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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 April 2001 (26.04.2001)

PCT

(10) International Publication Number
WO 01/29025 A2

(51) International Patent Classification[7]: C07D 401/00

(21) International Application Number: PCT/US00/28625

(22) International Filing Date: 16 October 2000 (16.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/160,356 19 October 1999 (19.10.1999) US

(71) Applicant *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ARRINGTON, Kenneth, L.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **BILODEAU, Mark, T.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **FRALEY, Mark, E.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **HARTMAN, George, D.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **HOFFMAN, William, F.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **HUNGATE, Randall, W.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **KIM, Yuntae** [KP/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/29025 A2

(54) Title: TYROSINE KINASE INHIBITORS

(57) Abstract: The present invention relates to compounds which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compositions which contain these compounds, and methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals.

TITLE OF THE INVENTION

TYROSINE KINASE INHIBITORS

RELATED APPLICATIONS

This application claims priority under 35 U.S.C. § 119(e) from U.S. Provisional Application 60/160,356 filed October 19th, 1999.

BACKGROUND OF THE INVENTION

The present invention relates to compounds which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compositions which contain these compounds, and methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals.

Tyrosine kinases are a class of enzymes that catalyze the transfer of the terminal phosphate of adenosine triphosphate to tyrosine residues in protein substrates. Tyrosine kinases are believed, by way of substrate phosphorylation, to play critical roles in signal transduction for a number of cell functions. Though the exact mechanism of signal transduction is still unclear, tyrosine kinases have been shown to be important contributing factors in cell proliferation, carcinogenesis and cell differentiation.

Tyrosine kinases can be categorized as receptor type or non-receptor type. Receptor type tyrosine kinases have an extracellular, a transmembrane, and an intracellular portion, while non-receptor type tyrosine kinases are wholly intracellular.

The receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. In fact, about twenty different subfamilies of receptor-type tyrosine kinases have been identified. One tyrosine kinase subfamily, designated the HER subfamily, is comprised of EGFR, HER2, HER3, and HER4. Ligands of this subfamily of

receptors include epithileal growth factor, TGF-α, amphiregulin, HB-EGF, betacellulin and heregulin. Another subfamily of these receptor-type tyrosine kinases is the insulin subfamily, which includes INS-R, IGF-IR, and IR-R. The PDGF subfamily includes the PDGF-α and β receptors, CSFIR, c-kit and FLK-II. Then there is the FLK family which is comprised of the kinase insert domain receptor (KDR), fetal liver kinase-1 (FLK-1), fetal liver kinase-4 (FLK-4) and the fms-like tyrosine kinase-1 (flt-1). The PDGF and FLK families are usually considered together due to the similarities of the two groups. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., *DN&P* 7(6):334-339, 1994, which is hereby incorporated by reference.

The non-receptor type of tyrosine kinases is also comprised of numerous subfamilies, including Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack, and LIMK. Each of these subfamilies is further sub-divided into varying receptors. For example, the Src subfamily is one of the largest and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, and Yrk. The Src subfamily of enzymes has been linked to oncogenesis. For a more detailed discussion of the non-receptor type of tyrosine kinases, see Bolen *Oncogene*, 8:2025-2031 (1993), which is hereby incorporated by reference.

Both receptor-type and non-receptor type tyrosine kinases are implicated in cellular signaling pathways leading to numerous pathogenic conditions, including cancer, psoriasis and hyperimmune responses.

Several receptor-type tyrosine kinases, and the growth factors that bind thereto, have been suggested to play a role in angiogenesis, although some may promote angiogenesis indirectly (Mustonen and Alitalo, *J. Cell Biol.* 129:895-898, 1995). One such receptor-type tyrosine kinase is fetal liver kinase 1 or FLK-1. The human analog of FLK-1 is the kinase insert domain-containing receptor KDR, which is also known as vascular endothelial cell growth factor receptor 2 or VEGFR-2, since it binds VEGF with high affinity. Finally, the murine version of this receptor has also been called NYK (Oelrichs et al., *Oncogene* 8(1):11-15, 1993). VEGF and KDR are a ligand-receptor pair

that play an important role in the proliferation of vascular endothelial cells, and the formation and sprouting of blood vessels, termed vasculogenesis and angiogenesis, respectively.

Angiogenesis is characterized by excessive activity of vascular endothelial growth factor (VEGF). VEGF is actually comprised of a family of ligands (Klagsburn and D'Amore, *Cytokine &Growth Factor Reviews* 7:259-270, 1996). VEGF binds the high affinity membrane-spanning tyrosine kinase receptor KDR and the related fms-like tyrosine kinase-1, also known as Flt-1 or vascular endothelial cell growth factor receptor 1 (VEGFR-1). Cell culture and gene knockout experiments indicate that each receptor contributes to different aspects of angiogenesis. KDR mediates the mitogenic function of VEGF whereas Flt-1 appears to modulate non-mitogenic functions such as those associated with cellular adhesion. Inhibiting KDR thus modulates the level of mitogenic VEGF activity. In fact, tumor growth has been shown to be susceptible to the antiangiogenic effects of VEGF receptor antagonists. (Kim et al., Nature *362*, pp. 841-844, 1993).

Solid tumors can therefore be treated by tyrosine kinase inhibitors since these tumors depend on angiogenesis for the formation of the blood vessels necessary to support their growth. These solid tumors include histiocytic lymphoma, cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung, including lung adenocarcinoma and small cell lung cancer. Additional examples include cancers in which overexpression or activation of Raf-activating oncogenes (e.g., K-ras, erb-B) is observed. Such cancers include pancreatic and breast carcinoma. Accordingly, inhibitors of these tyrosine kinases are useful for the prevention and treatment of proliferative diseases dependent on these enzymes.

The angiogenic activity of VEGF is not limited to tumors. VEGF accounts for most of the angiogenic activity produced in or near the retina in diabetic retinopathy. This vascular growth in the retina leads to visual degeneration culminating in blindness. Ocular VEGF mRNA and protein are

elevated by conditions such as retinal vein occlusion in primates and decreased pO_2 levels in mice that lead to neovascularization. Intraocular injections of anti-VEGF monoclonal antibodies or VEGF receptor immunofusions inhibit ocular neovascularization in both primate and rodent models. Regardless of the cause of induction of VEGF in human diabetic retinopathy, inhibition of ocular VEGF is useful in treating the disease.

Expression of VEGF is also significantly increased in hypoxic regions of animal and human tumors adjacent to areas of necrosis. VEGF is also upregulated by the expression of the oncogenes ras, raf, src and mutant p53 (all of which are relevant to targeting cancer). Monoclonal anti-VEGF antibodies inhibit the growth of human tumors in nude mice. Although these same tumor cells continue to express VEGF in culture, the antibodies do not diminish their mitotic rate. Thus tumor-derived VEGF does not function as an autocrine mitogenic factor. Therefore, VEGF contributes to tumor growth in vivo by promoting angiogenesis through its paracrine vascular endothelial cell chemotactic and mitogenic activities. These monoclonal antibodies also inhibit the growth of typically less well vascularized human colon cancers in athymic mice and decrease the number of tumors arising from inoculated cells.

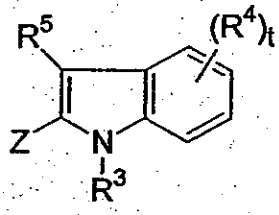
Viral expression of a VEGF-binding construct of Flk-1, Flt-1, the mouse KDR receptor homologue, truncated to eliminate the cytoplasmic tyrosine kinase domains but retaining a membrane anchor, virtually abolishes the growth of a transplantable glioblastoma in mice presumably by the dominant negative mechanism of heterodimer formation with membrane spanning endothelial cell VEGF receptors. Embryonic stem cells, which normally grow as solid tumors in nude mice, do not produce detectable tumors if both VEGF alleles are knocked out. Taken together, these data indicate the role of VEGF in the growth of solid tumors. Inhibition of KDR or Flt-1 is implicated in pathological angiogenesis, and these receptors are useful in the treatment of diseases in which angiogenesis is part of the overall pathology, e.g., inflammation, diabetic retinal vascularization, as well as various forms of

cancer since tumor growth is known to be dependent on angiogenesis. (Weidner et al., N. Engl. J. Med., *324*, pp. 1-8, 1991).

Accordingly, the identification of small compounds which specifically inhibit, regulate and/or modulate the signal transduction of tyrosine kinases is desirable and is an object of this invention.

SUMMARY OF THE INVENTION

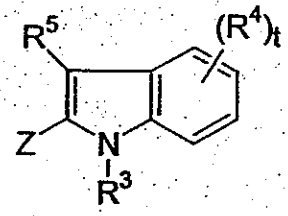
The present invention relates to compounds that are capable of inhibiting, modulating and/or regulating signal transduction of both receptor-type and non-receptor type tyrosine kinases. One embodiment of the present invention is illustrated by a compound of Formula I , and the pharmaceutically acceptable salts and stereoisomers thereof:



I

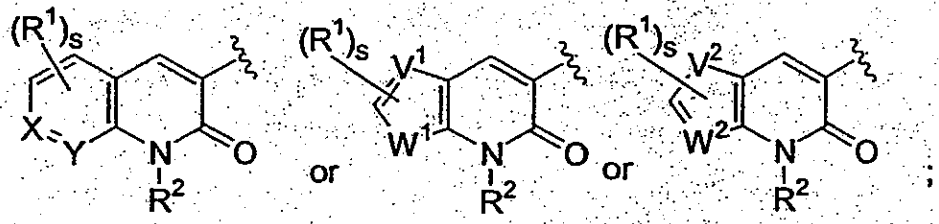
DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of kinases and are illustrated by a compound of Formula I:



I

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein

Z is  ;

W^1 is S, O, or N-R;

V^1 is N or C;

W^2 is N or C;

V^2 is S, O, or N-R;

a is 0 or 1;

b is 0 or 1;

m is 0, 1, or 2;

s is 1 or 2;

t is 1, 2, or 3;

X=Y is C=N, N=C, or C=C;

R is H or C_1-C_6 alkyl;

R^1 and R^5 are independently selected from:

1) H,
2) $(C=O)_aO_bC_1$-C_{10} alkyl,
3) $(C=O)_aO_b$aryl,
4) $(C=O)_aO_bC_2$-C_{10} alkenyl,
5) $(C=O)_aO_bC_2$-C_{10} alkynyl,
6) CO_2H,

7) halo,
8) OH,
9) O_bC_1-C_6 perfluoroalkyl,
10) $(C=O)_aNR^7R^8$,
11) CN,
12) $(C=O)_aO_bC_3$-C_8 cycloalkyl, and
13) $(C=O)_aO_b$heterocyclyl,

said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^6;

R^2 and R^3 are independently selected from:

1) H,
2) $(C=O)O_aC_1$-C_6 alkyl,
3) $(C=O)O_a$aryl,
4) C_1-C_6 alkyl,
5) SO_2R^a, and
6) aryl;

R^4 is selected from:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) $(C=O)_aO_bC_2$-C_{10} alkenyl,
4) $(C=O)_aO_bC_2$-C_{10} alkynyl,
5) CO_2H,
6) halo,
7) OH,
8) O_bC_1-C_6 perfluoroalkyl,
9) $(C=O)_aNR^7R^8$,

10) CN,

11) $(C=O)_aO_bC_3$-C_8 cycloalkyl, and

12) $(C=O)_aO_b$heterocyclyl,

said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^6;

R^6 is:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,

2) $(C=O)_aO_b$aryl,

3) C_2-C_{10} alkenyl,

4) C_2-C_{10} alkynyl,

5) $(C=O)_aO_b$ heterocyclyl,

6) CO_2H,

7) halo,

8) CN,

9) OH,

10) O_bC_1-C_6 perfluoroalkyl,

11) $O_a(C=O)_bNR^7R^8$,

12) oxo,

13) CHO,

14) $(N=O)R^7R^8$, or

15) $(C=O)_aO_bC_3$-C_8 cycloalkyl,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selcted from R^{6a};

R^{6a} is selected from:

1) $(C=O)_rO_s(C_1$-$C_{10})$alkyl, wherein r and s are independently 0 or 1,

2) $O_r(C_1$-$C_3)$perfluoroalkyl, wherein r is 0 or 1,

3) $(C_0\text{-}C_6)$alkylene-$S(O)_mR^a$, wherein m is 0, 1, or 2,

4) oxo,

5) OH,

6) halo,

7) CN,

8) $(C_2\text{-}C_{10})$alkenyl,

9) $(C_2\text{-}C_{10})$alkynyl,

10) $(C_3\text{-}C_6)$cycloalkyl,

11) $(C_0\text{-}C_6)$alkylene-aryl,

12) $(C_0\text{-}C_6)$alkylene-heterocyclyl,

13) $(C_0\text{-}C_6)$alkylene-$N(R^b)_2$,

14) $C(O)R^a$,

15) $(C_0\text{-}C_6)$alkylene-CO_2R^a,

16) C(O)H, and

17) $(C_0\text{-}C_6)$alkylene-CO_2H,

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1\text{-}C_6)$alkoxy, halogen, CO_2H, CN, $O(C{=}O)C_1\text{-}C_6$ alkyl, oxo, and $N(R^b)_2$;

R^7 and R^8 are independently selected from:

1) H,

2) $(C{=}O)O_bC_1\text{-}C_{10}$ alkyl,

3) $(C{=}O)O_bC_3\text{-}C_8$ cycloalkyl,

4) $(C{=}O)O_b$aryl,

5) $(C{=}O)O_b$heterocyclyl,

6) $C_1\text{-}C_{10}$ alkyl,

7) aryl,

8) $C_2\text{-}C_{10}$ alkenyl,

9) C_2-C_{10} alkynyl,

10) heterocyclyl,

11) C_3-C_8 cycloalkyl,

12) SO_2R^a, and

13) $(C=O)NR^b{}_2$,

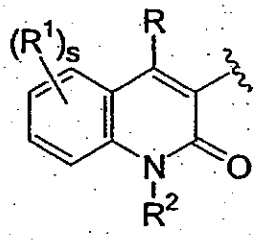
said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from $R6^a$, or

R^7 and R^8 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocylcic or bicyclic heterocycle optionally substituted with one or more substituents selected from R^{6a};

R^a is $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, aryl, or heterocyclyl; and

R^b is H, $(C_1$-$C_6)$alkyl, aryl, heterocyclyl, $(C_3$-$C_6)$cycloalkyl, $(C=O)OC_1$-C_6 alkyl, $(C=O)C_1$-C_6 alkyl or $S(O)_2R^a$.

A second embodiment of the invention is a compound of Formula I, wherein

Z is 

A further embodiment of the present invention is illustrated by a compound of Formula I, with Z as defined immediately above, wherein

s is 1, and

t is 1 or 2;

R^1 and R^5 are independently selected from:

1) H,
2) $(C=O)_aO_bC_1$-C_6 alkyl,
3) $(C=O)_aO_b$aryl,
4) $(C=O)_aO_bC_2$-C_6 alkenyl,
5) $(C=O)_aO_bC_2$-C_6 alkynyl,
6) CO_2H,
7) halo,
8) OH,
9) O_bC_1-C_3 perfluoroalkyl,
10) $(C=O)_aNR^7R^8$,
11) CN,
12) $(C=O)_aO_bC_3$-C_6 cycloalkyl, and
13) $(C=O)_aO_b$heterocyclyl,

said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^6;

R^4 is selected from:

1) $(C=O)_aO_bC_1$-C_6 alkyl,
2) $(C=O)_aO_b$aryl,
3) $(C=O)_aO_bC_2$-C_6 alkenyl,
4) $(C=O)_aO_bC_2$-C_6 alkynyl,
5) CO_2H,

6) halo,
7) OH,
8) O_bC_1-C_3 perfluoroalkyl,
9) $(C=O)_aNR^7R^8$,
10) CN,
11) $(C=O)_aO_bC_3$-C_6 cycloalkyl, and
12) $(C=O)_aO_b$heterocyclyl,

said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^6;

R^6 is:

1) $(C=O)_aO_bC_1$-C_6 alkyl,
2) $(C=O)_aO_b$aryl,
3) C_2-C_6 alkenyl,
4) C_2-C_6 alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) CO_2H,
7) halo,
8) CN,
9) OH,
10) O_bC_1-C_3 perfluoroalkyl,
11) $O_a(C=O)_bNR^7R^8$,
12) oxo,
13) CHO,
14) $(N=O)R^7R^8$, or
15) $(C=O)_aO_bC_3$-C_6 cycloalkyl,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl is optionally substituted with one or more substituents selcted from R^{6a};

R^{6a} is selected from:

1) $(C=O)_rO_s(C_1\text{-}C_6)$alkyl, wherein r and s are independently 0 or 1,
2) $O_r(C_1\text{-}C_3)$perfluoroalkyl, wherein r is 0 or 1,
3) $(C_0\text{-}C_6)$alkylene-$S(O)_mR^a$, wherein m is 0, 1, or 2,
4) oxo,
5) OH,
6) halo,
7) CN,
8) $(C_2\text{-}C_6)$alkenyl,
9) $(C_2\text{-}C_6)$alkynyl,
10) $(C_3\text{-}C_6)$cycloalkyl,
11) $(C_0\text{-}C_6)$alkylene-aryl,
12) $(C_0\text{-}C_6)$alkylene-heterocyclyl,
13) $(C_0\text{-}C_6)$alkylene-$N(R^b)_2$,
14) $C(O)R^a$,
15) $(C_0\text{-}C_6)$alkylene-CO_2R^a,
16) C(O)H, and
17) $(C_0\text{-}C_6)$alkylene-CO_2H,

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1\text{-}C_6)$alkoxy, halogen, CO_2H, CN, $O(C=O)C_1\text{-}C_6$ alkyl, oxo, and $N(R^b)_2$; and

R^7 and R^8 are independently selected from:

1) H,
2) $(C=O)O_bC_1\text{-}C_6$ alkyl,
3) $(C=O)O_bC_3\text{-}C_6$ cycloalkyl,
4) $(C=O)O_b$aryl,

5) $(C=O)O_b$heterocyclyl,

6) C_1-C_6 alkyl,

7) aryl,

8) C_2-C_6 alkenyl,

9) C_2-C_6 alkynyl,

10) heterocyclyl,

11) C_3-C_6 cycloalkyl,

12) SO_2R^a, and

13) $(C=O)NR^b{}_2$,

said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from $R6^a$, or

R^7 and R^8 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocylcic or bicyclic heterocycle optionally substituted with one or more substituents selected from R^{6a}.

Another embodiment is the compound described immediately above wherein R^2, R^3, and R^5 are further defined as H.

And yet another embodiment is wherein t is further defined as 1, s is 1, and R^1 is H.

Also encompassed by the present invention is the compound of Formula I as further defined immediately above and wherein R^4 is selected from:

1) OC_1-C_6 alkyleneNR^7R^8,

2) $(C=O)_aC_0$-C_6 alkylene-Q, wherein Q is H, OH, CO_2H, or OC_1-C_6 alkyl,

3) OC_0-C_6 alkylene-heterocyclyl, optionally substituted with one to three substituents selected from $R6^a$,

4) C_0-C_6 alkyleneNR^7R^8,

5) $(C=O)NR^7R^8$, and

6) OC_1-C_3 alkylene-$(C=O)NR^7R^8$.

A preferred embodiment is a compound selected from 3-{5-[3-(4-methyl-piperazin-1-yl)-propoxy]-1H-indol-2-yl}-1H-quinolin-2-one;
3-(5-{2-[(2-methoxyethyl)amino]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone;
3-[5-(2-{(2-methoxyethyl)[(2-methoxy-5-pyrimidinyl)methyl]amino}ethoxy)-1H-indol-2-yl]-2(1H)-quinolinone;
3-(5-{[(2S,4R)-4-methoxypyrrolidinyl]methoxy}-1H-indol-2-yl)-2(1H)-quinolinone;
3-[5-({(2S,4R)-4-methoxy-1-[(2-methyl-5-pyrimidinyl)methyl]pyrrolidinyl}methoxy)-1H-indol-2-yl]-2(1H)-quinolinone;
1-(2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}ethyl)-4-piperidine-carboxylic acid ethyl ester;
1-(2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}ethyl)-4-piperidinecarboxylic acid;
3-[(2S,4R)-4-methoxy-2-({[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}methyl)pyrrolidinyl]propanoic acid;
3-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one;
3-[5-(4-methanesulfonyl-1-oxy-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one;
3-[5-(4-acetyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one;
N-Cyclopropyl-N-[2-(2-oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-ylmethyl]-methanesulfonamide;
3-[5-(1-piperazinylcarbonyl)-1H-indol-2-yl]-2(1H)-quinolinone;
3-{5-[(4-methyl-1-piperazinyl)carbonyl]-1H-indol-2-yl}-2(1H)-quinolinone;

1-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]carbonyl}-4-piperidinaminium trifluoroacetate;

1-({[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}acetyl)piperazin-4-ium trifluoroacetate;

3-{5-[2-(1,1-dioxido-4-thiomorpholinyl)-2-oxoethoxy]-1H-indol-2-yl}-2(1H)-quinolinone;

N-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]methyl}-4-piperidine carboxamide;

3-{5-[1-(4-morpholinyl)ethyl]-1H-indol-2-yl}-2(1H)-quinolinone;

3-{5-[1-(1-pyrrolidinyl)ethyl]-1H-indol-2-yl}-2(1H)-quinolinone;

3-{5-[1-(4-acetyl-1-piperazinyl)ethyl]-1H-indol-2-yl}-2(1H)-quinolinone;

3-(5-{1-[4-(methylsulfonyl)-1-piperazinyl]ethyl}-1H-indol-2-yl)-2(1H)-quinolinone;

4-amino-N-[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]-1-piperidinecarboxamide; and

4-amino-N-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]methyl}-1-piperidinecarboxamide, or a pharmaceutically acceptable salt or stereoisomer thereof.

Also included within the scope of the present invention is a pharmaceutical composition which is comprised of a compound of Formula I as described above and a pharmaceutically acceptable carrier. The present invention also encompasses a method of treating or preventing cancer in a mammal in need of such treatment which is comprised of administering to said mammal a therapeutically effective amount of a compound of Formula I. Preferred cancers for treatment are selected from cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung. Another set of preferred forms of cancer are histiocytic lymphoma, lung adenocarcinoma, small cell lung cancers, pancreatic cancer, gioblastomas and breast carcinoma.

Also included is a method of treating or preventing a disease in which angiogenesis is implicated, which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula I. Such a disease in which angiogenesis is implicated is

ocular diseases such as retinal vascularization, diabetic retinopathy, age-related macular degeneration, and the like.

Also included within the scope of the present invention is a method of treating or preventing inflammatory diseases which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula 1. Examples of such inflammatory diseases are rheumatoid arthritis, psoriasis, contact dermatitis, delayed hypersensitivity reactions, and the like.

Also included is a method of treating or preventing a tyrosine kinase-dependent disease or condition in a mammal which comprises administering to a mammalian patient in need of such treatment a therapeutically effective amount of a compound of Formula I. The therapeutic amount varies according to the specific disease and is discernable to the skilled artisan without undue experimentation.

A method of treating or preventing retinal vascularization which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of compound of Formula 1 is also encompassed by the present invention. Methods of treating or preventing ocular diseases, such as diabetic retinopathy and age-related macular degeneration, are also part of the invention. Also included within the scope of the present invention is a method of treating or preventing inflammatory diseases, such as rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reactions, as well as treatment or prevention of bone associated pathologies selected from osteosarcoma, osteoarthritis, and rickets.

The invention also contemplates the use of the instantly claimed compounds in combination with a second compound selected from:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) retinoid receptor modulator,
4) a cytotoxic agent,

5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor, and
10) another angiogenesis inhibitor.

Preferred angiogenesis inhibitors are selected from the group consisting of a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP (matrix metalloprotease) inhibitor, an integrin blocker, interferon-α, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, and an antibody to VEGF. Preferred estrogen receptor modulators are tamoxifen and raloxifene.

Also included in the scope of the claims is a method of treating cancer which comprises administering a therapeutically effective amount of a compound of Formula 1 in combination with radiation therapy and/or in combination with a compound selected from:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) retinoid receptor modulator,
4) a cytotoxic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor, and
10) another angiogenesis inhibitor.

And yet another embodiment of the invention is a method of treating cancer which comprises administering a therapeutically effective

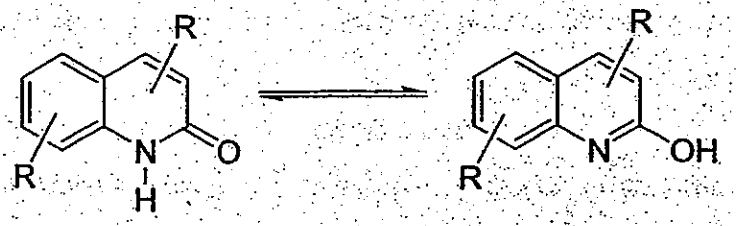
amount of a compound of Formula 1 in combination with paclitaxel or trastuzumab.

Also within the scope of the invention is a method of reducing or preventing tissue damage following a cerebral ischemic event which comprises administering a therapeutically effective amount of a compound of Formula I.

These and other aspects of the invention will be apparent from the teachings contained herein.

"Tyrosine kinase-dependent diseases or conditions" refers to pathologic conditions that depend on the activity of one or more tyrosine kinases. Tyrosine kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion and migration, and differentiation. Diseases associated with tyrosine kinase activities include the proliferation of tumor cells, the pathologic neovascularization that supports solid tumor growth, ocular neovascularization (diabetic retinopathy, age-related macular degeneration, and the like) and inflammation (psoriasis, rheumatoid arthritis, and the like).

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, being included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted. For example, any claim to compound A below is understood to include tautomeric structure B, and vice versa, as well as mixtures thereof.



A B

When any variable (e.g. R^4, R^6, R^{6a}, etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents indicate that the indicated bond may be attached to any of the substitutable ring atoms. If the ring system is polycyclic, it is intended that the bond be attached to any of the suitable carbon atoms on the proximal ring only.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted with one or more substituents" should be taken to be equivalent to the phrase "optionally substituted with at least one substituent" and in such cases the preferred embodiment will have from zero to three substituents.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C_1-C_{10}, as in "C_1-C_{10} alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear or branched arrangement. For example, "C_1-C_{10} alkyl" specifically includes methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *i*-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on. The term "cycloalkyl" means a monocyclic saturated aliphatic hydrocarbon

group having the specified number of carbon atoms. For example, "cycloalkyl" inlcudes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, and so on.

"Alkoxy" represents either a cyclic or non-cyclic alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Alkoxy" therefore encompasses the definitions of alkyl and cycloalkyl above.

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic carbon-carbon double bonds may be present. Thus, "C_2-C_6 alkenyl" means an alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl, 2-methylbutenyl and cyclohexenyl. The straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Thus, "C_2-C_6 alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups include ethynyl, propynyl, butynyl, 3-methylbutynyl and so on. The straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

In certain instances, substituents may be defined with a range of carbons that includes zero, such as (C_0-C_6)alkylene-aryl. If aryl is taken to be phenyl, this definition would include phenyl itself as well as -CH_2Ph, -CH_2CH_2Ph, $CH(CH_3)CH_2CH(CH_3)$Ph, and so on.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. In cases

where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. As with the definition of heterocycle below, "heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively.

As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo. The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 5- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, and includes bicyclic groups. "Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl,

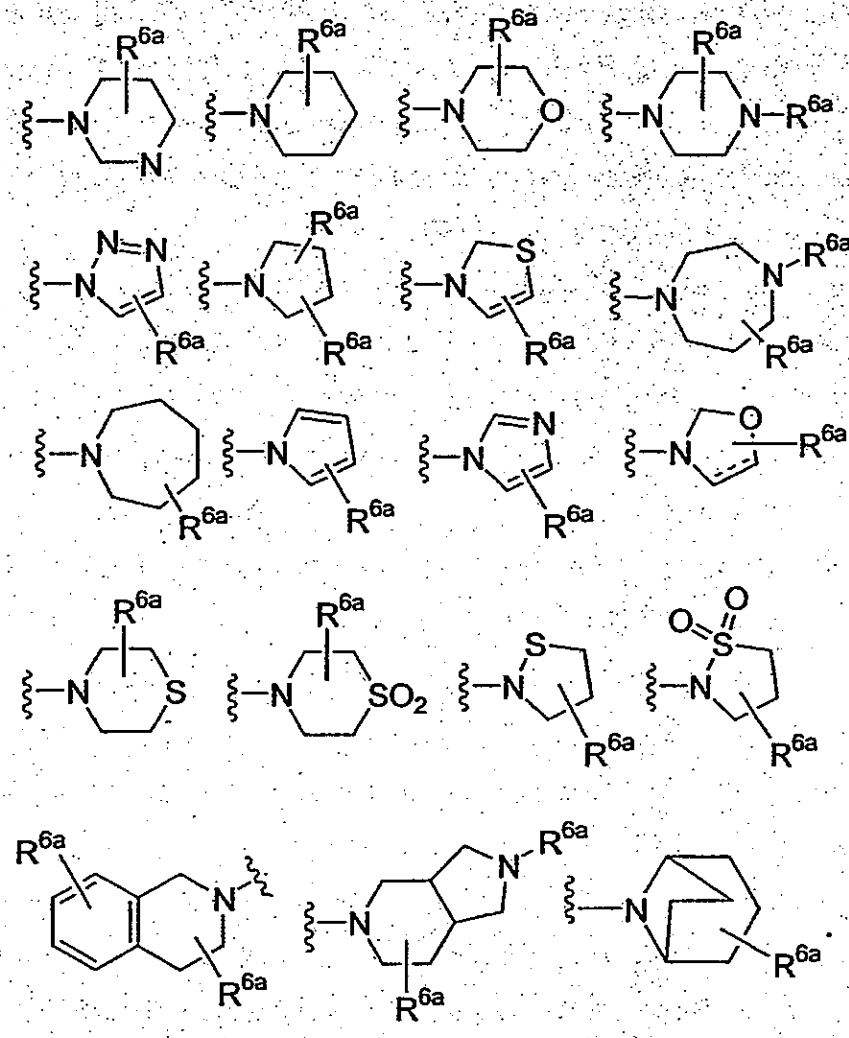
dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

The alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl substituents may be unsubstituted or unsubstituted, unless specifically defined otherwise. For example, a $(C_1\text{-}C_6)$alkyl may be substituted with one, two or three substituents selected from OH, oxo, halogen, alkoxy, dialkylamino, or heterocyclyl, such as morpholinyl, piperidinyl, and so on. In this case, if one substituent is oxo and the other is OH, the following are included in the definition: $\text{-C=O)CH}_2\text{CH(OH)CH}_3$, -(C=O)OH, $\text{-CH}_2\text{(OH)CH}_2\text{CH(O)}$, and so on.

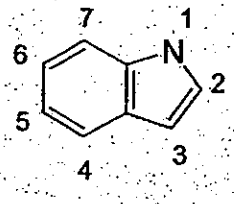
The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed inorganic or organic acids. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

In certain instances, R^7 and R^8 are defined such that they can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said heterocycle optionally substituted with one or more substituents selected from R^{6a}. Examples of the heterocycles that can thus be formed include, but are not limited to

the following, keeping in mind that the heterocycle is optionally substituted with one or more substituents chosen from R^{6a}:



Preferably R^1 is H. Also prefered is the definition of R^2 and R^3 as H. Preferably R^5 is H. The preferred heterocyclyl substituents are those shown immediately above plus pyrdidine, pyrimidine, pyrazine, pyridazine, tetramethylenesulfone, butyrolactone, tetrahydrofuran, furan, indole, and thiophene. Preferably t is 1 and R^4 is displaced at the 5-position of the indole, according to the following numbering scheme:



Preferably R^4 is defined as OC_1-C_6 alkyleneNR^{7}R^8, $(C=O)_aC_0$-C_6 alkylene-Q, wherein Q is H, OH, CO_2H, or OC_1-C_6 alkyl, OC_0-C_6 alkylene-heterocyclyl, optionally substituted with one to three substituents selected from R6^a, C_0-C_6 alkyleneNR^{7}R^8, (C=O)NR^{7}R^8, or OC_1-C_3 alkylene-(C=O)NR^{7}R^8. Most preferably R^4 is C_1-C_3 alkyleneNR^{7}R^8. Preferably R^7 and R^8 are defined such that they are be taken together with the nitrogen to which they are attached to form a monocyclic 5-7 membered heterocycle and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, and said heterocycle optionally substituted with one or more substituents selected from R^{6a}.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

The compounds of this invention may be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. These schemes, therefore, are not limited by the compounds listed or by any particular substituents employed for illustrative purposes. Substituent numbering as shown in the schemes does not necessarily correlate to that used in the claims.

