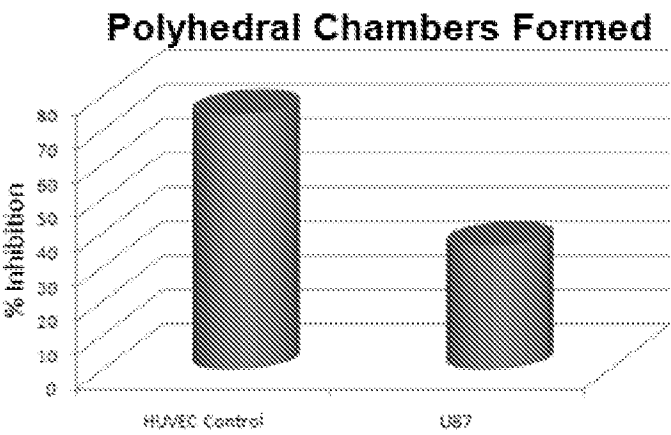


6A



6B

6C



6D

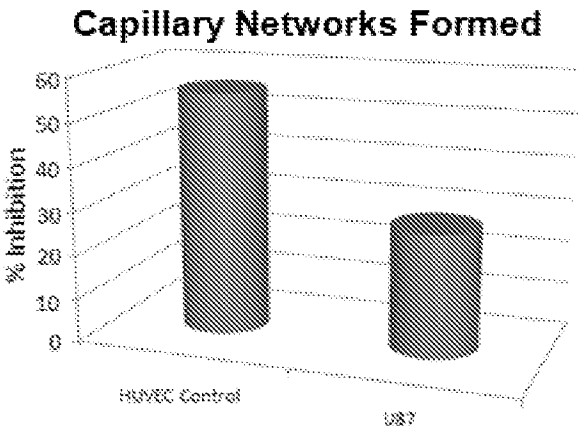
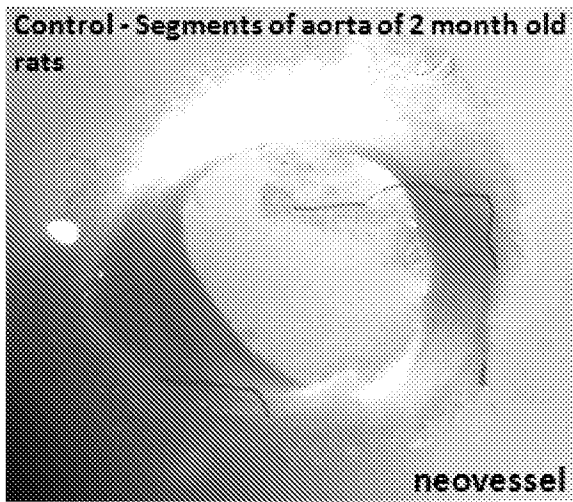


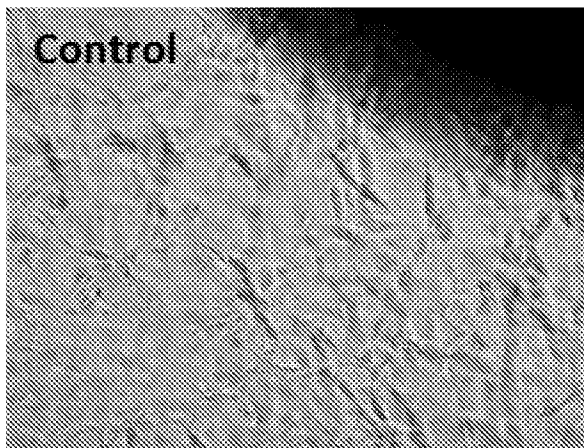
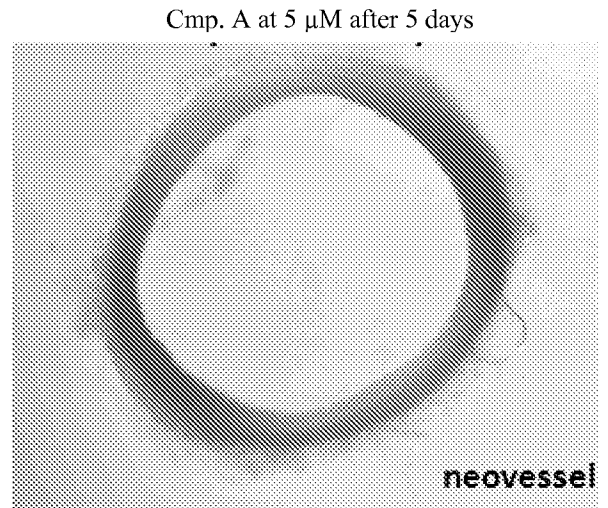
FIG. 6 A-D

