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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 June 2006 (01.06.2006)

PCT

(10) International Publication Number
WO 2006/058088 A2

(51) International Patent Classification:
C07D 209/88 (2006.01) ***C07D 317/66*** (2006.01)
C07D 495/04 (2006.01) ***C07D 209/94*** (2006.01)

(21) International Application Number:
PCT/US2005/042484

(22) International Filing Date:
23 November 2005 (23.11.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/629,889 23 November 2004 (23.11.2004) US
60/633,738 6 December 2004 (06.12.2004) US
60/639,283 27 December 2004 (27.12.2004) US

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)***:** ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, 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.

(54) Title: CARBAZOLE, CARBOLINE, AND INDOLE DERIVATIVES USEFUL IN THE INHIBITION OF VEGF PRODUCTION

(57) Abstract: In accordance with the present invention, compounds that inhibit the expression of VEGF post-transcriptionally have been identified, and methods for their use provided. In one aspect of the invention, compounds and compositions useful in the inhibition of BEGF production, and/or in the inhibition of angiogenesis, and/or in the treatment of cancer, diabetic retinopathy or exudative macular degeneration are provided. In another aspect of the invention, methods are provided for the inhibition of VEGF production, the inhibition of angiogenesis, and/or the treatment of cancer, diabetic retinopathy or exudative macular degeneration using the compounds of the invention.

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CARBAZOLE, CARBOLINE, AND INDOLE DERIVATIVES USEFUL IN THE INHIBITION OF VEGF PRODUCTION

RELATED APPLICATIONS

The present application claims priority to and the benefit under 35 U.S.C. §119 of U.S. Provisional Application No. 60/629, 889, filed November 23, 2004, which application is herein incorporated by reference in its entirety. The present application also claims priority to and the benefit under 35 U.S.C. §119 of U.S. Provisional Application No. 60/633,738, filed December 6, 2004, and U.S. Provisional Application No. 60/639,283, filed December 27, 2004. This application also incorporates by reference in their entirety, U.S. Provisional Patent Application Nos. 60/552,724 and 60/552,725, both of which were filed March 15, 2004.

FIELD OF THE INVENTION

The present invention relates to methods, compounds, and compositions for inhibiting angiogenesis. More particularly, the present invention relates to methods, compounds, and compositions for inhibiting VEGF production.

BACKGROUND OF THE INVENTION

Aberrant angiogenesis plays a critical role in the pathogenesis of numerous diseases, including malignant, ischemic, inflammatory and immune disorders (4, 18). The best-known of these disorders are cancer, exudative macular degeneration and diabetic retinopathy (DR), the last two of which are leading cause of blindness in the United States (6, 7). During the last decade our understanding of the molecular basis of angiogenesis has grown considerably. Numerous cytokines and growth factors that stimulate angiogenesis, such as VEGF, FGF-2, PDGF, IGF-1, TGF, TNF-α, G-CSF have been identified (2, 5, 19). Among these growth factors, Vascular Endothelial Growth Factor (VEGF) plays a central role in angiogenesis (18).

VEGF, also known as VEGF-A, was initially identified for its ability to induce vascular permeability and to promote vascular endothelial cell proliferation (23-25). VEGF is encoded by a single gene that gives rise to four isoforms by alternative splicing (26). All four isoforms share the same unusually long and GC rich 5'-UTR, as well as a 3'-UTR that includes multiple RNA stability determinants. The receptors VEGFR-2 (also known as KDR or Flk-1) and VEGFR-1 (previously known as Flt1) recognize the dimeric form of VEGF (27, 28). The highly specific VEGFR-2 receptor is expressed on endothelial cells. VEGF binding to the VEGFR-2 receptor activates the receptor's tyrosine kinase activity, leading to endothelial cell proliferation, differentiation and primitive vessel formation (29). VEGFR-1 inhibits endothelial cell growth either by acting as a decoy or by suppressing signaling pathways through VEGFR-2 (30).

Over 30 years ago, it was proposed that inhibition of tumor angiogenesis could be an effective approach for the treatment of cancer (31). VEGF and its receptor have been demonstrated to have a central role in tumor angiogenesis, especially in the early stages of tumor growth (33). Indeed, increased levels of VEGF expression have been correlated with microvessel density in primary tumor tissues (34). Moreover, increased levels of the VEGF transcript are found in virtually all of the common solid tumors (35). In general, tumor-bearing patients have higher levels of VEGF compared to those in tumor-free individuals, and high VEGF levels in serum/plasma are associated with poor prognosis (36). Consistent with the role of VEGF in tumor angiogenesis, VEGF null embryonic stem cells showed a dramatically reduced ability to form tumors in nude mice (37). Direct evidence for the involvement of VEGF in tumorgenesis was demonstrated by using specific antibodies against VEGF in human xenografts implanted in nude mice (38, 39). In these studies, the inhibition of tumor growth correlated positively with decreased vessel formation in the antibody-treated tumors. Subsequent experiments using the soluble receptors substantiated the importance of VEGF activity in tumor growth (40), and demonstrated that inactivation of VEGF by specific antibody treatment directly resulted in a nearly complete suppression of tumor-associated neovascularization (41, 42).

In exudative macular degeneration and diabetic retinopathy, pre-clinical experiments and clinical trials have demonstrated that over production of VEGF is critical for aberrant retinal or choroidal neovascularization (reviewed in 6). Evidence has been obtained that intra-ocular VEGF levels are strongly correlated with active retinal/choroidal neovascularization (CNV) in patients with diseases such as diabetic retinopathy and wet form macular degeneration (43, 44). In addition, studies using transgenic mice demonstrated that overexpression of VEGF in retinal pigment epithelial cells or photoreceptor cells results in choroidal or retinal neovascularization (45, 46). In recent studies neutralizing antibodies, soluble receptor, receptor antagonists, or siRNA have proven efficacious in reducing VEGF-mediated blood vessel formation in animal models and in the clinic. (17, 47-50)

VEGF expression is regulated by a number of factors and agents including cytokines, growth factors, steroid hormones and chemicals, and mutations that modulate the activity of oncogenes such as ras or the tumor suppressor gene VHL (51, 52). Nevertheless, hypoxia is the most significant physiologic signal for regulating VEGF expression. Hypoxia results in enhanced VEGF expression by increasing both the transcription rate and stability of the VEGF transcript (8-10). Hypoxia-inducible factor 1α (HIF-1α) is a transcription factor that increases VEGF gene expression in cells undergoing hypoxia by binding to the hypoxia response element (HRE) located in the VEGF promoter (53, 54). The stability of VEGF mRNA is also greatly enhanced as a consequence of the binding of factors to elements in the 3'-UTR (55). In addition, the translation initiation of the VEGF transcript is uniquely regulated. Under hypoxic conditions, translation of most cellular transcripts mediated by cap-dependent translation initiation process is greatly impaired (56). Initiation of translation of the VEGF mRNA, however, is unique under hypoxic conditions in that it is mediated via an internal ribosome entry site (IRES) within the VEGF 5'UTR (9-12).

There is a large body of experimental evidence indicating that tumor growth can be inhibited by the prevention of neovascularization (40, 72). Tumor vessels are generally immature and constantly undergo remodeling (4, 73). Active and aberrant angiogenesis is the result of a disruption in the normal balance of pro-angiogenic and anti-angiogenic factors, including various cytokines, growth factors and steroid hormones. Despite the complexity of the regulation of tumor angiogenesis, accumulated evidence indicates that targeting a single proangiogenic factor might be sufficient to inhibit tumor angiogenesis and suppress tumor growth (38, 74, 75). Among many angiogenesis targets, VEGF and its receptor are most attractive (4, 27). As noted above, treatment with a monoclonal antibody specifically targeting VEGF inhibited the growth of tumors in human xenografts implanted in nude mice. Subsequently, various approaches designed to inactivate VEGF signaling have been tested in tumor models and have proven to be highly effective in a broad range of tumor cell lines including various carcinomas, sarcomas and gliomas (35, 38, 74-76). In addition, inhibition of VEGF by anti-VEGF antibody did not result in significant side effects in fully developed rodents or primates (77, 78). Taken together, these results indicate that VEGF is a valid target for the development of tumor therapy. Indeed, a number of clinical trials are underway using VEGF inhibitors (3, 39).

Although several pro-angiogenic factors are implicated in the pathology of exudative age-related macular degeneration, VEGF appears to be the most critical in the pathogenesis and development of this disease (6, 90). Data from preclinical experiments and clinical trials have demonstrated that blockade of VEGF alone is sufficient to alleviate or stabilize disease progression (17, 47-50). For example, inhibition of VEGFR signaling by a specific tyrosine kinase inhibitor is sufficient to completely prevent retinal neovascularization in a murine retinopathy of prematurity model (79). Furthermore, it has recently been demonstrated that small interfering RNAs (siRNA) directed against murine VEGF significantly inhibited ocular neovascularization after laser photocoagulation in a mouse model (80). These results indicate that selective inhibition of VEGF expression is achievable and offer validation of this approach for the treatment of ocular neovascular diseases such as exudative macular degeneration and diabetic retinopathy.

Three approaches have been used to inhibit VEGF activity, including (1) neutralization of VEGF activity by using a specific antibody, soluble VEGF receptor or aptamer oligos against the VEGF/VEGFR interaction (38, 40, 41, 72, 74, 117, 118); (2) inhibition of VEGFR mediated signal transduction by specific small molecule tyrosine kinase inhibitors (75, 82, 119); and (3) inhibition of VEGF/VEGFR expression by using antisense, siRNA or ribozyme (80, 83, 84, 85). Although all of these approaches show significant inhibition of angiogenesis *in vivo*, they all possess significant limitations. For example, therapeutic proteins (antibody and soluble receptors) or oligos (antisense, siRNA and ribozyme) are large molecules with poor permeability that usually require parenteral administration and are costly to produce. For treatment of chronic ocular neovascularization, multiple injections may be impractical due to potential complications such as retinal detachment and procedure related infection. Moreover, tyrosine kinase inhibitors have the potential for limited specificity. VEGF is constitutively expressed at a low level in normal eyes and other tissues and thus it may be harmful to completely suppress VEGF function by administration of antibody or tyrosine kinase inhibitors systemically, especially for patients with AMD and DR many of whom are also hypertensive (86-89).

Thus, there remains a need to develop, characterize, and optimize lead molecules for the development of novel anti-angiogenesis drugs. Accordingly, it is an object of the present invention to provide such compounds. In addition, it is also an object of the invention to provide compositions and methods for anti-angiogenesis.

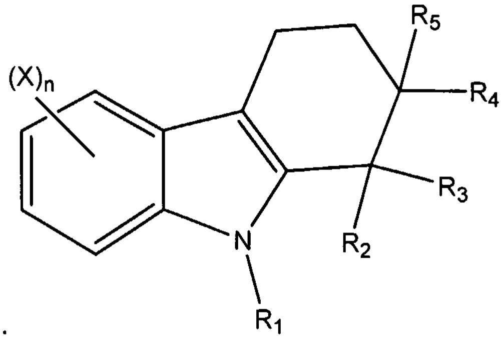
All documents referred to herein are incorporated by reference into the present application as though fully set forth herein.

SUMMARY OF THE INVENTION

In accordance with the present invention, compounds that inhibit the expression of VEGF post-transcriptionally have been identified, and methods for their use provided.

In one aspect of the invention, compounds of Formulas (I) to (VIII) are provided which are useful in the inhibition of VEGF production, in the inhibition of angiogenesis, and/or in the treatment of cancer, diabetic retinopathy, rheumatoid arthritis, psoriasis, atherosclerosis, obesity, chronic inflammation or exudative macular degeneration.

In one embodiment, the present invention includes and provides compounds of formula (I)



(I)

wherein

X is hydrogen, a hydroxyl group; a halogen; a nitro group; a cyano group; a C_1 to C_5 alkoxy group, optionally substituted with at least one halogen; a C_1 to C_6 alkyl group, optionally substituted with at least one halogen; an optionally substituted amine; an optionally substituted carbonyl; or an optionally substituted sulfonyl;

R_1 is a hydrogen; a C_1 to C_6 alkyl group, optionally substituted with at least one halogen or a C_6 to C_8 aryl group, wherein the aryl group is optionally substituted with at least one halogen; a C_6 to C_8 aryl group, optionally substituted with at least one halogen; –C(O)–R_a; –C(O)O–R_{aa}; or –S(O_2)–aryl;

R_2 is hydrogen; C_1 to C_4 alkyl; or may be taken together with R_3;

R_3 is hydrogen; C_1 to C_4 alkyl; a C_6 to C_8 aryl group, optionally substituted with at least one halogen or C_1 to C_5 alkoxy group; or R_3 may be taken together with R_2 to form (=O), =N–R_b, or a cycloalkyl group, optionally substituted with a C_1 to C_6 alkyl–C_6 to C_8 aryl group or a C_6 to C_8 aryl group;

R_4 and R_5 may each independently be hydrogen; a C_1 to C_6 alkyl group; or R_4 and R_5 may be taken together to form =CH–cycloalkyl, =CH–amino; or =CH–aryl, wherein the cycloalkyl and aryl groups are optionally substituted with at least one halogen group, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, $-CF_3$, $-OCF_3$, $-NO_2$, –CN, or $-N(CH_3)_2$, and the amino group is optionally substituted with at least one C_1 to C_4 alkyl group;

R_a is a C_1 to C_6 alkyl group; a C_1 to C_5 alkoxy group; a naphthyl group; $-CF_3$; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, naphthyl group, $-CF_3$, $-OCF_3$, $-NO_2$, –CN, or $-N(CH_3)_2$;

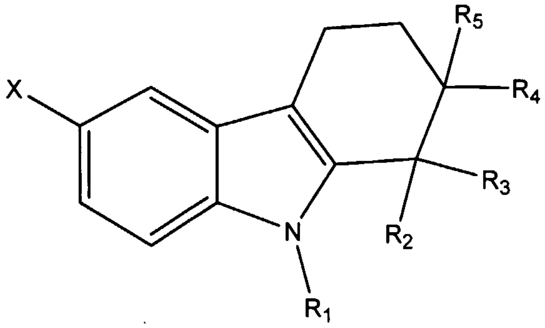
R_{aa} is a C_1 to C_6 alkyl group; a naphthyl group; $-CF_3$; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, naphthyl group, $-CF_3$, $-OCF_3$, $-NO_2$, –CN, or $-N(CH_3)_2$;

R_b is a hydroxyl group or pyrrolyl group; and

n is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compounds.

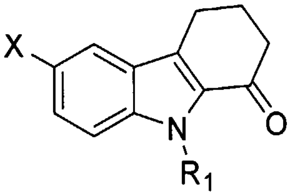
In another embodiment, the present invention includes and provides compounds of Formula (Ia)



(Ia)

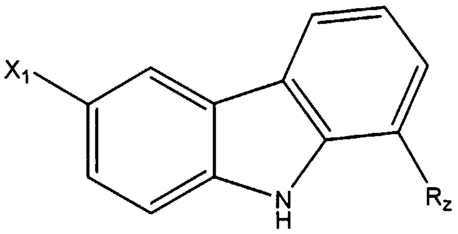
wherein X, R_1, R_2, R_3, R_4, and R_5 are as described above with regard to Formula (I).

In another embodiment, the present invention includes and provides compounds of Formula (Ib)



(Ib)

In another embodiment, the present invention includes and provides compounds of Formula (II)



(II)

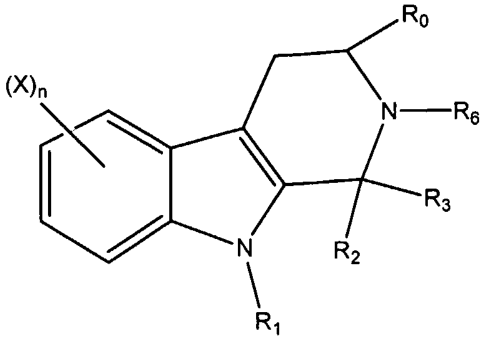
wherein

X_1 is a halogen; and

R_z is a heteroaryl group;

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compounds.

In another embodiment, the present invention includes and provides compounds of Formula (III)



(III)

wherein

X is a hydroxyl group; a halogen; a nitro group; a cyano group; a C_1 to C_5 alkoxy group, optionally substituted with at least one halogen; a C_1 to C_6 alkyl group, optionally substituted with at least one halogen; an optionally substituted amine; an optionally substituted carbonyl; or an optionally substituted sulfonyl;

R_0 is H or –C(O)O–(C_1-C_6 alkyl);

R_1 is a hydrogen; a C_1 to C_6 alkyl group, optionally substituted with at least one halogen or a C_6 to C_8 aryl group, wherein the aryl group is optionally substituted with at least one halogen; a C_6 to C_8 aryl group, optionally substituted with at least one halogen; –C(O)–R_a; –C(O)O–R_{aa}; or –S(O_2)–aryl;

R_2 is hydrogen; C_1 to C_4 alkyl; or may be taken together with R_3;

R_3 is hydrogen; C_1 to C_4 alkyl; a C_6 to C_8 aryl group, optionally substituted with at least one halogen or C_1 to C_5 alkoxy group; or R_3 may be taken together with R_2 to form (=O), =N–R_b, or a cycloalkyl group, optionally substituted with a C_1 to C_6 alkyl–C_6 to C_8 aryl group or a C_6 to C_8 aryl group;

R_a is a C_1 to C_6 alkyl group; a C_1 to C_5 alkoxy group; a naphthyl group; -CF_3; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, naphthyl group, –CF_3, –OCF_3, –NO_2, –CN, or –$N(CH_3)_2$;

R_{aa} is a C_1 to C_6 alkyl group; a naphthyl group; -CF_3; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, naphthyl group, –CF_3, –OCF_3, –NO_2, –CN, or –$N(CH_3)_2$;

R_b is a hydroxyl group or pyrrolyl group; and

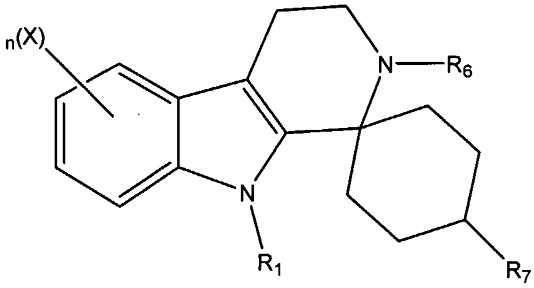
n is 0, 1, 2, 3 or 4;

R_6 is hydrogen; a C_1 to C_6 alkyl group, optionally substituted with a C_6 to C_8 aryl group, wherein the aryl group is optionally substituted with at least one halogen; –C(O)–R_a; –C(O)O–R_{aa}; –C(O)–NH–R_c; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen; and

R_c is a C_1 to C_6 alkyl or C_5 to C_6 cycloalkyl;

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compounds.