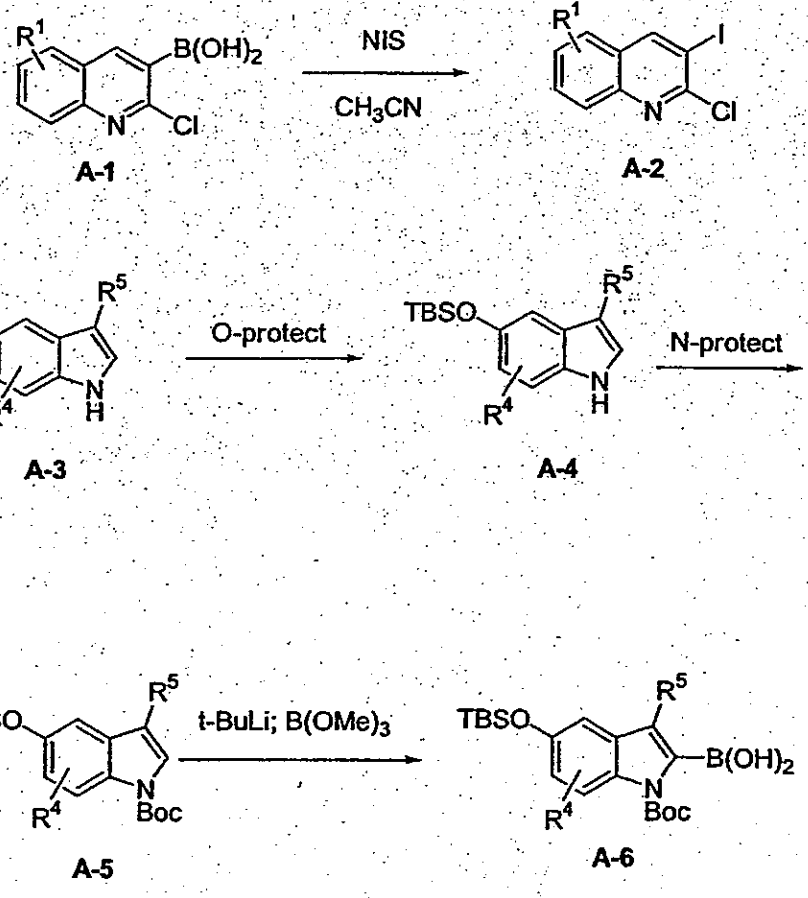
SCHEMES

As shown in Scheme A, the quinoline reagent **A-2** can be synthesized by the general procedures taught in Marsais, F; Godard, A.; Queguiner, G. *J. Heterocyclic Chem.* **1989**, *26*, 1589-1594). Derivatives with varying substitution can be made by modifying this procedure and use of standard synthetic protocols known in the art. Also shown in Scheme 1 is the preparation of the indole intermediate **A-6.**

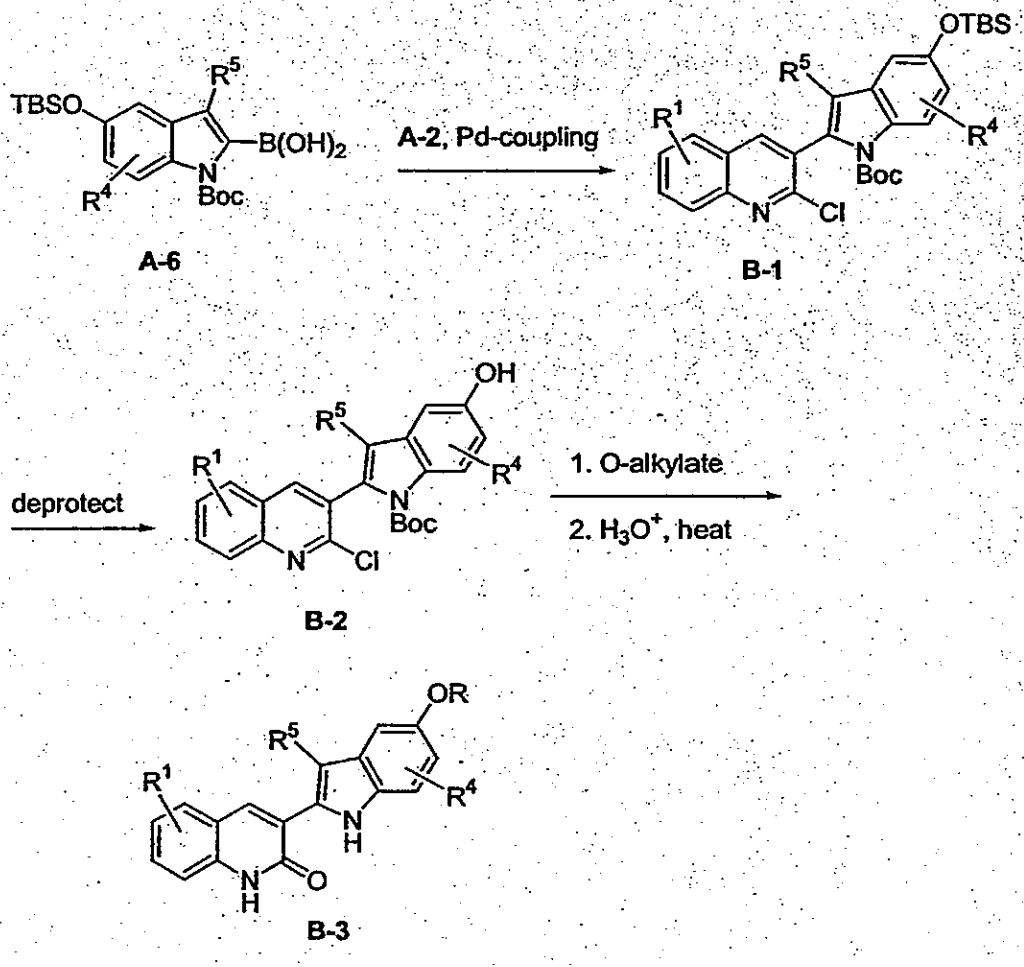
Scheme B illustrates one possible protocol for the coupling of the indole and quinolone intermediates to produce the desired compounds. Scheme C illustrates one possible synthetic route to the synthesis of a representative compound of the present invention, 3-(5-methoxy-1H-pyrrolo[2,3-c]pyridin-2-yl)-1H-quinolin-2-one, **C-6.**

Scheme D shows the synthesis of the iodo-naphthyridines and iodo-pyrido-pyridines. The resulting iodo compounds can the be coupled with appropriate indole boronic acid as taught in the other schemes to arrive at the desired product. The starting chloro-compounds can be prepared according to the method taught by D.J. Pokorny and W.W. Paudler in J. Org. Chem. 1972, 37, 3101.

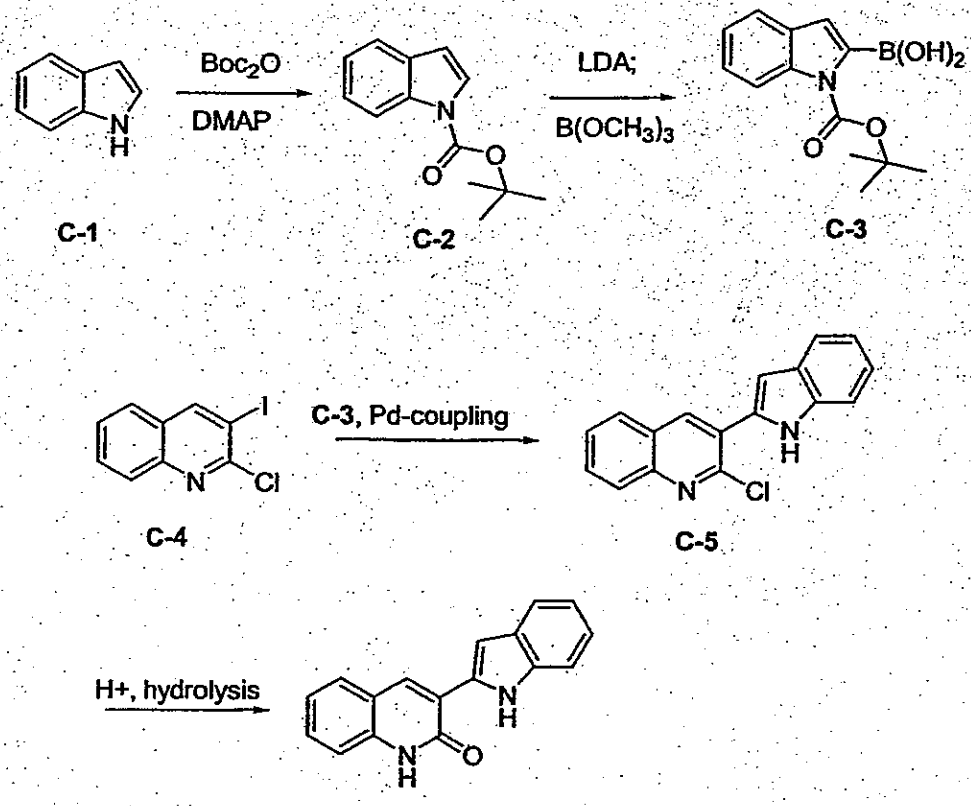
SCHEME A


R1
B(OH)2
N
Cl
A-1
NIS
CH3CN
R1
I
N
Cl
A-2
HO
R5
N
H
R4
A-3
O-protect
TBSO
R5
N
H
R4
A-4
N-protect
TBSO
R5
N
Boc
R4
A-5
t-BuLi; B(OMe)3
TBSO
R5
B(OH)2
N
Boc
R4
A-6

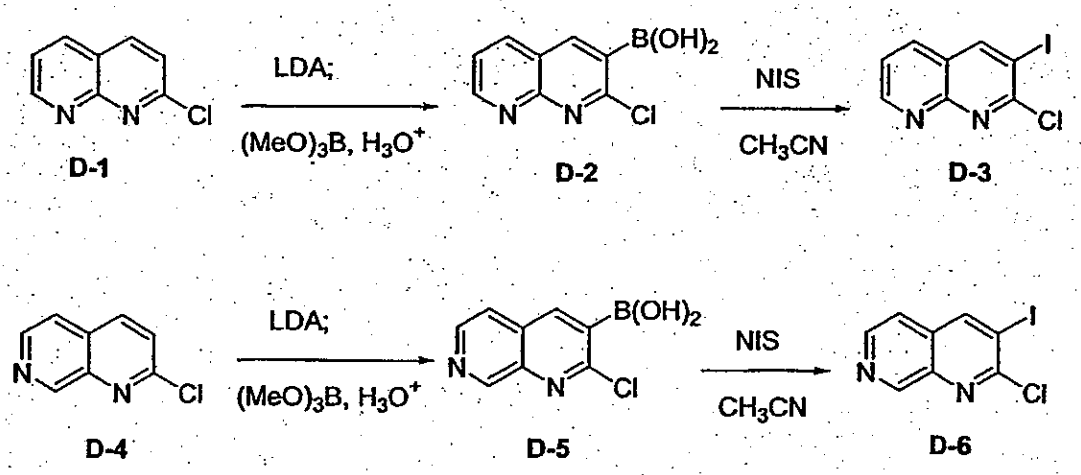
SCHEME B


TBSO
R5
B(OH)2
N
Boc
R4
A-6
A-2, Pd-coupling
OTBS
R5
R1
R4
N
Boc
N
Cl
B-1
deprotect
OH
R5
R1
R4
N
Boc
N
Cl
B-2
1. O-alkylate
2. H3O+, heat
OR
R5
R1
R4
N
H
N
H
O
B-3

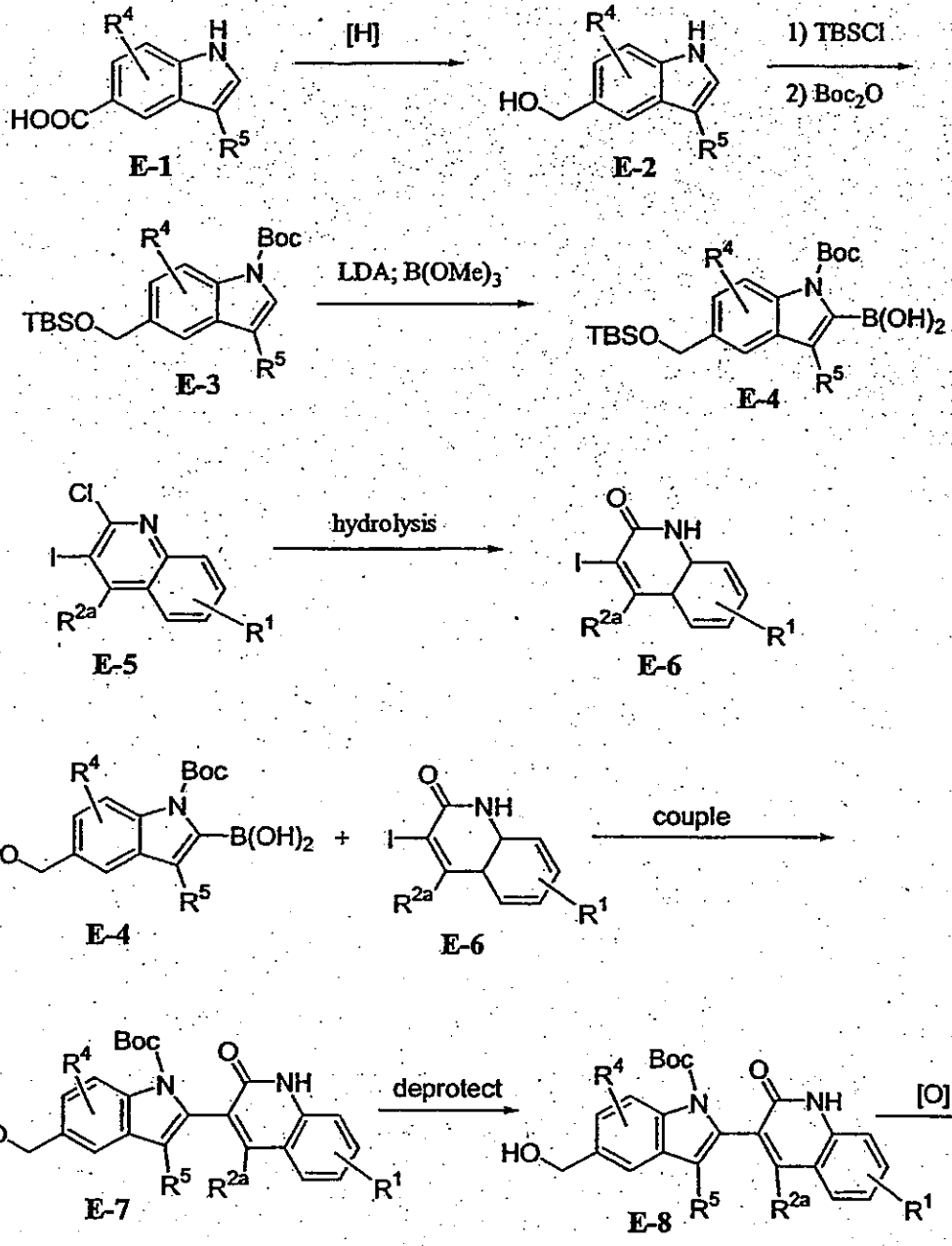
SCHEME C



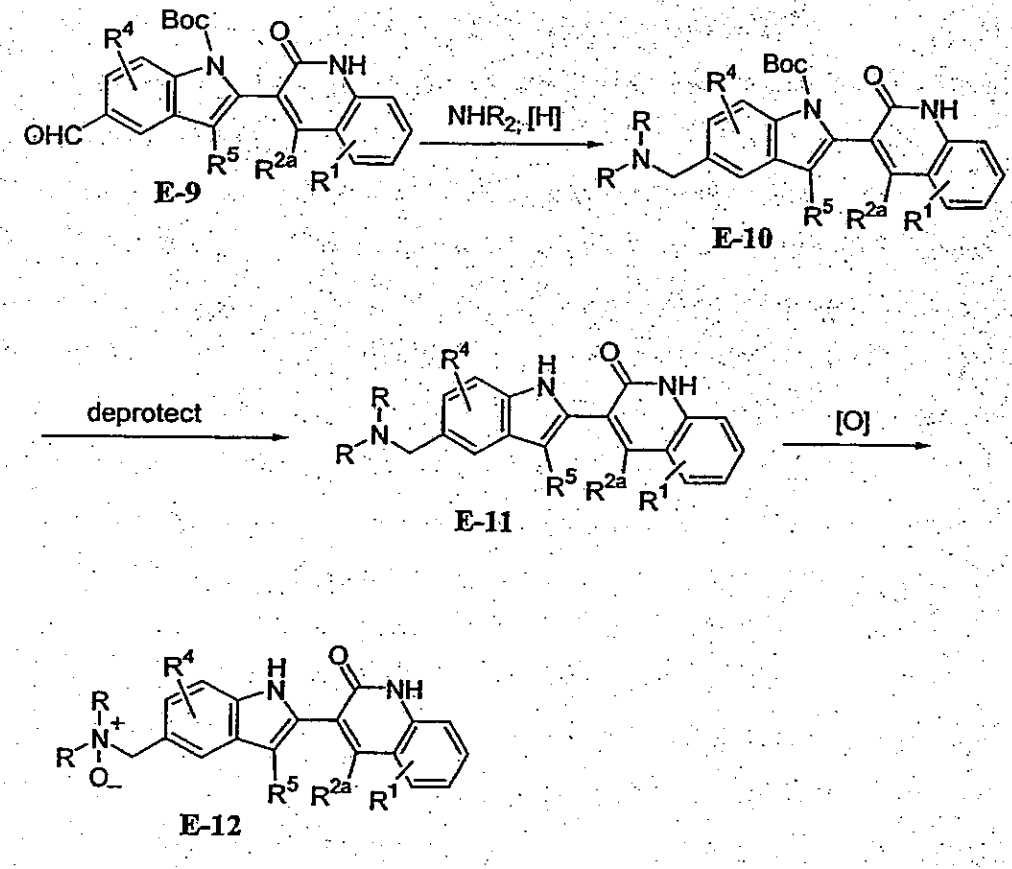
SCHEME D



SCHEME E


R4
H
N
HOOC
R5
E-1
[H]
HO
E-2
1) TBSCl
2) Boc2O
Boc
TBSO
E-3
LDA; B(OMe)3
B(OH)2
E-4
Cl
I
R2a
R1
hydrolysis
O
NH
E-5
E-6
couple
+
deprotect
[O]
E-7
E-8

SCHEME E (cont'd)



UTILITY

The instant compounds are useful as pharmaceutical agents for mammals, especially for humans, in the treatment of tyrosine kinase dependent diseases. Such diseases include the proliferation of tumor cells, the pathologic neovascularization (or angiogenesis) that supports solid tumor growth, ocular neovascularization (diabetic retinopathy, age-related macular degeneration, and the like) and inflammation (psoriasis, rheumatoid arthritis, and the like).

The compounds of the instant invention may be administered to patients for use in the treatment of cancer. The instant compounds inhibit tumor angiogenesis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 55:4575-4580, 1995). The anti-angiogenesis properties of

the instant compounds are also useful in the treatment of certain forms of blindness related to retinal vascularization.

The disclosed compounds are also useful in the treatment of certain bone-related pathologies, such as osteosarcoma, osteoarthritis, and rickets, also known as oncogenic osteomalacia. (Hasegawa et al., Skeletal Radiol., *28*, pp.41-45, 1999; Gerber et al., Nature Medicine, Vol. 5, No. 6, pp.623-628, June 1999). And since VEGF directly promotes osteoclastic bone resorption through KDR/Flk-1 expressed in mature osteoclasts (FEBS Let. 473:161-164 (2000); Endocrinology, 141:1667 (2000)), the instant compounds are also useful to treat and prevent conditions related to bone resorption, such as osteoporosis and Paget's disease.

The claimed compounds can also be used to reduce or prevent tissue damage which occurs after cerebral ischemic events, such as stroke, by reducing cerebral edema, tissue damage, and reperfusion injury following ischemia. (*Drug News Perspect* 11:265-270 (1998); *J. Clin. Invest.* 104:1613-1620 (1999)).

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use of a chemotherapeutic compound according to this invention, the compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and

intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The compounds of the instant invention may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, in the case of bone-related disorders, combinations that would be useful include those with antiresorptive bisphosphonates, such as alendronate and risedronate; integrin blockers (defined further below), such as $\alpha_v\beta_3$ antagonists; conjugated estrogens used in hormone replacement therapy, such as PREMPRO®, PREMARIN® and ENDOMETRION®; selective estrogen receptor modulators (SERMs), such as raloxifene, droloxifene, CP-336,156 (Pfizer) and lasofoxifene; cathespin K inhibitors; and ATP proton pump inhibitors.

The instant compounds are also useful in combination with known anti-cancer agents. Such known anti-cancer agents include the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors.

"Estrogen receptor modulators" refers to compounds which interfere or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081 , toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenylhydrazone, and SH646.

"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism.

Examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

"Retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl)retinamide, N-4-carboxyphenyl retinamide,

"Cytotoxic agents" refer to compounds which cause cell death primarily by interfering directly with the cell's functioning or inhibit or interfere with cell myosis, including alkylating agents, tumor necrosis factors, intercalators, microtubulin inhibitors, and topoisomerase inhibitors.

Examples of cytotoxic agents include, but are not limited to, tirapazimine, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methylpyridine) platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin.

Examples of microtubulin inhibitors include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl)

benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, and BMS188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H)propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexohydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c] quinolin-7-one, and dimesna.

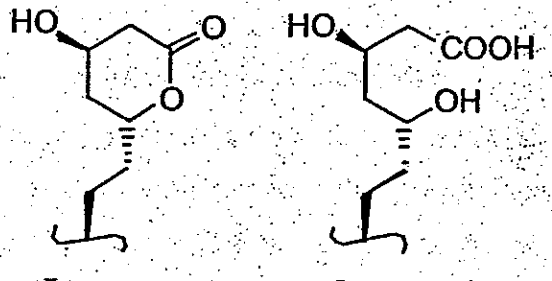
"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-

glutamic acid, aminopterin, 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone. "Antiproliferative agents" also includes monoclonal antibodies to growth factors, other than those listed under "angiogenesis inhibitors", such as trastuzumab, and tumor suppressor genes, such as p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Patent No. 6,069,134, for example).

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33. The terms "HMG-CoA reductase inhibitor" and "inhibitor of HMG-CoA reductase" have the same meaning when used herein.

Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see US Patent No. 4,231,938; 4,294,926; 4,319,039), simvastatin (ZOCOR®; see US Patent No. 4,444,784; 4,820,850; 4,916,239), pravastatin (PRAVACHOL®; see US Patent Nos. 4,346,227; 4,537,859; 4,410,629; 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see US Patent Nos. 5,354,772; 4,911,165; 4,929,437; 5,189,164; 5,118,853; 5,290,946; 5,356,896), atorvastatin (LIPITOR®; see US Patent Nos. 5,273,995; 4,681,893; 5,489,691; 5,342,952) and cerivastatin (also known as rivastatin and BAYCHOL®; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free

acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention. An illustration of the lactone portion and its corresponding open-acid form is shown below as structures I and II.



Lactone I

Open-Acid II

In HMG-CoA reductase inhibitors where an open-acid form can exist, salt and ester forms may preferably be formed from the open-acid, and all such forms are included within the meaning of the term "HMG-CoA reductase inhibitor" as used herein. Preferably, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin, and most preferably simvastatin. Herein, the term "pharmaceutically acceptable salts" with respect to the HMG-CoA reductase inhibitor shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenzimidazole, diethylamine, piperazine, and tris(hydroxymethyl) aminomethane. Further examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate,

gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

Ester derivatives of the described HMG-CoA reductase inhibitor compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

"Prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). Examples of prenyl-protein transferase inhibiting compounds include (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, (-)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, 5(S)-n-butyl-1-(2,3-dimethylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, (S)-1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl)-2-piperazinone, 5(S)-n-Butyl-1-(2-methylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, 1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-2-piperazinone, 1-(2,2-diphenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]piperidine, 4-{5-[4-Hydroxymethyl-4-(4-chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl} benzonitrile, 4-{5-[4-hydroxymethyl-4-(3-chlorobenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile, 4-{3-[4-(2-oxo-2H-pyridin-1-yl)benzyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(5-chloro-2-oxo-2H-[1,2']bipyridin-5'-

ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(2-Oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl}benzonitrile, 18,19-dihydro-19-oxo-5*H*,17*H*-6,10:12,16-dimetheno-1H-imidazo[4,3-*c*][1,11,4]dioxaazacyclo - nonadecine-9-carbonitrile, (±)-19,20-Dihydro-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxatriaza-cyclooctadecine-9-carbonitrile, 19,20-dihydro-19-oxo-5*H*,17*H*-18,21-ethano-6,10:12,16-dimetheno-22*H*-imidazo[3,4-*h*][1,8,11,14]oxatriazacycloeicosine-9-carbonitrile, and (±)-19,20-Dihydro-3-methyl-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxa-triazacyclooctadecine-9-carbonitrile.

Other examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U. S. Pat. No. 5,420,245, U. S. Pat. No. 5,523,430, U. S. Pat. No. 5,532,359, U. S. Pat. No. 5,510,510, U. S. Pat. No. 5,589,485, U. S. Pat. No. 5,602,098, European Pat. Publ. 0 618 221, European Pat. Publ. 0 675 112, European Pat. Publ. 0 604 181, European Pat. Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Pat. No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Pat. No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U. S. Pat. No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see European J. of Cancer, Vol. 35, No. 9, pp.1394-1401 (1999).

Examples of HIV protease inhibitors include amprenavir, abacavir, CGP-73547, CGP-61755, DMP-450, indinavir, nelfinavir, tipranavir, ritonavir, saquinavir, ABT-378, AG 1776, and BMS-232,632. Examples of reverse transcriptase inhibitors include delaviridine, efavirenz, GS-840, HB Y097, lamivudine, nevirapine, AZT, 3TC, ddC, and ddI.

"Angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR20), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-α, interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxygenase-2 inhibitors like celecoxib and rofecoxib (PNAS, Vol. 89, p. 7384 (1992); JNCI, Vol. 69, p. 475 (1982); Arch. Opthalmol., Vol. 108, p.573 (1990); Anat. Rec., Vol. 238, p. 68 (1994); FEBS Letters, Vol. 372, p. 83 (1995); Clin, Orthop. Vol. 313, p. 76 (1995); J. Mol. Endocrinol., Vol. 16, p.107 (1996); Jpn. J. Pharmacol., Vol. 75, p. 105 (1997); Cancer Res., Vol. 57, p. 1625 (1997); Cell, Vol. 93, p. 705 (1998); Intl. J. Mol. Med., Vol. 2, p. 715 (1998); J. Biol. Chem., Vol. 274, p. 9116 (1999)), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez et al., J. Lab. Clin. Med. 105:141-145 (1985)), and antibodies to VEGF. (see, Nature Biotechnology, Vol. 17, pp.963-968 (October 1999); Kim et al., Nature, *362*, 841-844 (1993)).

Other examples of angiogenesis inhibitors include, but are not limited to, endostation, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide,CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-

pyrrolocarbonylimino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

The instant compounds are also useful, alone or in combination with platelet fibrinogen receptor (GP IIb/IIIa) antagonists, such as tirofiban, to inhibit metastasis of cancerous cells. Tumor cells can activate platelets largely via thrombin generation. This activation is associated with the release of VEGF. The release of VEGF enhances metastasis by increasing extravasation at points of adhesion to

vascular endothelium (Amirkhosravi, *Platelets* 10, 285-292, 1999). Therefore, the present compounds can serve to inhibit metastasis, alone or in combination with GP IIb/IIIa) antagonists. Examples of other fibrinogen receptor antagonists include abciximab, eptifibatide, sibrafiban, lamifiban, lotrafiban, cromofiban, and CT50352.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term "treating cancer" or "treatment of cancer" refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically

effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's bloodstream by local bolus injection.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

ASSAYS

The compounds of the instant invention described in the Examples were tested by the assays described below and were found to have kinase inhibitory activity. Other assays are known in the literature and could be readily performed by those of skill in the art. (see, for example, Dhanabal et al., *Cancer Res.* 59:189-197; Xin et al., *J. Biol. Chem.* 274:9116-9121; Sheu et al., *Anticancer Res.* 18:4435-4441; Ausprunk et al., *Dev. Biol.* 38:237-248; Gimbrone et al., *J. Natl. Cancer Inst.* 52:413-427; Nicosia et al., *In Vitro* 18:538-549).

I. VEGF RECEPTOR KINASE ASSAY

VEGF receptor kinase activity is measured by incorporation of radio-labeled phosphate into polyglutamic acid, tyrosine, 4:1 (pEY) substrate. The phosphorylated pEY product is trapped onto a filter membrane and the incorporation of radio-labeled phosphate quantified by scintillation counting.

MATERIALS

VEGF Receptor Kinase

The intracellular tyrosine kinase domains of human KDR (Terman, B.I. et al. Oncogene (1991) vol. 6, pp. 1677-1683.) and Flt-1 (Shibuya, M. et al. Oncogene (1990) vol. 5, pp. 519-524) were cloned as glutathione S-transferase (GST) gene fusion proteins. This was accomplished by cloning the cytoplasmic domain of the KDR kinase as an in frame fusion at the carboxy terminus of the GST gene. Soluble recombinant GST-kinase domain fusion proteins were expressed in Spodoptera frugiperda (Sf21) insect cells (Invitrogen) using a baculovirus expression vector (pAcG2T, Pharmingen).

The other materials used and their compositions were as follows:

Lysis buffer: 50 mM Tris pH 7.4, 0.5 M NaCl, 5 mM DTT, 1 mM EDTA, 0.5% triton X-100, 10 % glycerol, 10 mg/mL of each leupeptin, pepstatin and aprotinin and 1mM phenylmethylsulfonyl fluoride (all Sigma).

Wash buffer: 50 mM Tris pH 7.4, 0.5 M NaCl, 5 mM DTT, 1 mM EDTA, 0.05% triton X-100, 10 % glycerol, 10 mg/mL of each leupeptin, pepstatin and aprotinin and 1mM phenylmethylsulfonyl fluoride.

Dialysis buffer: 50 mM Tris pH 7.4, 0.5 M NaCl, 5 mM DTT, 1 mM EDTA, 0.05% triton X-100, 50 % glycerol, 10 mg/mL of each leupeptin, pepstatin and aprotinin and 1mM phenylmethylsuflonyl fluoride.

10 X reaction buffer: 200 mM Tris, pH 7.4, 1.0 M NaCl, 50 mM $MnCl_2$, 10 mM DTT and 5 mg/mL bovine serum albumin (Sigma).

Enzyme dilution buffer: 50 mM Tris, pH 7.4, 0.1 M NaCl, 1 mM DTT, 10 % glycerol, 100 mg/mL BSA.

10 X Substrate: 750 µg/mL poly (glutamic acid, tyrosine; 4:1) (Sigma).

Stop solution: 30% trichloroacetic acid, 0.2 M sodium pyrophosphate (both Fisher).

Wash solution: 15% trichloroacetic acid, 0.2 M sodium pyrophosphate.

Filter plates: Millipore #MAFC NOB, GF/C glass fiber 96 well plate.

METHOD

A. Protein purification

1. Sf21 cells were infected with recombinant virus at a multiplicity of infection of 5 virus particles/ cell and grown at 27°C for 48 hours.

2. All steps were performed at 4°C Infected cells were harvested by centrifugation at 1000 X g and lysed at 4°C for 30 minutes with 1/10 volume of lysis buffer followed by centrifugation at 100,000Xg for 1 hour. The supernatant was then passed over a glutathione Sepharose column (Pharmacia) equilibrated in lysis buffer and washed with 5 volumes of the same buffer followed by 5 volumes of wash buffer. Recombinant GST-KDR protein was eluted with wash buffer/10 mM reduced glutathione (Sigma) and dialyzed against dialysis buffer.

B. VEGF receptor kinase assay

1. Add 5 µl of inhibitor or control to the assay in 50% DMSO.

2. Add 35 µl of reaction mix containing 5 µl of 10 X reaction buffer, 5 µl 25 mM ATP/10 µCi [^{33}P]ATP (Amersham), and 5 µl 10 X substrate.

3. Start the reaction by the addition of 10 µl of KDR (25 nM) in enzyme dilution buffer.

4. Mix and incubate at room temperature for 15 minutes.

5. Stop by the addition of 50 µl stop solution.

6. Incubate for 15 minutes at 4°C

7. Transfer a 90µl aliquot to filter plate.

8. Aspirate and wash 3 times with wash solution.

9. Add 30 µl of scintillation cocktail, seal plate and count in a Wallac Microbeta scintillation counter.

II. HUMAN UMBILICAL VEIN ENDOTHELIAL CELL MITOGENESIS ASSAY

Human umbilical vein endothelial cells (HUVECs) in culture proliferate in response to VEGF treatment and can be used as an assay system to quantify the effects of KDR kinase inhibitors on VEGF stimulation. In the assay described, quiescent HUVEC monolayers are treated with vehicle or test compound 2 hours prior to addition of VEGF or basic fibroblast growth factor (bFGF). The mitogenic response to VEGF or bFGF is determined by measuring the incorporation of [^{3}H]thymidine into cellular DNA.

MATERIALS

HUVECs: HUVECs frozen as primary culture isolates are obtained from Clonetics Corp. Cells are maintained in Endothelial Growth Medium (EGM; Clonetics) and are used for mitogenic assays described in passages 3-7 below.

Culture Plates: NUNCLON 96-well polystyrene tissue culture plates (NUNC #167008).

Assay Medium: Dulbecco's modification of Eagle's medium containing 1 g/mL glucose (low-glucose DMEM; Mediatech) plus 10% (v/v) fetal bovine serum (Clonetics).

Test Compounds: Working stocks of test compounds are diluted serially in 100% dimethylsulfoxide (DMSO) to 400-fold greater than their desired final concentrations. Final dilutions to 1X concentration are made directly into Assay Medium immediately prior to addition to cells.

10X Growth Factors: Solutions of human $VEGF_{165}$ (500 ng/mL; R&D Systems) and bFGF (10 ng/mL; R&D Systems) are prepared in Assay Medium.

10X [^{3}H]Thymidine: [Methyl-^{3}H]thymidine (20 Ci/mmol; Dupont-NEN) is diluted to 80 μCi/mL in low-glucose DMEM.

Cell Wash Medium: Hank's balanced salt solution (Mediatech) containing 1 mg/mL bovine serum albumin (Boehringer-Mannheim).

Cell Lysis Solution: 1 N NaOH, 2% (w/v) Na_2CO_3.

METHOD

1. HUVEC monolayers maintained in EGM are harvested by trypsinization and plated at a density of 4000 cells per 100 µL Assay Medium per well in 96-well plates. Cells are growth-arrested for 24 hours at 37°C in a humidified atmosphere containing 5% CO_2.

2. Growth-arrest medium is replaced by 100 µL Assay Medium containing either vehicle (0.25% [v/v] DMSO) or the desired final concentration of test compound. All determinations are performed in triplicate. Cells are then incubated at 37°C with 5% CO_2 for 2 hours to allow test compounds to enter cells.

3. After the 2-hour pretreatment period, cells are stimulated by addition of 10 µL/well of either Assay Medium, 10X VEGF solution or 10X bFGF solution. Cells are then incubated at 37°C and 5% CO_2.