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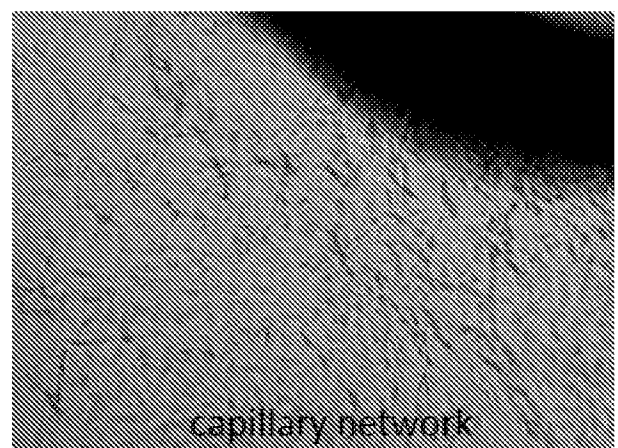
7A



7B



7C



7D

FIG. 7 A-D

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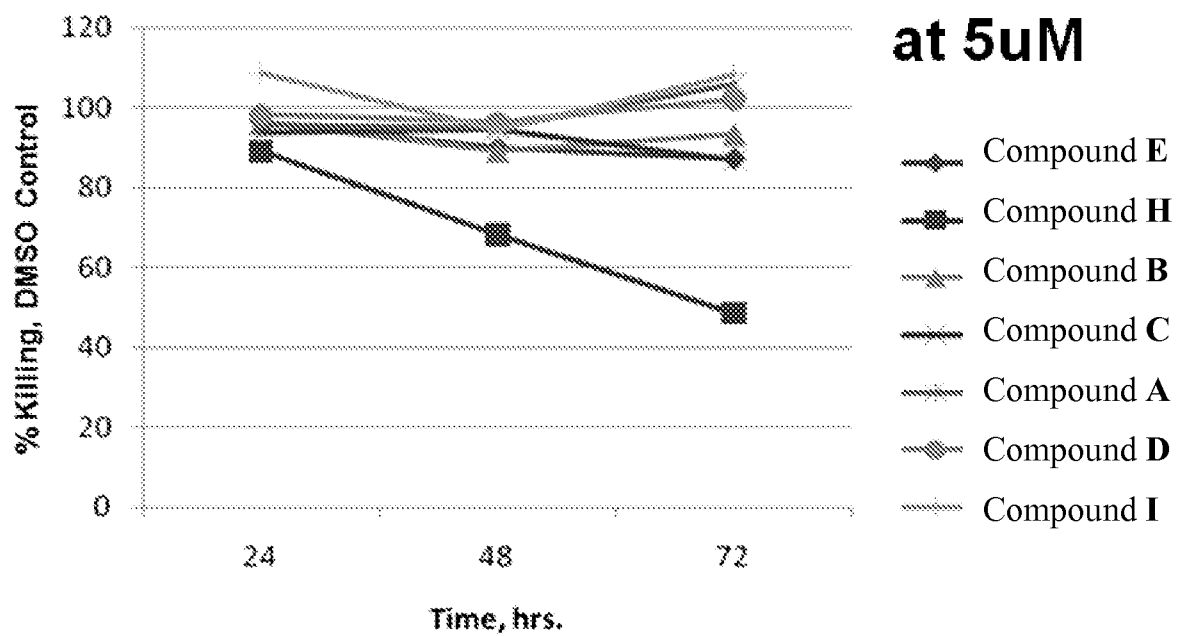


FIG. 8