In a further embodiment, the present invention also includes and provides compounds of Formula (IIIa)



(IIIa)

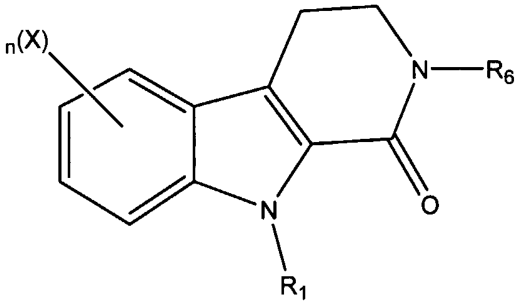
wherein

X, R_1, R_6, and n are as described above with regard to Formula (III); and

R_7 is hydrogen, a phenyl, or a benzyl group;

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compounds of Formula (IIIa).

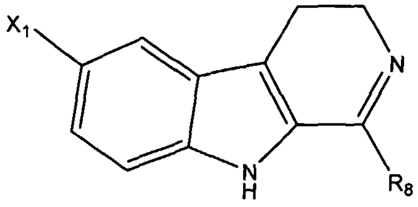
In another embodiment, the present invention also includes and provides compounds of Formula (IIIb)



(IIIb)

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compounds of Formula (IIIb).

In a further embodiment, the present invention includes and provides compounds of Formula (IV)



(IV)

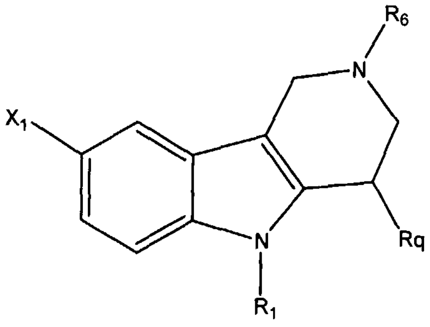
wherein

X_1 is a halogen; and

R_8 is a C_6 to C_8 aryl group, optionally substituted with at least one halogen or alkoxy group.

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compounds.

In yet another embodiment, the present invention includes and provides compounds of Formula (V)



(V)

wherein

X_1 is a halogen;

R_1 is a hydrogen; a C_1 to C_6 alkyl group, optionally substituted with at least one halogen or a C_6 to C_8 aryl group, wherein the aryl group is optionally substituted with at least one halogen; a C_6 to C_8 aryl group, optionally substituted with at least one halogen; $-C(O)-R_a$; $-C(O)O-R_{aa}$; or $-S(O_2)-$aryl;

R_a is a C_1 to C_6 alkyl group; a C_1 to C_5 alkoxy group; a naphthyl group; $-CF_3$; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, naphthyl group, $-CF_3$, $-OCF_3$, $-NO_2$, $-CN$, or $-N(CH_3)_2$;

R_{aa} is a C_1 to C_6 alkyl group; a naphthyl group; $-CF_3$; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, naphthyl group, $-CF_3$, $-OCF_3$, $-NO_2$, $-CN$, or $-N(CH_3)_2$;

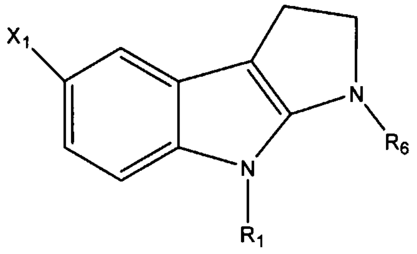
R_6 is hydrogen; a C_1 to C_6 alkyl group, optionally substituted with a C_6 to C_8 aryl group, wherein the aryl group is optionally substituted with at least one halogen; –C(O)–R_a; –C(O)O–R_{aa}; –C(O)–NH–R_c; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen;

R_c is a C_1 to C_6 alkyl or C_5 to C_6 cycloalkyl; and

R_q is hydrogen, phenyl, or -OH;

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compounds.

In another embodiment, the present invention includes and provides compounds of Formula (VI)



(VI)

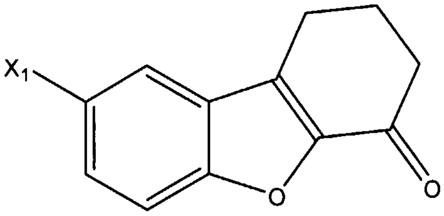
wherein

X_1 is a halogen; and

R_1 and R_6 are as defined above with regard to Formula (III);

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compounds.

In another embodiment, the present invention includes and provides compounds of Formula (VII)

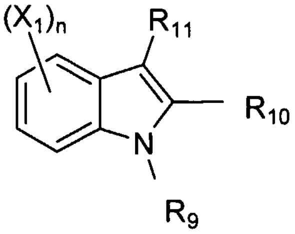


(VII)

wherein X_1 is a halogen;

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compounds.

In still other embodiments, the present invention includes and provides compounds of Formula (VIII)



(VIII)

wherein

X_1 is a halogen;

R_9 is hydrogen or –C(O)–alkyl;

R_{10} is hydrogen; $-CH_2-R_d$; $-C(O)-NH-R_d$; or $-CH_2-NH-R_d$;

R_{11} is hydrogen; a C_1 to C_6 alkyl group; $-CH=N-CH_2-CH(OH)-R_d$; or $-(CH_2)_m-NH-R_e$;

R_d is a C_6 to C_8 aryl group, optionally substituted with at least one halogen or alkoxy group;

R_e is $-C(O)-R_f$ or $-(CH_2)_p-CH(OH)-R_{ff}$;

R_f is a C_1 to C_6 alkyl group; a C_1 to C_5 alkoxy group; a pyridinyl group; a C_5 to C_8 heteroaryl group; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen or alkoxy group;

R_{ff} is a C_1 to C_6 alkyl group; a pyridinyl group; a C_5 to C_8 heteroaryl group; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen or alkoxy group;

m is 1, 2, or 3;

n is 0, 1, or 2; and

p is 1, 2 or 3;

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compounds.

In another embodiment, the present invention includes and provides the use of one or more compounds of the invention in the preparation of pharmaceutical compositions.

In a further embodiment, the present invention includes and provides pharmaceutical compositions comprising one or more compounds of the present invention.

In another embodiment of the invention, the present invention includes and provides methods for the inhibition of VEGF production, and/or the inhibition of angiogenesis, and/or the treatment of cancer, diabetic retinopathy, rheumatoid arthritis, psoriasis, atherosclerosis, obesity, chronic inflammation or exudative macular degeneration using one or more compounds or one or more pharmaceutical compositions of the present invention. In yet another embodiment of the invention, the present invention includes and provides methods for the inhibition of VEGF production, and/or the inhibition of angiogenesis, and/or the treatment of cancer, diabetic retinopathy, rheumatoid arthritis, psoriasis, atherosclerosis, obesity, chronic inflammation or exudative macular degeneration using one or more compounds and one or more pharmaceutical compositions of the present invention.

In another embodiment, the present invention includes and provides methods for inhibition of VEGF production. In another embodiment, the present invention includes and provides methods for inhibition of angiogenesis. In one embodiment, the invention is directed to methods for inhibiting VEGF production comprising administering a VEGF-inhibiting amount of at least one compound or pharmaceutical composition of the invention to a subject in need thereof.

In another embodiment, the present invention includes and provides methods for inhibiting angiogenesis comprising administering an anti-angiogenic amount of at least one compound or pharmaceutical composition of the invention to a subject in need thereof.

In an embodiment, the present invention includes and provides methods for inhibiting VEGF production and methods of inhibiting angiogenesis comprising administering a VEGF-inhibiting or angiogenesis-inhibiting amount of one or more compounds of Formula (I) to Formula (VIII) and/or one or more pharmaceutical compositions of the compounds of Formula (I) to Formula (VIII).

In another more preferred embodiment, the present invention includes and provides methods that comprise administering a therapeutically effective amount of one or more compounds selected from the group consisting of Compounds Numbers. 2, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24, or one or more pharmaceutical compositions thereof.

In another embodiment, the present invention is directed to methods for treating cancer, diabetic retinopathy, rheumatoid arthritis, psoriasis, atherosclerosis, obesity, chronic inflammation or exudative macular degeneration, the methods comprising administering a therapeutically effective amount of one or more compound or one or more pharmaceutical composition of the invention to a subject in need thereof. In a preferred embodiment, the present invention includes and provides methods that comprise administration of a therapeutic amount of one or more compound of Formula (I) to Formula (VIII) or one or more pharmaceutical composition capable of delivering a therapeutic amount of one or more compounds of Formula (I) to Formula (VIII). In a more preferred embodiment, the present invention includes and provides methods that comprise administering a therapeutically effective amount of at least one compound selected from the group consisting of Compounds Numbers. 2, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24.

These and other aspects of the invention will be more clearly understood with reference for example, to the following preferred embodiments, detailed description, and claims.

CERTAIN EMBODIMENTS

Embodiment 1. A method for inhibiting VEGF production in a subject, comprising administering a VEGF-inhibiting amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII) or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

Embodiment 2. A method for inhibiting angiogenesis in a subject, comprising administering an anti-angiogenic amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

Embodiment 3. A method for treating cancer in a subject, comprising administering a therapeutically effective amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

Embodiment 4. A method for treating diabetic retinopathy in a subject, comprising administering a therapeutically effective amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

Embodiment 5. A method for treating exudative macular degeneration in a subject, comprising administering a therapeutically effective amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

Embodiment 6. A method for treating rheumatoid arthritis in a subject, comprising administering a therapeutically effective amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

Embodiment 7. A method for treating psoriasis in a subject, comprising administering a therapeutically effective amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

Embodiment 8. A method for atherosclerosis in a subject, comprising administering a therapeutically effective amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

Embodiment 9. A method for treating obesity in a subject, comprising administering a therapeutically effective amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

Embodiment 10. A method for treating chronic inflammation in a subject, comprising administering a therapeutically effective amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

Embodiment 11. A method according to any of embodiments 1-10, wherein the compound is compounds Numbers. 2, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24.

Embodiment 12. A pharmaceutical composition comprising a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, and a pharmaceutically acceptable excipient.

Embodiment 13. A pharmaceutical composition according to embodiment 12, wherein the compound is selected from the group consisting of compound Numbers 2, 4 5, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24.

DETAILED DESCRIPTION OF THE INVENTION

Up-regulation of Vascular Endothelial Growth Factor (VEGF), a key factor for angiogenesis, is an important contributor to the pathogenesis of cancers, diabetic retinopathy, and exudative macular degeneration (reviewed for example in 1-7). In accordance with the present invention, compounds that inhibit the expression of VEGF post-transcriptionally have been identified, and methods for their use provided. The compounds of the invention have low nanomolar activity for the inhibition of VEGF expression.

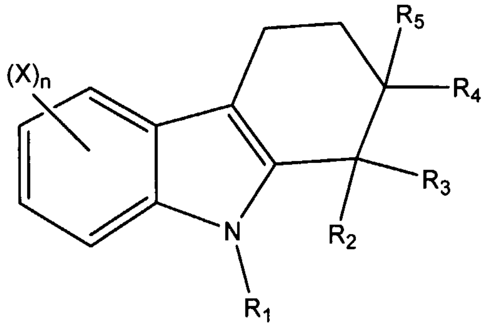
As recognized by one of skill in the art, certain compounds of the invention may include a chiral center, and as such may exist as racemic mixtures or as enantiomerically pure compositions. For example, the compounds may exist as R or S isomers in enantiomerically pure compositions. As used herein, "enantiomerically pure" refers to compositions consisting substantially of a single isomer, preferably consisting of 75%, 80%, 85%, 90%, 92%, 95%, 98%, 99%, or 100% of a single isomer.

A. Compounds of the Invention

In one aspect of the invention, compounds of the invention are provided which are useful in the inhibition of VEGF production or in the inhibition of angiogenesis or in the inhibition of VEGF production and in the inhibition of angiogenesis. In another aspect of the invention, compounds of the invention are provided which are useful in the treatment of cancer, diabetic retinopathy or exudative macular degeneration or in the treatment of any combination of cancer, diabetic retinopathy or exudative macular degeneration.

In an embodiment, the compounds of the invention specifically inhibit VEGF production. In another embodiment, the compounds of the invention inhibit VEGF expression as well as that of other angiogenesis factors such as for example FGF-2. In this regard, pan-angiogenic inhibitors may be preferred in methods of inhibiting tumor growth, while VEGF specific inhibitors may be preferred for the treatment of ocular neovascular disorders (17).

Preferred compounds of the present invention useful in the inhibition of VEGF production include those of Formula (I) as shown below.



(I)

wherein

X is hydrogen; a hydroxyl group; a halogen; a nitro group; a cyano group; a C_1 to C_5 alkoxy group, optionally substituted with at least one halogen; a C_1 to C_6 alkyl group, optionally substituted with at least one halogen; an optionally substituted amine; an optionally substituted carbonyl; or an optionally substituted sulfonyl;

R_1 is a hydrogen; a C_1 to C_6 alkyl group, optionally substituted with at least one halogen or a C_6 to C_8 aryl group, wherein the aryl group is optionally substituted with at least one halogen; a C_6 to C_8 aryl group, optionally substituted with at least one halogen; $-C(O)-R_a$; $-C(O)O-R_{aa}$; or $-S(O_2)-$aryl;

R_2 is hydrogen; C_1 to C_4 alkyl; or may be taken together with R_3;

R_3 is hydrogen; C_1 to C_4 alkyl; a C_6 to C_8 aryl group, optionally substituted with at least one halogen or C_1 to C_5 alkoxy group; or R_3 may be taken together with R_2 to form (=O), $=N-R_b$, or a cycloalkyl group, optionally substituted with a C_1 to C_6 alkyl–C_6 to C_8 aryl group or a C_6 to C_8 aryl group;

R_4 and R_5 may each independently be hydrogen; a C_1 to C_6 alkyl group; or R_4 and R_5 may be taken together to form =CH–cycloalkyl, =CH–amino; or =CH–aryl, wherein the cycloalkyl and aryl groups are optionally substituted with at least one halogen group, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, $-CF_3$, $-OCF_3$, $-NO_2$, –CN, or $-N(CH_3)_2$, and the amino group is optionally substituted with at least one C_1 to C_4 alkyl group;

R_a is a C_1 to C_6 alkyl group; a C_1 to C_5 alkoxy group; a naphthyl group; $-CF_3$; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, naphthyl group, $-CF_3$, $-OCF_3$, $-NO_2$, –CN, or $-N(CH_3)_2$;

R_{aa} is a C_1 to C_6 alkyl group; a naphthyl group; $-CF_3$; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, naphthyl group, $-CF_3$, $-OCF_3$, $-NO_2$, –CN, or $-N(CH_3)_2$;

R_b is a hydroxy group or pyrrolyl group, and

n is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound.

In certain preferred embodiments of Formula (I), X is selected from F, Cl, Br, $-CH_3$, $-CH_2-CH_3$, $-CF_3$, and $-O-CF_3$. In other preferred embodiments of Formula (I), n is 1. In further preferred embodiments of Formula (I), X is selected from F, Cl, Br, $-CH_3$, $-CH_2-CH_3$, $-CF_3$, and $-O-CF_3$; and n is 1. In a preferred embodiment of Formula (I), X is selected from Cl or Br. In another preferred embodiment of Formula (I), X is Cl. In a further preferred embodiment of Formula (I), X is Br. In an even more preferred embodiment of Formula (I), X is selected from Cl or Br and n is 1. In another even more preferred embodiment of Formula

(I), X is Cl and n is 1. In another even more preferred embodiment of Formula (I), X is Br and n is 1.

In an embodiment of Formula (I), X is an optionally substituted amine. In an embodiment, X is a monosubstituted amine. In another embodiment, X is a disubstituted amine. In a further embodiment, X is a monoalkyl amine. In a further embodiment, X is a dialkyl amine. In an embodiment, X is a monoalkyl amine that is substituted with one or more halogens. In another embodiment, X is a dialkyl amine that is substituted with one or more halogens. In an embodiment, X is a monoalkyl amine that is substituted with one or more fluorines. In another embodiment, X is a dialkyl amine that is substituted with one or more fluorine.

In another embodiment of Formula (I), X is an optionally substituted carbonyl. In an embodiment, the carbonyl is unsubstituted and has the form –C(O)H. In an embodiment, X is a carbonyl that is substituted with a C_1 to C_6 alkyl (e.g., C(O)–(C_1 to C_6 alkyl). In another embodiment, X is a carbonyl that is substituted with a C_1 to C_6 alkyl, wherein the alkyl is substituted with one or more halogens. In another embodiment, X is a carbonyl that is substituted with a C_1 to C_6 alkyl group, wherein the alkyl group is substituted with one or more fluorines.

In another embodiment of Formula (I), X is an optionally substituted sulfonyl. In an embodiment, X is a sulfonyl substituted with a C_1 to C_6 alkyl group. In another embodiment of Formula (I), X is an optionally substituted sulfonyl. In an embodiment, X is a sulfonyl substituted with a C_1 to C_6 alkyl group, wherein the alkyl group is substituted with one or more halogens. In an embodiment, X is a sulfonyl substituted with a C_1 to C_6 alkyl group, wherein the alkyl group is substituted with one or more fluorines.

In other embodiments of Formula (I), R_1 is a hydrogen; a C_1 to C_6 alkyl group, optionally substituted with at least one halogen or a C_6 to C_8 aryl group, wherein the C_6 to C_8 aryl group is optionally substituted with at least one halogen; –C(O)–R_a; –C(O)O–R_{aa}; or –S(O_2)–aryl, wherein R_a and R_{aa} are as defined above for Formula (I).

In a preferred embodiment of Formula (I), R_1 is hydrogen. In another preferred embodiment of Formula (I), R_1 is a C_1 to C_6 alkyl group, optionally substituted with a C_6 to C_8 aryl group. In a further preferred embodiment, R_1 is a methyl group, optionally substituted with a C_6 to C_8 aryl group. In another preferred embodiment of Formula (I), R_1 is a C_1 to C_6 alkyl group, optionally substituted with a phenyl group. In another preferred embodiment of Formula (I), R_1 is a methyl group, optionally substituted with a phenyl group.

In a preferred embodiment of Formula (I), R_1 is –C(O)(O)–C_6 to C_8 aryl. In another preferred embodiment of Formula (I), R_1 is –C(O)(O)–phenyl.

In another preferred embodiment of Formula (I), R_1 is –C(O)–bicyclic aromatic group. In another preferred embodiment of Formula (I), R_1 is –C(O)–naphthyl.

In another preferred embodiment of Formula (I), R_1 is –C(O)–C_1 to C_6 alkyl. In a further preferred embodiment of Formula (I), R_1 is –C(O)–methyl.