4. After 24 hours in the presence of growth factors, 10X [^{3}H]thymidine (10 µL/well) is added.

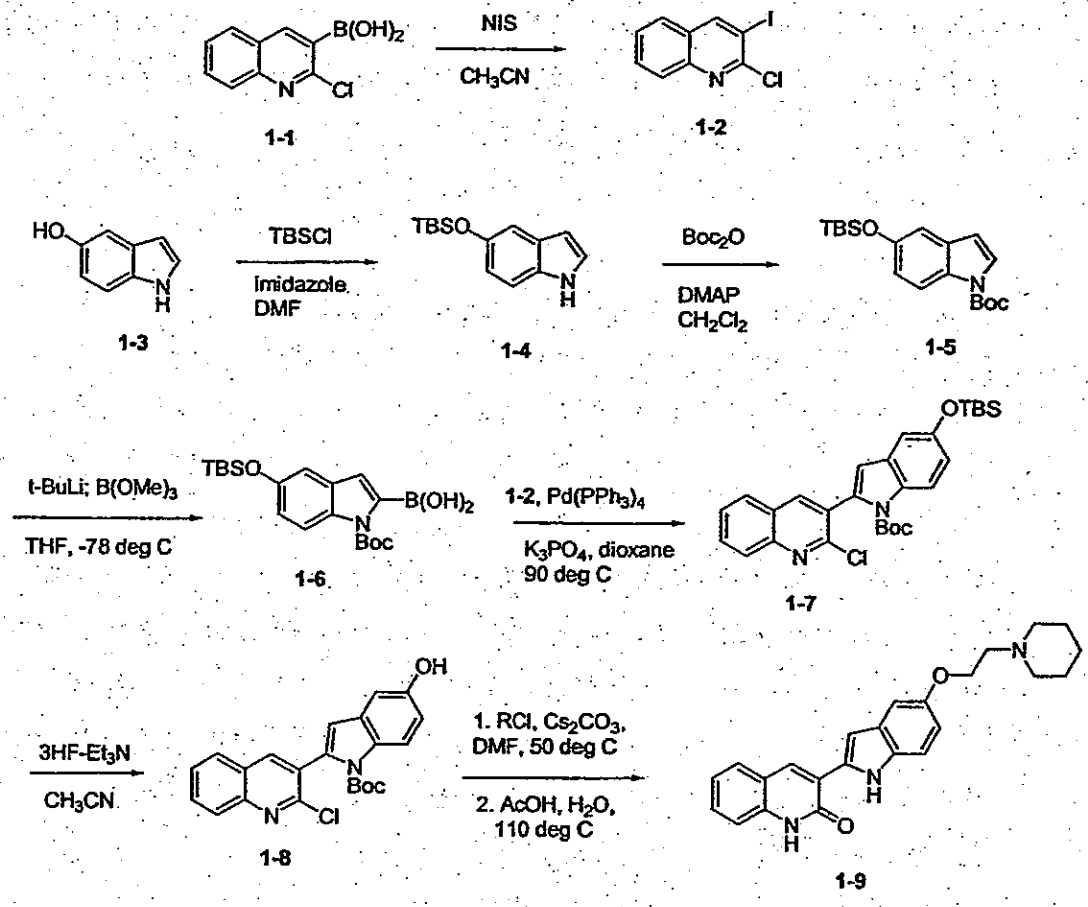
5. Three days after addition of [^{3}H]thymidine, medium is removed by aspiration, and cells are washed twice with Cell Wash Medium (400 µL/well followed by 200 µL/well). The washed, adherent cells are then solubilized by addition of Cell Lysis Solution (100 µL/well) and warming to 37°C for 30 minutes. Cell lysates are transferred to 7-mL glass scintillation vials containing 150 µL of water. Scintillation cocktail (5 mL/vial) is added, and cell-associated radioactivity is determined by liquid scintillation spectroscopy.

Based upon the foregoing assays the compounds of Formula I are inhibitors of VEGF and thus are useful for the inhibition of angiogenesis, such as in the treatment of ocular disease, e.g., diabetic retinopathy and in the treatment of cancers, e.g., solid tumors. The instant compounds inhibit VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC_{50} values between 0.001 - 5.0 µM. These compounds also show selectivity over

related tyrosine kinases (e.g., FGFR1 and the Src family; for relationship between Src kinases and VEGFR kinases, see Eliceiri et al., Molecular Cell, Vol. 4, pp.915-924, December 1999).

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be illustrative of the invention and not limiting of the reasonable scope thereof.



SCHEME 1

2-Chloro-3-iodo-quinoline (1-2)

A suspension of 3-(2-chloro)-quinolineboronic acid (1-1, 5.05 g, 24.3 mmol, 1 equiv, prepared by the method of Marsais, F; Godard, A.; Queguiner, G. *J. Heterocyclic Chem.* **1989**, *26*, 1589-1594) and *N*-iodosuccinimide (5.48 g, 24.4 mmol, 1.00 equiv) in acetonitrile (300 mL) was stirred at 23°C in the dark for 20 h. The reaction mixture was concentrated to dryness, and the resulting yellow solid was partitioned between saturated aqueous sodium bicarbonate solution and dichloromethane. The organic layer was washed with water, then dried over magnesium sulfate and concentrated to give 2-chloro-3-iodo-quinoline as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.99 (br d, 1H, J = 8.4 Hz), 7.75 (br t, 1H, J = 7.7 Hz), 7.72 (br d, 1H, J = 7.8 Hz), 7.57 (br t, 1H, J = 7.6 Hz).

5-(tert-Butyl-dimethyl-silanyloxy)-1H-indole (1-4)

A solution of 5-hydroxyindole 1-3 (5.50 g, 41.3 mmol, 1 equiv), *tert*-butyldimethylsilyl chloride (7.47 g, 49.6 mmol, 1.20 equiv), and imidazole (7.03 g, 103 mmol, 2.50 equiv) in *N*, *N*-dimethylformamide (20 mL) was stirred at 23°C for 20 h. The reaction mixture was concentrated, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water (3x), then dried over magnesium sulfate and concentrated. The residue was purified by flash column chromatography (40% dichloromethane in hexanes, then 60% dichloromethane in hexanes) to give 5-(tert-butyl-dimethyl-silanyloxy)-1H-indole as a colorless oil which solidified upon standing. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (br s, 1H), 7.22 (d, 1H, J = 8.7 Hz), 7.17 (t, 1H, J = 2.8 Hz), 7.06 (d, 1H, J = 2.3 Hz), 6.76 (dd, 1H, J = 8.6, 2.3 Hz), 6.44 (m, 1H), 1.00 (s, 9H), 0.19 (s, 6H).

5-(tert-Butyl-dimethyl-silanyloxy)-indole-1-carboxylic acid tert-butyl ester (1-5)

A solution of 5-(tert-butyl-dimethyl-silanyloxy)-1H-indole 1-4 (10.2 g, 41.3 mmol, 1 equiv), di-*tert*-butyl dicarbonate (14.4 g, 66.0 equiv, 1.60 equiv), and 4-dimethylaminopyridine (1.01 g, 8.25 mmol, 0.200 equiv) in dichloromethane (100 mL) was stirred at 23°C for 20 h. The reaction ixture was concentrated, and the residue was purified by flash column chromatography (40% dichloromethane in hexanes) to afford 5-(tert-butyl-dimethyl-silanyloxy)-indole-1-carboxylic acid tert-butyl ester (1-5) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (br d, 1H, J = 7.5 Hz), 7.54 (br d, 1H, J = 3.1 Hz), 6.98 (d, 1H, J = 2.4 Hz), 6.83 (dd, 1H, J = 9.0, 2.4 Hz), 6.45 (d, 1H, J = 3.7 Hz), 1.66 (s, 9H), 1.00 (s, 9H), 0.20 (s, 6H).

1-(tert-Butoxycarbonyl)-5-{[tert-butyl(dimethyl)silyl]oxy}-1H-indol-2-ylboronic acid (1-6)

A solution of *tert*-butyllithium in pentane (1.7 M, 20.7 mL, 35.2 mmol, 1.20 equiv) was added to a solution of 5-(tert-butyl-dimethyl-silanyloxy)-indole-1-carboxylic acid tert-butyl ester (1-5, 10.2 g, 29.3 mmol, 1 equiv) in tetrahydrofuran (100 mL) at –78°C. The resulting light-brown solution was stirred at –78°C for 30 min, then trimethylborate (6.67 mL, 58.7 mmol, 2.00 equiv) was added. The resulting mixture was warmed to 0°C, then diluted with saturated aqueous ammonium chloride solution (100 mL) and ethyl ether (200 mL). The aqueous layer was made acidic with aqueous 10% potassium hydrogensulfate solution. The organic layer was separated, then washed with brine, dried over magnesium sulfate, and concentrated. The residual yellow solid was triturated with hexanes to give 1-(tert-butoxycarbonyl)-5-{[tert-butyl(dimethyl)silyl]oxy}-1H-indol-2-ylboronic acid (1-6) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, 1H, J = 8.9 Hz), 7.37 (s, 1H), 7.01 (d, 1H, J = 2.4 Hz), 6.97 (br s, 2H), 6.88 (dd, 1H, J = 9.0, 2.4 Hz), 1.73 (s, 9H), 1.00 (s, 9H), 0.20 (s, 6H).

tert-Butyl 5-{[tert-butyl(dimethyl)silyl]oxy}-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (1-7)

A deoxygenated mixture of 1-(tert-butoxycarbonyl)-5-{[tert-butyl(dimethyl)silyl]oxy}-1H-indol-2-ylboronic acid **1-6** (4.10 g, 10.5 mmol, 1 equiv), 2-chloro-3-iodo-quinoline (1-2, 3.64 g, 12.6 mmol, 1.20 equiv), potassium phosphate (6.67 g, 31.4 mmol, 3.00 equiv), and tetrakis(triphenylphosphine)palladium (0.605 g, 0.524 mmol, 0.050 equiv) in dioxane (100 mL) was heated at 90°C for 20 h. The reaction mixture was cooled, then partitioned between a mixture of water and ethyl acetate. The organic layer was separated, washed with brine, dried over magnesium sulfate, and concentrated. The residue was purified by flash column chromatography (20% dichloromethane in hexanes, grading to 90% dichloromethane in hexanes) to give tert-butyl 5-{[tert-butyl(dimethyl)silyl]oxy}-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (**1-7**) as a tan-colored foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.15 (d, 1H, J = 9.0 Hz), 8.07 (d, 1H, J = 8.2 Hz), 7.86 (d, 1H, J = 7.8 Hz), 7.77 (br t, 1H, J = 8.4 Hz), 7.60 (br t, 1H, J = 8.1 Hz), 7.03 (d, 1H, J = 2.4 Hz), 6.92 (dd, 1H, J = 9.0, 2.4 Hz), 6.55 (s, 1H), 1.26 (s, 9H), 1.02 (s, 9H), 0.23 (s, 6H).

tert-Butyl 2-(2-chloro-3-quinolinyl)-5-hydroxy-1H-indole-1-carboxylate (**1-8**)

A solution of tert-butyl 5-{[tert-butyl(dimethyl)silyl]oxy}-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate **1-7** (2.50 g, 4.91 mmol, 1 equiv) and triethylamine trihydrofluoride (3.60 mL, 22.1 mmol, 4.50 equiv) in acetonitrile (100 mL) was stirred at 23°C for 20 h. The reaction mixture was concentrated, and the residue was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated to tert-butyl 2-(2-chloro-3-quinolinyl)-5-hydroxy-1H-indole-1-carboxylate (**1-8**) as a tan colored foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, 1H, J = 9.0 Hz), 8.17 (s, 1H), 8.07 (d, 1H, J = 8.4 Hz), 7.86 (d, 1H, J = 8.1 Hz), 7.77 (br t, 1H, J = 8.4 Hz), 7.61 (br t, 1H, J = 8.1 Hz), 7.03 (d, 1H, J = 2.6 Hz), 6.93 (dd, 1H, J = 8.8, 2.6 Hz), 6.55 (s, 1H), 1.26 (s, 9H).

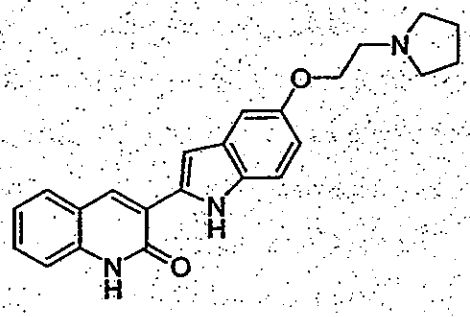
3-[5-(2-Piperidin-1-yl-ethoxy)-1H-indol-2-yl]-1H-quinolin-2-one (1-9)

A mixture of tert-butyl 2-(2-chloro-3-quinolinyl)-5-hydroxy-1H-indole-1-carboxylate **1-8** (395 mg, 1.00 mmol, 1 equiv), 1-(2-chloroethyl)-piperidine hydrochloride (276 mg, 1.50 mmol, 1.50 equiv), and cesium carbonate (978 mg, 3.00 mmol, 3.00 equiv) in *N, N*-dimethylformamide (5 mL) was heated at 50°C for 2 h. The reaction mixture was concentrated, and the residue was partitioned between water and ethyl acetate. The organic layer was washed with water then brine, dried over magnesium sulfate, and concentrated to give a pale-yellow foam. The foam was dissolved in a 1:1 mixture of water and acetic acid (60 mL), and the resulting solution was heated at 110°C for 12 h. The reaction mixture was concentrated, and the residue was stirred in aqueous saturated sodium bicarbonate solution which yielded a tan solid. The tan solid was filtered, then suspended in warm ethanol (2 x 20 mL) and filtered to give 3-[5-(2-piperidin-1-yl-ethoxy)-1H-indol-2-yl]-1H-quinolin-2-one (**1-9**) as a yellow solid. The ethanolic filtrate was concentrated and the residue purified by flash column chromatography (5% ethanol saturated with ammonia in ethyl acetate to afford additional **1-9**. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.14 (s, 1H), 11.41 (s, 1H), 8.50 (s, 1H), 7.73 (br d, 1H, J = 7.9 Hz), 7.51 (br t, 1H, J = 7.6 Hz), 7.41 (d, 1H, J = 8.6 Hz), 7.37 (br d, 1H, J = 8.2 Hz), 7.24 (br t, 1H, J = 7.7 Hz), 7.21 (br s, 1H), 7.06 (br s, 1H), 6.76 (dd, 1H, J = 8.6, 2.2 Hz), 4.06 (t, 2H, J = 5.9 Hz), 2.67 (t, 3H, J = 5.5 Hz), 2.45 (br m, 4H), 1.51 (br m, 4H), 1.39 (br m, 2H).

Compounds **1-10** through **1-19** below and Compounds **1-20** through **1-55** in Table 1 below were prepared by simple modifications of the protocols described above. The alkyl halides used in the following examples were either commercially available or prepared by alkylation of the corresponding amine with either 1-bromo-2-chloroethane in the presence of potassium carbonate in acetone by the method of Miyahara, M.; Sueyoshi, S.; Kamiya, S. *Chem. Pahrm. Bull.* **1985**, *33*, 5557-5561, or 1-bromo-3-chloropropane in benzene according to the method of Adams and Whitmore *J. Am. Chem. Soc.* **1945**, *67*, 735. In some cases, the mesylates of

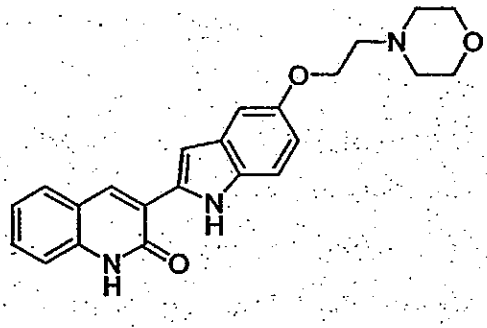
commercially available or readily available alcohols were prepared (MsCl, Et_3N) and utilized in place of the corresponding alkyl chlorides.

3-[5-(2-Pyrrolidin-1-yl-ethoxy)-1H-indol-2-yl]-1H-quinolin-2-one (1-10)



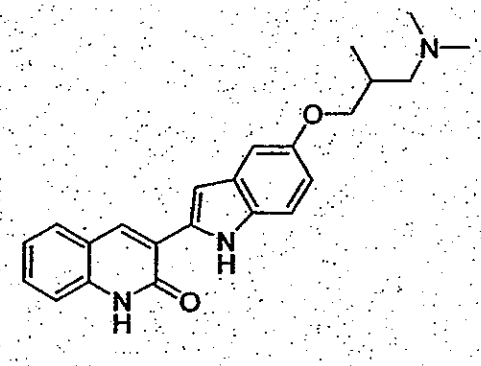
^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.14 (s, 1H), 11.41 (s, 1H), 8.50 (s, 1H), 7.73 (br d, 1H, J = 7.7 Hz), 7.51 (br t, 1H, J = 7.2 Hz), 7.41 (d, 1H, J = 8.6 Hz), 7.37 (br d, 1H, J = 8.2 Hz), 7.24 (br t, 1H, J = 7.7 Hz), 7.21 (d, 1H, J = 1.3 Hz), 7.06 (d, 1H, J = 2.2 Hz), 6.76 (dd, 1H, J = 8.6, 2.2 Hz), 4.07 (t, 2H, J = 5.9 Hz), 2.81 (t, 3H, J = 5.9 Hz), 2.55 (br m, 4H), 1.70 (br m, 4H).

3-[5-(2-Morpholin-4-yl-ethoxy)-1H-indol-2-yl]-1H-quinolin-2-one (1-11)



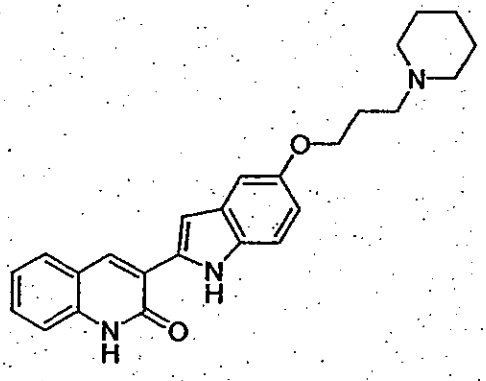
^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.15 (s, 1H), 11.42 (s, 1H), 8.51 (s, 1H), 7.73 (br d, 1H, J = 7.9 Hz), 7.51 (br t, 1H, J = 7.3 Hz), 7.41 (d, 1H, J = 8.8 Hz), 7.37 (br d, 1H, J = 8.2 Hz), 7.24 (br t, 1H, J = 7.6 Hz), 7.21 (br s, 1H), 7.07 (d, 1H, J = 1.7 Hz), 6.76 (dd, 1H, J = 8.7, 1.8 Hz), 4.09 (t, 2H, J = 5.8 Hz), 3.59 (br t, 4H, J = 4.5 Hz), 2.71 (t, 3H, J = 5.7 Hz), 2.50 (br m, 4H).

3-[5-(3-dimethylamino-2-methyl-propoxy)-1H-indol-2-yl]-1H-quinolin-2-one (1-12)



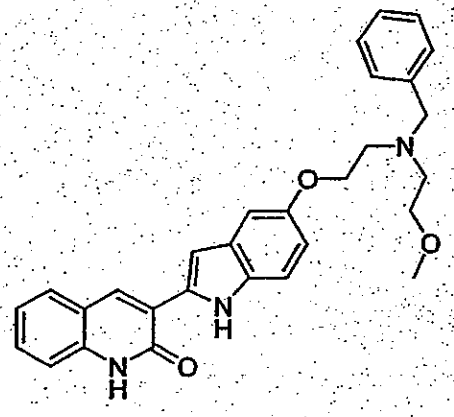
^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.15 (s, 1H), 11.41 (s, 1H), 8.50 (s, 1H), 7.73 (br d, 1H, J = 7.9 Hz), 7.51 (br t, 1H, J = 8.2 Hz), 7.41 (d, 1H, J = 8.8 Hz), 7.37 (br d, 1H, J = 8.2 Hz), 7.24 (br t, 1H, J = 7.9 Hz), 7.20 (d, 1H, J = 1.1 Hz), 7.03 (d, 1H, J = 2.0 Hz), 6.76 (dd, 1H, J = 8.8, 2.4 Hz), 3.95 (dd, 1H, J = 9.3, 4.4 Hz), 3.77 (dd, 1H J = 9.2, 6.2 Hz), 2.31 (m, 1H), 2.15 (s, 6H), 2.10 (m, 2H), 1.01 (d, 3H, J = 6.0 Hz).

3-[5-(3-piperidin-1-yl-propoxy)-1H-indol-2-yl]-1H-quinolin-2-one (1-13)



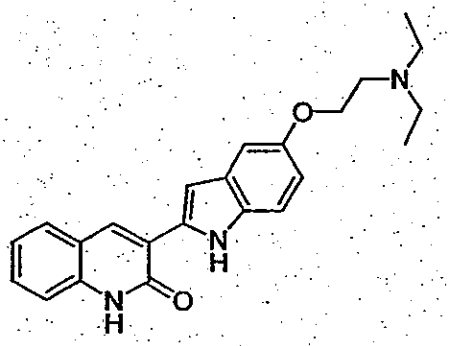
^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.15 (s, 1H), 11.41 (s, 1H), 8.50 (s, 1H), 7.73 (br d, 1H, J = 8.0 Hz), 7.51 (br t, 1H, J = 7.2 Hz), 7.41 (d, 1H, J = 8.8 Hz), 7.37 (br d, 1H, J = 8.2 Hz), 7.24 (br t, 1H, J = 7.7 Hz), 7.21 (br s, 1H), 7.04 (d, 1H, J = 2.1 Hz), 6.76 (dd, 1H, J = 8.7, 2.3 Hz), 3.99 (t, 2H, J = 6.4 Hz), 2.41 (t, 2H, J = 7.1 Hz), 2.34 (br m, 4H), 1.87 (pentet, 2H, J = 7.2 Hz), 1.50 (br m, 4H), 1.39 m, 2H).

3-(5-{2-[benzyl-(2-methoxy-ethyl)-amino]-ethoxy}-1H-indol-2-yl)-1H-quinolin-2-one (1-14)



^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.15 (s, 1H), 11.41 (s, 1H), 8.50 (s, 1H), 7.73 (br d, 1H, J = 7.7 Hz), 7.51 (br t, 1H, J = 7.1 Hz), 7.40 (d, 1H, J = 8.8 Hz), 7.37 (br d, 1H, J = 8.2 Hz), 7.37 (br d, 2H, J = 9.0 Hz), 7.32 (br t, 2H, J = 7.9 Hz), 7.24 (br t, 1H, J = 7.9 Hz), 7.24 (br t, 1H, J = 7.9 Hz), 7.20 (d, 1H, J = 2.0 Hz), 7.02 (d, 1H, J = 2.2 Hz), 6.73 (dd, 1H, J = 8.6, 2.2 Hz), 4.05 (t, 2H, J = 6.0 Hz), 3.75 (s, 2H), 3.46 (t, 2H, J = 6.0 Hz), 3.23 (s, 3H), 2.89 (t, 2H, J = 6.2 Hz), 2.74 (t, 2H, J = 6.2 Hz).

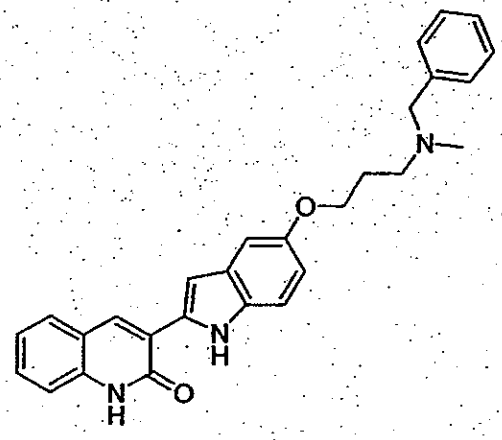
3-[5-(2-diethylamino-ethoxy)-1H-indol-2-yl]-1H-quinolin-2-one (1-15)



^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.15 (s, 1H), 11.41 (s, 1H), 8.51 (s, 1H), 7.73 (br d, 1H, J = 7.9 Hz), 7.51 (br t, 1H, J = 7.9 Hz), 7.41 (d, 1H, J = 8.8 Hz), 7.37 (br d, 1H, J = 8.1 Hz), 7.24 (br t, 1H, J = 7.3 Hz), 7.21 (br s, 1H), 7.05 (d, 1H, J = 2.2 Hz), 6.75

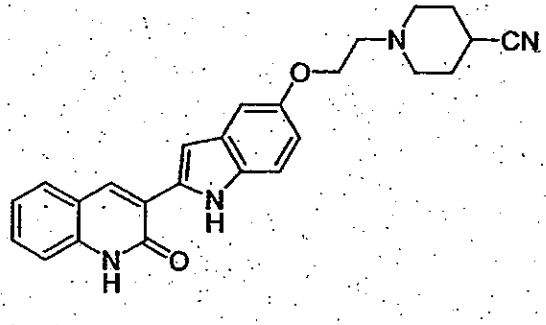
(dd, 1H, J = 8.8, 2.4 Hz), 4.02 (t, 2H, J = 6.4 Hz), 2.79 (t, 2H, J = 6.2 Hz), 2.57 (q, 4H, J = 7.1 Hz), 0.99 (t, 6H, J = 7.1 Hz).

3-{5-[3-(benzyl-methyl-amino)-propoxy]-1H-indol-2-yl}-1H-quinolin-2-one (1-16)



^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.14 (s, 1H), 11.42 (s, 1H), 8.50 (s, 1H), 7.73 (br d, 1H, J = 7.7 Hz), 7.51 (br t, 1H, J = 7.3 Hz), 7.41 (d, 1H, J = 8.8 Hz), 7.37 (br d, 1H, J = 8.2 Hz), 7.32 (br m, 5H), 7.24 (br t, 1H, J = 7.5 Hz), 7.22 (br s, 1H), 7.04 (d, 1H, J = 1.7 Hz), 6.73 (dd, 1H, J = 8.6, 2.2 Hz), 4.03 (br m, 2H), 3.50 (br s, 2H), 2.70 (br m, 2H), 2.16 (br s, 3H), 1.94 (br m, 2H).

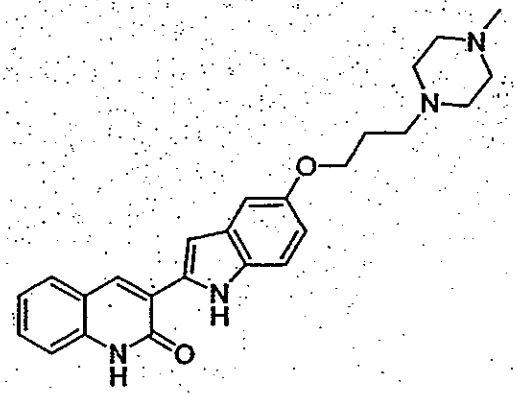
1-{2-[2-(2-oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-yloxy]-ethyl}-piperidine-4-carbonitrile (1-17)



^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.14 (s, 1H), 11.41 (s, 1H), 8.50 (s, 1H), 7.73 (br d, 1H, J = 7.5 Hz), 7.51 (br t, 1H, J = 7.8 Hz), 7.41 (d, 1H, J = 8.6 Hz), 7.37 (br d, 1H,

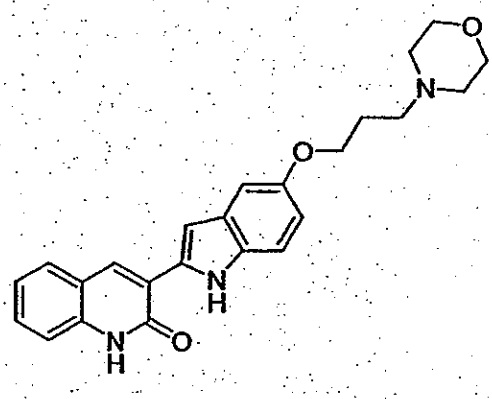
J = 7.9 Hz), 7.24 (br t, 1H, J = 7.1 Hz), 7.21 (d, 1H, J = 1.3 Hz), 7.06 (d, 1H, J = 2.2 Hz), 6.76 (dd, 1H, J = 8.6, 2.4 Hz), 4.07 (t, 2H, J = 5.7 Hz), 2.86 (m, 1H), 2.72 (t, 2H, J = 5.7 Hz), 2.67 (m, 2H), 2.41 (m, 2H), 1.87 (m, 2H), 1.72 (m, 2H).

3-{5-[3-(4-methyl-piperazin-1-yl)-propoxy]-1H-indol-2-yl}-1H-quinolin-2-one (**1-18**)



^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.15 (s, 1H), 11.41 (s, 1H), 8.49 (s, 1H), 7.72 (br d, 1H, J = 7.9 Hz), 7.51 (br t, 1H, J = 7.7 Hz), 7.40 (d, 1H, J = 8.8 Hz), 7.37 (br d, 1H, J = 8.2 Hz), 7.24 (br t, 1H, J = 7.5 Hz), 7.20 (br s, 1H), 7.03 (br s, 1H), 6.75 (dd, 1H, J = 8.8, 1.8 Hz), 3.99 (t, 2H, J = 6.4 Hz), 2.44 (t, 3H, J = 7.1 Hz), 2.36 (br m, 8H), 2.15 (s, 3H), 1.87 (m, 2H).

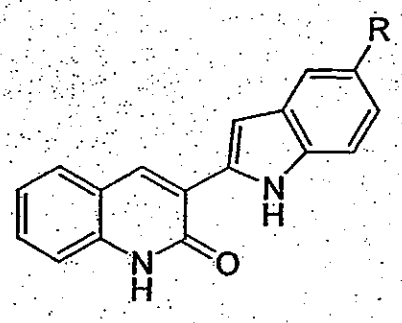
3-[5-(3-morpholin-4-yl-propoxy)-1H-indol-2-yl]-1H-quinolin-2-one (**1-19**)

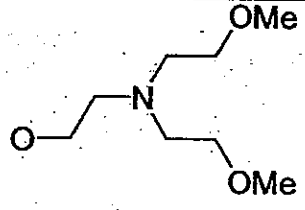
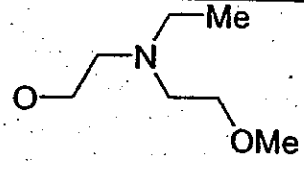
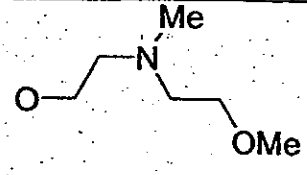
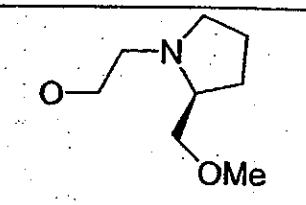


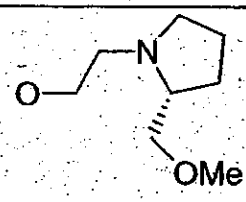
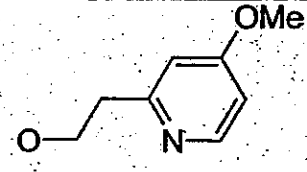
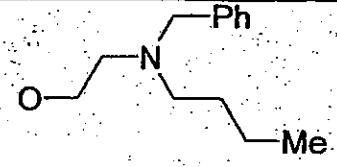
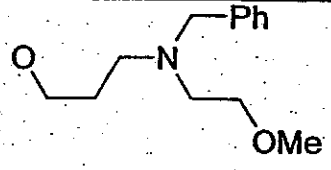
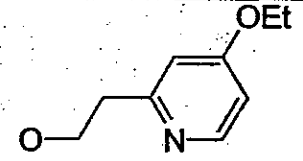
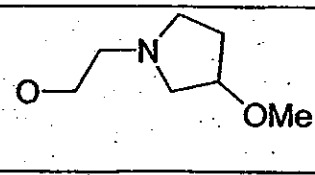
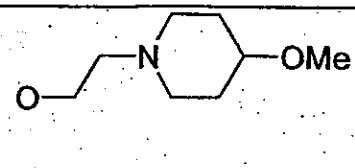
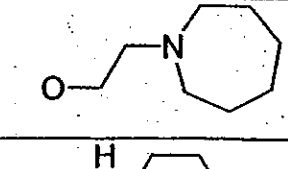
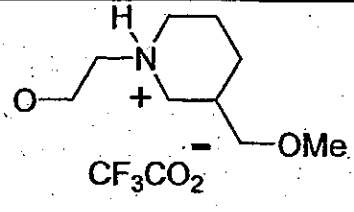
^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.14 (s, 1H), 11.41 (s, 1H), 8.50 (s, 1H), 7.73 (br d, 1H, J = 7.1 Hz), 7.51 (br t, 1H, J = 7.6 Hz), 7.41 (d, 1H, J = 8.8 Hz), 7.37 (br d, 1H,

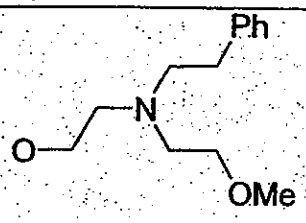
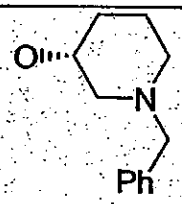
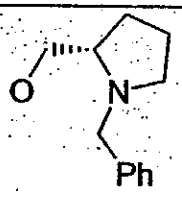
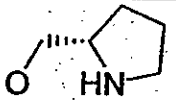
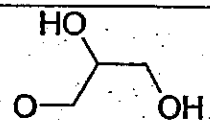
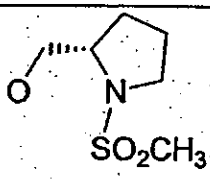
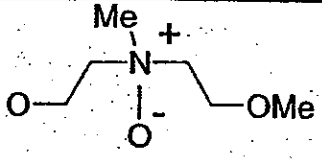
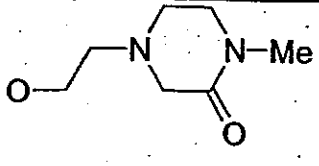
J = 8.2 Hz), 7.24 (br t, 1H, J = 7.7 Hz), 7.21 (d, 1H, J = 1.5 Hz), 7.04 (d, 1H, J = 2.2 Hz), 6.76 (dd, 1H, J = 8.6, 2.2 Hz), 4.01 (t, 2H, J = 6.4 Hz), 3.58 (t, 4H, J = 4.6 Hz), 2.45 (t, 2H, J = 7.1 Hz), 2.38 (br m, 4H), 1.89 (pentet, 2H, J = 7.0 Hz).

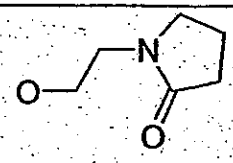
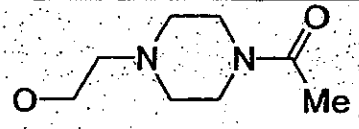
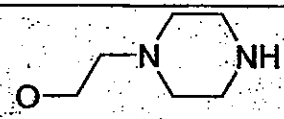
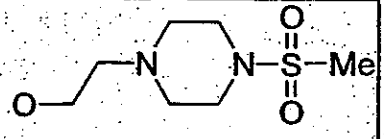
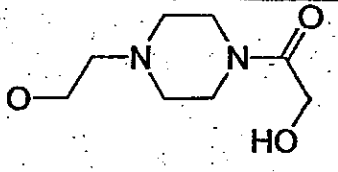
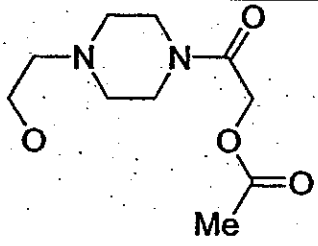
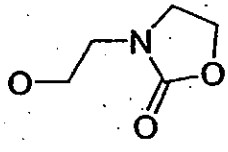
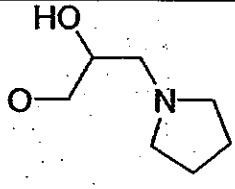
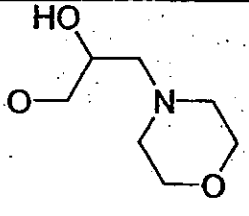
TABLE 1



Compound No.	Name	R
1-20	3-(5-{2-[bis(2-methoxyethyl)amino] ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone	
1-21	3-(5-{2-[ethyl(2-methoxyethyl)amino]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone	
1-22	3-(5-{2-[(2-methoxyethyl)(methyl)amino]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone	
1-23	3-(5-{2-[(2S)-2-(methoxymethyl)pyrrolidinyl]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone	

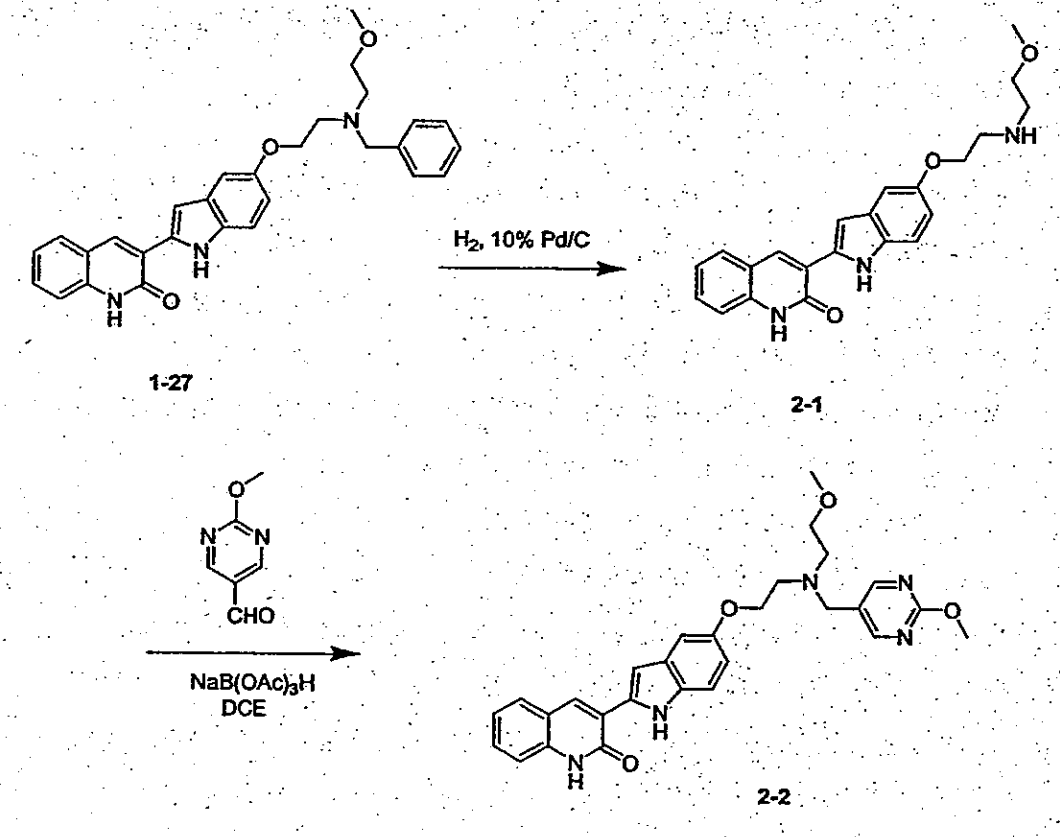
1-24	3-(5-{2-[(2R)-2-(methoxymethyl)pyrrolidinyl]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone	
1-25	3-{5-[(4-methoxy-2-pyridinyl)methoxy]-1H-indol-2-yl}-2(1H)-quinolinone	
1-26	3-(5-{2-[benzyl(butyl)amino]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone	
1-27	3-(5-{3-[benzyl(2-methoxyethyl)amino]propoxy}-1H-indol-2-yl)-2(1H)-quinolinone	
1-28	3-{5-[(4-ethoxy-2-pyridinyl)methoxy]-1H-indol-2-yl}-2(1H)-quinolinone	
1-29	3-{5-[2-(3-methoxy-1-pyrrolidinyl)ethoxy]-1H-indol-2-yl}-2(1H)-quinolinone	
1-30	3-{5-[2-(4-methoxy-1-piperidinyl)ethoxy]-1H-indol-2-yl}-2(1H)-quinolinone	
1-31	3-{5-[2-(1-azepanyl)ethoxy]-1H-indol-2-yl}-2(1H)-quinolinone	
1-32	3-(methoxymethyl)-1-(2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}ethyl)piperidinium trifluoroacetate	

1-33	3-(5-{2-[(2-methoxyethyl)(2-phenylethyl)amino]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone	
1-34	3-(5-{[(3R)-1-benzylpiperidinyl]oxy}-1H-indol-2-yl)-2(1H)-quinolinone	
1-35	3-(5-{[(2S)-1-benzylpyrrolidinyl]methoxy}-1H-indol-2-yl)-2(1H)-quinolinone	
1-36	3-{5-[(2S)-pyrrolidinylmethoxy]-1H-indol-2-yl}-2(1H)-quinolinone	
1-37	3-(5-methoxy-1H-indol-2-yl)-2(1H)-quinolinone	OMe
1-38	3-[5-(2-methoxyethoxy)-1H-indol-2-yl]-2(1H)-quinolinone	OCH_2CH_2OMe
1-39	3-[5-(2,3-dihydroxypropoxy)-1H-indol-2-yl]-2(1H)-quinolinone	
1-40	3-(5-{[(2S)-1-(methylsulfonyl)pyrrolidinyl]methoxy}-1H-indol-2-yl)-2(1H)-quinolinone	
1-41	3-(5-{2-[(2-methoxyethyl)(methyl)nitroryl]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone	
1-42	3-{5-[2-(4-methyl-3-oxo-1-piperazinyl)ethoxy]-1H-indol-2-yl}-2(1H)-quinolinone	

1-43	3-{5-[2-(2-oxo-1-pyrrolidinyl)ethoxy]-1H-indol-2-yl}-2(1H)-quinolinone	
1-44	3-{5-[2-(4-acetyl-1-piperazinyl)ethoxy]-1H-indol-2-yl}-2(1H)-quinolinone	
1-45	3-{5-[2-(1-piperazinyl)ethoxy]-1H-indol-2-yl}-2(1H)-quinolinone	
1-46	3-(5-{2-[4-(methylsulfonyl)-1-piperazinyl]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone	
1-47	3-{5-[2-(4-glycoloyl-1-piperazinyl)ethoxy]-1H-indol-2-yl}-2(1H)-quinolinone	
1-48	2-oxo-2-[4-(2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}ethyl)-1-piperazinyl]ethyl acetate	
1-49	3-{5-[2-(2-oxo-1,3-oxazolidin-3-yl)ethoxy]-1H-indol-2-yl}-2(1H)-quinolinone	
1-50	3-{5-[2-hydroxy-3-(1-pyrrolidinyl)propoxy]-1H-indol-2-yl}-2(1H)-quinolinone	
1-51	3-{5-[2-hydroxy-3-(4-morpholinyl)propoxy]-1H-indol-2-yl}-2(1H)-quinolinone	

1-52	{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}acetic acid	OCH_2CO_2H
1-53	{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}acetonitrile	OCH_2CN
1-54	3-(5-hydroxy-1H-indol-2-yl)-2(1H)-quinolinone	OH
1-55	3-(1H-indol-2-yl)-2(1H)-quinolinone	H

SCHEME 2



3-(5-{2-[(2-methoxyethyl)amino]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone (2-1)

10 % Pd/C (840 mg) was added to a solution (150 mL) of 3-(5-{2-[Benzyl-(2-methoxyethyl)-amino]-ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone, Compound **1-27**, (840 mg, 1.8 mmol) in EtOAc (150 mL), and the resulting mixture was stirred under

a hydrogen balloon for 18 h. The catalyst was removed by filtration and the filtrate concentrated to a yellow solid which was purified by chromatography on a silica column. Elution with EtOAc to 25 % NH3-EtOH/EtOAc gave 3-(5-{2-[(2-methoxyethyl)amino]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone (**2-1**) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.05 (s, 1H), 9.65 (br s, 1H), 8.32 (s, 1H), 7.67 (d, 1H, J = 8 Hz), 7.51 (t, 1H, J = 8 Hz), 7.34 (d, 1H, J = 8 Hz), 7.29 (t, 1H, J = 8 Hz), 7.24 (d, 1H, J = 8 Hz), 7.09 (s, 1H), 6.96 (s, 1H), 6.90 (dd, 1H, J = 8, 2 Hz), 4.15 (t, 2H, J = 5 Hz), 3.55 (t, 2H, J = 5 Hz), 3.38 (s, 3H), 3.07 (t, 2H, J = 5 Hz), 2.91 (t, 2H, J = 5 Hz).

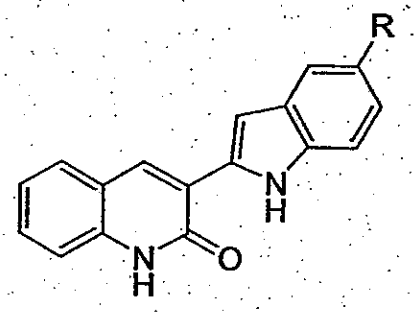
3-[5-(2-{(2-methoxyethyl)[(2-methoxy-5-pyrimidinyl)methyl]amino}ethoxy)-1H-indol-2-yl]-2(1H)-quinolinone (**2-2**)

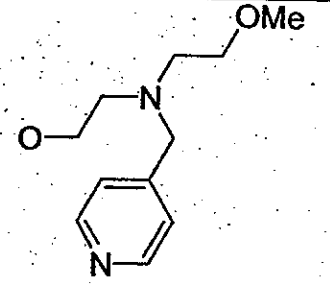
A solution of 3-(5-{2-[(2-methoxyethyl)amino]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone **2-1** (150 mg, 0.4 mmol), 2-methoxypyrimidine-5-carboxaldehyde (110 mg, 0.8 mmol) and sodium triacetoxyborohydride (168 mg, 0.8 mmol) in DCE (25 mL) was stirred under ambient conditions for 18 h. The reaction mixture was concentrated, and the residue was partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was suspended in ethyl ether with the aid of sonication, then filtered and air dried to provide 3-[5-(2-{(2-methoxyethyl)[(2-methoxy-5-pyrimidinyl)methyl]amino}ethoxy)-1H-indol-2-yl]-2(1H)-quinolinone (**2-2**) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.05 (s, 1H), 9.60 (s, 1H), 8.53 (s, 2H), 8.33 (s, 1H), 7.68 (d, 1H, J = 8 Hz), 7.52 (t, 1H, J = 8 Hz), 7.34 (d, 1H, J = 8 Hz), 7.27 (t, 1H, J = 8 Hz), 7.22 (d, 1H, J =8 Hz), 7.05 (s, 1H), 6.96 (s, 1H), 6.86 (dd, 1H, J = 8, 2 Hz), 4.13 (t, 2H, J = 6 Hz), 4.01 (s, 3H), 3.80 (s, 2H), 3.53 (t, 2H, J = 6 Hz), 3.34 (s, 3H), 3.01 (t, 2H, J = 6 Hz), 2.84 (t, 2H, J = 6Hz).

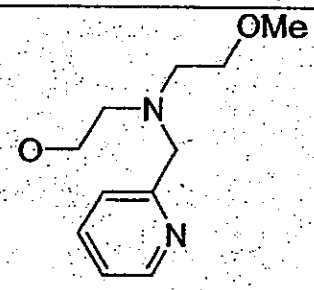
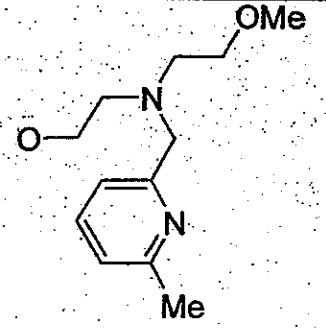
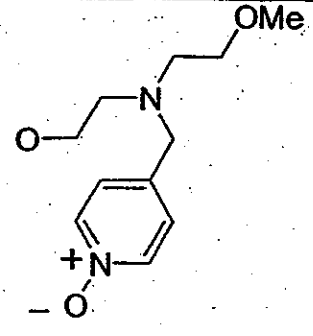
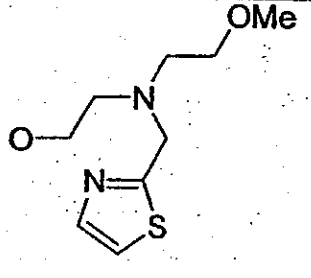
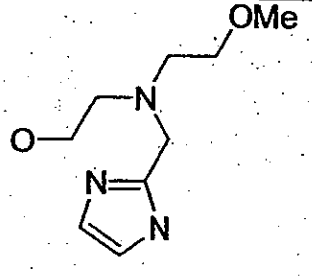
Compounds **2-3** through **2-12** in Table 2 were prepared by simple modifications to the protocols described above. Selected NMR spectra for **2-3** and **2-4** are as follow: **2-3**,

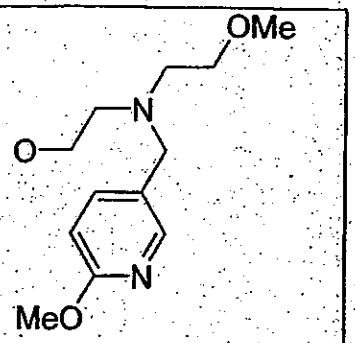
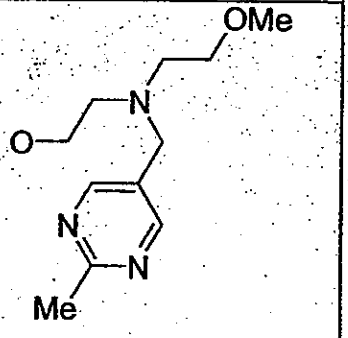
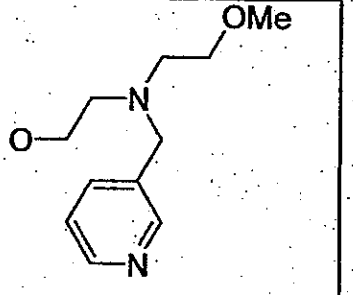
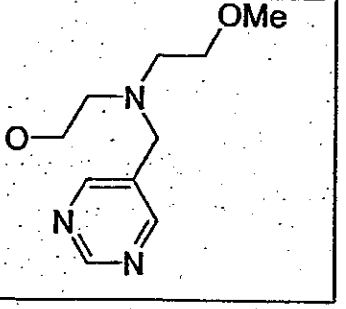
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.05 (s, 1H), 9.65 (s, 1H), 8.54 (dd, 1H, *J* = 4, 1 Hz), 8.33 (s, 1H), 7.68 (d, 1H, *J* =7 Hz), 7.52 (t, 1H, *J* =8 Hz), 7.33 (m, 3 H), 7.28 (t, 1H, *J* =7 Hz), 7.24 (d, 1H, *J* =8 Hz), 7.03 (d, 1H, J= *2* Hz), 6.96 (d, 1H, *J* =2 Hz), 6.85 (dd, 1H, *J* = 8, 2 Hz), 4.13 (t, 2H, *J* =6 Hz), 3.85 (s, 2H), 3.53 (t, 2H, *J* = 6 Hz), 3.33 (s, 3H), 3.03 (t, 2H, *J* =6 Hz), 2.86 (t, 2H, *J* = 6 Hz). **2-4**, ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.05 (s,1H), 9.40 (br s, 1H), 8.53 (d, 1H, *J* = 5 Hz), 8.32 (s, 1H), 7.68 (d, 1H, *J* = 8 Hz), 7.64 (t, 1H, *J* = 7 Hz), 7.56 (d, 1H, *J* = 8 Hz), 7.51 (t, 1H, *J* = 8 Hz), 7.34-7.21 (m, 3H), 7.14 (t, 1H, *J* = 7 Hz), 7.05 (s, 1H), 6.95 (s,1H), 6.85 (d, 1H, *J* = 8 Hz), 4.14 (t, 2H, *J* = 6 Hz), 3.99 (s, 2H), 3.55 (t, 2H, *J* = 6 Hz), 3.33 (s, 3H), 3.09 (t, 2H, *J* = 6 Hz), 2.93 (t, 2H, *J* = 6 Hz).

TABLE 2

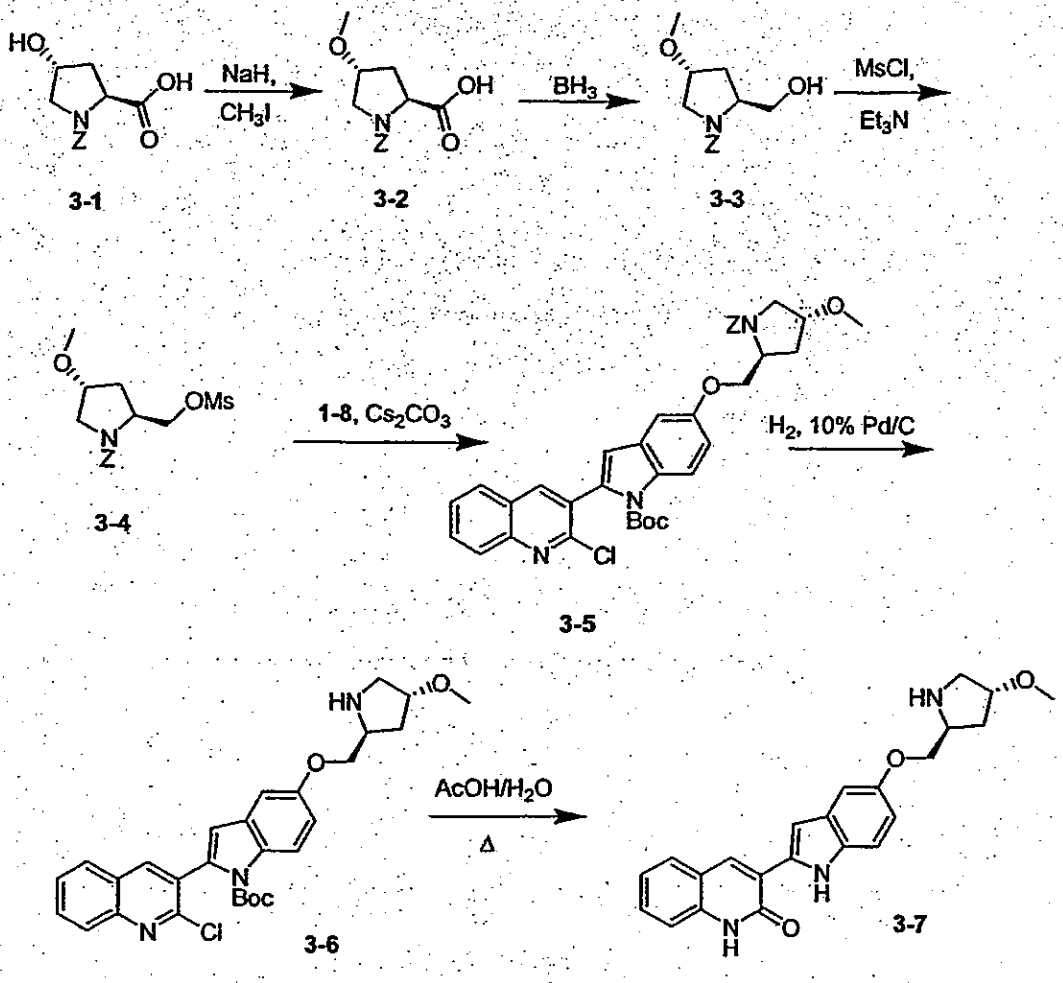


Compound No.	Name	R
2-3	3-(5-{2-[(2-methoxyethyl)(4-pyridinyl-methyl)amino]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone	

2-4	3-(5-{2-[(2-methoxyethyl)(2-pyridinyl-methyl)amino]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone	
2-5	3-[5-(2-{(2-methoxyethyl)[(6-methyl-2-pyridinyl)methyl]amino}ethoxy)-1H-indol-2-yl]-2(1H)-quinolinone	
2-6	3-[5-(2-{(2-methoxyethyl)[(1-oxido-4-pyridinyl)methyl]amino}ethoxy)-1H-indol-2-yl]-2(1H)-quinolinone	
2-7	3-(5-{2-[(2-methoxyethyl)(1,3-thiazol-2-ylmethyl)amino]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone	
2-8	3-(5-{2-[(1H-imidazol-2-ylmethyl)(2-methoxyethyl)amino]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone	

2-9	3-[5-(2-{(2-methoxyethyl)[(6-methoxy-3-pyridinyl)methyl]amino}ethoxy)-1H-indol-2-yl]-2(1H)-quinolinone	
2-10	3-[5-(2-{(2-methoxyethyl)[(2-methyl-5-pyrimidinyl)methyl]amino}ethoxy)-1H-indol-2-yl]-2(1H)-quinolinone	
2-11	3-(5-{2-[(2-methoxyethyl)(3-pyridinyl-methyl)amino]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone	
2-12	3-(5-{2-[(2-methoxyethyl)(5-pyrimidinyl-methyl)amino]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone	

SCHEME 3



(2S,4R)-1-[(benzyloxy)carbonyl]-4-methoxy-2-pyrrolidinecarboxylic acid (3-2)

Sodium hydride (543 mg, 22.6 mmol, 2.00 equiv) was carefully added to a solution of (2S,4R)-1-[(benzyloxy)carbonyl]-4-hydroxy-2-pyrrolidinecarboxylic acid (**3-1**, 3.00 g, 11.3 mmol, 1 equiv) in THF (100 mL) at 0°C, and resulting mixture was stirred for 20 minutes. Iodomethane (2.11 mL, 33.9 mmol, 3.00 equiv) was added, and the mixture was warmed to 23°C and stirred for 20 h. The reaction mixture was then diluted with saturated sodium bicarbonate solution washed with ethyl acetate (2 x 100 mL). The aqueous layer was then acidified with 1 N HCl solution to pH 3 and extracted with

ethyl acetate (100 mL). This organic layer was then dried over sodium sulfate and concentrated to provide (2S,4R)-1-[(benzyloxy)carbonyl]-4-methoxy-2-pyrrolidinecarboxylic acid (3-2) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) major rotamer: δ 7.40-7.25 (br m, 5H), 5.20 (s, 2H), 4.52 (t, 1H, J = 7.4 Hz), 4.00 (m, 1H), 3.67 (dd, 1H, J = 11.4, 2.8 Hz), 3.57 (dd, 1H, J = 11.4, 4.6 Hz), 3.32 (s, 3H), 2.34 (m, 2H).

Benzyl (2S,4R)-2-(hydroxymethyl)-4-methoxy-1-pyrrolidinecarboxylate (3-3)

A solution of borane-tetrahydrofuran complex in THF (1M, 53.0 mL, 53.0 mmol, 3.50 equiv) was added to a solution of (2S,4R)-1-[(benzyloxy)carbonyl]-4-methoxy-2-pyrrolidinecarboxylic acid (3-2, 4.23 g, 15.1 mmol, 1 equiv) in THF (200 mL) at 0°C. The resulting mixture was warmed to 23°C and stirred for 1 h. Excess borane was carefully quenched with water. The mixture was then partitioned between a 1:1 mixture of saturated sodium carbonate solution and brine (300 mL) and ethyl acetate (300 mL). The organic layer was dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (100% hexane initally, grading to 100% EtOAc) to provide benzyl (2S,4R)-2-(hydroxymethyl)-4-methoxy-1-pyrrolidinecarboxylate (3-3) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) major rotamer: δ 7.37-7.25 (br m, 5H), 5.18 (d, 1H, J = 12.4 Hz), 5.13 (d, 1H, J = 12.2 Hz), 4.51 (dd, 1H, J = 8.3, 2.2 Hz), 3.86 (m, 1H), 3.78 (dd, 1H, J = 11.7, 2.2 Hz), 3.72 (br d, 1H, J = 11.7 Hz), 3.61 (ddd, 1H, J = 9.8, 7.4, 2.2 Hz), 3.44 (dd, 1H, J = 12.2, 4.4 Hz), 3.30 (s, 3H), 2.18 (m, 1H), 1.64 (m, 1H).

Benzyl (2S,4R)-4-methoxy-2-{[(methylsulfonyl)oxy]methyl}-1-pyrrolidinecarboxylate (3-4)

Methanesulfonyl chloride (0.175 mL, 2.26 mmol, 1.2 equiv) was added to a solution of (2S,4R)-2-(hydroxymethyl)-4-methoxy-1-pyrrolidinecarboxylate (3-3, 0.500 g, 1.88 mmol, 1 equiv) and triethylamine (0.394 mL, 2.83 mmol, 1.50 equiv) in

dichloromethane (30 mL) at 0° C. The resulting mixture was warmed to 23°C and stirred for 1 h. The reaction mixture was partitioned between saturated sodium bicarbonate solution and dichloromethane (2 x 40 mL). The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (100% hexane initially, grading to 100% EtOAc) to provide benzyl (2S,4R)-4-methoxy-2-{[(methylsulfonyl)oxy]methyl}-1-pyrrolidinecarboxylate (3-4) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) major rotamer: δ 7.37-7.25 (br m, 5H), 5.17 (d, 1H, J = 11.8 Hz), 5.10 (d, 1H, J = 11.8 Hz), 4.65 (dd, 1H, J = 8.3, 3.8 Hz), 4.24 (br m, 2H), 3.95 (m, 1H), 3.68 (br d, 1H, J = 12.0 Hz), 3.45 (dd, 1H, J = 12.0, 4.4 Hz), 3.30 (s, 3H), 2.88 (s, 3H), 2.39 (m, 1H), 2.12 (m, 1H).

tert-Butyl 5-({(2S,4R)-1-[(benzyloxy)carbonyl]-4-methoxypyrrolidinyl}methoxy)-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (3-5)

A mixture of benzyl (2S,4R)-4-methoxy-2-{[(methylsulfonyl)oxy]methyl}-1-pyrrolidinecarboxylate (3-4, 380 mg, 1.11 mmol, 1 equiv), 2-B (437 mg, 1.11 mmol, 1.00 equiv), and cesium carbonate (433 mg, 1.33 mmol, 1.20 equiv) in DMF (5.0 mL) was heated at 70°C for 3 h. The reaction mixture was partitioned between water and ethyl acetate (2 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (100% hexane, grading to 40% EtOAc in hexane) to give tert-butyl 5-({(2S,4R)-1-[(benzyloxy)carbonyl]-4-methoxypyrrolidinyl}methoxy)-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (3-5). ^{1}H NMR (400 MHz, $CDCl_3$) major rotamer: δ 8.17 (m, 2H), 8.08 (d, 1H, J = 8.5 Hz), 7.87 (br d, 1H, J = 8.6 Hz), 7.78 (t, 1H, J = 8.4 Hz), 7.61 (t, 1H, J = 8.4 Hz), 7.38-7.22 (br m, 5H), 7.10 (br s, 1H), 6.94 (br m, 1H), 6.56 (s, 1H), 5.17 (br s, 2H), 4.35 (br m, 2H), 4.16 (br m, 2H), 3.60 (br m, 2H), 3.34 (s, 3H), 2.88 (s, 3H), 2.32 (m, 1H), 2.23 (m, 1H).

tert-Butyl 2-(2-chloro-3-quinolinyl)-5-{[(2S,4R)-4-methoxypyrrolidinyl]methoxy}-1H-indole-1-carboxylate (3-6)

A mixture of tert-butyl 5-({(2S,4R)-1-[(benzyloxy)carbonyl]-4-methoxypyrrolidinyl}methoxy)-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (3-5, 295 mg, 0.459 mmol, 1 equiv) and 10% palladium on carbon (200 mg, 0.188 mmol, 0.410 equiv) in ethanol (10 mL) was stirred under a hydrogen balloon for 1.5 h. The catalyst was filtered onto a pad of celite and washed with ethanol (20 mL). The filtrate was concnetrated, and the residue was purified by reverse-phase liquid chromotography (H_2O/CH_3CN gradient w/ 0.1% TFA present) to give tert-butyl 2-(2-chloro-3-quinolinyl)-5-{[(2S,4R)-4-methoxypyrrolidinyl]methoxy}-1H-indole-1-carboxylate (3-6). ^{1}H NMR (300 MHz, CD_3OD) δ 8.41 (s, 1H), 8.23 (d, 1H, J = 9.3 Hz), 8.02 (br t, 2H, J = 7.1 Hz), 7.86 (br t, 1H, J = 7.9 Hz), 7.70 (br t, 1H, J = 8.1 Hz), 7.25 (d, 1H, J = 2.4 Hz), 7.09 (dd, 1H, J = 9.0, 2.7), 6.73 (s, 1H), 4.45 (m, 1H), 4.23 (br m, 3H), 3.51 (br d, 1H, J = 12.7 Hz), 3.41 (dd, 1H, J = 12.7, 3.4 Hz), 3.40 (s, 3H), 2.47 (m, 1H), 2.06 (m, 1H).

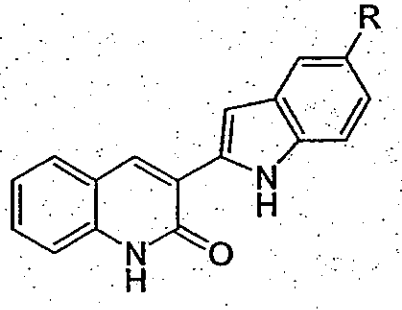
3-(5-{[(2S,4R)-4-methoxypyrrolidinyl]methoxy}-1H-indol-2-yl)-2(1H)-quinolinone (3-7)

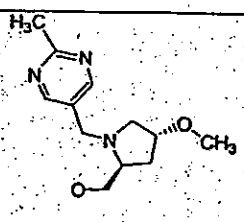
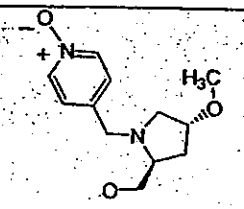
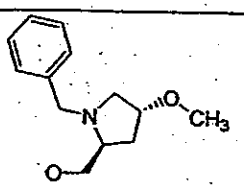
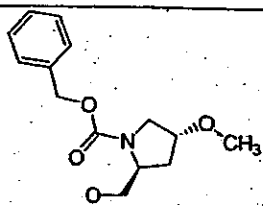
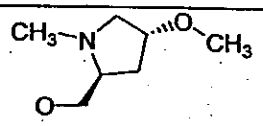
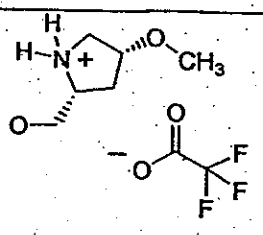
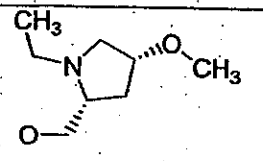
A solution of tert-butyl 2-(2-chloro-3-quinolinyl)-5-{[(2S,4R)-4-methoxypyrrolidinyl]methoxy}-1H-indole-1-carboxylate (6-6, 29 mg, 0.057 mmol) was heated in a 8:1 mixture of acetic acid and water (5 mL) at 90°C for 1.5 h. The reaction mixture was cooled and concentrated, and the residue was purified by reverse-phase liquid chromotography (H_2O/CH_3CN gradient w/ 0.1% TFA present) to give 3-(5-{[(2S,4R)-4-methoxypyrrolidinyl]methoxy}-1H-indol-2-yl)-2(1H)-quinolinone (3-7) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (s, 1H), 7.75 (d, 1H, J = 7.8 Hz), 7.53 (br t, 1H, J = 7.8 Hz), 7.38 (d, 1H, J = 8.9 Hz), 7.38 (d, 1H, J = 8.1 Hz), 7.29 (br t, 1H, J = 7.3 Hz), 7.19 (s, 1H), 7.17 (d, 1H, J = 2.4 Hz), 6.89 (dd, 1H, J = 8.8, 2.4 Hz), 4.39 (dd, 1H, J = 10.2, 2.8 Hz), 4.25 (m, 1H), 4.20 (m,

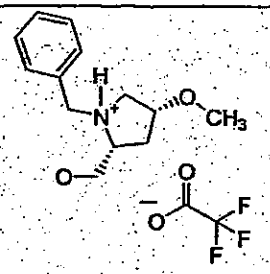
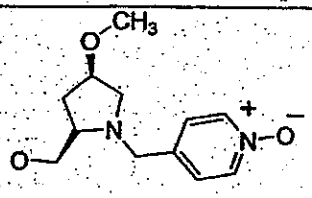
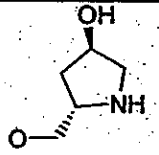
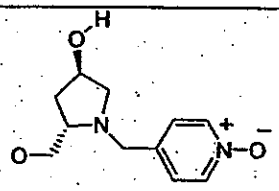
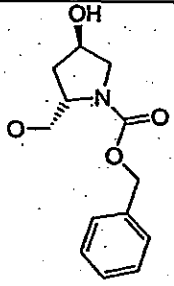
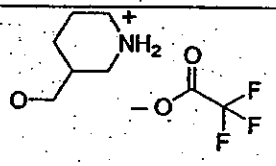
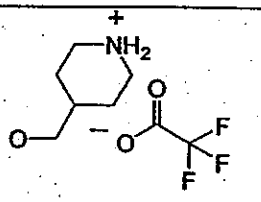
1H), 4.14 (m, 1H), 3.49 (dd, 1H, J = 13.9, 6.9 Hz), 3.41 (dd, 1H, J = 12.6, 3.6 Hz), 3.39 (s, 3H), 2.45 (br dd, 1H, J = 13.9, 6.5 Hz), 2.05 (m, 1H).