In a preferred embodiment of Formula (I), R_1 is –C(O)–C_6 to C_8 aryl. In another preferred embodiment of Formula (I), R_1 is –C(O)–C_6 to C_8 aryl, wherein the C_6 to C_8 aryl is substituted with halogen. In another preferred embodiment of Formula (I), R_1 is –C(O)– C_6 to C_8 aryl, wherein the C_6 to C_8 aryl is substituted with chlorine or bromine. In another preferred embodiment of Formula (I), R_1 is –C(O)–C_6 to C_8 aryl, wherein the C_6 to C_8 aryl is substituted with chlorine. In another preferred embodiment of Formula (I), R_1 is –C(O)–C_6 to C_8 aryl, wherein the C_6 to C_8 aryl is substituted with bromine.

In another preferred embodiment of Formula (I), R_1 is –C(O)–C_6 to C_8 aryl, wherein the C_6 to C_8 aryl is substituted with –OCF_3. In another preferred embodiment of Formula (I), R_1 is –C(O)–phenyl, wherein the phenyl is substituted with –OCF_3.

In another preferred embodiment of Formula (I), R_1 is –C(O)–C_6 to C_8 aryl, wherein the C_6 to C_8 aryl is substituted with a halogen. In another preferred embodiment of Formula (I), R_1 is –C(O)–C_6 to C_8 aryl, wherein the C_6 to C_8 aryl is substituted with chlorine. In another preferred embodiment of Formula (I), R_1 is –C(O)–C_6 to C_8 aryl, wherein the C_6 to C_8 aryl is substituted with bromine. In another preferred embodiment of Formula (I), R_1 is –C(O)–phenyl, wherein the phenyl is substituted with a halogen. In another preferred embodiment of Formula (I), R_1 is –C(O)–phenyl, wherein the phenyl is substituted with chlorine. In another preferred embodiment of Formula (I), R_1 is –C(O)–phenyl, wherein the phenyl is substituted with bromine.

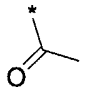
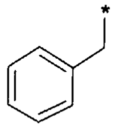
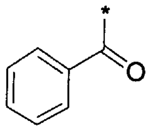
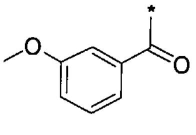
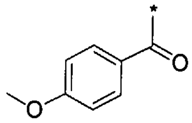
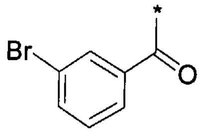
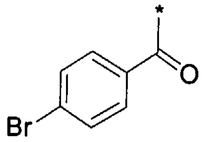
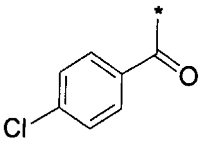
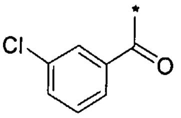
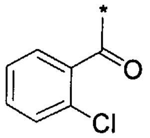
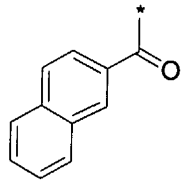
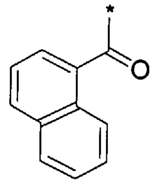
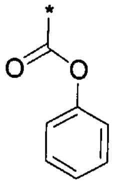
In another preferred embodiment of Formula (I), R_1 is –C(O)–C_6 to C_8 aryl, wherein the C_6 to C_8 aryl is substituted with –OCF_3. In another preferred embodiment of Formula (I), R_1 is –C(O)–C_6 to C_8 aryl, wherein the C_6 to C_8 aryl is substituted with–NO_2. In another preferred embodiment of Formula (I), R_1 is –C(O)–C_6 to C_8 aryl, wherein the C_6 to C_8 aryl is substituted with —CN. In another preferred embodiment of Formula (I), R_1 is –C(O)–phenyl, wherein the phenyl is substituted with –OCF_3. In another preferred embodiment of Formula (I), R_1 is –C(O)–phenyl, wherein the phenyl is substituted with–NO_2. In another preferred embodiment of Formula (I), R_1 is –C(O)–phenyl, wherein the phenyl is substituted with —CN.

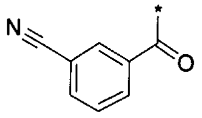
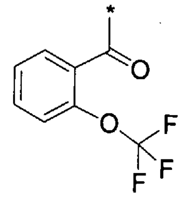
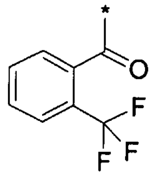
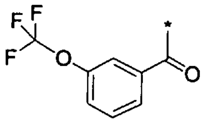
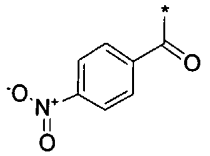
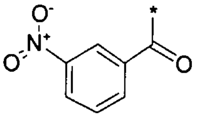
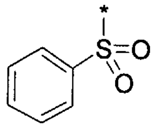
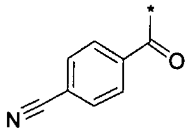
In a preferred embodiment of Formula (I), R_1 is –S(O$_2$)–aryl. In another preferred embodiment of Formula (I), R_1 is –S(O$_2$)–phenyl.

In a preferred embodiment of Formula (I), R_2 and R_3 are both hydrogens. In another preferred embodiment of Formula (I), R_2 and R_3 are taken together to form (=O). In another preferred embodiment of Formula (I), R_2 and R_3 are taken together to form =N–R_b, wherein R_b is defined as above in Formula (I). In another preferred embodiment of Formula (I), R_2 and R_3 are taken together to form =N–hydroxyl. In another preferred embodiment of Formula (I), R_2 and R_3 are taken together to form =N–pyrrolyl.

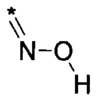
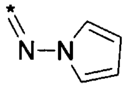
In an embodiment of Formula (I), R_4 and R_5 are taken together to form =CH–aryl and preferred aryl substituents include –CH_3, –CF_3, –NO_2, –CN, –OCH_3, –$OC(CH_3)_3$, –OCF_3, F, Br, and Cl. In another embodiment of Formula (I), R_4 and R_5 are taken together to form =CH–aryl and preferred aryl substituents are independently selected from the group consisting of F and –OCH_3. In another preferred embodiment of Formula (I), R_4 and R_5 taken together form =CH–aryl, wherein aryl is a phenyl group. In another preferred embodiment of Formula (I), R_4 and R_5 taken together form =CH–aryl, wherein aryl is substituted phenyl group, and preferred phenyl substituents include –CH_3, –CF_3, –NO_2, –CN, –OCH_3, –$OC(CH_3)_3$, –OCF_3, F, Br, and Cl. In another preferred embodiment of Formula (I), R_4 and R_5 taken together comprise a substituted phenyl group, and preferred phenyl substituents are independently selected from the group consisting of F and –OCH_3.

In another preferred embodiment of Formula (I), R_1 is selected from the following substituents:

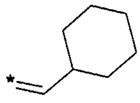
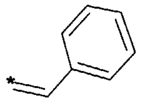
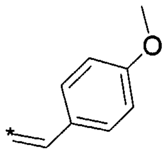
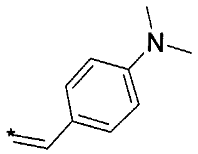
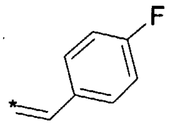
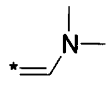
H				
				
				

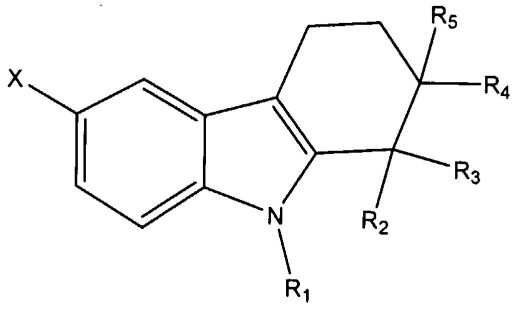
In yet another preferred embodiment of Formula (I), R_2 and R_3 together form:

In yet another preferred embodiment of Formula (I), R_4 and R_5 may be independently selected from the group consisting of:

				
	and H			

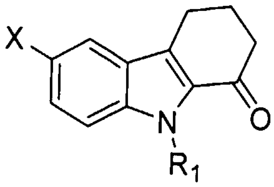
Preferred compounds within Formula (I) include the following compounds of Formula (Ia) as shown below.



(Ia)

wherein X, R_1, R_2, R_3, R_4, and R_5 are as described above with regard to Formula (I).

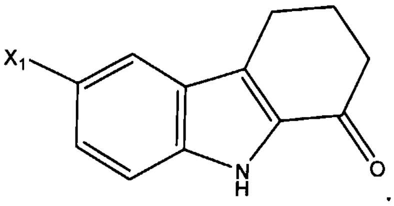
In another embodiment, preferred compounds of Formula (I) include those of Formula (Ib) as shown below



(Ib)

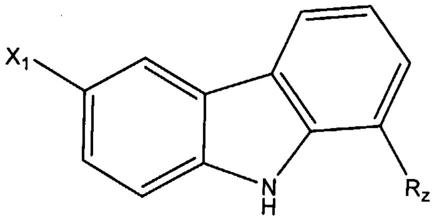
wherein R_1 is hydrogen and X is a halogen.

A preferred embodiment of compounds of formula (Ib) where R_1 is hydrogen and X_1 is a halogen is shown by the following:



In an embodiment, a compound of Formula (I) is not a compound of Formula (Ia). In another embodiment, a compound of Formula (I) is not a compound of Formula (Ib).

In yet another embodiment, preferred compounds of the invention include those of Formula (II) shown below.

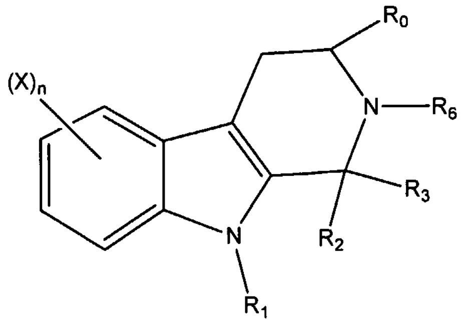


(II)

wherein X_1 is a halogen and R_z is a heteroaryl group.

In a preferred embodiment of Formula (II), X_1 is a halogen and R_z is a five to six membered heteroaryl group. In another preferred embodiment of Formula (II), X_1 is a halogen and R_z is a five to six membered heteroaryl group containing one or more endocyclic nitrogen atoms. In another preferred embodiment of Formula (II), X_1 is a halogen and R_z is a five to six membered heteroaryl group containing one endocyclic nitrogen atom. In a further preferred embodiment of Formula (II), X_1 is a halogen and R_z is a pyrrolyl group. In another preferred embodiment of Formula (II), X_1 is bromine and R_z is a pyrrolyl group.

In yet another embodiment, preferred compounds of the present invention useful in the inhibition of VEGF expression include those of Formula (III) as shown below.



(III)

wherein

X, R_1, R_2, R_3, R_a, R_{aa},R_b, and n are as described above with reference to Formula (I);

R_0 is H or –C(O)O–(C_1-C_6 alkyl);

R_6 is hydrogen; a C_1 to C_6 alkyl group, optionally substituted with a C_6 to C_8 aryl group, wherein the aryl group is optionally substituted with at least one halogen; –C(O)–R_a; –C(O)O–R_{aa}; –C(O)–NH–R_c; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen; and

R_c is a C_1 to C_6 alkyl or C_5 to C_6 cycloalkyl;

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound.

In a preferred embodiment of Formula (III), n is 1. In another preferred embodiment, n is 0.

In another preferred embodiment of Formula (III), X is a halogen. In a preferred embodiment of Formula (III), X is Br or Cl. In another preferred embodiment of Formula (III), X is Br. In another preferred embodiment of Formula (III), X is Cl.

In a preferred embodiment of Formula (III), R_1 is a hydrogen; –C(O)–R_a; –C(O)O–R_{aa}; –S(O_2)–aryl; or a C_1 to C_6 alkyl group, optionally substituted with at least one C_6 to C_8 aryl group, wherein the aryl group is optionally substituted with at least one halogen.

In a preferred embodiment of Formula (III), R_1 is –C(O)(O)–R_{aa}. In a preferred embodiment of Formula (III), R_1 is –C(O)(O)–C_6 to C_8 aryl. In a preferred embodiment of Formula (III), R_1 is –C(O)(O)–phenyl.

In a preferred embodiment of Formula (III), R_1 is a hydrogen.

In a preferred embodiment of Formula (III), R_1 is a C_1 to C_6 alkyl group, optionally substituted with at least one C_6 to C_8 aryl group, wherein the aryl group is optionally substituted with at least one halogen. In another preferred embodiment of Formula (III), R_1 is a C_1 to C_6 alkyl group, optionally substituted with at least one phenyl group, wherein the phenyl group is optionally substituted with at least one halogen. In another preferred embodiment of Formula

(III), R_1 is a C_1 to C_6 alkyl group, optionally substituted with at least one phenyl group, wherein the phenyl group is substituted with chlorine.

In another preferred embodiment of Formula (III), R_1 is a methyl group, optionally substituted with at least one phenyl group, wherein the phenyl group is optionally substituted with at least one halogen. In another preferred embodiment of Formula (III), R_1 is a methyl group, optionally substituted with at least one phenyl group, wherein the phenyl group is substituted with chlorine.

In another preferred embodiment of Formula (III), R_1 is –S(O_2)–aryl. In another preferred embodiment of Formula (III), R_1 is –S(O_2)–phenyl.

In another preferred embodiment of Formula (III), R_1 is –C(O)–R_a. In a preferred embodiment of Formula (III), R_1 is –C(O)–C_1 to C_5 alkoxy. In a preferred embodiment of Formula (III), R_1 is –C(O)–ethoxy.

In another preferred embodiment of Formula (III), R_1 is –C(O)–naphthyl.

In a preferred embodiment of Formula (III), R_1 is –C(O)–C_6 to C_8 aryl group. In another preferred embodiment of Formula (III), R_1 is –C(O)–C_6 to C_8 aryl group, wherein the C_6 to C_8 aryl group is substituted with at least one halogen. In another preferred embodiment of Formula (III), R_1 is –C(O)–C_6 to C_8 aryl group, wherein the C_6 to C_8 aryl group is substituted with chlorine or bromine. In another preferred embodiment of Formula (III), R_1 is –C(O)–C_6 to C_8 aryl group, wherein the C_6 to C_8 aryl group is substituted with chlorine. In another preferred embodiment of Formula (III), R_1 is –C(O)–C_6 to C_8 aryl group, wherein the C_6 to C_8 aryl group is substituted with bromine.

In a preferred embodiment of Formula (III), R_1 is –C(O)–C_6 to C_8 aryl group, wherein the C_6 to C_8 aryl group is substituted with a C_1 to C_5 alkoxy group. In another preferred embodiment of Formula (III), R_1 is –C(O)–C_6 to C_8 aryl group, wherein the C_6 to C_8 aryl group is substituted with a methoxy group.

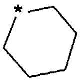
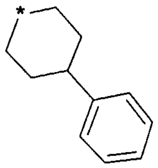
In a preferred embodiment of Formula (III), R_1 is –C(O)–C_6 to C_8 aryl group, wherein the C_6 to C_8 aryl group is substituted with –CF_3. In a preferred embodiment of Formula (III), R_1 is –C(O)–C_6 to C_8 aryl group, wherein the C_6 to C_8 aryl group is substituted with –OCF_3. In a preferred embodiment of Formula (III), R_1 is –C(O)–C_6 to C_8 aryl group, wherein the C_6 to C_8 aryl group is substituted with –NO_2. In a preferred embodiment of Formula (III), R_1 is –C(O)–C_6 to C_8 aryl group, wherein the C_6 to C_8 aryl group is substituted with –CN. In a preferred embodiment of Formula (III), R_1 is –C(O)–phenyl, wherein the phenyl group is substituted with –CF_3. In a preferred embodiment of Formula (III), R_1 is –C(O)–phenyl, wherein the phenyl group is substituted with –OCF_3. In a preferred embodiment of Formula (III), R_1 is –C(O)–

phenyl, wherein the phenyl group is substituted with $-NO_2$. In a preferred embodiment of Formula (III), R_1 is –C(O)–phenyl, wherein the phenyl group is substituted with –CN.

In a preferred embodiment of Formula (III), R_1 is –C(O)–phenyl group. In a preferred embodiment of Formula (III), R_1 is –C(O)–phenyl group, wherein the phenyl group is substituted with at least one halogen. In another preferred embodiment of Formula (III), R_1 is –C(O)–phenyl group, wherein the phenyl group is substituted with chlorine or bromine. In another preferred embodiment of Formula (III), R_1 is –C(O)–phenyl, wherein the phenyl group is substituted with chlorine. In another preferred embodiment of Formula (III), R_1 is –C(O)–phenyl, wherein the phenyl group is substituted with bromine.

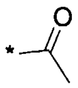
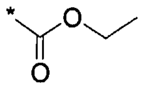
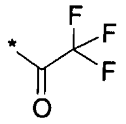
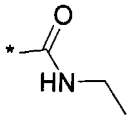
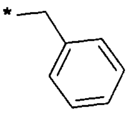
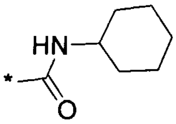
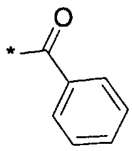
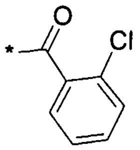
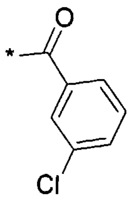
In a preferred embodiment of Formula (III), R_1 is –C(O)–phenyl, wherein the phenyl group is substituted with a C_1 to C_5 alkoxy group. In another preferred embodiment of Formula (III), R_1 is –C(O)–phenyl, wherein the phenyl group is substituted with a methoxy group.

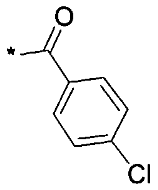
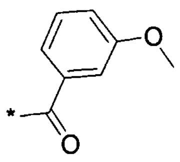
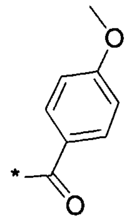
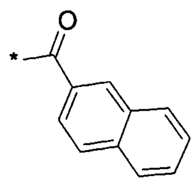
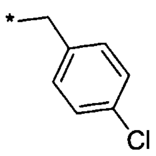
Preferred embodiments of Formula (III) include those wherein R_2 and R_3 are both hydrogen. Other preferred embodiments of Formula (III) include those wherein R_2 and R_3 are both C_1 to C_4 alkyl groups. Other preferred embodiments of Formula (III) include those wherein R_2 and R_3 are both methyl groups. Further preferred embodiments of Formula (III) include those wherein R_2 and R_3 together form:

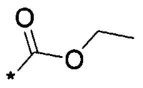
With reference to Formula (III), in an embodiment, preferred aryl substituents include: $-CH_3$, $-CF_3$, $-NO_2$, –CN, $-OCH_3$, $-OC(CH_3)_3$, $-OCF_3$, F, Br, and Cl.

In yet other preferred embodiments of Formula (III), R_6 is selected from:

H				
				

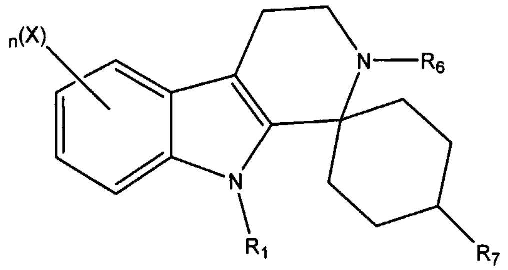
				

In other preferred embodiments of Formula (III), R_0 is hydrogen. In yet other preferred embodiments of Formula (III), R_0 is:



In yet another preferred embodiment, Formula III compounds are enantiomerically pure compositions.

Preferred compounds within Formula (III) include the following compounds of Formula (IIIa) as shown below.

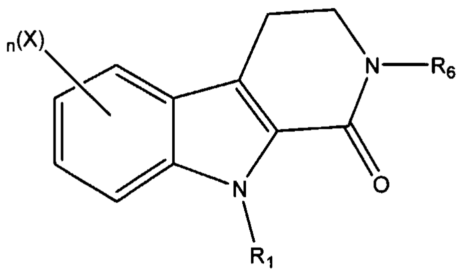


(IIIa)

wherein X, R_1, R_6, and n are as described above with regard to Formula (III), and R_7 is hydrogen, a phenyl, or a benzyl group.

In another preferred embodiment, compound of Formula (IIIa) are provided, wherein R_7 is hydrogen or a phenyl group.

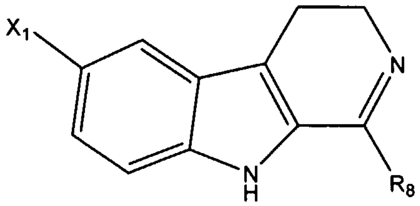
Other preferred compounds within Formula (III) include the following compounds of Formula (IIIb) as shown below.



(IIIb)

wherein X, R_1, R_6, and n are as described above with regard to Formula (III).

In another embodiment, preferred compounds of the invention include those of Formula (IV), as shown below.



(IV)

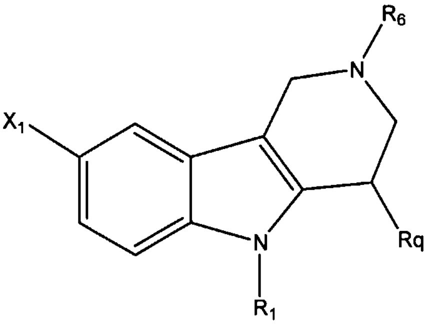
wherein

X_1 is a halogen; and

R_8 is a C_6 to C_8 aryl group, optionally substituted with at least one halogen or alkoxy group.

In a preferred embodiment of Formula (IV), X_1 is chlorine. In another preferred embodiment of Formula (IV), R_8 is a C_6 to C_8 aryl group. In another preferred embodiment of Formula (IV), R_8 is a C_6 to C_8 aryl group substituted with a C_1 to C_4 alkoxy group. In another preferred embodiment of Formula (IV), R_8 is a C_6 to C_8 aryl group substituted with a methoxy group. In another preferred embodiment of Formula (IV), R_8 is a phenyl group. In another preferred embodiment of Formula (IV), R_8 is a phenyl group substituted with a C_1 to C_4 alkoxy group. In another preferred embodiment of Formula (IV), R_8 is a phenyl group substituted with a methoxy group.

In yet another embodiment, preferred compounds of the invention include those of Formula (V), as shown below.



(V)

wherein

X_1 is a halogen;

R_q is hydrogen, phenyl, or -OH; and

R_1 and R_6 are as defined above with regard to Formula (III).

In a preferred embodiment of Formula (V), X_1 is chlorine or bromine. In another preferred embodiment, X_1 is chlorine. In a further preferred embodiment, X_1 is bromine.

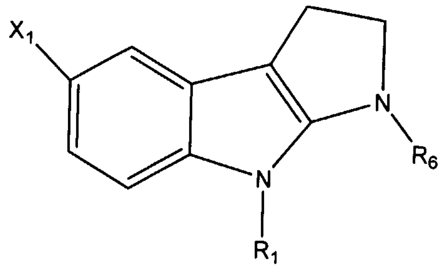
In a preferred embodiment of Formula (V), R_1 is hydrogen.

In a preferred embodiment of Formula (V), R_q is hydrogen. In another preferred embodiment of Formula (V), R_q is phenyl or -OH.

In a preferred embodiment of Formula (V), R_6 is hydrogen. In another preferred embodiment of Formula (V), R_6 is –C(O)O-alkyl. In another preferred embodiment, R_6 is -C(O)O-ethyl.

In yet another preferred embodiment, Formula V compounds are enantiomerically pure compositions.

In another embodiment, preferred compounds of the invention include those of Formula (VI) as shown below.

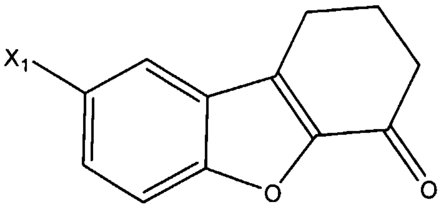


(VI)

wherein X_1 is a halogen, and R_1 and R_6 are as defined above with regard to Formula (III).

In a preferred embodiment of Formula (VI), X_1 is chlorine. In another preferred embodiment of Formula (VI), R_1 is hydrogen. In another preferred embodiment of Formula (VI), R_6 is –C(O)-R_a, wherein R_a is a C_1 to C_5 alkyl or phenyl group. In another preferred embodiment of Formula (VI), R_6 is –C(O)-R_a, wherein R_a is a C_1 to C_5 alkyl. In another preferred embodiment of Formula (VI), R_6 is -C(O)-R_a, wherein R_a is a methyl group. In a preferred embodiment of Formula (VI), R_1 is hydrogen and R_6 is -C(O)-R_a, wherein R_a is a C_1 to C_5 alkyl or phenyl group. In a preferred embodiment of Formula (VI), R_1 is hydrogen and R_6 is –C(O)-R_a, wherein R_a is a phenyl group. In a preferred embodiment of Formula (VI), R_1 is hydrogen and R_6 is –C(O)-R_a, wherein R_a is a C_1 to C_5 alkyl group. In a preferred embodiment of Formula (VI), R_1 is hydrogen and R_6 is –C(O)-R_a, wherein R_a is a methyl group.

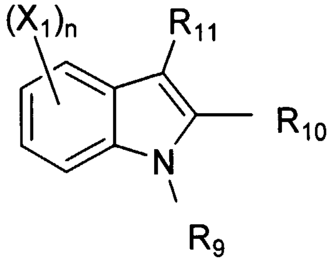
In yet another embodiment, preferred compounds of the invention include those of Formula (VII) as shown below.



(VII)

wherein X_1 is a halogen.

Yet other preferred compounds of the present invention useful in the inhibition of VEGF expression include those of Formula (VIII), as shown below:



(VIII)

wherein

X_1 is a halogen;

R_9 is hydrogen or –C(O)–alkyl;

R_{10} is hydrogen; $-CH_2-R_d$; -C(O)–NH–R_d; or $-CH_2-NH-R_d$;

R_{11} is hydrogen; a C_1 to C_6 alkyl group; $-CH=N-CH_2-CH(OH)-R_d$; or $-(CH_2)_m-NH-R_e$;

R_d is a C_6 to C_8 aryl group, optionally substituted with at least one halogen or alkoxy group;

R_e is $-C(O)-R_f$ or $-(CH_2)_p-CH(OH)-R_{ff}$;

R_f is a C_1 to C_6 alkyl group; a C_1 to C_5 alkoxy group; a pyridinyl group; a C_5 to C_8 heteroaryl group; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen or alkoxy group;

R_{ff} is a C_1 to C_6 alkyl group; a pyridinyl group; a C_5 to C_8 heteroaryl group; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen or alkoxy group;

m is 1, 2, or 3;

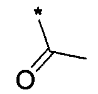
n is 0, 1, or 2; and

p is 1, 2 or 3.

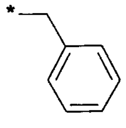
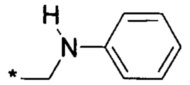
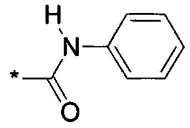
In preferred embodiments of Formula (VIII), n is 1. In other preferred embodiments of Formula (VIII), n is 0.

In preferred embodiments of Formula (VIII), X_1 is chlorine or bromine.

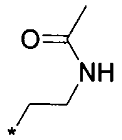
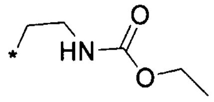
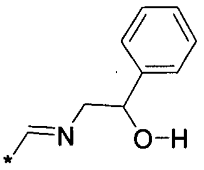
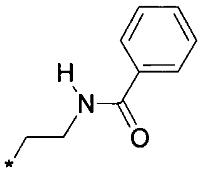
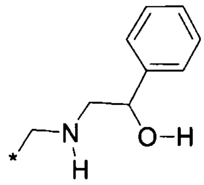
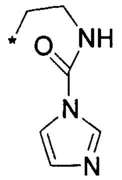
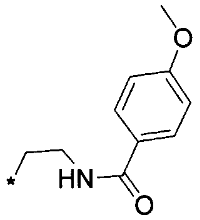
In other preferred embodiments, R_9 is selected from:

H	

In still yet other preferred embodiments of Formula (VIII), R_{10} is selected from:

		
H		

In additional preferred embodiments of Formula (VIII), R_{11} is selected from the following:

H				
				

As used herein, the term "alkyl" generally refers to saturated hydrocarbyl radicals of straight, branched or cyclic configuration including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, cyclohexyl, n-heptyl, octyl, n-octyl, and the like. In some embodiments, alkyl substituents may be C_1 to C_8, C_1 to C_6, or C_1 to C_4 alkyl groups.

In certain embodiments, the alkyl group may be optionally substituted with one or more halogen or alkoxy groups. For instance, the alkyl group may be a haloalkyl, dihaloalkyl, or trihaloalkyl.

As used herein, "alkylene" generally refers to linear, branched or cyclic alkene radicals having one or more carbon-carbon double bonds, such as C_2 to C_6 alkylene groups including 3-propenyl.

As used herein, "aryl" refers to a carbocyclic aromatic ring structure. Included in the scope of aryl groups are aromatic rings having from five to twenty carbon atoms. Aryl ring structures include compounds having one or more ring structures, such as mono-, bi-, or tricyclic compounds. Examples of aryl groups that include phenyl, tolyl, anthracenyl, fluorenyl, indenyl, azulenyl, phenanthrenyl (*i.e.*, phenanthrene), and naphthyl (*i.e.*, naphthalene) ring structures. In certain embodiments, the aryl group may be optionally substituted.

As used herein, "heteroaryl" refers to cyclic aromatic ring structures in which one or more atoms in the ring, the heteroatom(s), is an element other than carbon. Heteroatoms are typically O, S or N atoms. Included within the scope of heteroaryl, and independently selectable, are O, N, and S heteroaryl ring structures. The ring structure may include compounds having one or more ring structures, such as mono-, bi-, or tricyclic compounds. In some embodiments, the heteroaryl groups may be selected from heteroaryl groups that contain two or more heteroatoms, three or more heteroatoms, or four or more heteroatoms. Heteroaryl ring structures may be selected from those that contain five or more atoms, six or more atoms, or eight or more atoms. Examples of heteroaryl ring structures include: acridine, benzimidazole, benzoxazole, benzodioxole, benzofuran, 1,3-diazine, 1,2-diazine, 1,2-diazole, 1,4-diazanaphthalene, furan, furazan, imidazole, indole, isoxazole, isoquinoline, isothiazole, oxazole, purine, pyridazine, pyrazole, pyridine, pyrazine, pyrimidine, pyrrole, quinoline, quinoxaline, thiazole, thiophene, 1,3,5-triazine, 1,2,4-triazine, 1,2,3-triazine, tetrazole and quinazoline.

As used herein, "heterocycle" refers to cyclic ring structures in which one or more atoms in the ring, the heteroatom(s), is an element other than carbon. Heteroatoms are typically O, S or N atoms. Included within the scope of heterocycle, and independently selectable, are O, N, and S heterocycle ring structures. The ring structure may include compounds having one or more ring structures, such as mono-, bi-, or tricyclic compounds. Examples of heterocyclo groups include morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl or tetrahydrothiopyranyl and the like. In certain embodiments, the heterocycle may optionally be substituted.

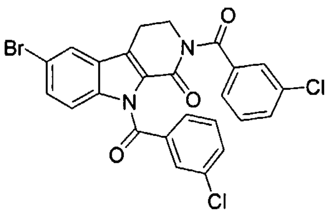
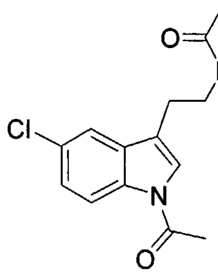
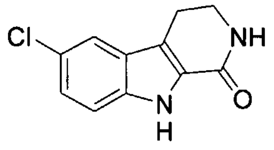
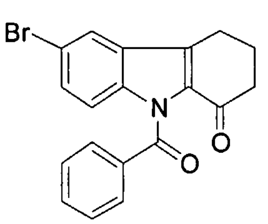
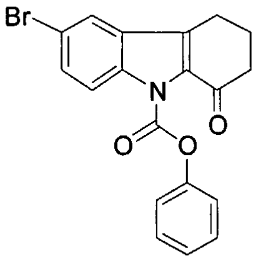
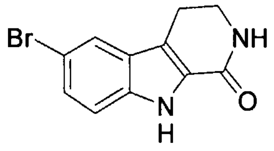
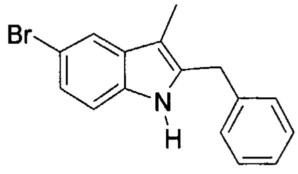
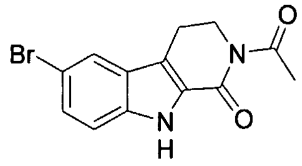
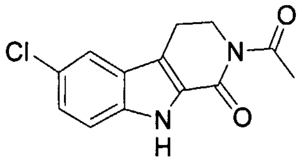
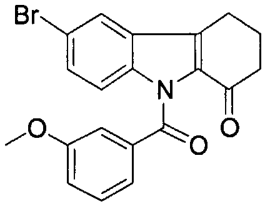
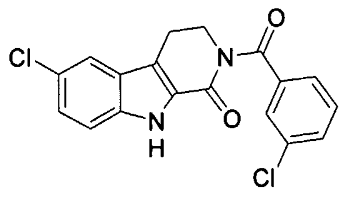
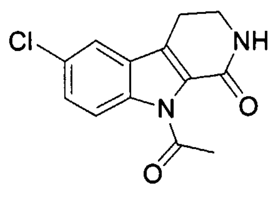
As used herein, "alkoxy" generally refers to a group with the structure –O-R. In certain embodiments, R may be an alkyl group, such as a C_1 to C_8 or C_1 to C_5 alkyl group. In certain embodiments, the R group of the alkoxy may optionally be substituted with at least one halogen. For example, the R group of the alkoxy may be a haloalkyl, dihaloalkyl, or trihaloalkyl.

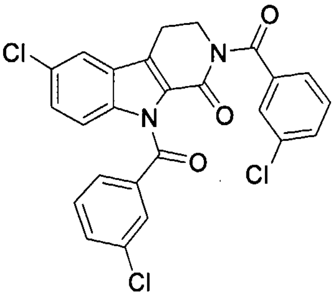
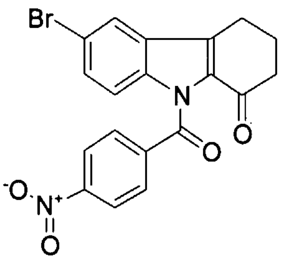
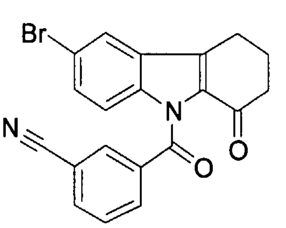
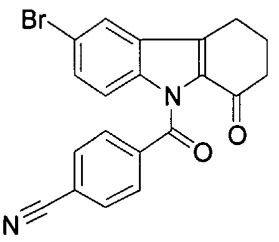
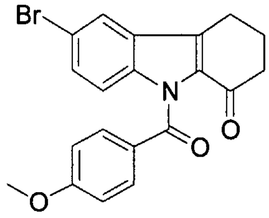
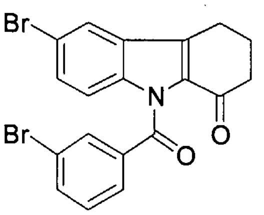
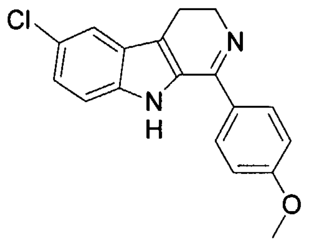
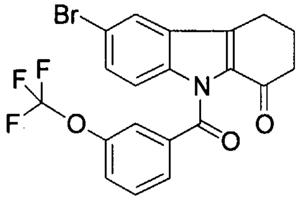
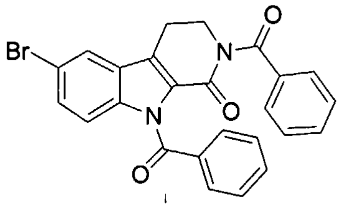
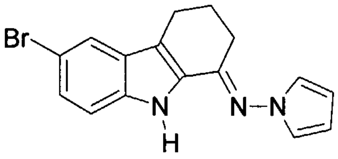
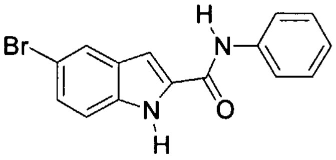
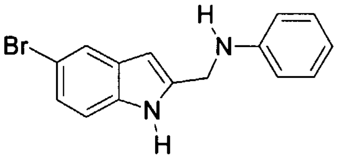
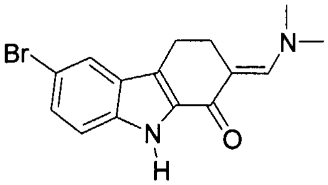
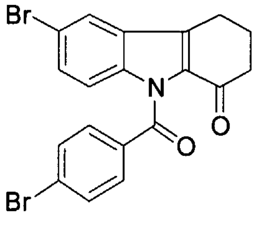
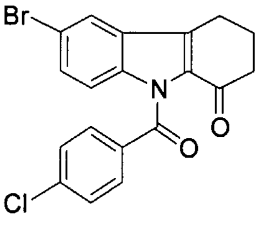
For the purposes of this invention, halo substituents may be independently selected from the halogens such as fluorine, chlorine, bromine, iodine, and astatine.