Compounds **3-8** through **3-21** in Table 3 below were prepared by simple modifications of the protocols described above. For examples **3-13** through **3-15**, (2R,4R)-1-[(benzyloxy)carbonyl]-4-hydroxy-2-pyrrolidinecarboxylic acid was used as the starting material. For examples **3-17** through **3-19**, TBSCl was used in place of iodomethane in the first step of sequence described in Scheme 3. For examples **3-20** and **3-21**, 1-(tert-butoxycarbonyl)-4-piperidinecarboxylic acid and 1-(tert-butoxycarbonyl)-3-piperidinecarboxylic acid were used as starting material, respectively. Selected NMR spectra for **3-8** and **3-9** are as follow: **3-8**, ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.1 (s, 1H), 9.27 (br s, 1H), 8.62 (s, 2H), 8.32 (s, 1H), 7.68 (d, 1H, J = 8 Hz), 7.51 (t, 1H, J = 8 Hz), 7.34 (d, 1H, J = 8 Hz), 7.29 (t, 1H, J = 7 Hz), 7.19 (d, 1H, J = 8 Hz), 7.07 (d, 1H, J = 2 Hz), 6.96 (br s, 1H), 6.87 (dd, 1H, J = 8, 2 Hz), 4.25 (d, 1H, J = 14 Hz), 4.05 (m, 2H), 3.94 (m, 1H), 3.58 (d, 1H, J = 14 Hz), 3.36-3.22 (m, 2H), 3.30 (s, 3H), 2.71 (s, 3H), 2.38 (m, 1H), 2.12 (m, 1H), 1.96 (m, 1H). **3-9**, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.2 (s, 1H), 11.4 (s, 1H), 8.51 (s, 1H), 8.13 (d, 2H, J = 7 Hz), 7.72 (d, 1H, J = 7 Hz), 7.51 (t, 1H, J = 8 Hz), 7.42-7.32 (m, 4 H), 7.24 (t, 1H, J = 8Hz), 7.20 (s, 1H), 7.05 (s, 1H), 6.74 (dd, 1H, J = 8, 2 Hz), 4.13 (d, 1H, J =14 Hz), 4.04 (m, 1H), 3.91 (m, 2H), 3.54 (d, 1H, J = 14 Hz), 3.20 (s, 3H), 3.20-3.13 (m, 2H), 2.31 (m, 1H), 2.01 (m, 1H), 1.86 (m, 1H).

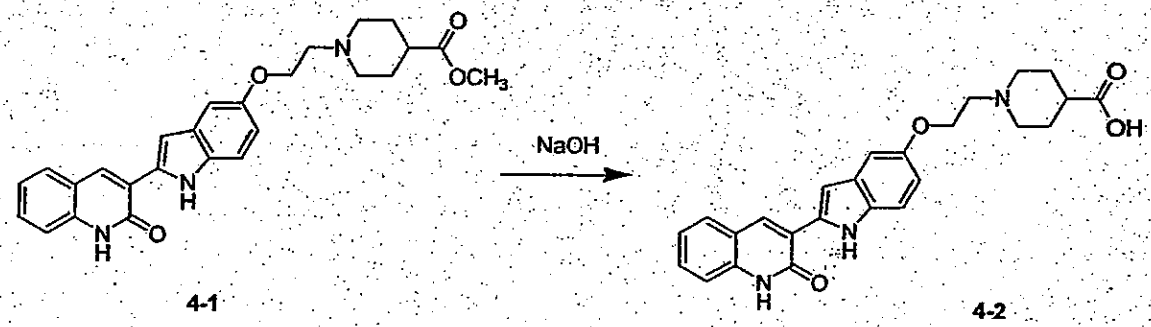
TABLE 3



Compound No.	Compound	R
3-8	3-[5-({(2S,4R)-4-methoxy-1-[(2-methyl-5-pyrimidinyl)methyl]pyrrolidinyl} methoxy)-1H-indol-2-yl]-2(1H)-quinolinone	
3-9	3-[5-({(2S,4R)-4-methoxy-1-[(1-oxido-4-pyridinyl)methyl]pyrrolidinyl}methoxy)-1H-indol-2-yl]-2(1H)-quinolinone	
3-10	3-(5-{[(2S,4R)-1-benzyl-4-methoxypyrrolidinyl]methoxy}-1H-indol-2-yl)-2(1H)-quinolinone	
3-11	benzyl (2S,4R)-4-methoxy-2-({[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}methyl)-1-pyrrolidinecarboxylate	
3-12	3-(5-{[(2S,4R)-4-methoxy-1-methylpyrrolidinyl]methoxy}-1H-indol-2-yl)-2(1H)-quinolinone	
3-13	(2R,4R)-4-methoxy-2-({[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy} methyl)pyrrolidinium trifluoroacetate	
3-14	3-(5-{[(2R,4R)-1-ethyl-4-methoxypyrrolidinyl]methoxy}-1H-indol-2-yl)-2(1H)-quinolinone	

3-15	(2R,4R)-1-benzyl-4-methoxy-2-({[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}methyl)pyrrolidinium trifluoroacetate	
3-16	3-[5-({(2R,4R)-4-methoxy-1-[(1-oxido-4-pyridinyl)methyl]pyrrolidinyl}methoxy)-1H-indol-2-yl]-2(1H)-quinolinone	
3-17	3-(5-{[(2S,4R)-4-hydroxypyrrolidinyl]methoxy}-1H-indol-2-yl)-2(1H)-quinolinone	
3-18	3-[5-({(2S,4R)-4-hydroxy-1-[(1-oxido-4-pyridinyl)methyl]pyrrolidinyl}methoxy)-1H-indol-2-yl]-2(1H)-quinolinone	
3-19	benzyl (2R,4R)-4-hydroxy-2-({[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}methyl)-1-pyrrolidinecarboxylate	
3-20	3-({[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}methyl)piperidinium trifluoroacetate	
3-21	4-({[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}methyl)piperidinium trifluoroacetate	

SCHEME 4



1-(2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}ethyl)-4-piperidine-carboxylic acid ethyl ester (4-1)

Compound 4-1 was synthesized by the protcol described in Scheme 1 above.

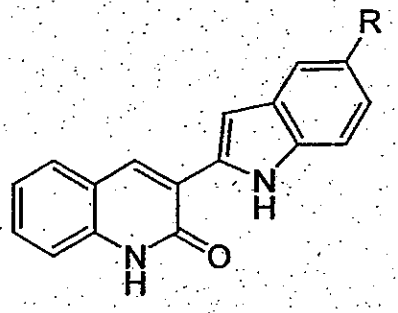
1-(2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}ethyl)-4-piperidinecarboxylic acid (4-2)

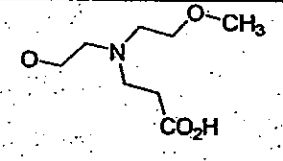
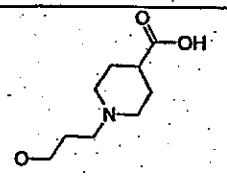
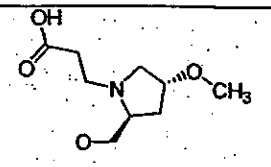
1-(2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}ethyl)-4-piperidine-carboxylic acid ethyl ester (4-1, 138 mg, 0.30 mmol, 1 equiv) was dissolved in MeOH (20 mL). 1 N NaOH (6 mL, 20 equiv) was added and the solution warmed at 50°C for 5 h. The reaction was concentrated, and the residue was suspended in 4 mL of water. This suspension was neutralized with 1 N HCl to provide 1-(2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}ethyl)-4-piperidinecarboxylic acid (4-2) as a yellow solid. ^{1}H NMR (400 MHz, CD3OD) δ 8.45 (s, 1H), 7.74 (d, 1H, J = 8 Hz), 7.53 (t, 1H, J = 8 Hz), 7.38 (m, 2H), 7.28 (t, 1H, J = 8 Hz), 7.19 (s, 1H), 7.16 (s, 1H), 6.88 (dd, 1H, J =9, 2 Hz), 4.34 (t, 2H, J = 5 Hz), 3.53 (m, 2H), 3.47 (m, 2H), 3.07 (m, 2 H), 2.42 (m, 1H), 2.11 (m, 2H), 1.95 (m, 2H).

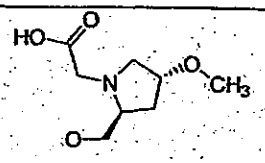
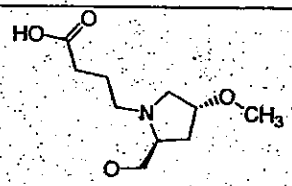
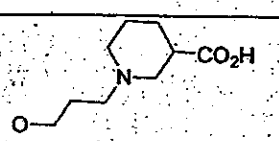
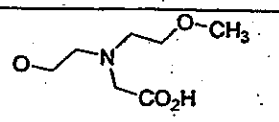
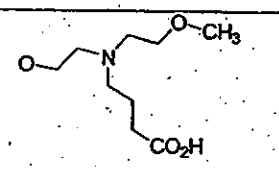
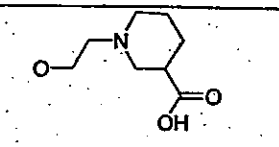
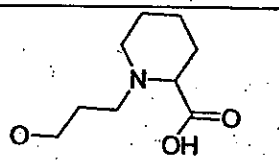
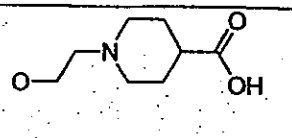
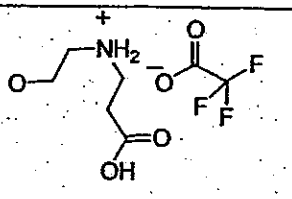
Compounds 4-3 through 4-16 in Table 4 below were made by simple modifications of the hydrolysis conditions described above. The corresponding ester precursors were prepared by alkylation chemistry analogous to that depicted in Schemes 1 and 3.

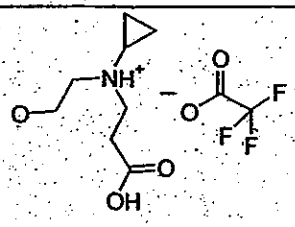
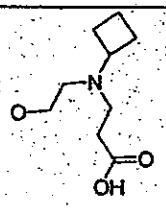
Selected NMR spectra for 4-3 and 4-4 are as follow: 4-3, ^{1}H NMR(400 MHz, CD_3OD) δ 8.44 (s, 1H), 7.74 (d, 1H, J = 8 Hz), 7.52 (t, 1H, J = 7 Hz), 7.34 (d, 1H, J = 8 Hz), 7.28 (t, 1H, J = 7 Hz), 7.18 (br s, 1H), 6.92 (d, 1H, J = 8 Hz), 4.36 (t, 2H, J = 5Hz), 3.74 (t, 2H, J = 5 Hz), 3.62 (t, 2H, J = 5 Hz), 3.45 (m, 4H), 3.36 (s, 3H), 2.61 (t, 2H, J = 5 Hz). 4-4, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.1 (s, 1H), 11.5 (s, 1H), 8.50 (s, 1H), 7.73 (d, 1H, J = 8 Hz), 7.51 (t, 1H, J = 8 Hz), 7.42 (d, 1H, J = 8 Hz), 7.37 (d, 1H, J = 8 Hz), 7.25 (t, 1H, J = 8 Hz), 7.21 (s, 1H), 7.05 (s, 1H), 6.76 (dd, 1H, J = 8, 2 Hz), 4.02 (m, 2H), 3.15- 2.75 (m, 4H), 2.4-1.5 (m, 9H).

TABLE 4

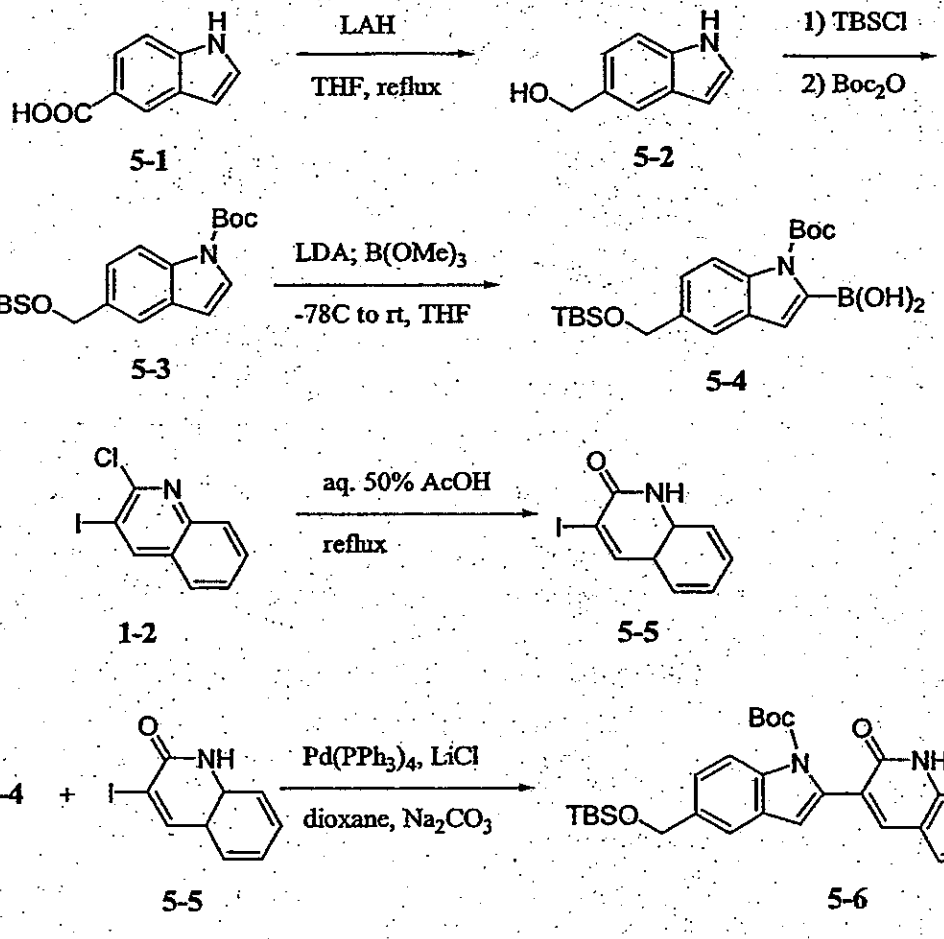


Compound No.	Compound	R
4-3	N-(2-methoxyethyl)-N-(2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}ethyl)-beta-alanine	
4-4	1-(3-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}propyl)-4-piperidinecarboxylic acid	
4-5	3-[(2S,4R)-4-methoxy-2-({[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}methyl)pyrrolidinyl]propanoic acid	

4-6	[(2S,4R)-4-methoxy-2-({[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}methyl)pyrrolidinyl]acetic acid	
4-7	4-[(2S,4R)-4-methoxy-2-({[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}methyl)pyrrolidinyl]butanoic acid	
4-8	1-(3-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}propyl)-3-piperidinecarboxylic acid	
4-9	[(2-methoxyethyl)(2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}ethyl)amino]acetic acid	
4-10	4-[(2-methoxyethyl)(2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}ethyl)amino]butanoic acid	
4-11	1-(2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}ethyl)-3-piperidinecarboxylic acid	
4-12	1-(3-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}propyl)-2-piperidinecarboxylic acid	
4-13	1-(2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}ethyl)-4-piperidinecarboxylic acid	
4-14	2-carboxy-N-(2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}ethyl) ethanaminium trifluoroacetate	

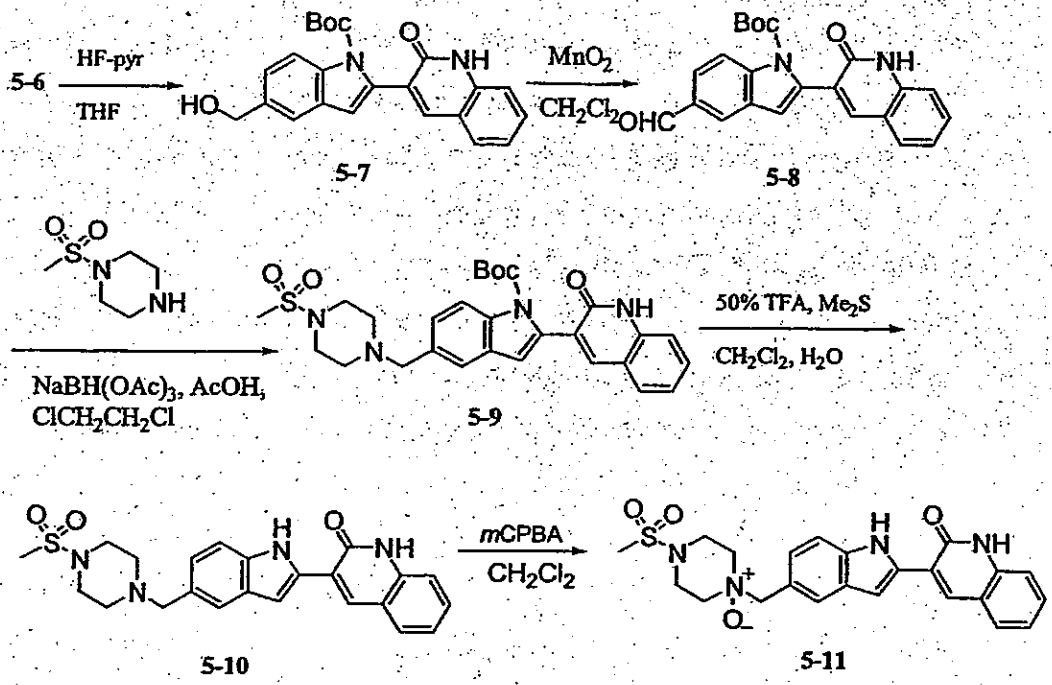
4-15	N-(2-carboxyethyl)-N-(2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}ethyl)cyclopropanaminium trifluoroacetate	
4-16	N-cyclobutyl-N-(2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}ethyl)-beta-alanine	

SCHEME 5



5

SCHEME 5 (cont'd)



(1H-Indol-5-yl)-methanol (5-2)

To a mechanically stirred solution of 1H-Indole-5-carboxylic acid (5-1, 20.01 g, 124 mmol) in THF (500 mL) was added at ambient temperature slowly a solution of 1M-LAH in toluene (186 mL, 186 mmol, 1.5 equiv). The reaction mixture was heated at reflux for 1 h, quenched with ice, partitioned between ethylacetate and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, separated, dried ($MgSO_4$) and concentrated in vacuo. The crude product solidified upon standing under the reduced pressure. The crude solid was suspended in hexanes (200 mL) and ethyl acetate (10 mL), stirred overnight, collected by filtration and air-dried to afford the desired product as a light brown solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 7.62 (s, 1H), 7.36 (d, 1H, J = 8.4 Hz), 7.23 (d, 1H, J = 8.4 Hz), 7.20 (s, 1H), 6.54 (s, 1H), 4.75 (s, 2H), 1.68 (s, 1H).

5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-indole-1-carboxylic acid *tert*-butyl ester (5-3)

A stirred solution of (1H-Indol-5-yl)-methanol (5-2, 16.5 g, 112.1 mmol) in dichloromethane (300 mL) was subsequently treated at ambient temperature with diisopropylethylamine (39 mL, 224.2 mmol, 2 equiv), *tert*-butyldimethylsilyl chloride (18.6 g, 123.3 mmol, 1.1 equiv), and 4-(N,N-dimethylamino)pyridine (1.37g, 11.2 mmol, 0.1 equiv). The reaction mixture was stirred at RT for 30 min, concentrated in vacuo, partitioned between ethyl acetate and 0.5N-HCl. The organic layer was washed with brine, separated, dried ($MgSO_4$), concentrated in vacuo to give the crude silylether as a light brown solid. The crude product and di-tert-butyl dicarbonate (26.9, 123.3 mmol) were dissolved in dichrolomethane (300 mL) and stirred at ambient temperature in the presence of 4-(N,N-dimethylamino)pyridine (1.37g, 11.2 mmol) for 2 h. The reaction mixture was concentrated in vacuo, partitioned between ethyl acetate and 0.5N-HCl. The organic layer was washed with brine, separated, dried ($MgSO_4$) and concentrated in vacuo to give the crude oil. Chromatography (SiO_2, 10% ethyl acetate in hexanes) afforded 5-(tert-Butyl-dimethyl-silanyloxymethyl)-indole-1-carboxylic acid tert-butyl ester (5-3) as a white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, 1H, J = 8.0 Hz), 7.47 (d, 1H, J = 3.2 Hz), 7.41 (s, 1H), 7.15 (d, 1H, J = 7.7 Hz), 6.44 (d, 1H, J = 3.6 Hz), 4.72 (s, 2H), 1.56 (s, 9H), 0.84 (s, 9H), 0.00 (s, 6H).

5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-indole-1-*tert*-butyloxycarbonylindole-2-boronic acid (5-4)

To a stirred solution of 5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-indole-1-carboxylic acid *tert*-butyl ester (5-3, 38.6g, 106.7 mmol) in tetrahydrofuran (400 mL) was slowly added at –78°C a solution of lithiun diisopropylamide in tetrahydrofuran (2M, 80.1 mL, 160.1 mmol, 1.5 equiv). The reaction mixture was stirred at the same temperature for 1 h, treated with trimethylborate, warmed up to ambient temperature, and partitioned between ethyl acetate and 0.5N-HCl. The organic layer was washed with brine, separated, dried ($MgSO_4$) and concentrated in vacuo to give the crude solid.

Trituation of the crude product with hexanes followed by filtration and air-drying afforded the desired boronic acid (**5-4**) as a white powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, 1H, J = 6.8 Hz), 7.54 (s, 1H), 7.47 (s, 1H), 7.32 (d, 1H, J = 6.8 Hz), 7.10 (s, 1H), 4.82 (s, 2H), 1.74 (s, 9H), 0.95 (s, 9H), 0.11 (s, 6H).

3-Iodo-1H-quinolin-2-one (**5-5**)

The 2-chloro-3-iodoquinoline (**1-2**, 30.0 g) was weighed into a 250 mL flask and suspended in of 50% aqueous acetic acid (125 mL). The mixture was heated to 100°C and allowed to reflux for 16 h to completion by TLC analysis of the crude reaction mixture. The mixture was allowed to cool to ambient temperature followed by dilution with 200 mL of water. The resulting a suspension of the desired product was isolated by vacuum filtration follows by washing with water (50 mL). The water and traces of acetic acid were removed under vacuum for 5 h to afford the desired quinolinone as a tan powder (**5-5**); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.13 (br s, 1H), 8.71 (s, 1H), 7.65 (d, 1H, J = 7.5 Hz), 7.54 (m, 1H), 7.31 (d, 1H, J = 8.0 Hz), 7.20 (m, 1H).

5-Hydroxymethyl-2-(2-oxo-1,2-dihydro-quinolin-3-yl)-indole-1-carboxylic acid *tert*-butyl ester (**5-7**)

A stirred mixture of the iodoquinolinone (**5-5**, 10 g, 36.9 mmol, 1 equiv), the boronic acid (**5-4**, 7.5g, 18.45 mmol, 0.5 equiv), tetrakis(triphenylphosphine)palladium (1.71 g, 1.48 mmol, 0.04 equiv), and lithium chloride (4.69 g, 110.7 mmol, 3 equiv) in dioxane/2M-aqueous Na_2CO_3 was degassed and heated at 80°C until the boronic acid is not detected by thin layer chromatography. Additional boronic acid (0.2 equiv at a time) was added to the reaction mixture until all the iodoquinolinone (**5-5**) was consumed completely (1.5 equivalent of the boronic acid, **5-4**, in total, was required). The reaction mixture was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, separated, dried (MgSO4) and concentrated in vacuo. The crude oil (**5-6**) was dissolved in tetrahydrofuran (100 mL), transferred to the PEG bottle, treated at 0°C with HF-pyridine (15mL) and stirred for

1 h at ambient temperature. The reaction mixture was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, separated, dried ($MgSO_4$) and concentrated in vacuo. The crude solid was trituated with ethyl acetate and hexanes, collected by filtration and air-dried to afford the desired product (5-7) as a light yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.1 (s, 1H), 8.07 (s, 1H), 8.03 (d, 1H, J = 8.5 Hz), 7.74 (d, 1H, J = 7.5 Hz), 7.55 (s, 1H), 7.52 (t, 1H, J = 7.5 Hz), 7.35 (d, 1H, J = 8.5 Hz), 7.30 (d, 1H, J = 7.5 Hz), 7.22 (t, 1H, J = 7.5 Hz), 6.77 (s, 1H), 5.21 (t, 1H, J = 5.5 Hz), 4.60 (d, 2H, J = 5.5 Hz), 1.35 (s, 9H).

5-Formyl-2-(2-oxo-1,2-dihydro-quinolin-3-yl)-indole-1-carboxylic acid tert-butyl ester (5-8)

The pre-activated MnO_2 (34.5 g, 15 equiv) and the alcohol (5-7, 10.32 g, 1.0 equiv) were weighed into a 1 liter flask and suspended in dry dichloromethane (500 mL). The reaction mixture was heated to 45°C and was complete by thin layer chromatography after 1h. The mixture was allowed to cool to ambient temperature and the manganese oxide(s) were removed by vacuum filtration. The resulting pad of oxides on the filter were triturated with hot THF and the solvent filtered through under vacuum to remove any product from the oxides. The resulting filtrate was concentrated in vacuo to afford the crude aldehyde as a yellow solid. The solid was triturated with methanol (10 mL) and ethyl acetate (15 mL) followed by vacuum filtration to isolate the pure product. The light-yellow aldehyde was dried under vacuum (5-8); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.15 (s, 1H), 10.08 (s, 1H), 8.26 (d, 1H, J = 1.5 Hz), 8.24 (d, 1H, J = 8.5 Hz), 8.15 (s, 1H), 7.90 (dd, 1H, J = 8.5, 1.5 Hz), 7.77 (d, 1H, J = 7.5 Hz), 7.55 (m, 1H), 7.37 (d, 1H, J = 8.5 Hz), 7.24 (m, 1H), 7.01 (s, 1H).

5-(4-Methanesulfonyl-piperazin-1-ylmethyl)-2-(2-oxo-1,2-dihydro-quinolin-3-yl)-indole-1-carboxylic acid tert-butyl ester (5-9)

To a stirred solution of the aldehyde (**5-8**, 2.01 g, 5.15 mmol, 1 equiv) and N-methanesulfonylpiperazine acetic acid salt (4.62 g, 20.60 mmol, 4 equiv) in dichloroethane (400 mL) was added at ambient temperature acetic acid (1.2 mL). The reaction mixture was treated with sodium triacetoxyborohydride and stirred for 3h. The reaction stopped at 76% of conversion and treated with $MgSO_4$ and additional 1 g of the hydride. After further stirring for 1h the reaction was complete. The reaction mixture was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The organic layer was once again washed with saturated aqueous $NaHCO_3$, and then with brine, separated, dried with (Na_2SO_4) and concentrated in vacuo. The crude solid was dissolved in dimethylformamide and treated with the activated carbon. The filtrate solution (celite) was concentrated to syrup which was quickly trituated with methanol (100 mL). The resulting solid was collected by filtration, redissolved in dimethylformamide, concentrated to syrup, trituated with methanol (100 mL), collected by filtration and vacuum-dried to give 5-(4-Methanesulfonyl-piperazin-1-ylmethyl)-2-(2-oxo-1,2-dihydro-quinolin-3-yl)-indole-1-carboxylic acid tert-butyl ester (**5-9**) as a white powder; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.06 (s, 1H), 8.06 (s, 1H), 8.04 (d, 1H, J = 8.5 Hz), 7.74 (d, 1H, J = 8.0 Hz), 7.55 (s, 1H), 7.53 (dt, 1H, J = 8.0, 1.5 Hz), 7.35 (d, 1H, J = 8.5 Hz), 7.30 (dd, 1H, J = 8.5, 1.5 Hz), 7.22 (t, 1H, J = 7.5 Hz), 6.76 (s, 1H), 3.62 (s, 2H), 3.16 (m, 4H), 2.87 (s, 3H), 2.48 (m, 4H), 1.35 (s, 9H).

3-[5-(4-Methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one (**5-10**)

A mixture of 5-(4-Methanesulfonyl-piperazin-1-ylmethyl)-2-(2-oxo-1,2-dihydro-quinolin-3-yl)-indole-1-carboxylic acid tert-butyl ester (**5-9**, 1.02 g, 1.863 mmol), dimethylsulfide (1.2 mL), water (0.6 mL) and TFA (40 mL) in dichloromethane (40 mL) was stirred for 1.5 h. The reaction mixture was concentrated in vacuo, partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, separated, dried (Na_2SO_4), and concentrated in vacuo. The resulting crude solid was purified by reverse-phase liquid chromatography (H_2O/CH_3CN gradient

with 0.1% TFA present) to give trifluoroacetic acid salt of **5-10**. All the fractions containing the desired product was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, separated, dried (Na_2SO_4), and concentrated in vacuo to give 3-[5-(4-Methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one (**5-10**) as a bright yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.07 (s, 1H), 11.54 (s, 1H), 8.53 (s, 1H), 7.73 (d, 1H, J = 7.5 Hz), 7.52 (t, 1H, J = 7.5 Hz), 7.47 - 7.46 (m, 2H), 7.38 (d, 1H, J = 8.5 Hz), 7.29 (br s, 1H), 7.25 (t, 1H, J = 7.5 Hz), 7.08 (d, 1H, J = 9.0 Hz), 3.57 (s, 2H), 3.11 (m, 4H), 2.87 (s, 3H), 2.48 (m, 4H).

3-[5-(4-Methanesulfonyl-1-oxy-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one (**5-11**)

A solution of **5-10** (50g, 0.11 mmol, 1 equiv) in CH_2Cl_2 (125 mL) was treated at ambient temperature with *m*CPBA (70 %, 35 mg, 0.143 mmol). The reaction mixture was stirred for 1 h, concentrated in vacuo. The resulting crude solid was purified by reverse-phase liquid chromatography (H_2O/CH_3CN gradient with 0.1% TFA present) to give trifluoroacetic acid salt of **5-11**; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.57 (s, 1H); 12.22 (s, 1H); 11.86 (s,1H); 8.60 (s, 1H); 7.79 (bs,1H); 7.74 (d, 1H, J = 7.6 Hz); 7.64 (d,1H, J = 8.3 Hz); 7.54 (m,1H); 7.40 (m,2H); 7.28 (m,2H); 4.97 (s,2H); 3.85 (t, 2H, J = 11.7 Hz); 3.73 (d, 2H, J = 13.2 Hz); 3.61 (d, 2H, J = 12.5 Hz); 3.34 (t, 2H, J = 11.9 Hz); 3.04 (s,3H).