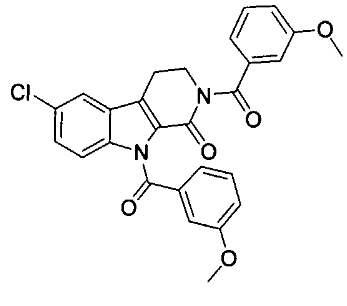
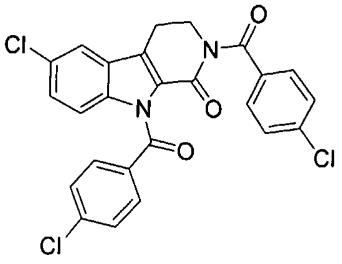
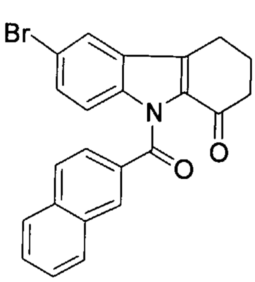
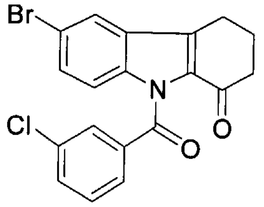
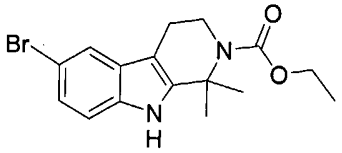
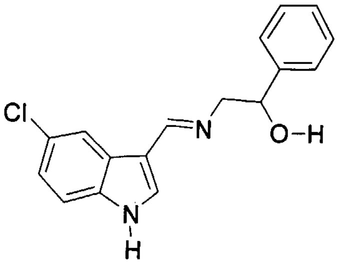
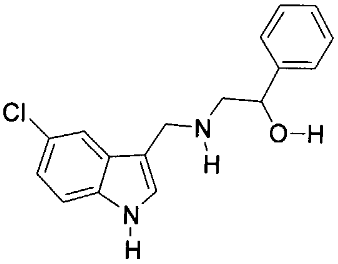
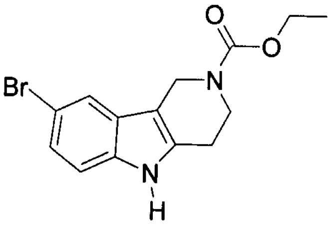
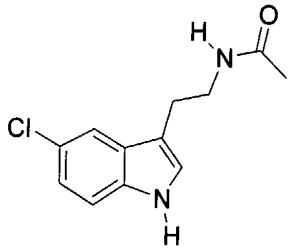
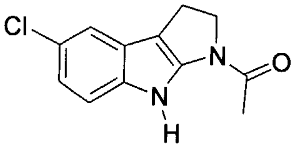
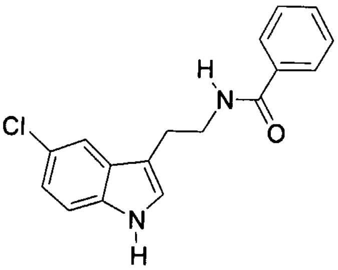
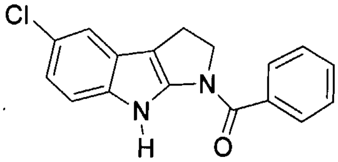
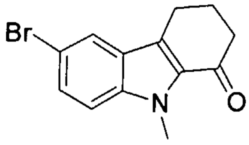
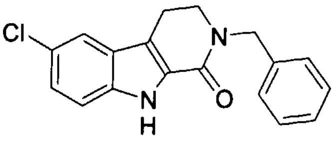
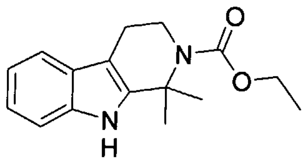
Also included within the scope of the present invention are pharmaceutically acceptable salts, hydrates, solvates, clathrates, polymorphs, racemates and stereoisomers of the compounds of Formulas (I) to (VIII).

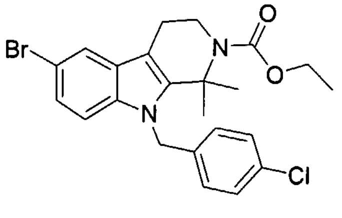
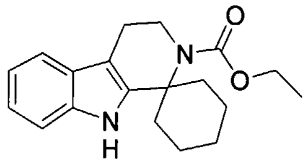
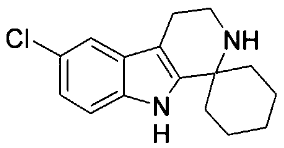
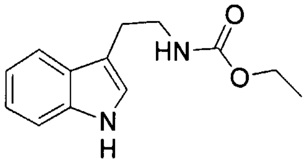
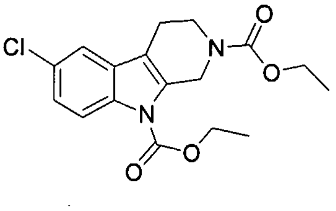
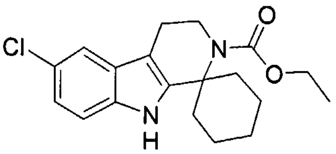
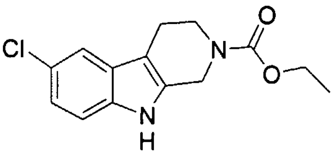
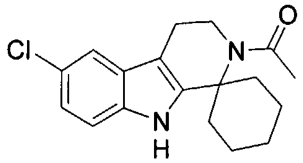
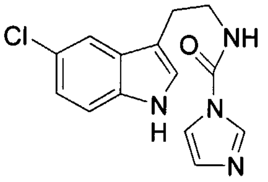
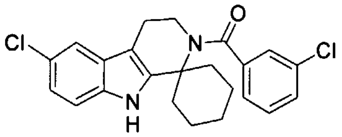
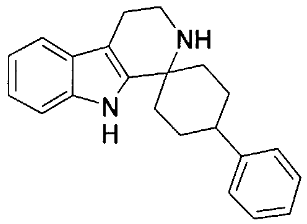
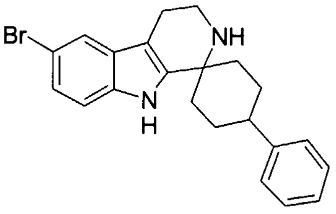
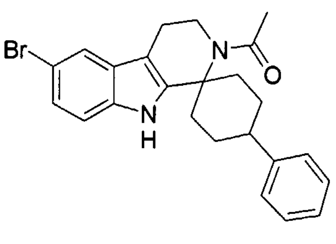
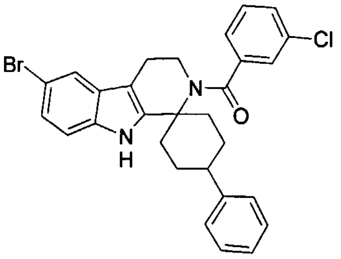
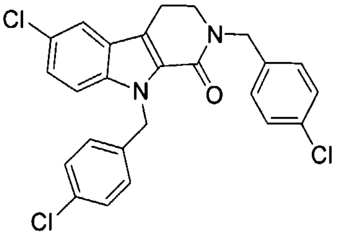
For the purposes of this invention, where one or more functionalities encompassing, such as for example without limitation, X, X_1, R_z, R_0, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_a, R_{aa}, R_b, R_c, R_d, R_e, R_f, and R_{ff} are incorporated into a molecule of Formula (I) to (VIII), including preferred embodiments, each functionality appearing at any location within the disclosed may be independently selected, and as appropriate, independently substituted. Further, where a more generic substituent is set forth for any position in the molecules of the present invention, it is understood that the generic substituent may be replaced with more specific substituents, and the resulting molecules are within the scope of the molecules of the present invention.

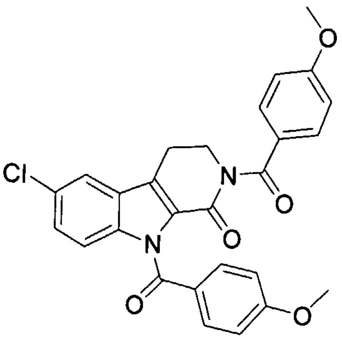
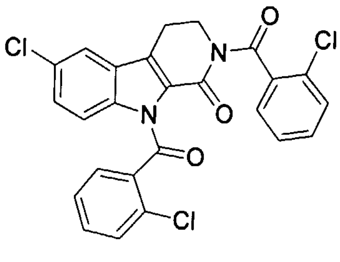
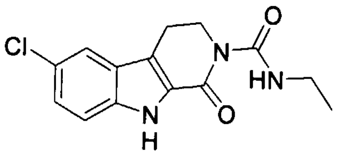
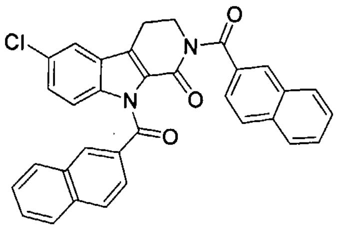
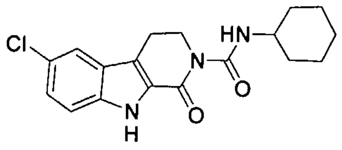
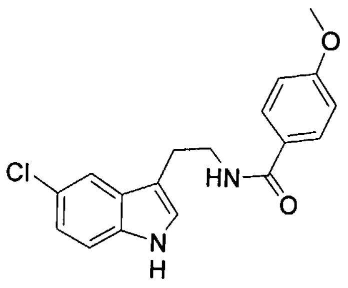
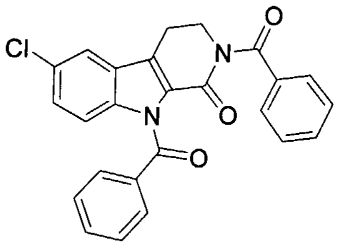
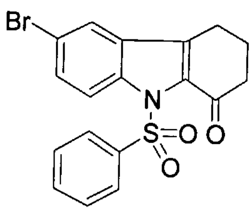
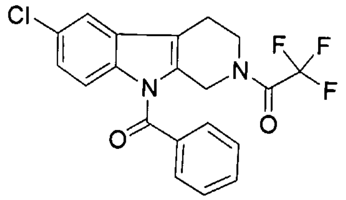
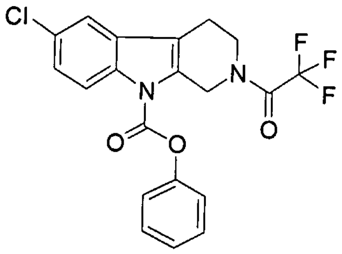
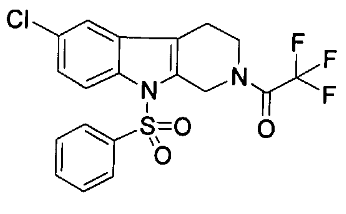
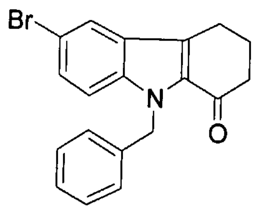
Preferred compounds of the invention include the following:

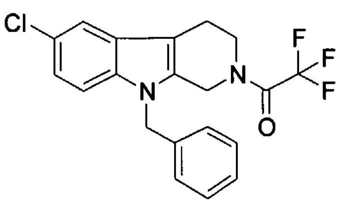
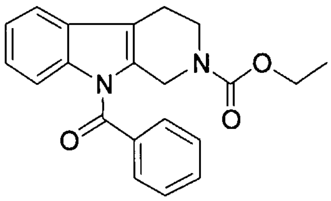
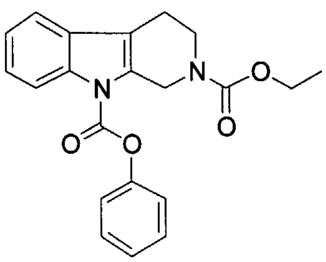
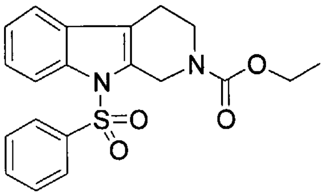
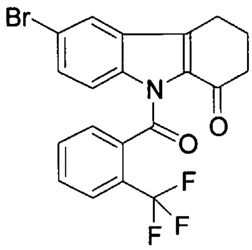
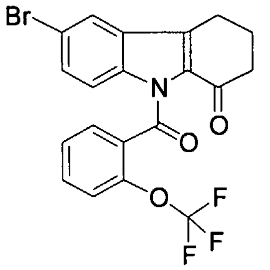
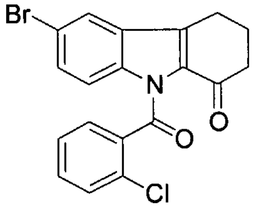
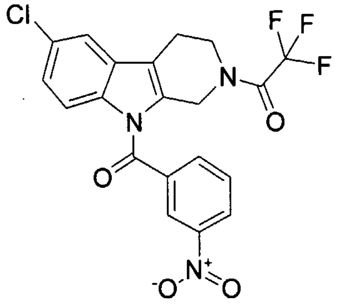
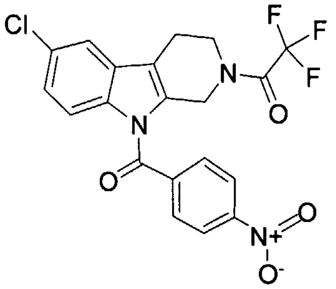
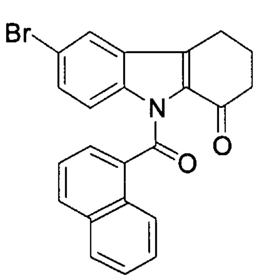
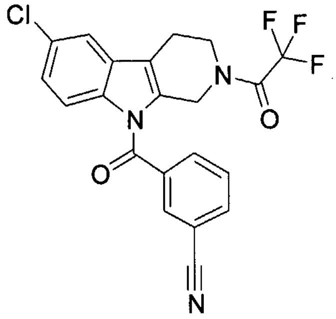
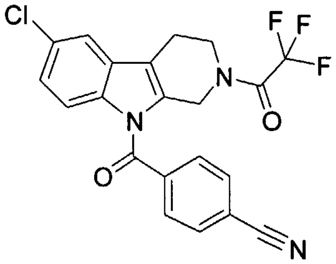
 **2**	 **4**	 **5**
 **6**	 **8**	 **9**
 **10**	 **11**	 **12**
 **13**	 **14**	 **15**

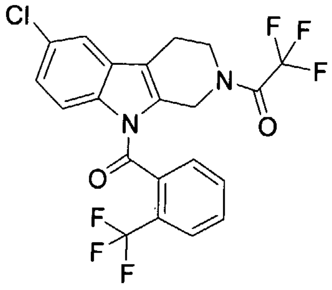
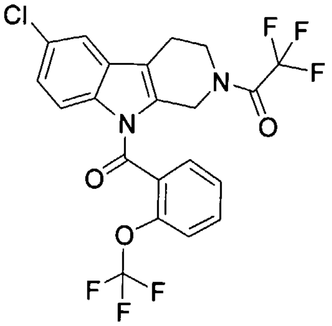
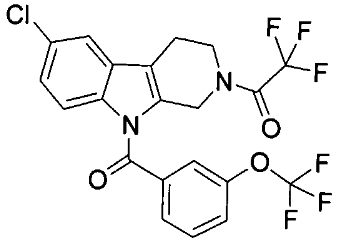
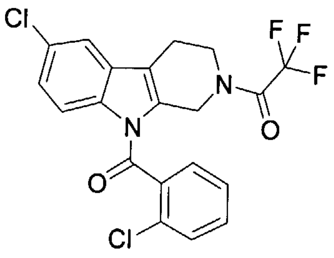
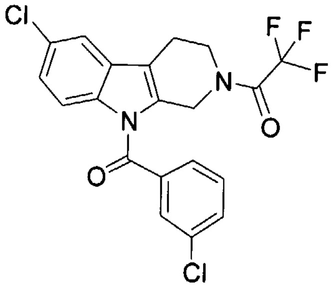
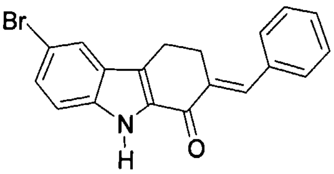
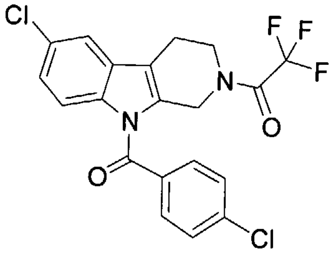
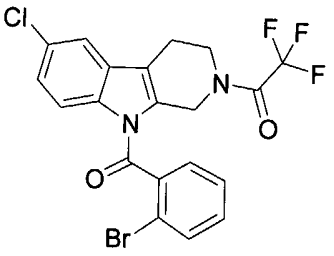
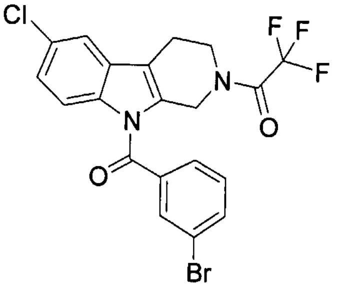
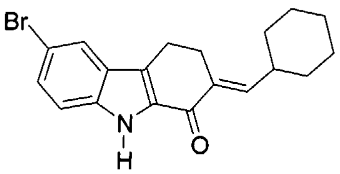
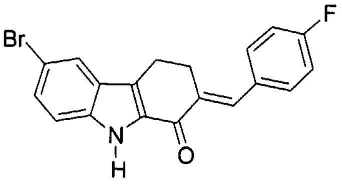
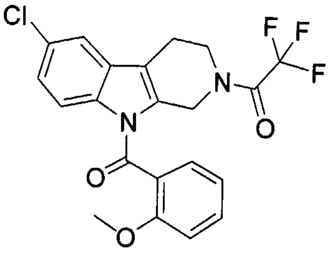
 **16**	 **17**	 **18**
 **19**	 **20**	 **21**
 **22**	 **23**	 **24**
 **27**	 **28**	 **29**
 **30**	 **32**	 **33**

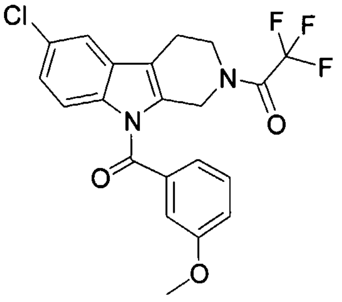
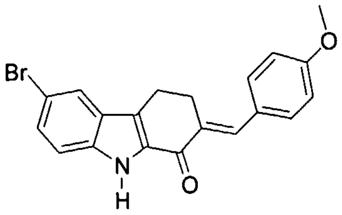
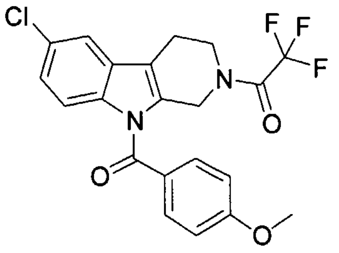
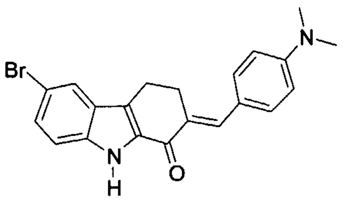
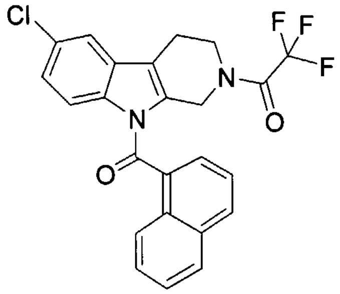
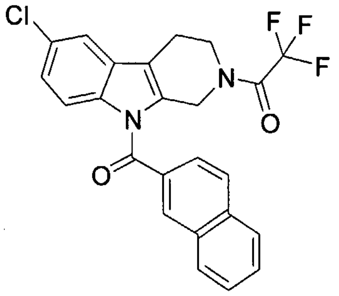
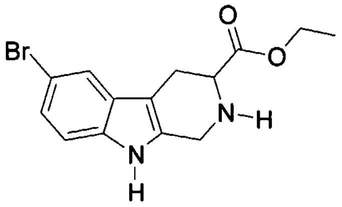
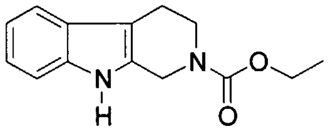
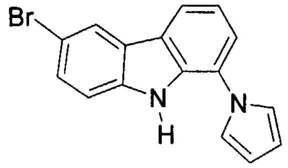
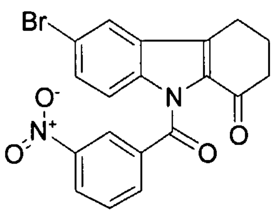
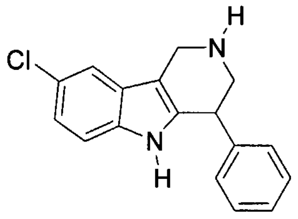
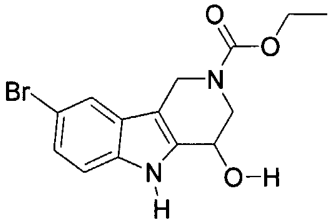
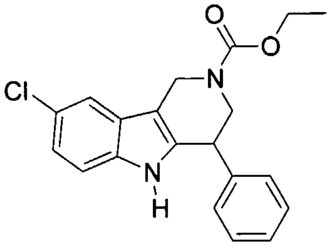
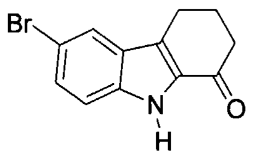
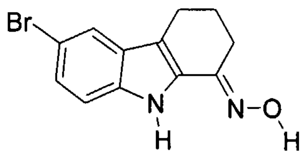
 **34**	 **35**	 **37**
 **38**	 **40**	 **43**
 **45**	 **46**	 **48**
 **49**	 **50**	 **51**
 **53**	 **56**	 **57**

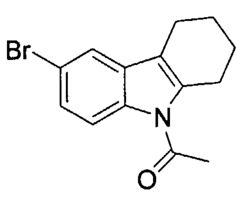
 **58**	 **59**	 **60**
 **61**	 **62**	 **63**
 **64**	 **65**	 **66**
 **67**	 **68**	 **69**
 **70**	 **71**	 **72**

 **73**	 **74**	 **75**
 **76**	 **77**	 **78**
 **79**	 **81**	 **82**
 **83**	 **84**	 **85**

 **124**	 **86**	 **87**
 88	 **89**	 **90**
 **91**	 **92**	 **93**
 **94**	 **95**	 **96**

 **97**	 **98**	 **99**
 **100**	 **102**	 **103**
 **104**	 **105**	 **106**
 **107**	 **108**	 **109**

 **110**	 **111**	 **112**
 **113**	 **114**	 **115**
 **116**	 **117**	 **119**
 **120**	 **121**	 **122**
 **123**	 **1**	 **41**

 **42**		

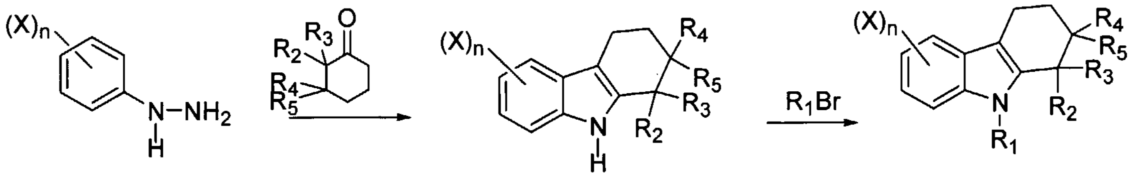
Particularly preferred compounds of the present invention are Compound Numbers: 2, 4, 5, 6, and 8 through 24.

The above compounds are listed only to provide examples that may be used in the methods of the invention. Based upon the instant disclosure, the skilled artisan would recognize other compounds intended to be included within the scope of the presently claimed invention that would be useful in the methods recited herein.

B. Preparation of Compounds of the Invention

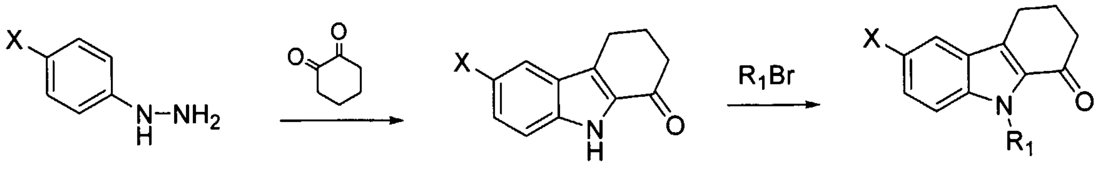
Compounds of the invention may be produced in any manner known in the art. By way of example, compounds of the invention may be prepared according to the following general schemes.

More specifically, a general scheme for preparing compounds of Formula (I) is depicted in **Scheme I** below.



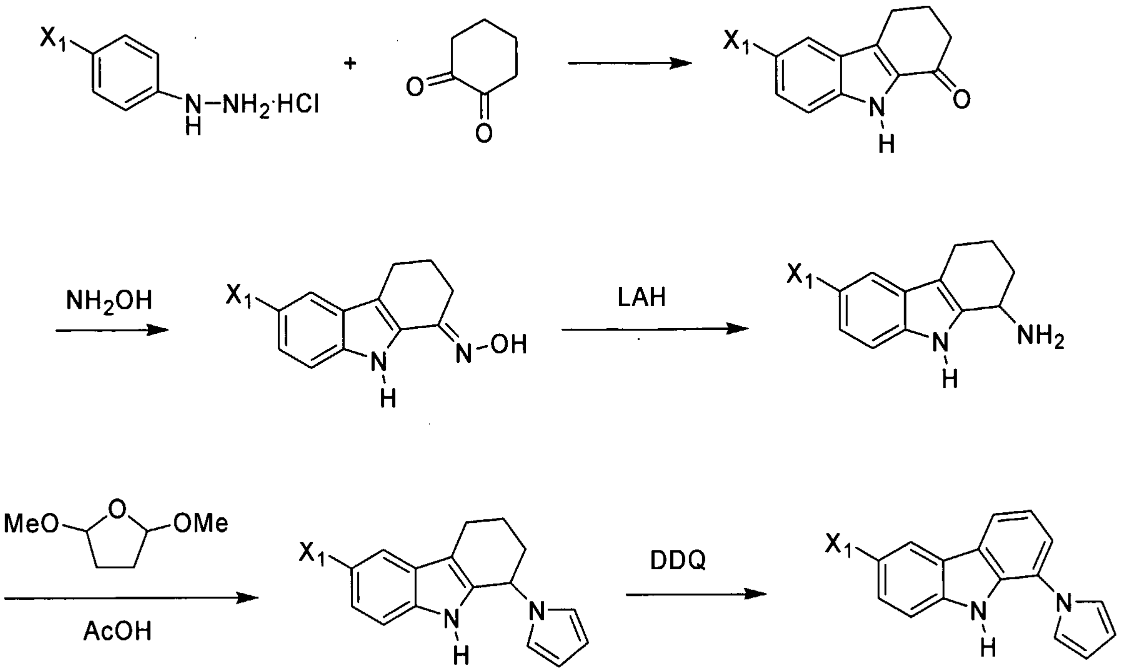
Scheme I

In another embodiment, compounds of Formula (Ib) may be prepared according to **Scheme Ib** below.



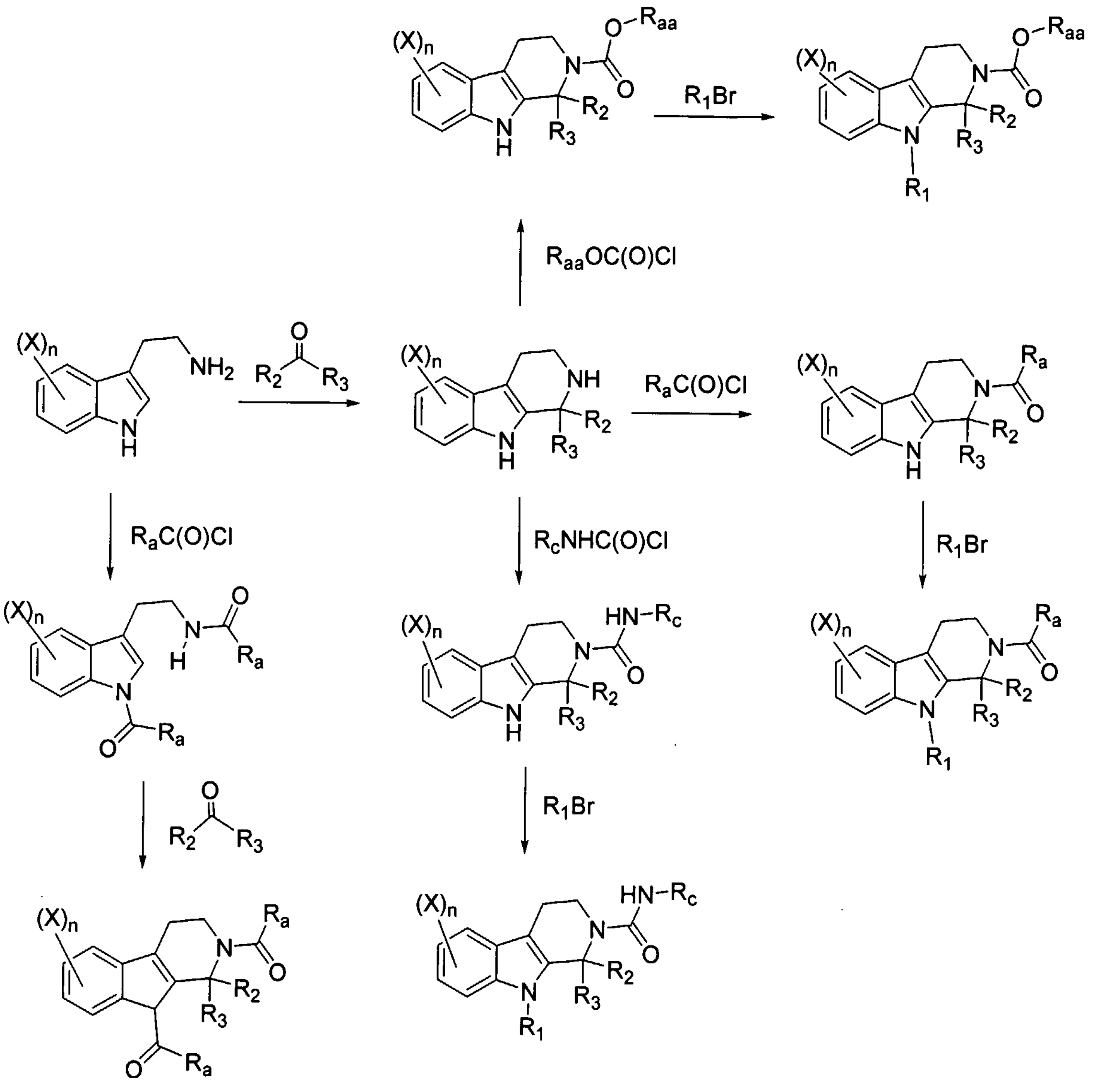
Scheme Ib

Compounds of Formula II may generally be prepared in accordance with **Scheme II**, shown below.



Scheme II

For compounds of Formula III where R_0 is hydrogen and R_6 is H, –C(O)–R_a, –C(O)O–R_{aa}, or –C(O)–NH–R_c, such compounds of Formula (III) can generally be prepared as illustrated in **Scheme III** below.

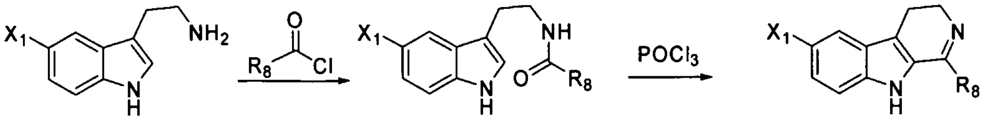


Scheme III

Scheme III shows that several compounds having identical R_1 and R_6 groups (indicated as –C(O)–R_a) may be made by reacting a 2-(1H-indol-3-yl)-ethylamine with the acid chloride R_a-C(O)Cl, followed by reaction with $R_2C(O)R_3$. Other compounds having identical R_1 and R_6 groups may be similarly prepared. For example, compounds having identical R_1 and R_6 groups of the form –C(O)O–R_{aa}, may be prepared by reacting the corresponding acid chlorides ($R_{a'}$-O-C(O)Cl) with a 2-(1H-indol-3-yl)-ethylamine, followed by a ring closure reaction with $R_2C(O)R_3$.

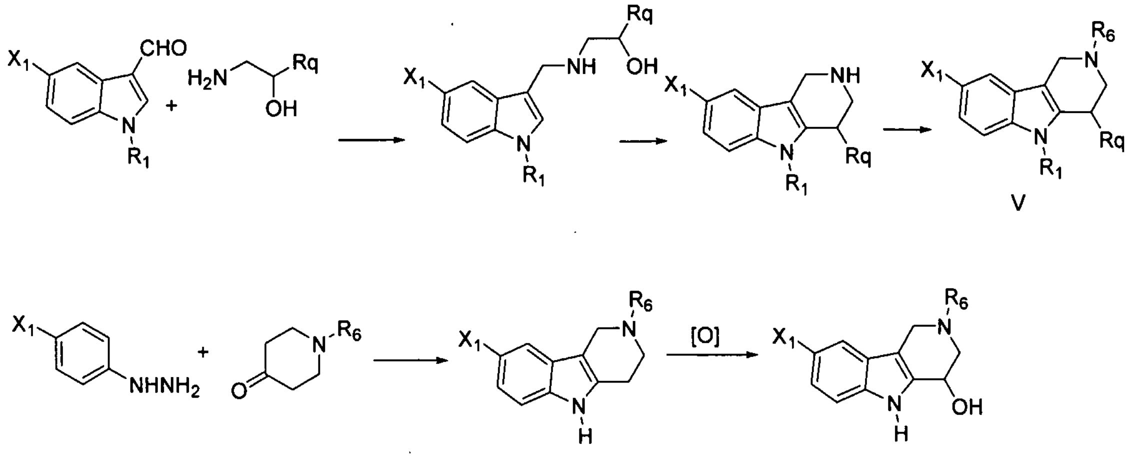
In a particular embodiment, compounds of Formula IIIb may be prepared by employing a phosgene-based procedure, exemplified for example in the synthesis of 6-bromo-2,3,4,9-tetrahydro-b-carbolin-1-one (compound 9, Example 1F).

Compounds of Formula IV can generally be prepared as illustrated in **Scheme IV** below.



Scheme IV

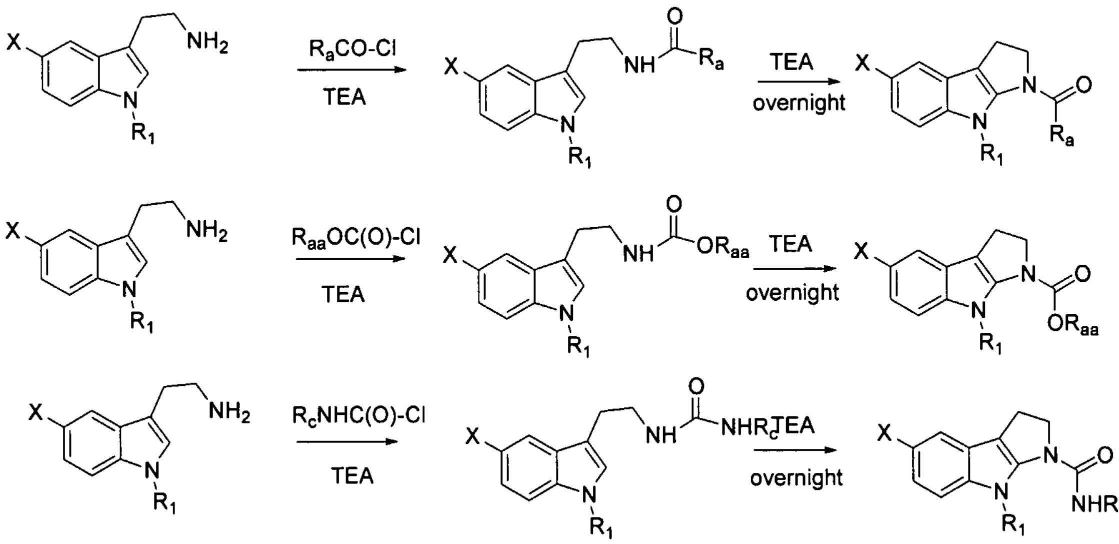
Compounds of Formula V can generally be prepared as illustrated in **Scheme V** below.