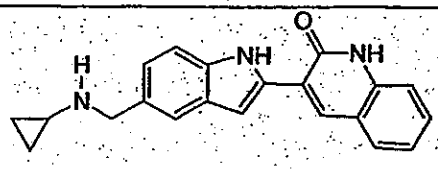
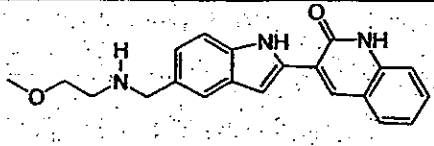
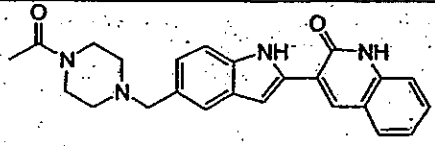
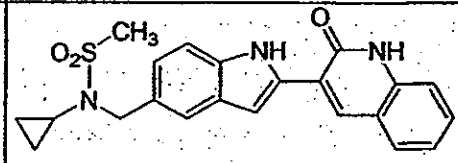
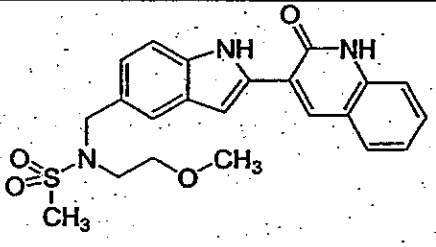
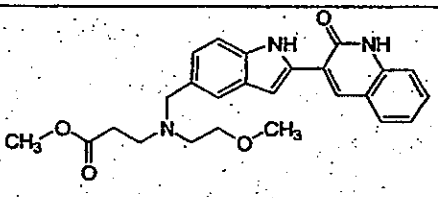
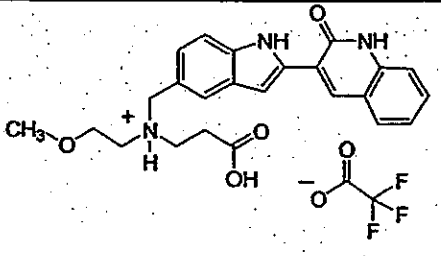
Compounds **5-12** through **5-65** in Table 5 below (except for **5-15, 16, 18, 29, 30** and **31**) were prepared by simple modifications of the protocols described above. Selected spectra are as follow: **5-14**, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (s, 1H), 11.52 (s, 1H), 8.52 (s, 1H), 7.73 (d, 1H, J = 7.5 Hz), 7.52 (dt, 1H, J = 8.5, 1.0 Hz), 7.46 (d, 1H, J = 9.0 Hz), 7.45 (s, 1H), 7.38 (d, 1H, J = 8.0 Hz), 7.29 (s, 1H), 7.25 (t, 1H, J = 7.5 Hz), 7.08 (dd, 1H, J = 8.0, 1.0 Hz), 3.55 (s, 2H), 3.42 (m, 4H), 2.38 (m, 2H), 2.32 (m, 2H), 1.97 (s, 3H); **5-20**, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.16 (s, 1H), 11.53 (s, 1H), 8.52 (s, 1H), 7.73 (d, 1H, J = 7.5 Hz), 7.52 (dt, 1H, J = 8.5, 1.0 Hz), 7.46 (d, 1H,

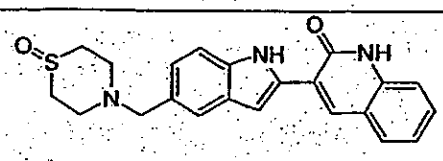
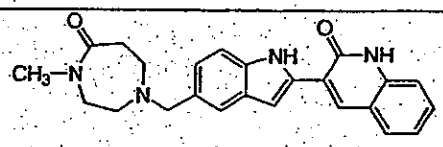
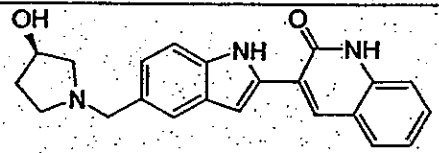
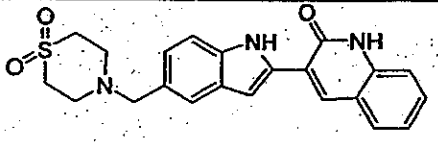
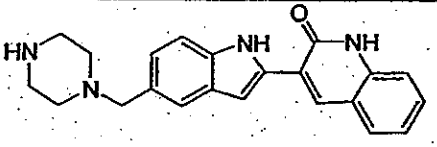
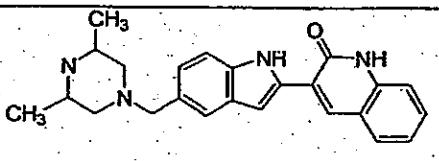
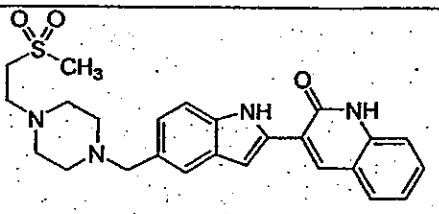
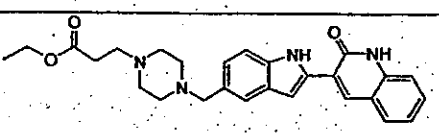
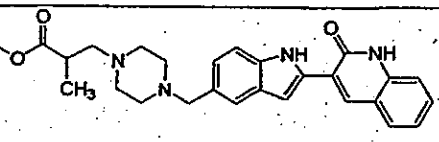
J = 9.0 Hz), 7.45 (s, 1H), 7.38 (d, 1H, J = 8.0 Hz), 7.29 (s, 1H), 7.25 (t, 1H, J = 7.5 Hz), 7.08 (dd, 1H, J = 8.0, 1.0 Hz), 3.61 (s, 2H), 3.42 (m, 2H), 2.83 (s, 3H), 2.54-2.50 (m, 6H); **5-23**, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (br s, 1H), 11.51 (s, 1H), 8.53 (s, 1H), 7.73 (d, 1H, J = 7.5 Hz), 7.52 (dt, 1H, J = 8.5, 1.0 Hz), 7.45 (d, 1H, J = 9.0 Hz), 7.44 (s, 1H), 7.38 (d, 1H, J = 8.0 Hz), 7.29 (s, 1H), 7.25 (t, 1H, J = 7.5 Hz), 7.08 (dd, 1H, J = 8.0, 1.0 Hz), 3.48 (s, 2H), 2.68 (m, 4H), 2.52 (s, 1H), 2.30 (m, 4H); **5-37**, ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.16 (br s, 1H), 11.53 (s, 1H), 8.52 (s, 1H), 7.73 (d, 1H, J = 7.5 Hz), 7.52 (dt, 1H, J = 8.5, 1.0 Hz), 7.47 (d, 1H, J = 9.0 Hz), 7.46 (s, 1H), 7.38 (d, 1H, J = 8.0 Hz), 7.29 (d, 1H, J = 1.0 Hz), 7.25 (t, 1H, J = 7.5 Hz), 7.08 (dd, 1H, J = 8.0, 1.0 Hz), 4.51 (t, 1H, J = 5.5 Hz), 4.06 (d, 1H, J = 5.5 Hz) 3.55 (s, 2H), 3.46 (m, 2H), 3.32 (m, 2H), 2.36 (m, 4H).

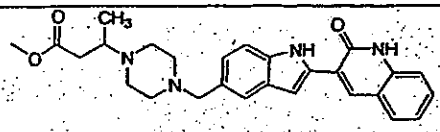
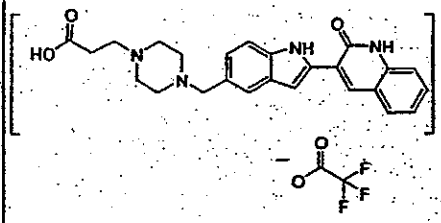
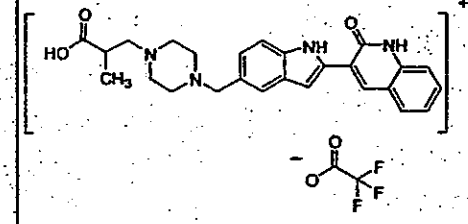
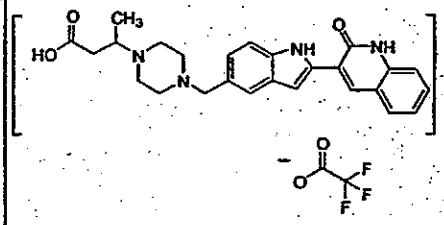
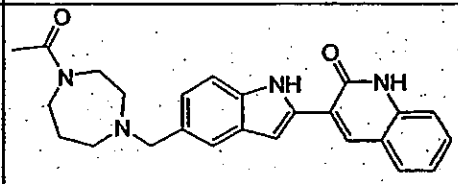
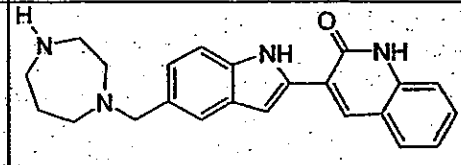
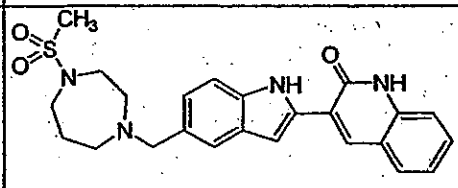
Sulfonamides (**5-15** and **16**) were prepared from the corresponding secondary amines (by treating **5-12** and **13**, respectively, with methanesulfonyl chloride and diisopropylethylamine in dichloromethane at ambient temperature).

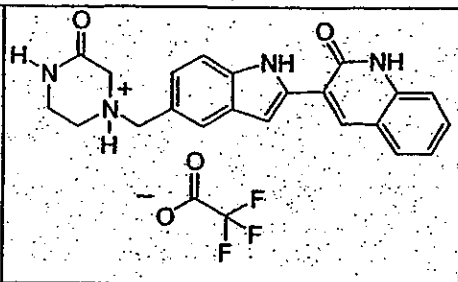
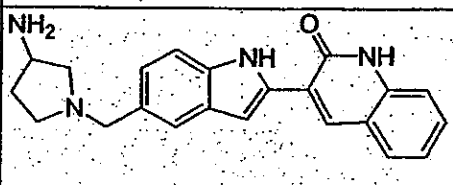
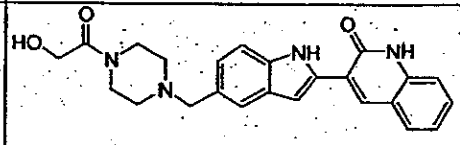
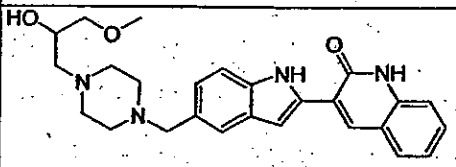
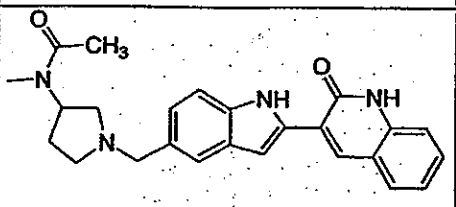
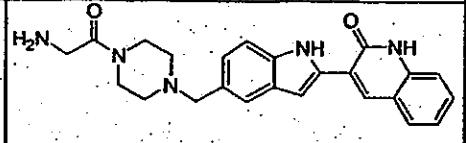
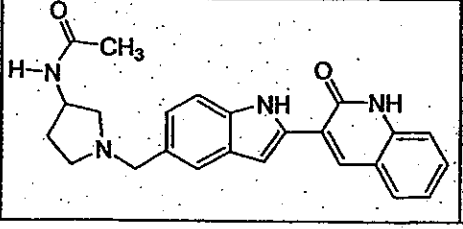
Carboxylic acids (**5-18**, **29**,**30** and **31**) were synthesized from the parent esters (**5-17**, **26**, **27** and **28**, respectively) by the hydrolysis (NaOH/EtOH at 90°C); The starting ester (**5-28**, 57 mg,.124 mmol) was dissolved in EtOH (1 mL) and 1N-NaOH (1 mL). The mixture was heated to 90°C. The reaction was monitored by LC/MS. The starting material had all converted to product after stirring for 7 hours. The reaction mixture was condensed, and residue was dissolved in trifluoroacetic acid. The excess trifluoroacetic acid was removed on the rotovap. The residue was taken up in water and the material was centrifuged. The water was decanted, and the solid was analyzed by HPLC for purity. The product (**5-31**) was isolated as a yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.06 (s, 1H); 11.77 (s,1H); 8.58 (s, 1H); 7.74 (d, 1H,); 7.60-7.52 (m,3H); 4.3 (bs,1H); 2.24 (m, 4H); 2.15 (m, 4H); 1.12 (bs,3H).

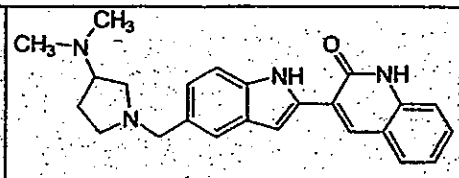
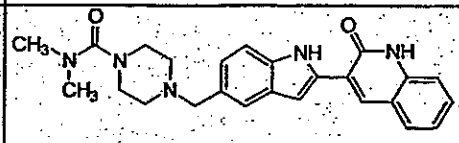
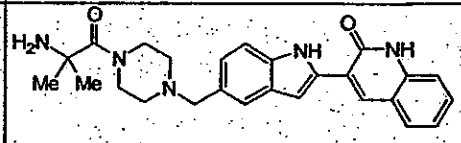
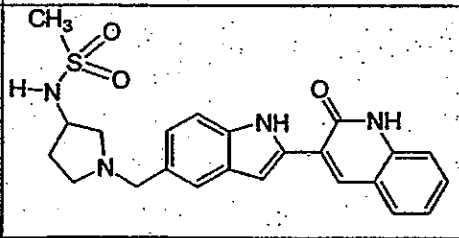
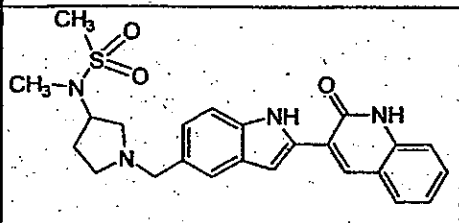
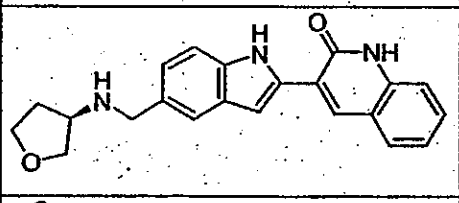
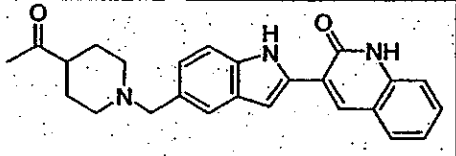
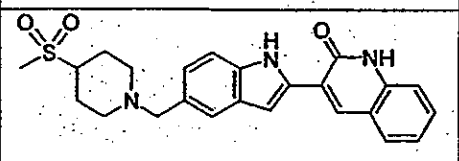
TABLE 5

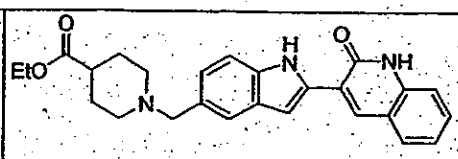
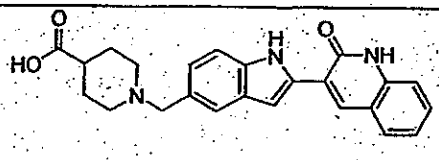
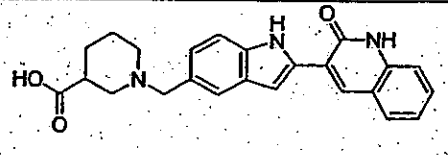
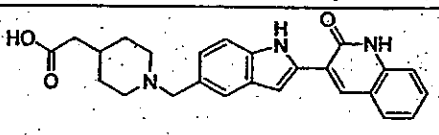
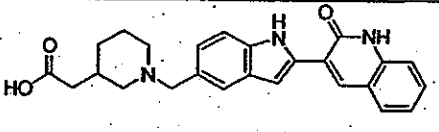
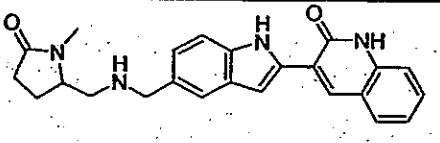
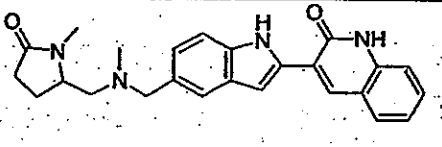
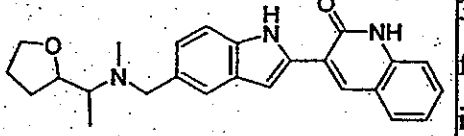
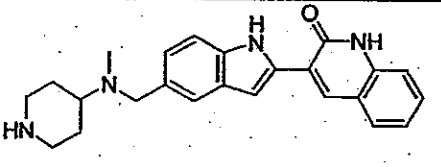
Compound No.	Structure	Compound Name
5-12		3-(5-Cyclopropylaminomethyl-1H-indol-2-yl)-1H-quinolin-2-one
5-13		3-{5-[(2-Methoxy-ethylamino)-methyl]-1H-indol-2-yl}-1H-quinolin-2-one
5-14		3-[5-(4-Acetyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one
5-15		*N*-Cyclopropyl-N-[2-(2-oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-ylmethyl]-methanesulfonamide
5-16		*N*-(2-Methoxy-ethyl)-*N*-[2-(2-oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-ylmethyl]-methanesulfonamide
5-17		3-{(2-Methoxy-ethyl)-[2-(2-oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-ylmethyl]-amino}-propionic acid methyl ester
5-18		(2-Carboxy-ethyl)-(2-methoxy-ethyl)-[2-(2-oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-ylmethyl]-ammonium; trifluoro-acetate

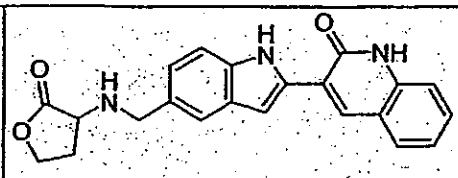
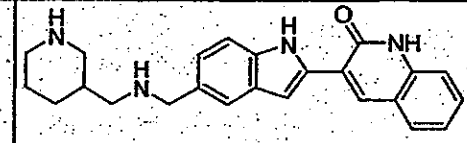
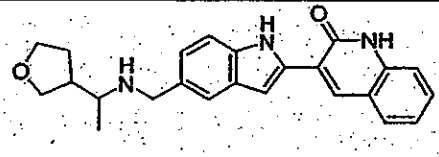
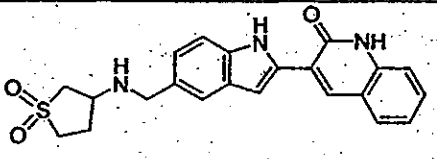
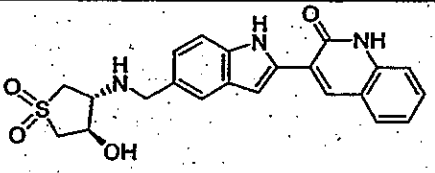
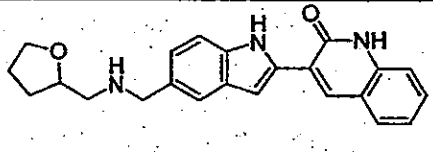
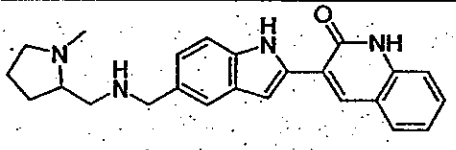
5-19		3-[5-(1-Oxo-1,4-thiomorpholin-4-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one
5-20		3-[5-(4-Methyl-5-oxo-[1,4]diazepan-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one
5-21		3-[5-(3-(*R*)-Hydroxy-pyrrolidin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one
5-22		3-[5-(1,1-Dioxo-1,4-thiomorpholin-4-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one
5-23		3-(5-Piperazin-1-ylmethyl-1H-indol-2-yl)-1H-quinolin-2-one
5-24		3-[5-(3,5-Dimethyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one
5-25		3-{5-[4-(2-Methanesulfonyl-ethyl)-piperazin-1-ylmethyl]-1H-indol-2-yl}-1H-quinolin-2-one
5-26		3-{4-[2-(2-Oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-ylmethyl]-piperazin-1-yl}-propionic acid ethyl ester
5-27		2-Methyl-3-{4-[2-(2-oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-ylmethyl]-piperazin-1-yl}-propionic acid methyl ester

5-28		3-{4-[2-(2-Oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-ylmethyl]-piperazin-1-yl}-butyric acid methyl ester
5-29		4-(2-Carboxy-ethyl)-1-[2-(2-oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-ylmethyl]-piperazin-1-ium; 2,2,2-trifluoro-acetate
5-30		4-(2-Carboxy-propyl)-1-[2-(2-oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-ylmethyl]-piperazin-1-ium; 2,2,2-trifluoro-acetate
5-31		4-(2-Carboxy-1-methyl-ethyl)-1-[2-(2-oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-ylmethyl]-piperazin-1-ium; 2,2,2-trifluoro-acetate
5-32		3-[5-(4-Acetyl-[1,4]diazepan-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one
5-33		3-(5-[1,4]Diazepan-1-ylmethyl-1H-indol-2-yl)-1H-quinolin-2-one
5-34		3-[5-(4-Methanesulfonyl-[1,4]diazepan-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one

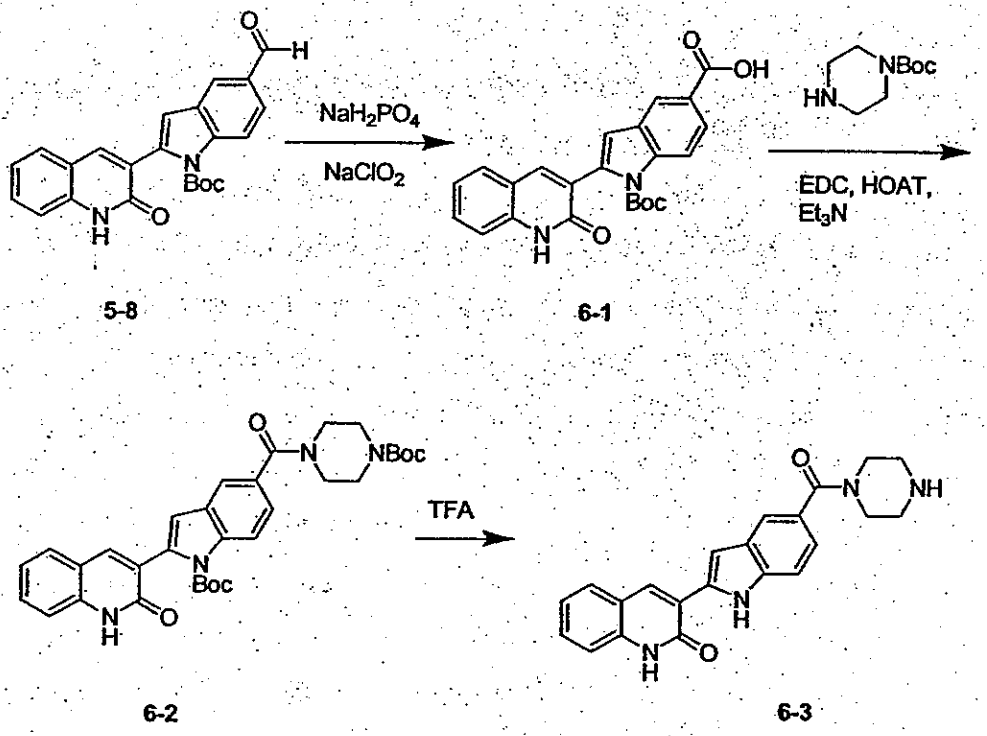
5-35		3-Oxo-1-[2-(2-oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-ylmethyl]-piperazin-1-ium; 2,2,2-trifluoro-acetate
5-36		3-[5-(3-amino-pyrrolidin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one
5-37		3-{5-[4-(2-Hydroxy-ethanoyl)-piperazin-1-ylmethyl]-1H-indol-2-yl}-1H-quinolin-2-one
5-38		3-{5-[4-(2-Hydroxy-3-methoxy-propyl)-piperazin-1-ylmethyl]-1H-indol-2-yl}-1H-quinolin-2-one
5-39		*N*-Methyl-*N*-{1-[2-(2-oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-ylmethyl]-pyrrolidin-3-yl}-acetamide
5-40		3-(5-{[4-(aminoacetyl)-1-piperazinyl]methyl}-1H-indol-2-yl)-2(1H)-quinolinone
5-41		*N*-{1-[2-(2-Oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-ylmethyl]-pyrrolidin-3-yl}-acetamide

5-42		3-[5-(3-Dimethylamino-pyrrolidin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one
5-43		4-[2-(2-Oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-ylmethyl]-piperazine-1-carboxylic acid dimethylamide
5-44		3-{5-[4-(2-Amino-2-methyl-propanoyl)-piperazin-1-ylmethyl]-1H-indol-2-yl}-1H-quinolin-2-one
5-45		*N*-{1-[2-(2-Oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-ylmethyl]-pyrrolidin-3-yl}-methanesulfonamide
5-46		*N*-Methyl-*N*-{1-[2-(2-oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-ylmethyl]-pyrrolidin-3-yl}-methanesulfonamide
5-47		3-(5-{[(3R)-tetrahydro-3-furanylamino]methyl}-1H-indol-2-yl)-2(1H)-quinolinone
5-48		3-(5-{[4-acetyl-1-piperidinyl]methyl}-1H-indol-2-yl)-2(1H)-quinolinone
5-49		3-(5-{[4-(methylsulfonyl)-1-piperidinyl]methyl}-1H-indol-2-yl)-2(1H)-quinolinone

5-50		ethyl-1-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]methyl}-4-piperdinecarboxylate
5-51		1-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]methyl}-4-piperdinecarboxylic acid
5-52		1-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]methyl}-3-piperdinecarboxylic acid
5-53		(1-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]methyl}-4-piperdinyl)acetic acid
5-54		(1-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]methyl}-3-piperdinyl)acetic acid
5-55		3-[5-({[(1-methyl-5-oxo-2-pyrrolidinyl)methyl]amino}methyl)-1H-indol-2-yl]-2(1H)-quinolinone
5-56		3-[5-({methyl[(1-methyl-5-oxo-2-pyrrolidinyl)methyl]amino}methyl)-1H-indol-2-yl]-2(1H)-quinolinone
5-57		3-(5-{[methyl(1-tetrahydro-2-furanylethyl)amino]methyl}-1H-indol-2-yl)-2(1H)-quinolinone
5-58		3-(5-{[methyl(4-piperidinyl)amino]methyl}-1H-indol-2-yl)-2(1H)-quinolinone

5-59		3-(5-{[2-oxotetrahydro-3-furanyl)amino] methyl}-1H-indol-2-yl)-2(1H)-quinolinone
5-60		3-(5-{[(3-piperidinylmethyl)amino] methyl}-1H-indol-2-yl)-2(1H)-quinolinone
5-61		3-(5-{[(1-tetrahydro-3-furanylethyl)amino] methyl}-1H-indol-2-yl)-2(1H)-quinolinone
5-62		3-(5-{[(1,1-dioxidotetrahydro-3-thienyl)amino] methyl}-1H-indol-2-yl)-2(1H)-quinolinone
5-63		3-(5-{[({3R,4R}-4-hydroxy-1,1-dioxidotetrahydro-3-thienyl)amino] methyl}-1H-indol-2-yl)-2(1H)-quinolinone
5-64		3-(5-{[(tetrahydro-2-furanylmethyl)amino] methyl}-1H-indol-2-yl)-2(1H)-quinolinone
5-65		3-(5-{[({1-methyl-2-pyrrolidinyl}methyl)amino] methyl}-1H-indol-2-yl)-2(1H)-quinolinone

SCHEME 6



2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indole-5-carboxylic acid (6-1)

A solution of 2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indole-5-carbaldehyde (5-8, 500 mg, 1.29 mmol, 1 equiv) in a 4:1 mixture of THF and t-BuOH was treated with 2-methyl butene (8 mL), an aqueous solution of sodium phosphate monobasic (0.14 M 355.2 mg, 2.57 mmol, 2.00 equiv), and sodium chlorite (232.8 mg, 2.57 mmol, 2.00 equiv). Additional solid sodium phosphate monobasic (380 mg, 2.76 mmol, 2.14 equiv) and sodium chlorite (300 mg, 3.32 mmol, 2.57 equiv) was added in 2 equal portions over 2.5 h. The reaction mixture was concentrated, and the residue dissolved in EtOAc (60 mL), then washed twice with a 25:1 mixture of aqueous 10% sodium bisulfite solution and 10% potassium hydrogen sulfate solution (2 x 50 mL). The organic layer was dried over sodium sulfate, concentrated, and combined with a precipitate in the aqueous layer which was filtered and dried to 2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indole-5-carboxylic acid (6-1) as an off-white solid. ^{1}H NMR (500 MHz, DMSO) δ 12.13 (s, 1H), 8.27 (s, 1H), 8.14 (m, 3H), 7.95 (d, 1H, J = 7.8 Hz),

7.76 (d, 1H, J = 7.8 Hz), 7.54 (t, 1H, J = 7.8), 7.36 (d, 1H, J = 7.8), 7.24 (t, 1H, J = 7.8) 1.36 (s, 9H).

tert-Butyl 5-{[4-(tert-butoxycarbonyl)-1-piperazinyl]carbonyl}-2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indole-1-carboxylate (6-2)

A solution of 2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indole-5-carboxylic acid (6-1, 130 mg, 0.321 mmol, 1 equiv), *tert*-butyl 1-piperazine carboxylate (71.8 mg, 0.39 mmol, 1.20 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (73.5 mg, 0.39 mmol, 1.20 equiv), 1-hydroxy-7-azabenzotriazole (52.5 mg, 0.39 mmol, 1.20 equiv), and triethylamine (112 µL, 0.80 mmol, 2.50 equiv) in DMF (5 mL) was stirred for 20 h. The solution was partitioned between EtOAc (3 x 100 mL) and water (120 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate, then concentrated to afford the tert-butyl 5-{[4-(tert-butoxycarbonyl)-1-piperazinyl]carbonyl}-2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indole-1-carboxylate (6-2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, 1H, J = 8.6 Hz), 7.95 (s, 1H), 7.69 (s, 1H), 7.62 (d, 1H, J = 7.6 Hz), 7.51 (t, 1H, J = 7.1 Hz), 7.41 (d, 1H, J = 6.6 Hz), 7.40 (d, 1H, J = 8.3 Hz), 7.25 (t, 1H, J = 7.2 Hz), 6.73 (s, 1H), 3.55-3.35 (br m, 8H), 1.48 (s, 9H), 1.39 (s, 9H).

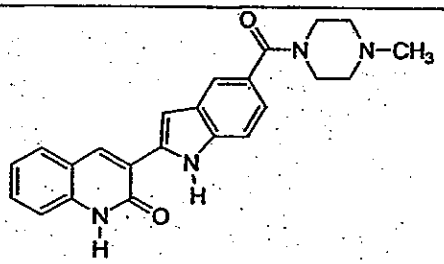
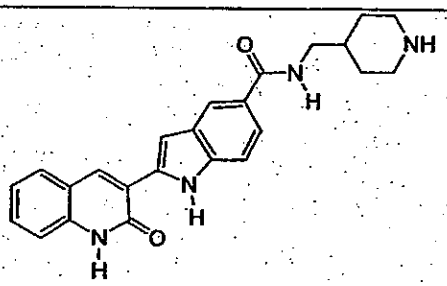
3-[5-(1-piperazinylcarbonyl)-1H-indol-2-yl]-2(1H)-quinolinone (6-3)

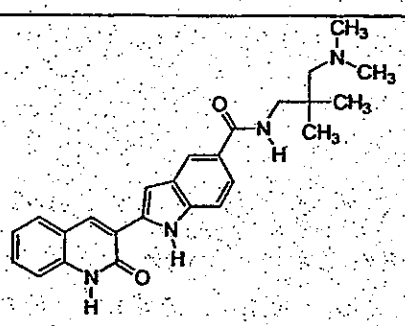
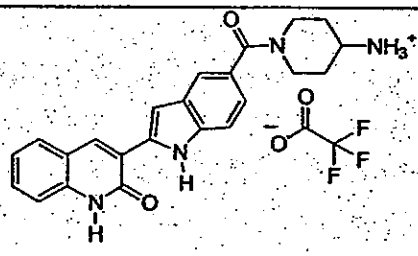
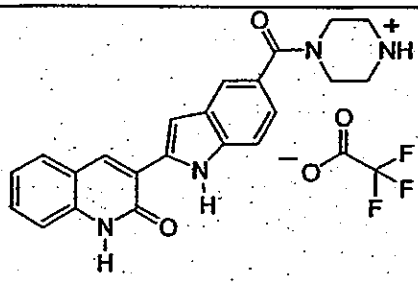
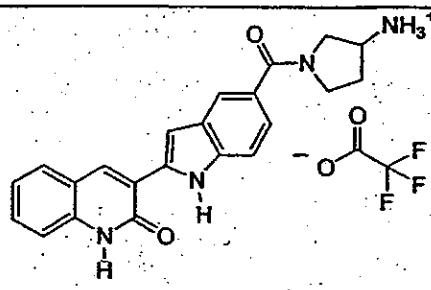
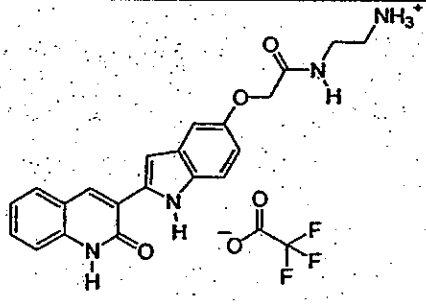
A solution of tert-butyl 5-{[4-(tert-butoxycarbonyl)-1-piperazinyl]carbonyl}-2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indole-1-carboxylate (6-2, 213 mg, 0.373 mmol, 1 equiv) in a 1:1 mixture of CH_2Cl_2 and trifluoroacetic acid (40 mL) was treated with 3 drops of DMSO and H_2O, and the resulting mixture was heated at reflux for 45 minutes. The solution was concentrated, and the residue was dried by azeotropic removal of water using a 90:10 mixture of toluene and methanol (100 mL). It was then purified by reverse phase chromatography (H_2O/CH_3CN gradient with 0.1% TFA present) to provide 3-[5-(1-piperazinylcarbonyl)-1H-indol-2-yl]-2(1H)-quinolinone (6-3) as a TFA salt (brown solid). ^{1}H NMR (500 MHz, DMSO) δ 12.21 (s, 1H), 11.83 (s, 1H), 8.59 (s, 1H), 7.75 (d, 1H, J = 7.9 Hz), 7.74 (s, 1H), 7.59 (d, 1H, J = 8.3

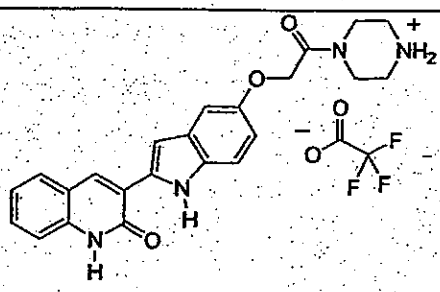
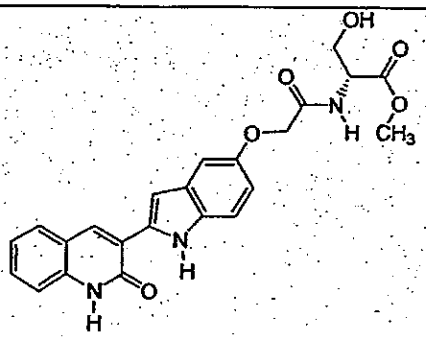
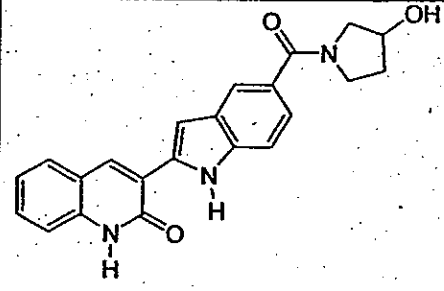
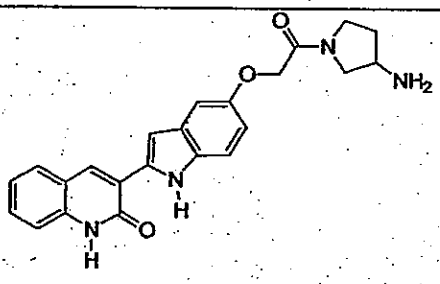
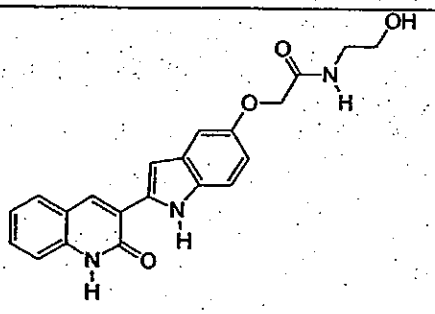
Hz), 7.54 (t, 1H, J = 7.6 Hz), 7.42 (s, 1H), 7.39 (d, 1H, J = 8.3 Hz), 7.25 (m, 2H), 3.86 – 3.15 (br m, 8H).