Scheme V

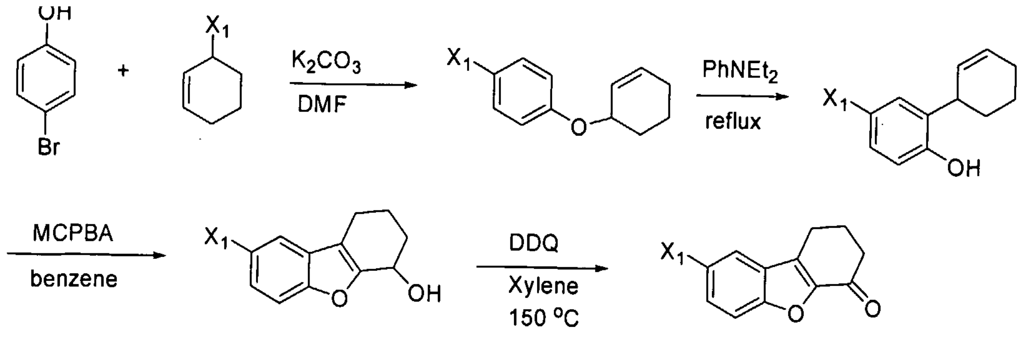
Ref: *Chem. Pharm. Bull.* 1987, 4700.

Compounds of Formula VI, for example where R_6 is –C(O)–R_a, –C(O)O–R_{aa}, or –C(O)–NH–R_c, can generally be prepared as illustrated in **Scheme VI** below.



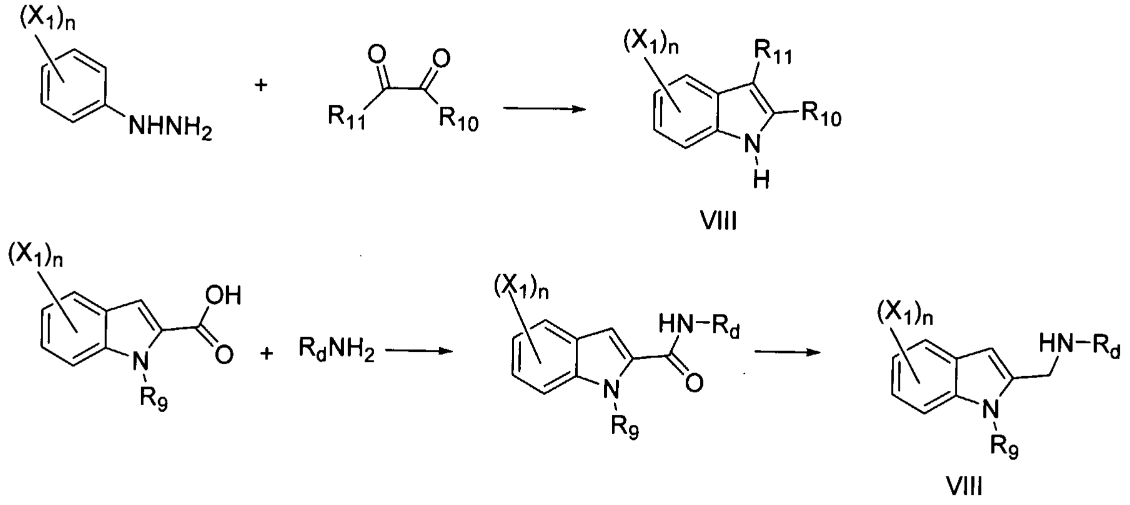
Scheme VI

Compounds of Formula VII can generally be prepared as illustrated in **Scheme VII** below.



Scheme VII

Compounds of Formula VIII can generally be prepared as illustrated in **Scheme VIII** below.



Scheme VIII

These and other reaction methodologies may be useful in preparing the compounds of the invention, as recognized by one of skill in the art. Various modifications to the above schemes and procedures will be apparent to one of skill in the art, and the invention is not limited specifically by the method of preparing the compounds of the invention.

In general, the synthesis methods described herein may employ a variety of commercially available starting materials, starting materials known in the literature, and readily-prepared starting materials prepared by employing standard synthetic methods and procedures. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard reference textbooks in the field. Although not limited to any one or several sources, recognized reference textbooks of organic synthesis include for example: Smith, M. B.; March, J. March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th ed.; John Wiley & Sons: New York, 2001; and Greene, T.W.; Wuts, P.G. M. Protective Groups in Organic Synthesis, 3rd; John Wiley & Sons:

New York, 1999. The foregoing descriptions of synthetic methods are designed to illustrate, but not limit, general procedures for the preparation of compounds of the invention.

C. Methods of the Invention

In another aspect of the invention, methods are provided for the inhibition of VEGF production. In a further aspect of the invention, methods are provided for the inhibition of angiogenesis. In yet another aspect of the present invention, methods are provided for the treatment of cancer, diabetic retinopathy, exudative macular degeneration, or any combination of such conditions by using the compounds described herein. In an embodiment, methods are provided for inhibition of both VEGF production and angiogenesis. In another embodiment, methods are provided for inhibition of VEGF production, inhibition of angiogenesis, or inhibition of both VEGF production and angiogenesis and treatment of one or more conditions selected from the group consisting of cancer, diabetic retinopathy, and exudative macular degeneration.

Without intending to be limited by theory, it is believed that the methods of the present invention act through a combination of mechanisms that modulate the activity of VEGF.

In one embodiment, the invention is directed to methods for inhibiting VEGF production comprising administering a VEGF-inhibiting amount of at least one compound of the invention to a subject in need thereof.

In another embodiment, methods for inhibiting angiogenesis are provided comprising administering an anti-angiogenic amount of at least one compound of the invention to a subject in need thereof.

In one embodiment, the methods of the invention include a method for inhibiting VEGF production in a subject, comprising administering a VEGF-inhibiting amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII) or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

In another embodiment, the methods of the invention include a method for inhibiting angiogenesis in a subject, comprising administering an anti-angiogenic amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

In another embodiment, the methods of the invention include a method for treating cancer in a subject, comprising administering a therapeutically effective amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

The methods of the invention also include a method for treating diabetic retinopathy in a subject, comprising administering a therapeutically effective amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

Another embodiment of the invention includes a method for treating exudative macular degeneration in a subject, comprising administering a therapeutically effective amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

In still another embodiment, the methods of the invention include a method for treating rheumatoid arthritis in a subject, comprising administering a therapeutically effective amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

In yet another embodiment, the methods of the invention include a method for treating psoriasis in a subject, comprising administering a therapeutically effective amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

In another embodiment, the methods of the invention include a method for treating atherosclerosis in a subject, comprising administering a therapeutically effective amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

In other embodiments, the methods of the invention include methods for treating obesity in a subject, comprising administering a therapeutically effective amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

In still other embodiment, the methods of the invention include methods for treating chronic inflammation in a subject, comprising administering a therapeutically effective amount of a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, to a subject in need thereof.

In other embodiments, methods for inhibiting VEGF production, inhibiting angiogenesis, treating cancer, diabetic retinopathy, rheumatoid arthritis, psoriasis, atherosclerosis, obesity, chronic inflammation or exudative macular degeneration are provided comprising administering a therapeutically effective amount of at least one compound of the invention to a subject in need thereof. In a preferred embodiment, one or more compounds of the invention used in the methods of the present invention is a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), or (VIII). In a more preferred embodiment, the methods of inhibiting VEGF production and/or inhibiting angiogenesis, and/or treating cancer, diabetic retinopathy, rheumatoid arthritis, psoriasis, atherosclerosis, obesity, chronic inflammation or exudative macular degeneration comprises administering a therapeutically effective amount of at least one compound selected from the group consisting of Compound Numbers. 2, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24.

According to the methods of the invention, one or more compounds may be administered to the subject via any drug delivery route known in the art. In a preferred embodiment, the subject is a mammal. In a more preferred embodiment, the subject is a human. Specific exemplary administration routes of administration include by way of non-limiting example, oral, ocular, rectal, buccal, topical, nasal, ophthalmic, subcutaneous, intramuscular, intraveneous (bolus and infusion), intracerebral, transdermal, and pulmonary.

The terms "VEGF-inhibiting amount", "anti-angiogenic amount", and "therapeutically effective amount", as used herein, refer to an amount of a pharmaceutical agent to treat, ameliorate, or prevent the identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by, for example, the assays disclosed in the following examples. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

For any compound, the therapeutically effective amount can be estimated initially either in cell culture assays, *e.g.*, of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index, and it can be expressed as the ratio, LD_{50}/ED_{50}. Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies may be used in formulating a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that include an ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

More specifically, the concentration-biological effect relationships observed with regard to the compound(s) of the present invention indicate an initial target plasma concentration ranging from approximately 5 μg/mL to approximately 100 μg/mL, preferably from approximately 10 μg/mL to approximately 50 μg/mL, more preferably from approximately 10 μg/mL to approximately 25 μg/mL. To achieve such plasma concentrations, the compounds of the invention may be administered at doses that vary from 0.1 μg to 100,000 mg, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and is generally available to practitioners in the art. In general the dose will be in the range of about 1mg/day to about 10g/day, or about 0.1g to about 3g/day, or about 0.3g to about 3g/day, or about 0.5g to about 2g/day, in single, divided, or continuous doses for a patient weighing between about 40 to about 100 kg (which dose may be adjusted for patients above or below this weight range, particularly children under 40 kg).

The exact dosage will be determined by the practitioner, in light of factors related to the subject that requires treatment. Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors, which may be taken into account, include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

D. Metabolites of the Compounds of the Invention

Also falling within the scope of the present invention are the in vivo metabolic products of the compounds described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising contacting a compound of this invention with a mammalian tissue or a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radio-labeled (*e.g.* C^{14} or H^3) compound of the invention, administering it in a detectable dose (*e.g.*, greater than about 0.5 mg/kg) to a mammal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours), and isolating its conversion products from urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, *e.g.*, by MS or NMR analysis. In general, analysis of metabolites may be done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no biological activity of their own.

E. Pharmaceutical Compositions of the Invention

While it is possible for the compounds of the present invention to be administered neat, it may be preferable to formulate the compounds as pharmaceutical compositions. As such, in yet another aspect of the invention, pharmaceutical compositions useful in the methods of the invention are provided. The pharmaceutical compositions of the invention may be formulated with pharmaceutically acceptable excipients such as carriers, solvents, stabilizers, adjuvants, diluents, *etc.*, depending upon the particular mode of administration and dosage form. The pharmaceutical compositions should generally be formulated to achieve a physiologically compatible pH, and may range from a pH of about 3 to a pH of about 11, preferably about pH 3 to about pH 7, depending on the formulation and route of administration. In another embodiment, pH may be adjusted to a range from about pH 4 to about pH 7. In alternative embodiments, it may be preferred that the pH is adjusted to a range from about pH 5 to about pH 8.

More particularly, the pharmaceutical compositions of the invention comprise a therapeutically or prophylactically effective amount of at least one compound of the present invention, together with one or more pharmaceutically acceptable excipients. Optionally, the pharmaceutical compositions of the invention may comprise a combination of compounds of the present invention, or may include a second active ingredient useful in the treatment of cancer, diabetic retinopathy, or exudative macular degeneration.

In one embodiment, a pharmaceutical composition of the invention comprises a compound selected from the group consisting of the compounds of Formula (I) to Formula (VIII), or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound, and a pharmaceutically acceptable excipient. In a more preferred embodiment, the pharmaceutical composition of the present invention comprises a pharmaceutically acceptable excipient and a compound selected from the group consisting of compound Numbers: 2, 4 5, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24.

Formulations of the present invention, *e.g.*, for parenteral or oral administration, are most typically solids, liquid solutions, emulsions or suspensions, while inhaleable formulations for pulmonary administration are generally liquids or powders, with powder formulations being generally preferred. A preferred pharmaceutical composition of the invention may also be formulated as a lyophilized solid that is reconstituted with a physiologically compatible solvent prior to administration. Alternative pharmaceutical compositions of the invention may be formulated as syrups, creams, ointments, tablets, and the like.

The term "pharmaceutically acceptable excipient" refers to an excipient for administration of a pharmaceutical agent, such as the compounds of the present invention. The term refers to any pharmaceutical excipient that may be administered without undue toxicity. Pharmaceutically acceptable excipients are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. Accordingly, there exists a wide variety of suitable formulations of pharmaceutical compositions of the present invention (*see, e.g.*, Remington's Pharmaceutical Sciences).

Suitable excipients may be carrier molecules that include large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, and inactive virus particles. Other exemplary excipients include antioxidants such as ascorbic acid; chelating agents such as EDTA; carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid; liquids such as oils, water, saline, glycerol and ethanol; wetting or emulsifying agents; pH buffering substances; and the like. Liposomes are also included within the definition of pharmaceutically acceptable excipients.

The pharmaceutical compositions of the invention may be formulated in any form suitable for the intended method of administration. When intended for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, non-aqueous solutions, dispersible powders or granules (including micronized particles or nanoparticles), emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation.

Pharmaceutically acceptable excipients particularly suitable for use in conjunction with tablets include, for example, inert diluents, such as celluloses, calcium or sodium carbonate, lactose, calcium or sodium phosphate; disintegrating agents, such as croscarmellose sodium, cross-linked povidone, maize starch, or alginic acid; binding agents, such as povidone, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example celluloses, lactose, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with non-aqueous or oil medium, such as glycerin, propylene glycol, polyethylene glycol, peanut oil, liquid paraffin or olive oil.

In another embodiment, pharmaceutical compositions of the invention may be formulated as suspensions comprising a compound of the present invention in admixture with at least one pharmaceutically acceptable excipient suitable for the manufacture of a suspension. In yet another embodiment, pharmaceutical compositions of the invention may be formulated as dispersible powders and granules suitable for preparation of a suspension by the addition of suitable excipients.

Excipients suitable for use in connection with suspensions include suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth, gum acacia, dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*, lecithin), a condensation product of an alkylene oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethyleneoxycethanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene sorbitan monooleate); and thickening agents, such as carbomer, beeswax, hard paraffin or cetyl alcohol. The suspensions may also contain one or more preservatives such as acetic acid, methyl and/or n-propyl p-hydroxy-benzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth; naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids; hexitol anhydrides, such as sorbitan monooleate; and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

Additionally, the pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous emulsion or oleaginous suspension. This emulsion or suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents, for example those which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,2-propane-diol. The sterile injectable preparation may also be prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

Generally, the compounds of the present invention useful in the methods of the present invention are substantially insoluble in water and are sparingly soluble in most pharmaceutically acceptable protic solvents and in vegetable oils. However, the compounds are generally soluble in medium chain fatty acids (*e.g.*, caprylic and capric acids) or triglycerides and have high solubility in propylene glycol esters of medium chain fatty acids. Also contemplated in the invention are compounds which have been modified by substitutions or additions of chemical or biochemical moieties which make them more suitable for delivery (*e.g.*, increase solubility, bioactivity, palatability, decrease adverse reactions, *etc.*), for example by esterification, glycosylation, PEGylation, etc.

In a preferred embodiment, the compounds of the present invention may be formulated for oral administration in a lipid-based formulation suitable for low solubility compounds. Lipid-based formulations can generally enhance the oral bioavailability of such compounds. As such, a preferred pharmaceutical composition of the invention comprises a therapeutically or prophylactically effective amount of a compound of the present invention, together with at least one pharmaceutically acceptable excipient selected from the group consisting of: medium chain fatty acids or propylene glycol esters thereof (*e.g.*, propylene glycol esters of edible fatty acids such as caprylic and capric fatty acids) and pharmaceutically acceptable surfactants such as polyoxyl 40 hydrogenated castor oil.

In an alternative preferred embodiment, cyclodextrins may be added as aqueous solubility enhancers. Preferred cyclodextrins include hydroxypropyl, hydroxyethyl, glucosyl, maltosyl, and maltotriosyl derivatives of α-, β-, and γ-cyclodextrin. A particularly preferred cyclodextrin solubility enhancer is hydroxypropyl-β-cyclodextrin (HPBC), which may be added to any of the above-described compositions to further improve the aqueous solubility characteristics of the compounds of the present invention. In one embodiment, the composition comprises 0.1% to 20% hydroxypropyl-β-cyclodextrin, more preferably 1% to 15% hydroxypropyl-β-cyclodextrin, and even more preferably from 2.5% to 10% hydroxypropyl-β-cyclodextrin. The amount of solubility enhancer employed will depend on the amount of the compound of the present invention in the composition.

F. Combination Therapy

It is also possible to combine any compound of the present invention with one or more other active ingredients useful in the treatment of cancer, including compounds, in a unitary dosage form, or in separate dosage forms intended for simultaneous or sequential administration to a patient in need of treatment. When administered sequentially, the combination may be administered in two or more administrations. In an alternative embodiment, it is possible to administer one or more compounds of the present invention and one or more additional active ingredients by different routes.

The skilled artisan will recognize that a variety of active ingredients may be administered in combination with the compounds of the present invention that may act to augment or synergistically enhance the VEGF-inhibiting and/or anti-angiogenesis activity of the compounds of the invention.

According to the methods of the invention, the combination of active ingredients may be: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by any other combination therapy regimen known in the art. When delivered in alternation therapy, the methods of the invention may comprise administering or delivering the active ingredients sequentially, *e.g.*, in separate solution, emulsion, suspension, tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, *i.e.*, serially, whereas in simultaneous therapy, effective dosages of two or more active ingredients are administered together. Various sequences of intermittent combination therapy may also be used.

To assist in understanding the present invention, the following Examples are included. The experiments relating to this invention should not, of course, be construed as specifically limiting the invention and such variations of the invention, now known or later developed, which would be within the purview of one skilled in the art are considered to fall within the scope of the invention as described herein and hereinafter claimed.

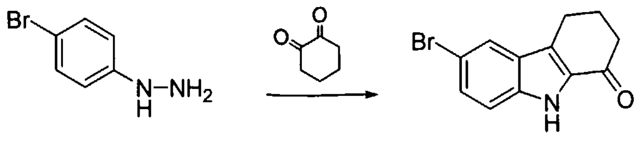
EXAMPLES

The present invention is described in more detail with reference to the following non-limiting examples, which are offered to more fully illustrate the invention, but are not to be construed as limiting the scope thereof. The examples illustrate the preparation of certain compounds of the invention, and the testing of these compounds *in vitro* and/or *in vivo*. Those of skill in the art will understand that the techniques described in these examples represent techniques described by the inventors to function well in the practice of the invention, and as such constitute preferred modes for the practice thereof. However, it should be understood that those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific methods that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1: Preparation of Compounds of the Invention

Compounds of the invention may be prepared according to the general schemes described above. By way of example, certain preferred compounds of the invention may be prepared as follows. Other preferred compounds of the invention may be similarly prepared (*e.g.*, the compounds of Table 1 below).