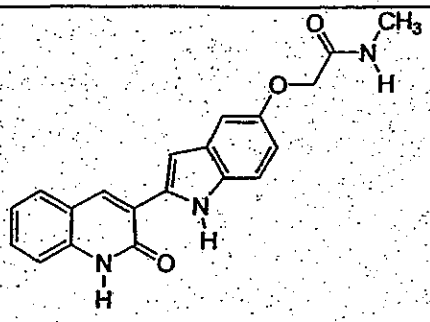
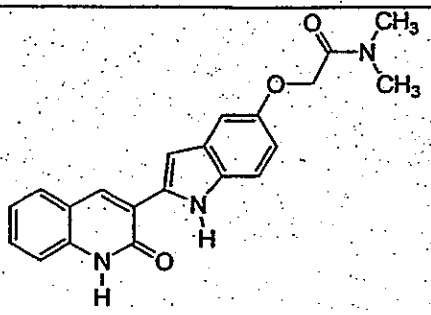
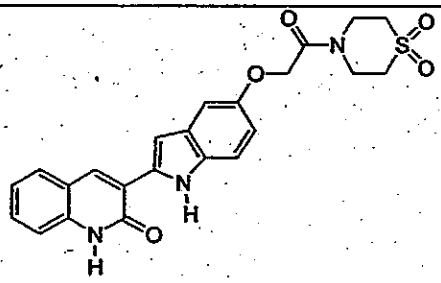
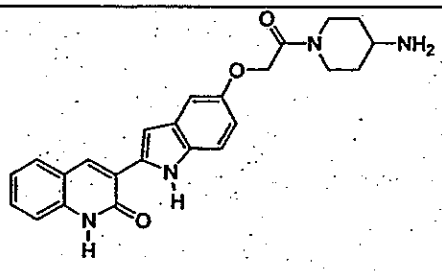
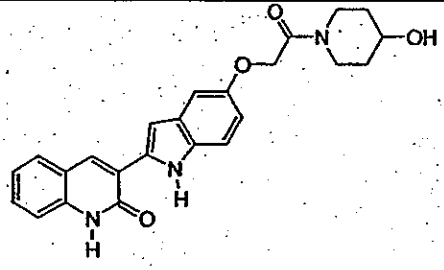
Compounds **6-4** through **6-22** in Table 6 below were prepared by simple modification of the protocols described above. Selected spectra are as follow: **6-4**, ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.21 (s, 1H), 11.77 (s, 1H), 8.58 (s, 1H), 7.75 (d, 1H, J = 8.0 Hz), 7.63 (s, 1H), 7.55 (m, 2H), 7.39 (s, 1H), 7.38 (d, 1H, J = 8.8 Hz), 7.60 (t, 1H, J = 7.6 Hz), 7.15 (d, 1H, J = 8.3 Hz), 3.53 (br m, 4H), 2.33 (br m, 4H), 2.21 (s, 3H). **6-5**, ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.79 (s, 1H), 8.58 (s, 1H), 8.36 (br t, 1H, J = 6 Hz), 8.13 (s, 1H), 7.75 (d, 1H, J = 8.1 Hz), 7.65 (d, 1H, J = 8.8 Hz), 7.55 (d, 1H, 8.8 Hz), 7.53 (t, 1H, J = 8.3 Hz), 7.40 (s, 1H), 7.38 (d, 1H, J = 8.3 Hz), 3.17 (br t, 2H, J = 5.7 Hz), 3.07 (br d, 2H, J = 12.9 Hz), 2.59 (m, 2H), 1.71 (br m, 3H), 1.17 (m, 2H).

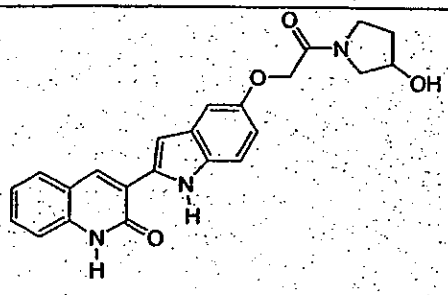
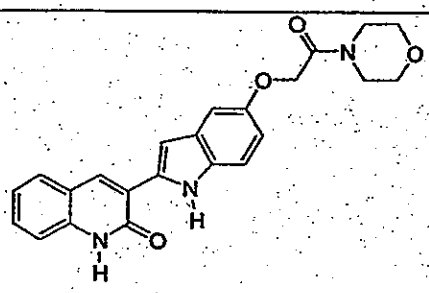
TABLE 6

Compound No.	Structure	Compound Name
6-4		3-{5-[(4-methyl-1-piperazinyl)carbonyl]-1H-indol-2-yl}-2(1H)-quinolinone
6-5		2-(2-oxo-1,2-dihydro-3-quinolinyl)-N-(4-piperidinylmethyl)-1H-indole-5-carboxamide

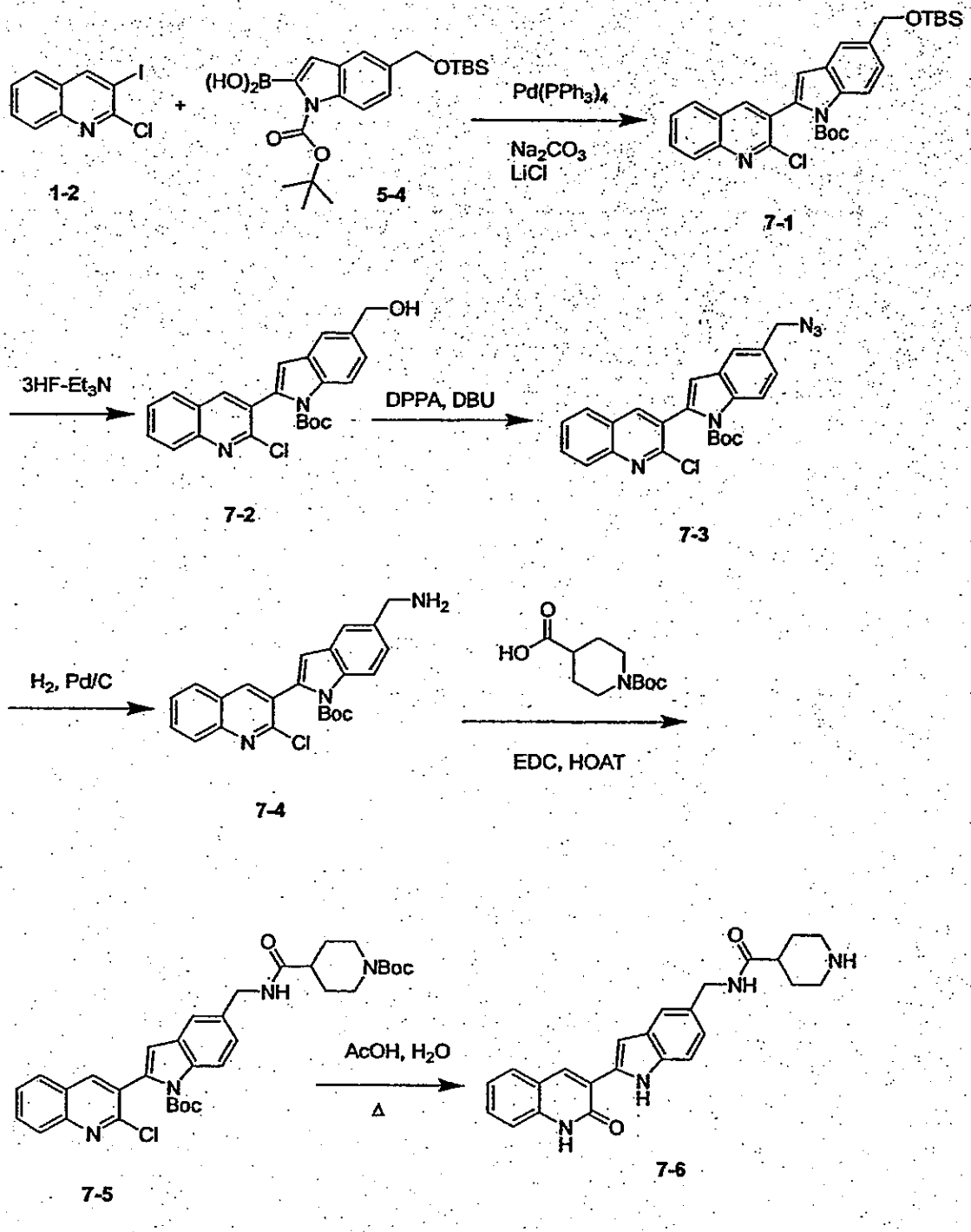
6-6		N-[3-(dimethylamino)-2,2-dimethylpropyl]-2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indole-5-carboxamide
6-7		1-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]carbonyl}-4-piperidinaminium trifluoroacetate
6-8		1-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]carbonyl}piperazin-4-ium trifluoroacetate
6-9		1-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]carbonyl}-3-pyrrolidinaminium trifluoroacetate
6-10		2-[({[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}acetyl)amino]ethanaminium trifluoroacetate

6-11		1-({[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}acetyl)piperazin-4-ium trifluoroacetate
6-12		methyl (2R)-3-hydroxy-2-[({[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}acetyl)amino]propanoate
6-13		3-{5-[(3-hydroxy-1-pyrrolidinyl)carbonyl]-1H-indol-2-yl}-2(1H)-quinolinone
6-14		3-{5-[2-(3-amino-1-pyrrolidinyl)-2-oxoethoxy]-1H-indol-2-yl}-2(1H)-quinolinone
6-15		N-(2-hydroxyethyl)-2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}acetamide

6-16		N-methyl-2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}acetamide
6-17		N,N-dimethyl-2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}acetamide
6-18		3-{5-[2-(1,1-dioxido-4-thiomorpholinyl)-2-oxoethoxy]-1H-indol-2-yl}-2(1H)-quinolinone
6-19		3-{5-[2-(4-amino-1-piperidinyl)-2-oxoethoxy]-1H-indol-2-yl}-2(1H)-quinolinone
6-20		3-{5-[2-(4-hydroxy-1-piperidinyl)-2-oxoethoxy]-1H-indol-2-yl}-2(1H)-quinolinone

6-21		3-{5-[2-(3-hydroxy-1-pyrrolidinyl)-2-oxoethoxy]-1H-indol-2-yl}-2(1H)-quinolinone
6-22		3-{5-[2-(4-morpholinyl)-2-oxoethoxy]-1H-indol-2-yl}-2(1H)-quinolinone

SCHEME 7


1-2
5-4
Pd(PPh3)4
Na2CO3
LiCl
7-1
3HF-Et3N
DPPA, DBU
7-2
7-3
H2, Pd/C
EDC, HOAT
7-4
AcOH, H2O
Δ
7-5
7-6

tert-butyl 5-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (7-1)

1-(tert-butoxycarbonyl)-5-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1H-indol-2-ylboronic acid (5-4, 5.60 g, 13.8 mmol, 2.00 equiv) was added in 4 equal portions over 8 hours to a deoxygenated solution of 2-chloro-3-iodoquinoline (1-2, 2.00 g, 6.91 mmol, 1 equiv), lithium chloride (0.878 g, 20.7 mmol, 3.00 equiv), tetrakis(triphenylphosphine)palladium (0.400 g, 0.346 mmol, 0.0500 equiv), and aqueous sodium carbonate solution (2M, 10.4 mL, 20.7 mmol, 3.00 equiv) in dioxane (50 mL) at 80°C, and the resulting mixture was heated an additional 12 h. The reaction mixture was cooled then partitioned between brine and ethyl acetate (2 x 200 mL). The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (100% hexane initially, grading to 50% EtOAc in hexane) to provide tert-butyl 5-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (7-1) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, 1H, J = 8.0 Hz), 8.18 (s, 1H), 8.07 (d, 1H, J = 8.2 Hz), 7.87 (d, 1H, J = 8.0 Hz), 7.77 (br t, 1H, J = 8.0 Hz), 7.61 (br t, 1H, J = 8.0 Hz), 7.58 (s, 1H), 7.45 (d, 1H, J = 8.0 Hz), 6.65 (s, 1H), 4.87 (s, 2H), 1.27 (s, 9H), 0.97 (s, 9H), 0.13 (s, 6H).

tert-butyl 2-(2-chloro-3-quinolinyl)-5-(hydroxymethyl)-1H-indole-1-carboxylate (7-2)

A solution of tert-butyl 5-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (7-1, 2.50 g, 4.78 mmol, 1 equiv) and triethylamine trihydrofluoride (3.89 mL, 23.9 mmol, 5.00 equiv) in acetonitrile (100 mL) was heated at 50°C for 3 h. The reaction mixture was carefully partitioned between saturated sodium bicarbonate solution and ethyl acetate (2 x 100 mL). The combined organic layers were dried over sodium sulfate and concentrated to give tert-butyl 2-(2-chloro-3-quinolinyl)-5-(hydroxymethyl)-1H-indole-1-carboxylate (7-2) as a tan foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, 1H, J = 8.5 Hz), 8.19 (s, 1H), 8.08 (d, 1H, J = 8.5 Hz), 7.87 (d, 1H, J = 8.1 Hz), 7.78 (br t, 1H, J = 8.0 Hz), 7.63 (s, 1H),

7.62 (br t, 1H, J = 8.0 Hz), 7.41 (d, 1H, J = 8.5 Hz), 6.66 (s, 1H), 4.82 (d, 2H, J = 4.9 Hz), 1.81 (br s, 1H), 1.27 (s, 9H).

tert-butyl 5-(azidomethyl)-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (7-3)

1,8-diazabicyclo[5.4.0]undec-7-ene (0.400 mL, 2.69 mmol, 1.10 equiv) was added dropowise over 2 min to a solution of tert-butyl 2-(2-chloro-3-quinolinyl)-5-(hydroxymethyl)-1H-indole-1-carboxylate (7-2, 1.00 g, 2.45 mmol, 1 equiv) and diphenylphosphoryl azide (0.580 mL, 2.69 mmol, 1.10 equiv) in THF (20 mL) at 0°C. The resulting mixture was warmed to 23°C and stirred for 20 h. The reaction mixture was partitioned between saturated sodium bicarbonate solution and ethyl acetate (2 x 75 mL). The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (100% hexane, grading to 50% EtOAc in hexane) to afford tert-butyl 5-(azidomethyl)-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (7-3) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, 1H, J = 8.5 Hz), 8.19 (s, 1H), 8.08 (d, 1H, J = 8.3 Hz), 7.88 (d, 1H, J = 7.8 Hz), 7.79 (br t, 1H, J = 8.1 Hz), 7.62 (br t, 1H, J = 8.0 Hz), 7.58 (s, 1H), 7.36 (dd, 1H, J = 8.6, 1.5 Hz), 6.68 (s, 1H), 4.46 (s, 2H), 1.27 (s, 9H).

tert-butyl 5-(aminomethyl)-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (7-4)

A mixture of tert-butyl 5-(azidomethyl)-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (7-3, 730 mg, 1.68 mmol) in EtOAc (50 mL) and 10 % Pd/C (146 mg) was stirred under a hydrogen balloon at 23°C for 2 h. The catalyst was filtered and washed with EtOAc (50 mL). The combined filtrate was concentrated to provide tert-butyl 5-(aminomethyl)-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (7-4) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, 1H, J = 8 Hz), 8.18 (s, 1H), 8.07 (d, 1H, J = 8 Hz), 7.86 (d, 1H, J = 8 Hz), 7.78 (t, 1H, J = 8 Hz), 7.61 (t, 1H, J = 8 Hz), 7.56 (s, 1H), 7.35 (dd, 1H, J = 8, 2 Hz), 6.64 (s, 1H), 4.00 (s, 2H), 1.27 (s, 9H).

tert-butyl 5-[({[1-(tert-butoxycarbonyl)-4-piperidinyl]carbonyl}amino)methyl]-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (7-5)

A solution of tert-butyl 5-(aminomethyl)-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (7-4, 204 mg, 0.5 mmol, 1 equiv), HOAT (68 mg, 0.5 mmol, 1 equiv), triethylamine (101 mg, 1.0 mmol, 2 equiv), EDC (144 mg, .75 mmol, 1.5 equiv) and 1-BOC-piperidine-4-carboxylic acid (126 mg, .55 mmol, 1.1 equiv) in DMF (5 mL) was stirred under ambient conditions for 18 hr. The reaction was concentrated, and the residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ solution. The organic layer was washed with brine, dried over magnesium sulfate and concentrated to provide tert-butyl 5-[({[1-(tert-butoxycarbonyl)-4-piperidinyl]carbonyl}amino)methyl]-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (7-5) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, 1H, J = 8Hz), 8.16 (s, 1H), 8.05 (d, 1H, J = 8 Hz), 7.85 (d, 1H, J = 8 Hz), 7.76 (t, 1H, J = 8 Hz), 7.59 (t, 1H, J = 8 Hz), 7.49 (s, 1H), 7.28 (dd, 1H, J = 8, 2 Hz), 6.61 (s, 1H), 4.48 (d, 2H, J = 5 Hz), 4.12 (m, 2H), 2.72 (m, 2H), 2.26 (m, 1H), 1.84 (m, 2H), 1.65 (m, 2H), 1.42 (s, 9H), 1.25 (s, 9H).

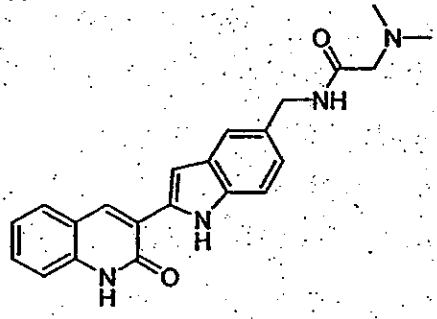
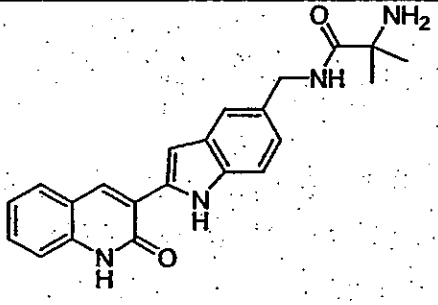
N-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]methyl}-4-piperidine carboxamide (7-6)

A solution of tert-butyl 5-[({[1-(tert-butoxycarbonyl)-4-piperidinyl]carbonyl} amino)methyl]-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (7-5, 310 mg, 0.5 mmol) in 50 % aqueous acetic acid (20 mL) was heated at 100°C for 18 hr. The reaction was concentrated, and the residue dissolved in a 1:1 mixture of methanol and aqueous 1 N NaOH solution. This solution stirred under ambient conditions for 2 h. The reaction mixture was concentrated, and the residue was purified reverse-phase liquid chromatography (H_2O/CH_3CN gradient w/ 0.1% TFA present) to provide the trifluoroacetic acid salt of N-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]methyl}-4-piperidinecarboxamide (7-6) as yellow solid. ^{1}H NMR (400 MHz, DMSO- d_6) δ 12.20 (s, 1H), 11.58 (s, 1H), 8.53 (b s, 2H), 8.41 (t, 1H, J = 5 Hz), 7.72 (d, 1H, J = 8 Hz), 7.52 (t, 1H, J = 8 Hz), 7.46 (d, 1H, J = 8 Hz), 7.42 (s, 1H), 7.38 (d,

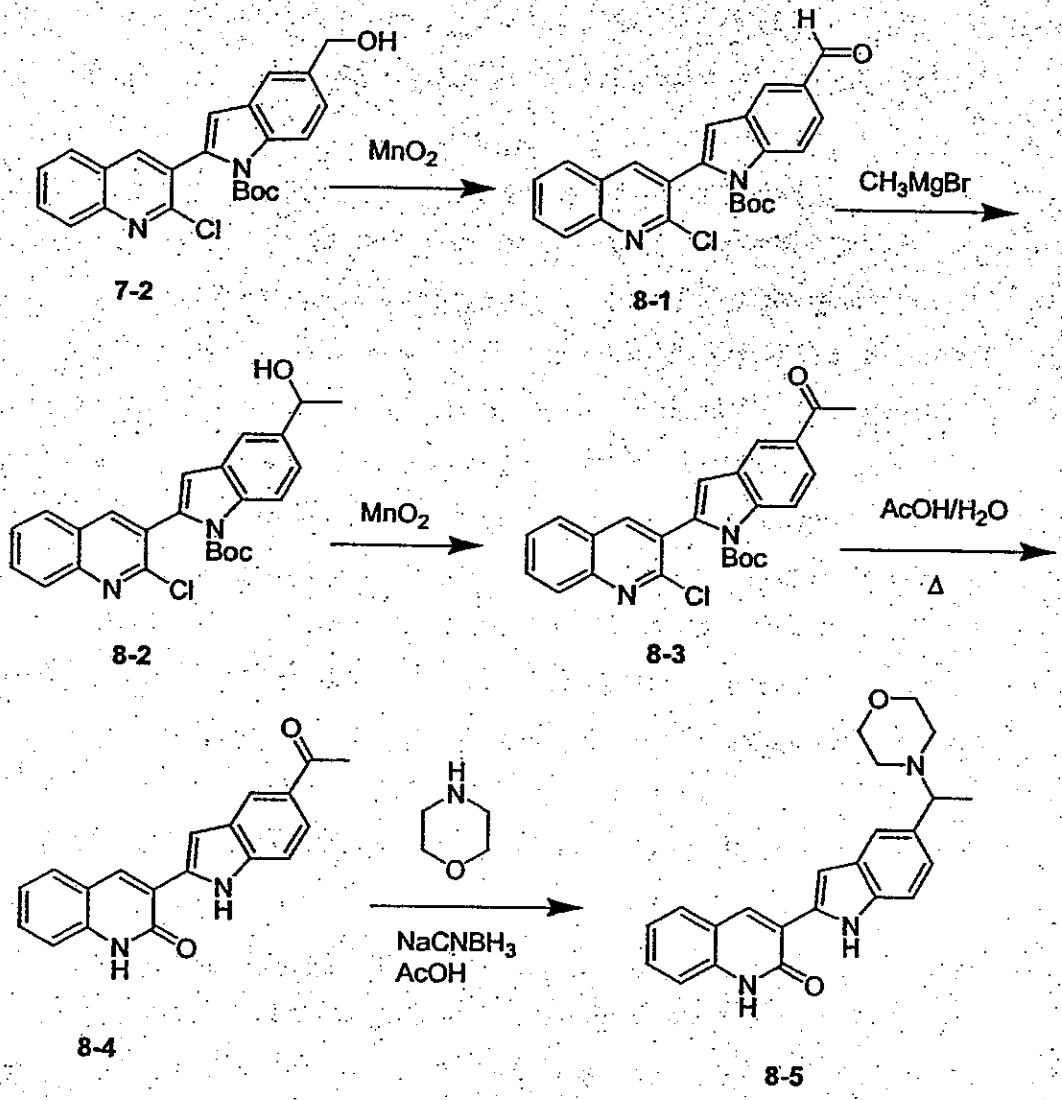
1H, J = 8 Hz), 7.29 (s, 1H), 7.25 (t, 1H, J = 8 Hz), 7.01 (dd, 1H, J = 8, 2 Hz), 4.33 (d, 2H, J = 5 Hz), 3.32 (m, 2H), 2.90 (m, 2H), 2.48 (m, 1H), 1.89 (m, 2H), 1.78 (m, 2H).

Compounds 7-7 and 7-8 in Table 7 below were prepared by simple modification of the protocols described above.

TABLE 7

Compound No.	Structure	Compound Name
7-7		2-(dimethylamino)-N-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]methyl}acetamide
7-8		2-amino-2-methyl-N-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]methyl}propanamide

SCHEME 8



tert-butyl 2-(2-chloro-3-quinolinyl)-5-formyl-1H-indole-1-carboxylate (8-1)

A mixture of tert-butyl 2-(2-chloro-3-quinolinyl)-5-(hydroxymethyl)-1H-indole-1-carboxylate (7-2, 800 mg, 1.96 mmol, 1 equiv) and MnO_2 (850 mg, 9.8 mmol, 5.00 equiv) in dichloromethane (100 mL) was heated at reflux for 1.5 h. Additional MnO_2 (700 mg, 8.05 mmol, 4.10 equiv) was added and heating was continued for 1 h. The catalyst was filtered and washed with dichloromethane (100 mL). The combined filtrate was concentrated to give tert-butyl 2-(2-chloro-3-quinolinyl)-5-formyl-1H-

indole-1-carboxylate (**8-1**) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.47 (d, 1H, J = 8.8 Hz), 8.22 (s, 1H), 8.16 (d, 1H, J = 1.0 Hz), 8.09 (d, 1H, J = 8.6 Hz), 7.95 (dd, 1H, J = 8.8, 1.7 Hz), 7.89 (d, 1H, J = 8.1 Hz), 7.81 (br t, 1H, J = 7.6 Hz), 7.64 (br t, 1H, J = 7.5 Hz), 6.80 (s, 1H), 1.27 (s, 9H).

tert-butyl 2-(2-chloro-3-quinolinyl)-5-(1-hydroxyethyl)-1H-indole-1-carboxylate (**8-2**)

A solution of methylmagnesium bromide in THF (3 M, 0.85 mL, 2.56 mmol, 1.3 equiv) was added to a solution of 2-(2-chloro-3-quinolinyl)-5-formyl-1H-indole-1-carboxylate (**8-1**, 800 mg, 2.0 mmol, 1 equiv) in THF (25 mL) at 0°C, and the resulting mixture was stirred for 30 minutes. The reaction mixture was partitioned between pH 7 phosphate buffer solution and ethyl acetate (2 x 100 mL). The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (100% hexane, grading to 70% EtOAc in hexane) to provide tert-butyl 2-(2-chloro-3-quinolinyl)-5-(1-hydroxyethyl)-1H-indole-1-carboxylate (**8-2**) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, 1H, J = 8.8 Hz), 8.18 (s, 1H), 8.08 (d, 1H, J = 8.5 Hz), 7.87 (d, 1H, J = 7.8 Hz), 7.78 (br t, 1H, J = 7.1 Hz), 7.64 (s, 1H), 7.61 (br t, 1H, J = 7.1 Hz), 7.42 (dd, 1H, J = 8.6, 1.5 Hz), 6.66 (s, 1H), 5.05 (m, 1H), 1.58 (d, 3H, J = 6.6 Hz), 1.27 (s, 9H).

tert-butyl 5-acetyl-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (**8-3**)

A mixture of 2-(2-chloro-3-quinolinyl)-5-(1-hydroxyethyl)-1H-indole-1-carboxylate (**8-2**, 840 mg, 1.99 mmol, 1 equiv) and MnO_2 (863 mg, 9.93 mmol, 5.00 equiv) in dichloromethane (30 mL) was heated at reflux for 1 h. Additional MnO_2 (500 mg, 5.75 mmol, 2.89 equiv) was added and heating was continued for 1 h. The catalyst was filtered and washed with dichloromethane (100 mL). The combined filtrate was concentrated to give tert-butyl 5-acetyl-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (**8-3**) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, 1H, J = 8.8 Hz), 8.27 (d, 1H, J = 0.7 Hz), 8.21 (s, 1H), 8.09 (d, 1H, J = 8.3 Hz), 8.04 (dd, 1H, J = 8.8, 1.2 Hz), 7.89 (d, 1H, J = 8.1 Hz), 7.80 (br t, 1H, J = 7.6 Hz), 7.63 (br t, 1H, J = 7.5 Hz), 6.76 (s, 1H), 2.70 (s, 3H), 1.27 (s, 9H).

3-(5-acetyl-1H-indol-2-yl)-2(1H)-quinolinone (8-4)

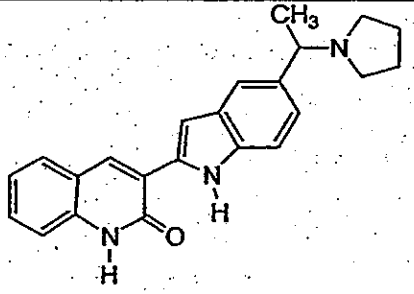
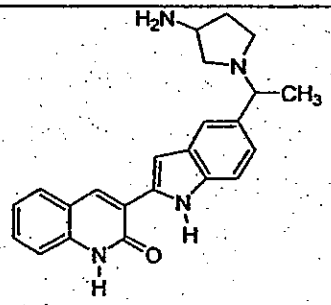
A solution of tert-butyl 5-acetyl-2-(2-chloro-3-quinolinyl)-1H-indole-1-carboxylate (8-3, 400 mg, 0.95 mmol) was heated in a 3:1 mixture of acetic acid and water at reflux for 20 h. The reaction mixture was cooled, then concentrated to dryness. The residue was suspended in ethyl ether (50 mL) with the aid of sonication, then filtered and air dried to give 3-(5-acetyl-1H-indol-2-yl)-2(1H)-quinolinone (8-4) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 12.22 (s, 1H), 11.94 (s, 1H), 8.59 (s, 1H), 8.31 (s, 1H), 7.76 (d, 2H, J = 7.9 Hz), 7.60 (d, 1H, J = 8.6 Hz), 7.55 (t, 1H, J = 7.5 Hz), 7.49 (s, 1H), 7.39 (d, 1H, J = 7.9 Hz), 7.26 (t, 1H, J = 7.5 Hz), 2.62 (s, 3H).

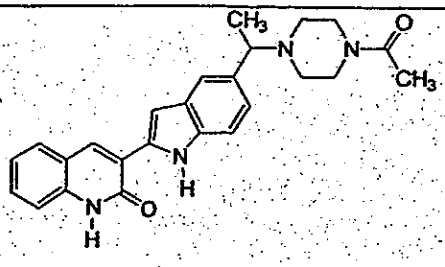
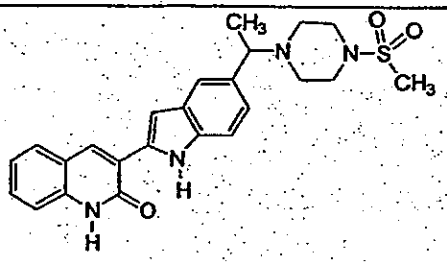
3-{5-[1-(4-morpholinyl)ethyl]-1H-indol-2-yl}-2(1H)-quinolinone (8-5)

A mixture of 3-(5-acetyl-1H-indol-2-yl)-2(1H)-quinolinone (8-4, 50.0 mg, 0.165 mmol, 1 equiv), morpholine (0.070 mL, 0.83 mmol, 5.0 equiv), acetic acid (0.050 mL, 0.83 mmol, 5.0 equiv), sodium cyanoborohydride (52 mg, 0.83 mmol, 5.0 equiv), and activated powdered 3 angstrom molecular sieves in anhydrous 20% dioxane in methanol (15 mL) was heated at 50°C for 8 h. Additional morpholine (0.070 mL, 0.83 mmol, 5.0 equiv), acetic acid (0.050 mL, 0.83 mmol, 5.0 equiv), and sodium cyanoborohydride (52 mg, 0.83 mmol, 5.0 equiv) was added, and this was repeated (3 x) every 8-12 hours over the course of two days. The reaction mixture was partitioned between a 1:1 mixture of saturated sodium carbonate solution and brine and ethyl acetate (100 mL). The organic layer was dried over sodium sulfate and concentrated. The residue was purified by reverse-phase liquid chromatography (H_2O/CH_3CN gradient w/ 0.1% TFA present) to provide 3-{5-[1-(4-morpholinyl)ethyl]-1H-indol-2-yl}-2(1H)-quinolinone (8-5) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.15 (s, 1H), 9.28 (br s, 1H), 8.37 (s, 1H), 7.72 (d, 1H, J = 8.0 Hz), 7.57 (s, 1H), 7.54 (br t, 1H, J = 7.6 Hz), 7.43 (d, 1H, J = 8.0 Hz), 7.32 (t, 1H, J = 7.6 Hz), 7.27 (d, 1H, J = 7.8 Hz), 7.22 (d, 1H, J = 7.9 Hz), 7.04 (s, 1H), 3.72 (m, 4H), 3.41 (q, 1H, J = 6.6 Hz), 2.56 (m, 2H), 2.43 (m, 2H), 1.46 (d, 3H, J = 6.6 Hz).

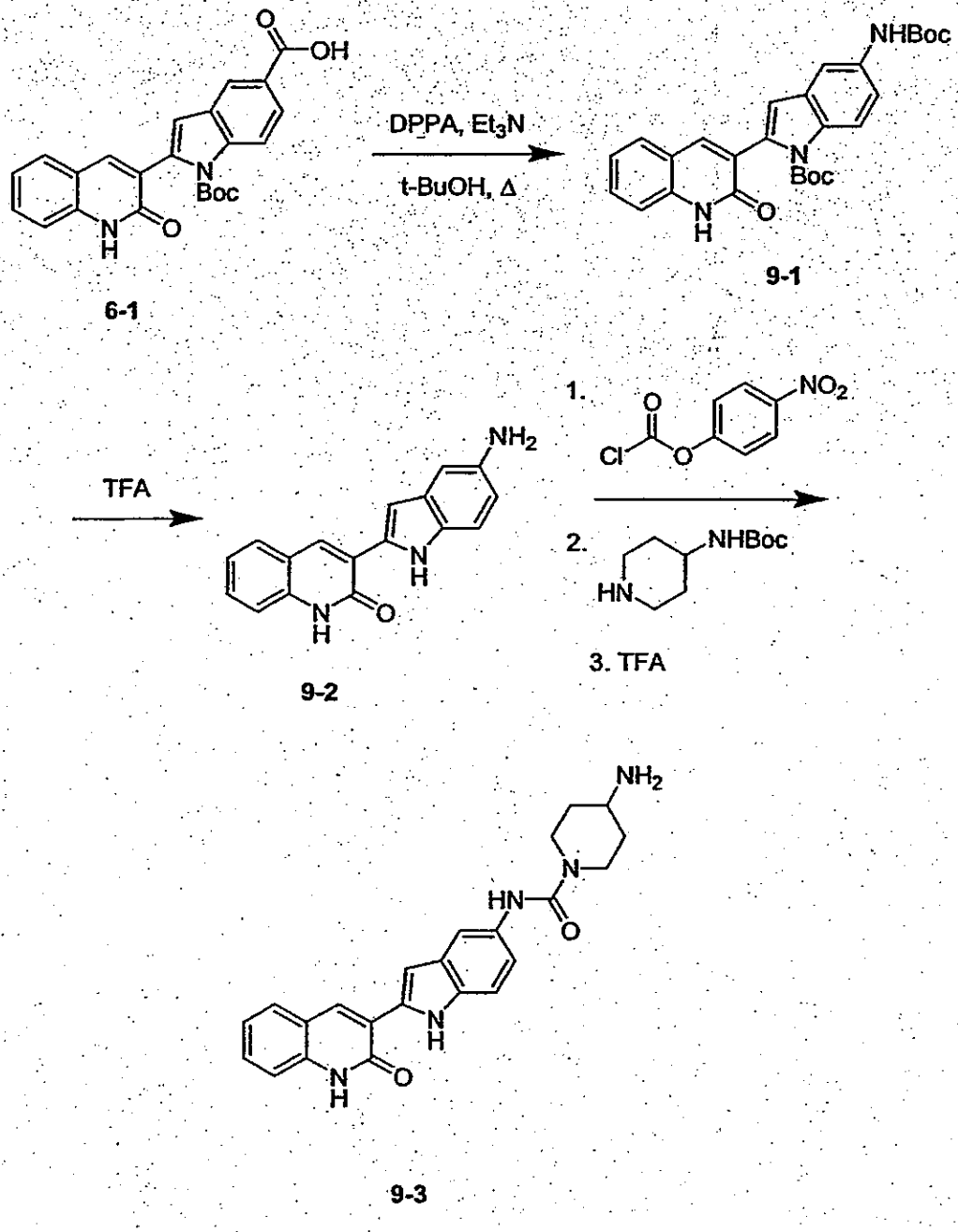
Compounds **8-6** through **8-9** in Table 8 below were made via minor modifications of the protocol shown in Scheme 8. Selected spectra are as follow: **8-6**, ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.13 (s, 1H), 9.76 (br s, 1H), 8.37 (s, 1H), 7.69 (d, 1H, J = 7.1 Hz), 7.60 (s, 1H), 7.52 (t, 1H, J = 7.6 Hz), 7.42 (d, 1H, J = 8.3 Hz), 7.30 (t, 1H, J = 7.6 Hz), 7.25 (d, 1H, J = 8.3 Hz), 7.24 (d, 1H, J = 8.5 Hz), 7.02 (d, 1H, J = 1.2 Hz), 3.34 (br m, 1H), 2.64 (br m, 2H), 2.45 (br m, 2H), 1.79 (br m, 3H), 1.50 (d, 3H, J = 6.6 Hz). **8-8**, ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.17 (s, 1H), 9.74 (br s, 1H), 8.36 (s, 1H), 7.69 (d, 1H, J = 7.1 Hz), 7.53 (s, 1H), 7.52 (t, 1H, J = 7.6 Hz), 7.43 (d, 1H, J = 8.3 Hz), 7.30 (t, 1H, J = 7.6 Hz), 7.25 (d, 1H, J = 8.3 Hz), 7.19 (dd, 1H, J = 8.5, 1.5 Hz), 7.02 (d, 1H, J = 1.2 Hz), 3.66 (m, 1H), 3.56 (m, 1H), 3.49 (q, 1H, J = 6.6 Hz), 3.43 (m, 2H), 2.55 (m, 1H), 2.46 (m, 2H), 2.40 (m, 1H), 2.05 (s, 3H), 1.46 (d, 3H, J = 6.6 Hz).

TABLE 8

Compound No.	Structure	Compound Name
8-6		3-{5-[1-(1-pyrrolidinyl)ethyl]-1H-indol-2-yl}-2(1H)-quinolinone
8-7		3-{5-[1-(3-amino-1-pyrrolidinyl) ethyl]-1H-indol-2-yl}-2(1H)-quinolinone

8-8		3-{5-[1-(4-acetyl-1-piperazinyl)ethyl]-1H-indol-2-yl}-2(1H)-quinolinone
8-9		3-(5-{1-[4-(methylsulfonyl)-1-piperazinyl]ethyl}-1H-indol-2-yl)-2(1H)-quinolinone

SCHEME 9


OH
O
N
Boc
N
H
O
6-1
DPPA, Et3N
t-BuOH, Δ
NHBoc
N
Boc
N
H
O
9-1
TFA
NH2
N
H
N
H
O
9-2
1.
O
Cl
O
NO2
2.
HN
NHBoc
3. TFA
NH2
N
HN
O
N
H
N
H
O
9-3

5

tert-butyl 5-{[(tert-butoxycarbonyl)amino]carbonyl}-2-(2-oxo-1,2-dihydroquinolin-3-yl)-1H-indole-1-carboxylate (9-1)

A solution of 1-(tert-butoxycarbonyl)-2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indole-5-carboxylic acid (6-1, 0.200 mg, 0.49 mmol, 1 equiv), diphenylphosphoryl azide (128 μL, 0.59 mmol, 1.2 equiv), and triethylamine (89 μL, 0.64 mmol, 1.3 equiv) in t-BuOH (30 mL) was heated at 100°C for 2 h. Cuprous chloride (4.9 mg, 0.05 mmol, 0.1 equiv) was added and the resulting mixture was heated at 100°C for 24 h. The solution was concentrated, and the residue was partitioned between and saturated aqueous $NaHCO_3$ solution (75 mL) and EtOAc (3 x 60 mL). The combined organic layers were washed once with water (150 mL) then brine (150 mL) and dried over sodium sulfate and concentrated. The residue was purified by reverse-phase liquid chromatography (H_2O/CH_3CN gradient with 0.1% TFA present) to provide tert-butyl 5-[(tert-butoxycarbonyl)amino]-2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indole-1-carboxylate (9-1). ^1H NMR (500 MHz, DMSO-d_6) δ 12.06 (s, 1H), 9.37 (bs, 1H), 8.05 (s, 1H) , 7.92 (d, 1H, J = 7.8 Hz), 7.82 (s, 1H), 7.52 (m, 2H), 7.35 (m, 2H), 7.21 (m, 2H), 6.72 (s, 1H), 1.50 (s, 9H), 1.34 (s, 9H).

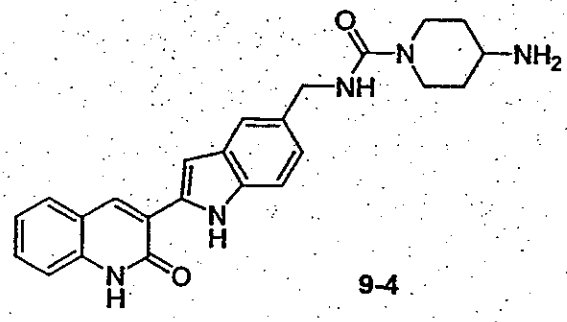
3-(5-amino-1H-indol-2-yl)-2(1H)-quinolinone (9-2)

A solution of tert-butyl 5-{[(tert-butoxycarbonyl)amino]carbonyl}-2-(2-oxo-1,2-dihydroquinolin-3-yl)-1H-indole-1-carboxylate (9-1, 340 mg) in a mixture of 1:1 CH_2Cl_2 and TFA (30 mL) was treated with 3 drops each of DMSO and H_2O, and the resulting mixture was heated at reflux for 45 min. The solution was concentrated, and the residue purified by reverse phase liquid chromatography (H_2O/CH_3CN gradient with 0.1% TFA present) to afford 3-(5-amino-1H-indol-2-yl)-2(1H)-quinolinone (9-2) as a yellow solid. ^1H NMR (500 MHz, CD_3OD) δ 8.42 (s, 1H), 7.74 (d, 1H, J = 7.8 Hz), 7.51 (t, 1H, J = 7.8 Hz), 7.36 (d, 1H, J = 8.3 Hz), 7.28 (d, 1H, J = 8.3 Hz), 7.25 (d, 1H, J = 8.3 Hz), 7.05 (s, 1H), 6.98 (d, 1H, J = 1.5 Hz), 6.74 (d, 1H, J = 2.0 Hz), 6.72 (d, 1H, J = 2.0 Hz).

4-amino-N-[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]-1-piperidinecarboxamide (9-3)

4-Nitrophenyl chloroformate (70 mg, 0.35 mmol, 1.5 equiv) and pyridine (0.030 mL, 0.35 mmol, 1.5 equiv) were sequentially added to a solution of 3-(5-amino-1H-indol-2-yl)-2(1H)-quinolinone (9-2, 64 mg, 0.23 mmol, 1 equiv) in dioxane (20 mL), and the resulting mixture was heated at 60°C for 1 h. tert-Butyl 4-piperidinylcarbamate (100 mg, 0.50 mmol, 2.2 equiv) was added, and the resulting mixture was heated at 60°C for 1 h. The reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate (100 mL). The organic layer was dried over sodium sulfate and concentrated. A solution of the residue in a 1:1 mixture of CH_2Cl_2 and TFA (15 mL) was treated with 2 drops of DMSO and 2 drops of H_2O. The resulting mixture was heated at reflux for 45 min, then concentrated. The residue was purified by reverse-phase chromatography (H_2O/CH_3CN gradient with 0.1% TFA present) to provide 4-amino-N-[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]-1-piperidinecarboxamide (9-3) as a TFA salt. ^1H NMR (500 MHz, CD_3OD) δ 8.45 (s, 1H), 7.75 (d, 1H, J = 8.1 Hz), 7.54 (t, 1H, J = 7.1 Hz), 7.53 (m, 1H), 7.38 (m, 2H), 7.28 (t, 1H, J = 7.1 Hz), 7.20 (s, 1H), 7.08 (dd, 1H, J = 2.0, 1.9 Hz), 4.29 (d, 2H, J = 6.9 Hz), 3.37 (m, 1H), 2.99 (t, 2H, J = 5.98 Hz), 2.05 (d, 2H, J = 6.1 Hz), 1.60 (qd, 2H, J = 4.4, 1.5 Hz).

4-Amino-N-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]methyl}-1-piperidinecarboxamide (9-4) was prepared starting from compound 7-4 using the protocol described above.

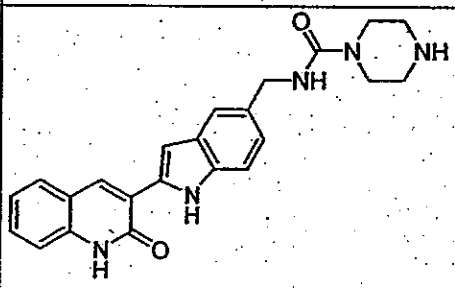
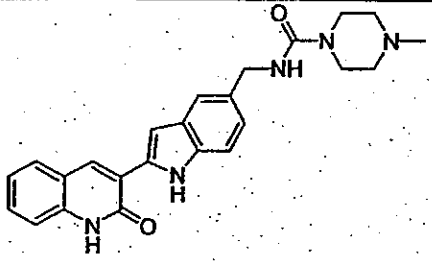


9-4

9-4, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.1 (s, 1H), 11.5 (s, 1H), 8.52 (s, 1H), 7.79 (br s, 2H), 7.72 (d, 1H, J = 8 Hz), 7.52 (t, 1H, J = 8 Hz), 7.43 (m, 2H), 7.37 (d, 1H, J = 8 Hz), 7.29 (s, 1H), 7.25 (t, 1H, J = 8 Hz), 7.06 (m, 2H), 4.31 (d, 2H, J = 5 Hz), 4.04 (d, 2H, J = 13 Hz), 3.20 (br s, 1H), 2.76 (t, 2H, J = 12 Hz), 1.83 (d, 2H, J = 13 Hz), 1.36 (m, 2H).

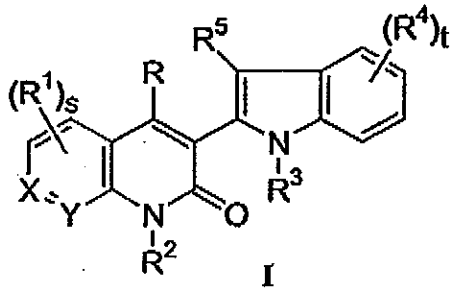
Compounds **9-5** and **9-6** in Table 9 below were prepared by simple modification of the protocols described above for compound **9-3**.

TABLE 9

Compound No.	Structure	Compound Name
9-5		N-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)1H-indol-5-yl]methyl}-1-piperazine carboxamide
9-6		4-methyl-N-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)1H-indol-5-yl]methyl}-1-piperazine carboxamide

What is claimed is:

1. A compound of Formula I



I

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein

a is 0 or 1;
b is 0 or 1;
m is 0, 1, or 2;
s is 1 or 2;
t is 1, 2, or 3;

X=Y is C=N, N=C, or C=C;

R is H or C_1-C_6 alkyl;

R^1 and R^5 are independently selected from:

1) H,
2) $(C=O)_aO_bC_1$-C_{10} alkyl,
3) $(C=O)_aO_b$aryl,
4) $(C=O)_aO_bC_2$-C_{10} alkenyl,
5) $(C=O)_aO_bC_2$-C_{10} alkynyl,
6) CO_2H,
7) halo,

8) OH,

9) O_bC_1-C_6 perfluoroalkyl,

10) $(C=O)_aNR^7R^8$,

11) CN,

12) $(C=O)_aO_bC_3$-C_8 cycloalkyl, and

13) $(C=O)_aO_b$heterocyclyl,

said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^6;

R^2 and R^3 are independently selected from:

1) H,

2) $(C=O)O_aC_1$-C_6 alkyl,

3) $(C=O)O_a$aryl,

4) C_1-C_6 alkyl,

5) SO_2R^a, and

6) aryl;

R^4 is selected from:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,

2) $(C=O)_aO_b$aryl,

3) $(C=O)_aO_bC_2$-C_{10} alkenyl,

4) $(C=O)_aO_bC_2$-C_{10} alkynyl,

5) CO_2H,

6) halo,

7) OH,

8) O_bC_1-C_6 perfluoroalkyl,

9) $(C=O)_aNR^7R^8$,

10) CN,

11) $(C=O)_aO_bC_3$-C_8 cycloalkyl, and

12) $(C=O)_aO_b$heterocyclyl,

said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^6;

R^6 is:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,

2) $(C=O)_aO_b$aryl,

3) C_2-C_{10} alkenyl,

4) C_2-C_{10} alkynyl,

5) $(C=O)_aO_b$ heterocyclyl,

6) CO_2H,

7) halo,

8) CN,

9) OH,

10) O_bC_1-C_6 perfluoroalkyl,

11) $O_a(C=O)NR^7R^8$,

12) oxo,

13) CHO,

14) NR^7R^8 or the N-oxide, or

15) $(C=O)_aO_bC_3$-C_8 cycloalkyl,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^{6a};

R^{6a} is selected from:

1) $(C=O)_rO_s(C_1$-$C_{10})$alkyl, wherein r and s are independently 0 or 1,

2) $O_r(C_1\text{-}C_3)$perfluoroalkyl, wherein r is 0 or 1,

3) $(C_0\text{-}C_6)$alkylene-$S(O)_mR^a$, wherein m is 0, 1, or 2,

4) oxo,

5) OH,

6) halo,

7) CN,

8) $(C_2\text{-}C_{10})$alkenyl,

9) $(C_2\text{-}C_{10})$alkynyl,

10) $(C_3\text{-}C_6)$cycloalkyl,

11) $(C_0\text{-}C_6)$alkylene-aryl,

12) $(C_0\text{-}C_6)$alkylene-heterocyclyl,

13) $(C_0\text{-}C_6)$alkylene-$N(R^b)_2$,

14) $C(O)R^a$,

15) $(C_1\text{-}C_6)$alkylene-CO_2R^a,

16) C(O)H, and

17) $(C_0\text{-}C_6)$alkylene-CO_2H,

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1\text{-}C_6)$alkoxy, halogen, CO_2H, CN, $O(C{=}O)C_1\text{-}C_6$ alkyl, oxo, and $N(R^b)_2$;

R^7 and R^8 are independently selected from:

1) H,

2) $(C{=}O)O_bC_1\text{-}C_{10}$ alkyl,

3) $(C{=}O)O_bC_3\text{-}C_8$ cycloalkyl,

4) $(C{=}O)O_b$aryl,

5) $(C{=}O)O_b$heterocyclyl,

6) $C_1\text{-}C_{10}$ alkyl,

7) aryl,
8) C_2-C_{10} alkenyl,
9) C_2-C_{10} alkynyl,
10) heterocyclyl,
11) C_3-C_8 cycloalkyl,
12) SO_2R^a, and
13) $(C=O)NR^b{}_2$,

said alkyl, cycloalkyl, aryl, heterocyclyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^{6a}, or

R^7 and R^8 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocylcic or bicyclic heterocycle optionally substituted with one or more substituents selected from R^{6a};

R^a is:

1) $(C_1$-$C_6)$alkyl,
2) $(C_3$-$C_6)$cycloalkyl,
3) aryl, or
4) heterocyclyl; and

R^b is:

1) H,
2) $(C_1$-$C_6)$alkyl,
3) aryl,
4) heterocyclyl,

5) $(C_3\text{-}C_6)$cycloalkyl,

6) $(C{=}O)OC_1\text{-}C_6$ alkyl,

7) $(C{=}O)C_1\text{-}C_6$ alkyl, or

8) $S(O)_2R^a$.

2. The compound of Claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein

s is 1;

t is 1 or 2;

X=Y is C=C;

R^1 and R^5 are independently selected from:

1) H,

2) $(C{=}O)_aO_bC_1\text{-}C_6$ alkyl,

3) $(C{=}O)_aO_b$aryl,

4) $(C{=}O)_aO_bC_2\text{-}C_6$ alkenyl,

5) $(C{=}O)_aO_bC_2\text{-}C_6$ alkynyl,

6) CO_2H,

7) halo,

8) OH,

9) $O_bC_1\text{-}C_3$ perfluoroalkyl,

10) $(C{=}O)_aNR^7R^8$,

11) CN,

12) $(C{=}O)_aO_bC_3\text{-}C_6$ cycloalkyl, and

13) $(C{=}O)_aO_b$heterocyclyl,

said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^6;

R^4 is selected from:

1) $(C=O)_aO_bC_1$-C_6 alkyl,
2) $(C=O)_aO_b$aryl,
3) $(C=O)_aO_bC_2$-C_6 alkenyl,
4) $(C=O)_aO_bC_2$-C_6 alkynyl,
5) CO_2H,
6) halo,
7) OH,
8) O_bC_1-C_3 perfluoroalkyl,
9) $(C=O)_aNR^7R^8$,
10) CN,
11) $(C=O)_aO_bC_3$-C_6 cycloalkyl, and
12) $(C=O)_aO_b$heterocyclyl,

said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R^6;

R^6 is:

1) $(C=O)_aO_bC_1$-C_6 alkyl,
2) $(C=O)_aO_b$aryl,
3) C_2-C_6 alkenyl,
4) C_2-C_6 alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) CO_2H,
7) halo,

8) CN,

9) OH,

10) O_bC_1-C_3 perfluoroalkyl, or

11) $O_a(C=O)NR^7R^8$,

12) oxo,

13) CHO,

14) NR^7R^8 or the N-oxide, or

15) $(C=O)_aO_bC_3$-C_6 cycloalkyl,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl is optionally substituted with one or more substituents selected from R^{6a};

R^{6a} is selected from:

1) $(C=O)_rO_s(C_1$-$C_6)$alkyl, wherein r and s are independently 0 or 1,

2) $O_r(C_1$-$C_3)$perfluoroalkyl, wherein r is 0 or 1,

3) $(C_0$-$C_6)$alkylene-$S(O)_mR^a$, wherein m is 0, 1, or 2,

4) oxo,

5) OH,

6) halo,

7) CN,

8) $(C_2$-$C_6)$alkenyl,

9) $(C_2$-$C_6)$alkynyl,

10) $(C_3$-$C_6)$cycloalkyl,

11) $(C_0$-$C_6)$alkylene-aryl,

12) $(C_0$-$C_6)$alkylene-heterocyclyl,

13) $(C_0$-$C_6)$alkylene-$N(R^b)_2$,

14) $C(O)R^a$,

15) $(C_1$-$C_6)$alkylene-CO_2R^a,

16) C(O)H, and

17) (C_0-C_6)alkylene-CO_2H,

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, (C_1-C_6)alkoxy, halogen, CO_2H, CN, O(C=O)C_1-C_6 alkyl, oxo, and $N(R^b)_2$; and

R^7 and R^8 are independently selected from:

1) H,

2) $(C=O)O_bC_1$-C_6 alkyl,

3) $(C=O)O_bC_3$-C_6 cycloalkyl,

4) $(C=O)O_b$aryl,

5) $(C=O)O_b$heterocyclyl,

6) C_1-C_6 alkyl,

7) aryl,

8) C_2-C_6 alkenyl,

9) C_2-C_6 alkynyl,

10) heterocyclyl,

11) C_3-C_6 cycloalkyl,

12) SO_2R^a, and

13) $(C=O)NR^b_2$,

said alkyl, cycloalkyl, aryl, heterocyclyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^{6a}, or

R^7 and R^8 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing,

in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclcic or bicyclic heterocycle optionally substituted with one or more substituents selected from R^{6a}.

3. The compound of Claim 2, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^2, R^3, and R^5 are H.

4. The compound of Claim 3, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein t is 1, s is 1, and R^1 is H.

5. A compound selected from:

3-{5-[3-(4-methyl-piperazin-1-yl)-propoxy]-1H-indol-2-yl}-1H-quinolin-2-one;

3-(5-{2-[(2-methoxyethyl)amino]ethoxy}-1H-indol-2-yl)-2(1H)-quinolinone;

3-[5-(2-{(2-methoxyethyl)[(2-methoxy-5-pyrimidinyl)methyl]amino}ethoxy)-1H-indol-2-yl]-2(1H)-quinolinone;

3-(5-{[(2S,4R)-4-methoxypyrrolidinyl]methoxy}-1H-indol--yl)-2(1H)-quinolinone;

3-[5-({(2S,4R)-4-methoxy-1-[(2-methyl-5-pyrimidinyl)methyl]pyrrolidinyl} methoxy)-1H-indol-2-yl]-2(1H)-quinolinone;

1-(2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}ethyl)-4-piperidine- carboxylic acid ethyl ester;

1-(2-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}ethyl)-4-piperidinecarboxylic acid;

3-[(2S,4R)-4-methoxy-2-({[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}methyl) pyrrolidinyl]propanoic acid;

3-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one;

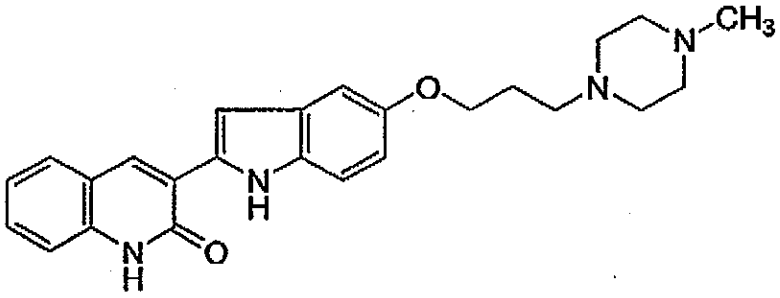
3-[5-(4-methanesulfonyl-1-oxy-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one;

3-[5-(4-acetyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one;

N-Cyclopropyl-N-[2-(2-oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-ylmethyl]-methanesulfonamide;

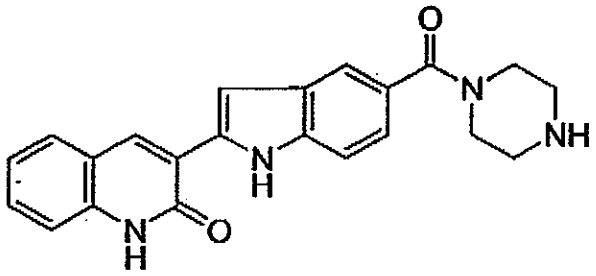
3-[5-(1-piperazinylcarbonyl)-1H-indol-2-yl]-2(1H)-quinolinone;
3-{5-[(4-methyl-1-piperazinyl)carbonyl]-1H-indol-2-yl}-2(1H)-quinolinone;
1-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]carbonyl}-4-piperidinaminium trifluoroacetate;
1-({[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]oxy}acetyl)piperazin-4-ium trifluoroacetate;
3-{5-[2-(1,1-dioxido-4-thiomorpholinyl)-2-oxoethoxy]-1H-indol-2-yl}-2(1H)-quinolinone;
N-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]methyl}-4-piperidine carboxamide;
3-{5-[1-(4-morpholinyl)ethyl]-1H-indol-2-yl}-2(1H)-quinolinone;
3-{5-[1-(1-pyrrolidinyl)ethyl]-1H-indol-2-yl}-2(1H)-quinolinone;
3-{5-[1-(4-acetyl-1-piperazinyl)ethyl]-1H-indol-2-yl}-2(1H)-quinolinone;
3-(5-{1-[4-(methylsulfonyl)-1-piperazinyl]ethyl}-1H-indol-2-yl)-2(1H)-quinolinone;
4-amino-N-[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]-1-piperidinecarboxamide; and
4-amino-N-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]methyl}-1-piperidinecarboxamide, or a pharmaceutically acceptable salt or stereoisomer thereof.

6. A compound which is 3-{5-[3-(4-methyl-piperazin-1-yl)-propoxy]-1H-indol-2-yl}-1H-quinolin-2-one



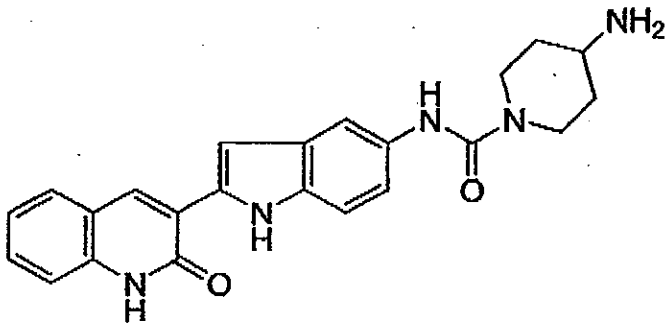
or a pharmaceutically acceptable salt thereof.

7. A compound which is 3-[5-(1-piperazinylcarbonyl)-1H-indol-2-yl]-2(1H)-quinolinone



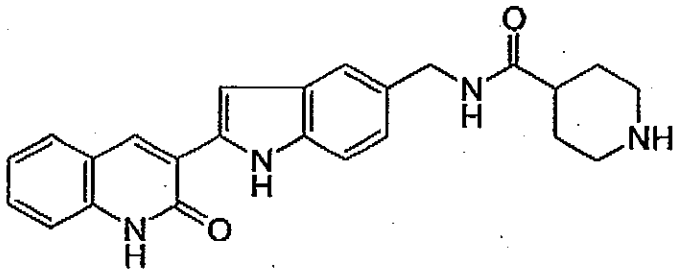
or a pharmaceutically acceptable salt thereof.

8. A compound which is 4-amino-N-[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]-1-piperidinecarboxamide



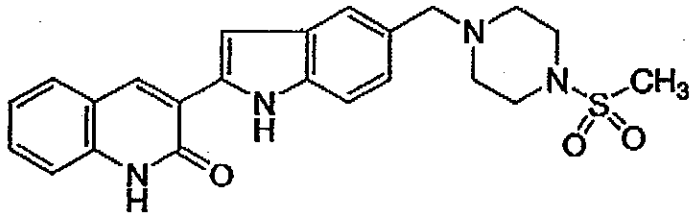
or a pharmaceutically acceptable salt thereof.

9. A compound which is N-{[2-(2-oxo-1,2-dihydro-3-quinolinyl)-1H-indol-5-yl]methyl}-4-piperidine carboxamide



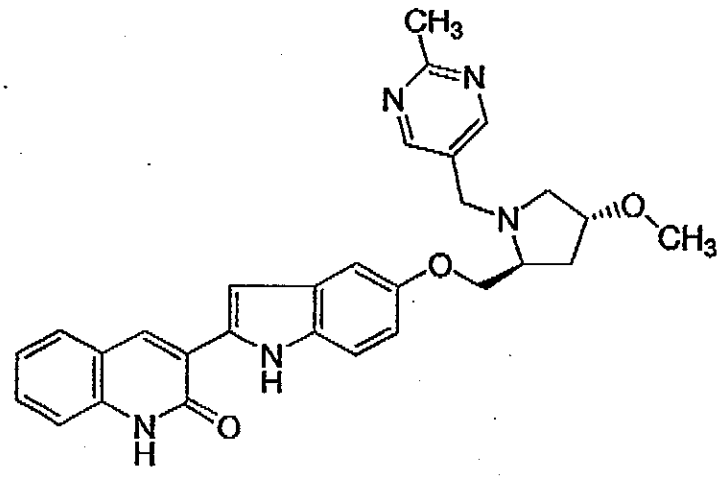
or a pharmaceutically acceptable salt thereof.

10. A compound which is 3-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one



or a pharmaceutically acceptable salt thereof.

11. A compound which is 3-[5-({(2S,4R)-4-methoxy-1-[(2-methyl-5-pyrimidinyl)methyl]pyrrolidinyl} methoxy)-1H-indol-2-yl]-2(1H)-quinolinone



or a pharmaceutically acceptable salt or stereoisomer thereof.

12. A pharmaceutical composition which is comprised of a compound in accordance with Claim 1 and a pharmaceutically acceptable carrier.

13. Use of a therapeutically effective amount of the compound according to Claim 1 in the manufacture of a medicament for the treatment of cancer in a mammal.

14. The use according to Claim 13 wherein the cancer is selected from cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung.

15. The use according to Claim 13 wherein the cancer is selected from histiocytic lymphoma, lung adenocarcinoma, small cell lungcancers, pancreatic cancer, gjoblastomas and breast carcinoma.

16. Use of a therapeutically effective amount of the compound according to Claim 1 in the manufacture of a medicament for the treatment of disease in which angiogenesis is implicated.

17. The use according to Claim 16 wherein the disease is an ocular disease.

18. The use of therapeutically effective amount of the compound according to Claim 1 for the manufacture of a medicament for the treatment of retinal vascularization in a mammal.

19. The use of therapeutically effective amount of the compound according to Claim 1 for the manufacture of a medicament for treating diabetic retinopathy

20. The use of therapeutically effective amount of the compound according to Claim 1 for the manufacture of a medicament for the treatment of age-related macular degeneration.

21. The use of therapeutically effective amount of the compound according to Claim 1 for the manufacture of a medicament for the treatment of inflammatory disease in a mammal.

22. The use according to Claim 21 wherein the inflammatory disease is selected from rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reactions.

23. The use of therapeutically effective amount of the compound according to Claim 1 in the manufacture of a medicament for the treatment of tyrosine kinase-dependent disease or condition in a mammal.

24. A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier.

25. A process for making a pharmaceutical composition which comprises combining a compound of Claim 1 with a pharmaceutically acceptable carrier.

26. The use of therapeutically effective amount of the compound according to Claim 1 in the manufacture of a medicament for the treatment of bone associated pathologies selected from osteosarcoma, osteoarthritis, and rickets.

27. The composition of Claim 12 further comprising a second compound selected from:

1) an estrogen receptor modulator,

2) an androgen receptor modulator,

3) retinoid receptor modulator,

4) a cytotoxic agent,

5) an antiproliferative agent,

6) a prenyl-protein transferase inhibitor,

7) an HMG-CoA reductase inhibitor,

8) an HIV protease inhibitor,

9) a reverse transcriptase inhibitor, and

10) another angiogenesis inhibitor.

28. The composition of Claim 27, wherein the second compound is another angiogenesis inhibitor selected from the group consisting of a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP inhibitor, an integrin blocker, interferon-a, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, and an antibody to VEGF.

29. The composition of Claim 27, wherein the second compound is an estrogen receptor modulator selected from tamoxifen and raloxifene.

30. The use of therapeutically effective amount of the compound according to Claim 1 in combination with radiation therapy for the treatment of cancer.

31. The use of therapeutically effective amount of the compound according to Claim 1 in combination with a compound selected from:

1) an estrogen receptor modulator,

2) an androgen receptor modulator,
3) retinoid receptor modulator,
4) a cytotoxic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor, and
10) another angiogenesis inhibitor,

in the manufacture of a medicament for the treatment of cancer in a mammal.

32. The use of a therapeutically effective amount of the compound of Claim 1 and a compound selected from:

1) an estrogen receptor modulator,
2) an androgen receptor modulator,
3) retinoid receptor modulator,
4) a cytotoxic agent,
5) an antiproliferative agent,
6) a prenyl-protein transferase inhibitor,
7) an HMG-CoA reductase inhibitor,
8) an HIV protease inhibitor,
9) a reverse transcriptase inhibitor, and
10) another angiogenesis inhibitor.

in the manufacture of a medicament wherein the medicament is administered to a mammal in combination with radiation for treating cancer in the mammal.

33. Use of effective amount of the compound according to Claim 1 and paclitaxel or trastuzumab in the manufacture of a medicament for treatment of cancer.

34. Use of a therapeutically effective amount of the compound of Claim 1 and a GPIIb/IIIa antagonist in the manufacture of a medicament for the treatment of cancer.

35. Use according to Claim 34 wherein the GPIIb/IIIa antagonist is tirofiban.

36. The use of a therapeutically effective amount of a compound according to Claim 1 in the manufacture of a medicament for reducing tissue damage following a cerebral ischemic event in a mammal.