A. *6-Bromo-2,3,4,9-tetrahydro-carbazol-1-one (Compound 1):*

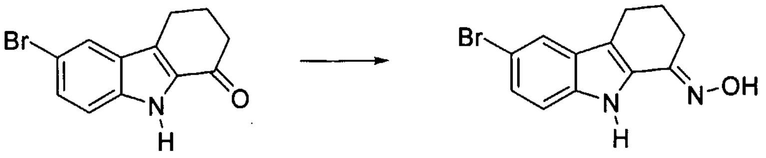


1

4-bromophenylhydrazine hydrochloride in a solution of methanol (MeOH, 250 mL) is added to a solution of 1,2-cyclohexanedione (10.03 g, 89 mmol) in a mixture of AcOH (225 mL) and con. HCl (80 mL) at 60°C over a period of 1.5 h. After the addition, the reaction mixture is stirred at room temperature overnight. The precipitated solid is filtered, washed with MeOH and dried. On evaporation, the filtrate yields a residue, which on washing with MeOH, gives additional product. The combined yield is 8.75 g (74%). ES-MS: 264.03 $(MH)^+$.

Compounds **31, 26, 25, 54 and 118** are synthesized by the same procedure using 4-trifluorophenylhydrazine, 4-chlorophenylhydrazine, 4-trifluoromethoxyphenylhydrazine, 4-methylphenylhydrazine, 2-bromophenylhydrazine and 3-bromophenylhydrazine respectively. Compound **39** is also synthesized by this procedure using 4-bromophenylhydrazine and cyclohexanone. Compound **10** is synthesized by using 4-bromophenylhydrazine and 1-phenyl-butan-2-one.

B. *6-Bromo-2,3,4,9-tetrahydro-carbazol-1-one oxime (Compound 41):*



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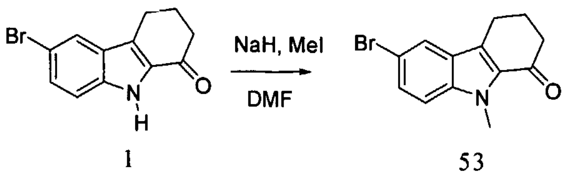
Compound **41** is prepared from Compound 1 as follows. Pyridine (5.64 ml, 39.8 mmol) is added to a mixture of Compound **1** (5.25g, 19.9 mmol) and hydroxylamine HCl salt (2.76g, 39.8 mmol) in ethanol (EtOH). The mixture is refluxed for about 1 h, and the solids are dissolved upon heating. The reaction mixture is then concentrated to dryness. The resulting sticky solid is treated and washed with hexanes (3x) to give a tan colored power of Compound **41**, 6.1g, 100%.

Compounds **44, 52** and **55** are synthesized by the same procedure as that of Compound **41**.

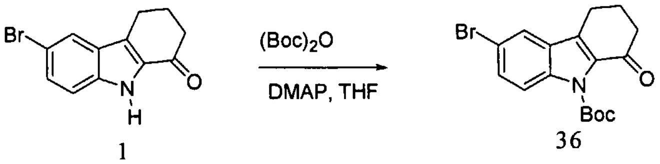
C. *6-Bromo-9-methyl-2,3,4,9-tetrahydro-carbazol-1-one (Compound 53):*

Compound **53** may be prepared as follows.



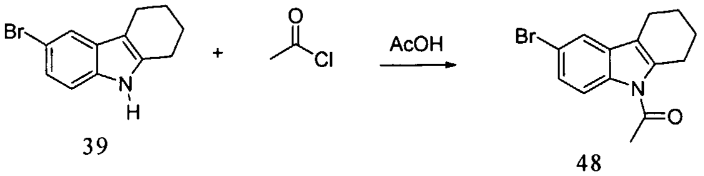
NaH (60% in mineral oil, 0.18 g, 4.5 mmol) is added to a solution of **1** (0.795 g, 3.0 mmol) in *N,N*-dimethylformamide (DMF, 20 ml) at 0 °C. The mixture is stirred at room temperature for 30 minutes, and MeI (0.56 ml, 9.0 mmol) is added. The mixture is stirred at room temperature for 2 days, quenched with water and concentrated to remove most of the DMF. The residue is taken into EtOAc, washed with saturated NH_4Cl and brine. The organics are concentrated and chromatographed (10% EtOAc in hexanes) to give **53** as a white solid, 0.27 g, 34%.

D. *6-Bromo-1-oxo-1,2,3,4-tetrahydro-carbazole-9-carboxylic acid tert-butyl ester (Compound 36):*



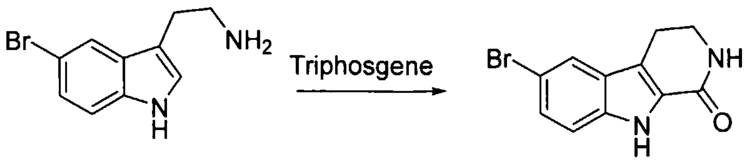
DMAP (dimethylaminopyridine, 0.55 g, 4.5 mmol) is added to a solution of **1** (0.795 g, 3.0 mmol) and Boc anhydride (di-*tert*-butyl pyrocarbonate, 0.785 g, 3.6 mmol) in THF (tetrahydrofuran, 30 ml). After stirring at room temperature for 2 days, the solution is concentrated. The residue is taken into ethyl acetate (EtOAc), washed with saturated NH_4Cl and brine. Evaporation of the solvents gives **36** as oil, 1.148 g, 100%.

E. *1-(6-Bromo-1,2,3,4-tetrahydro-carbazol-9-yl)-ethanone (Compound 48):*



To a suspension of **39** (0.75 g, 3.0 mmol) in acetic acid (3 ml) is added acetyl chloride (0.21 ml, 3.0 mmol). The mixture is heated to reflux, resulting in a clear solution. After 2 hours, the reaction solution is cooled to room temperature (rt). A solid is precipitated out. The solid **48** is filtered and washed with hexanes (2 ×), 0.24 g, 27%.

F. 6-Bromo-2,3,4,9-tetrahydro-b-carbolin-1-one (Compound 9):

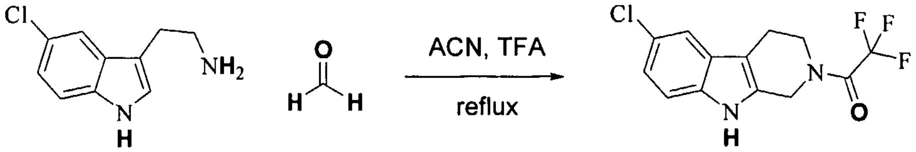


9

Triethylamine (10.92 mmol, 1.52 mL) and triphosgene (2.4 mmol, 712 mg) are added to a suspension of bromotryptamine (1g, 3.64 mmol) in 25 mL of dichloromethane at 0 °C. The suspension is stirred at room temperature for about 1 hour and concentrated under vacuum. The residue is redissolved in 20 mL of AcOH, and the solution is refluxed in oil bath at 120 °C for 2 hours followed by concentration. 1N NaOH is then added and the aqueous mixture extracted with dichloromethane. The combined organic layers are dried over K_2CO_3. The concentrated residue is recrystallized from ethyl acetate to give, e.g., 370 mg of desired product. The mother liquor is concentrated and purified on silica with 50% ethyl acetate in hexane to yield an additional amount, e.g., 220 mg, of the desired product **9**. Total 590 mg (61%).

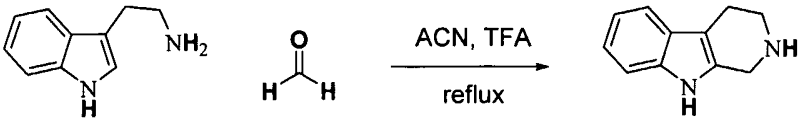
Compound **5** may be prepared in a similar manner.

G. 1-(6-Chloro-1,3,4,9-tetrahydro-β-carbolin-2-yl)-2,2,2-trifluoro-ethanone:



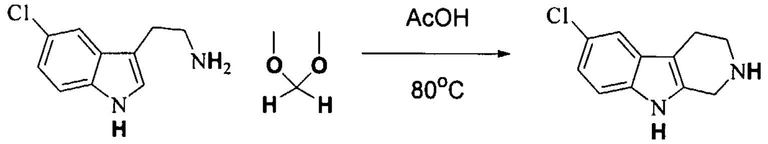
5-Chlorotryptamine hydrochloride (1.2 g, 5.14 mmol) is dissolved in 5% trifluoroacetic acid in acetonitrile and heated to reflux under nitrogen. A solution of aqueous formaldehyde (37%, 385 µL, 5.14 mmol) in acetonitrile (25 mL) is added dropwise to the heated reaction mixture over 15 minutes. After 3 hours of heating, the solvent is removed *in vacuo*, the crude mixture is taken up in ethyl acetate (200 mL), washed with saturated aqueous sodium bicarbonate (2 x 50 mL) and then brine (50 mL), and dried over anhydrous sodium sulfate. The solvent is removed *in vacuo* and purified on a silica gel column with a gradient of 10 – 20 % ethyl acetate in hexanes. The product is collected as a yellow oil (200 mg, 18%). LC/MS RT = 3.67. M/Z+ 305, 33%; 303, 100%; 190, 50%.

H. 2,3,4,9-tetrahydro-1H-β-carboline:



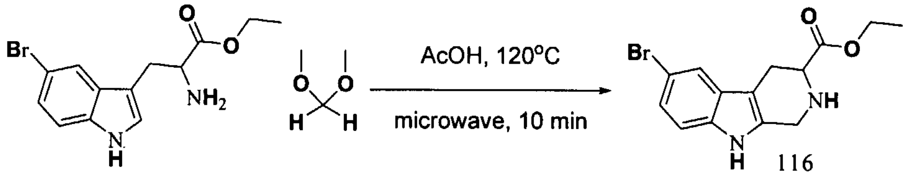
Tryptamine (1.0 g, 6.24 mmol) is suspended in 5% trifluoroacetic acid in acetonitrile (100 mL) and heated to reflux. A solution of aqueous formaldehyde (37%, 465 μL, 6.24 mmol) in acetonitrile (25 mL) is added dropwise to the heated reaction mixture over 30 minutes. After 24 hours of heating, the solvent is removed *in vacuo*, the crude mixture is taken up in ethyl acetate (50 mL), washed with saturated aqueous sodium bicarbonate (2 × 50 mL) and then brine (50 mL), and dried over anhydrous sodium sulfate. The crude brown oil (1.4 g) is used in downstream synthesis without further purification. LC/MS RT = 1.64 min. M/Z+ 173, 20%; 145, 20%; 144, 100%.

I: 6-Chloro-2,3,4,9-tetrahydro-1H-β-carboline:



5-Chlorotryptamine hydrochloride (2.0 g, 8.65 mmol) and dimethoxymethane (850 μL, 9.52 mmol) are dissolved in glacial acetic acid (50 mL) and heated to 80 °C under nitrogen. The reaction is stirred for 68 hours and cooled to room temperature. The precipitate is filtered and washed with acetonitrile (50 mL) and dried *in vacuo* to yield the product as the acetic acid salt (1.68g, 73%). LC/MS RT = 2.02 min. M/Z- 207, 33%; 205, 100%.

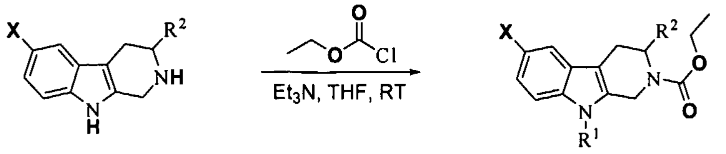
J. 6-Bromo-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid ethyl ester (Compound 116):



116

5-Bromotryptophan ethyl ester (685 mg, 2.2 mmol) and dimethoxymethane (215 μL, 2.42 mmol) are dissolved in glacial acetic acid (14 mL). The solution is divided into 7 portions and heated to 120 °C for 10 minutes in a CEM Explorer microwave synthesis system (CEM Corporation, Matthews, NC). After cooling to room temperature, the precipitate is filtered, washed with acetic acid (10 mL), and washed under a stream of nitrogen for 3 days. The product **116** is collected as the acetic acid salt (459 mg, 54%). LC/MS RT = 2.24 min. M/Z- 323, 100%; 321, 100%.

K. 6-Chloro-1,3,4,9-tetrahydro-β-carboline-2-carboxylic acid ethyl esters (Compounds 62, 64):



$X = Cl, R^1 = H, R^2 = H$: 64
$X = Cl, R^1 = CO_2Et, R^2 = H$: 62
$X = Br, R^1 = H, R^2 = H$
$X = Br, R^1 = H, R^2 = COOEt$

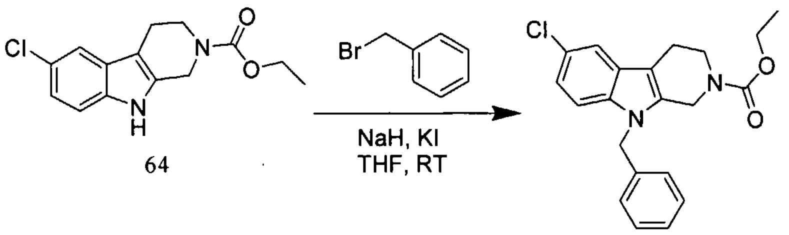
The acetic acid salt of 6-Chloro-2,3,4,9-tetrahydro-1H-β-carboline (1.79 g, 8.65 mmol) and triethylamine (6 mL, 43.3 mmol) are dissolved in dry THF (100 mL) at room temperature under nitrogen and stirred for 15 minutes. Ethyl chloroformate is added and the reaction is stirred overnight, salts are filtered off, and solvent is removed *in vacuo*. Purification by silica gel column chromatography using a gradient of 10 – 25 % ethyl acetate in hexanes yields the desired compound as an off white solid (1.0 g, 42%). LC/MS RT = 3.56 min. M/Z+ 281, 33%; 279, 100%. (114,116,117,118,119)

Compound **46** may be synthesized in a similar manner.

L. 6-Chloro-3,4-dihydro-1H-β-carboline-2,9-dicarboxylic acid diethyl ester:

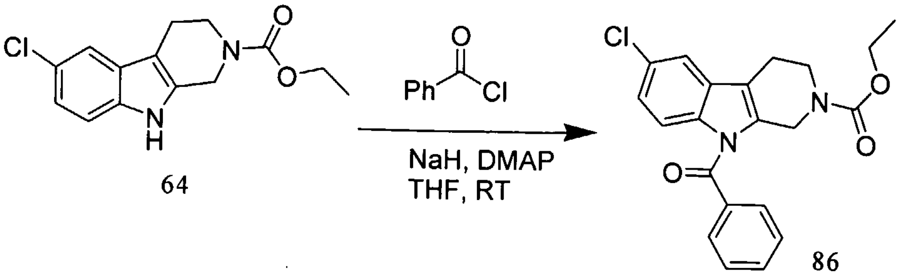
The title compound is isolated from the same silica gel column from which compound **64** is isolated. LC/MS RT = 4.17 min. M/Z+ 353, 33%; 351, 100%

M. 9-Benzyl-6-chloro-1,3,4,9-tetrahydro-b-carboline-2-carboxylic acid ethyl ester:



Compound **64** (56 mg, 0.2 mmol), a catalytic amount of potassium iodide, and benzyl bromide (50 μL, 0.4 mmol) are dissolved / suspended in THF (5 mL) at room temperature. Sodium hydride in mineral oil (60%, 25 mg, 0.6 mmol) is added to the reaction and stirred for 30 minutes at room temperature. 1 N aqueous HCl (1 mL) and water (8 mL) are added and the resulting solution is washed with dichloromethane (5 mL then 2 mL). The solvent is dried under a stream of nitrogen and purified by preparative HPLC. The final compound is collected as a glassy yellow solid (32 mg, 43%). LC/MS RT = 4.22 min. M/Z+ 371, 33%, 369, 100%.

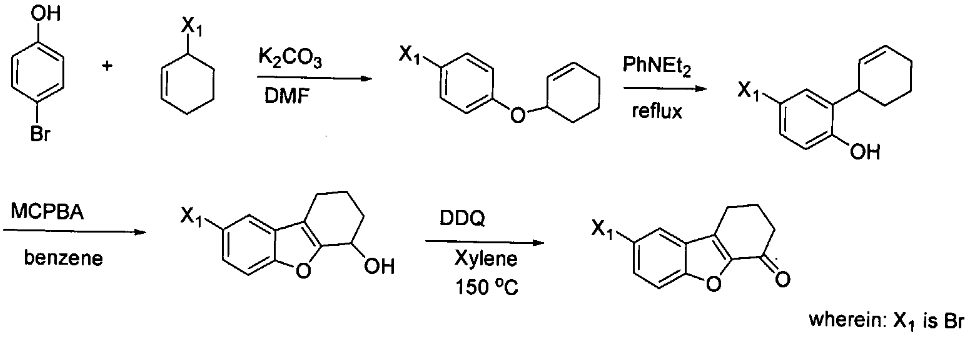
N. 9-Benzoyl-6-chloro-1,3,4,9-tetrahydro-b-carboline-2-carboxylic acid ethyl ester (Compound 86):



Compound **64** (56 mg, 0.2 mmol), a catalytic amount of 4-(dimethylamino)pyridine, and benzoyl chloride (46.5 µL, 0.4 mmol) are dissolved / suspended in THF (5 mL) at room temperature. Sodium hydride in mineral oil (60%, 25 mg, 0.6 mmol) is added to the reaction and stirred at room temperature for 20 hours. 1 N aqueous HCl (1 mL) and water (8 mL) are added and the resulting solution is washed with dichloromethane (5 mL then 2 mL). The solvent is dried under a stream of nitrogen and purified by preparative HPLC. The final compound **86** is collected as a glassy yellow solid (2 mg, 2%). LC/MS RT = 4.17 min. M/Z+ 385, 33%; 383, 100%.

Compounds **40, 57, 58, 59, 62, 63, 64, 87, 88** may be synthesized in a similar manner.

O. 8-Bromo-2,3-dihydro-1H-dibenzofuran-4-one (Compound 47):



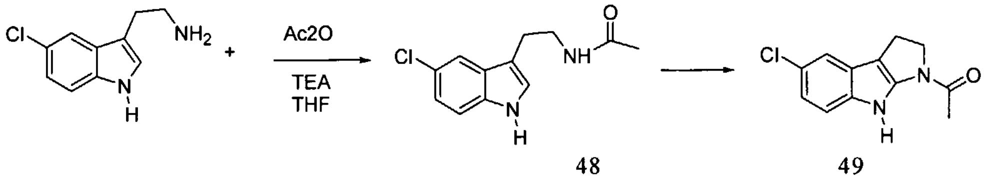
K_2CO_3 (4.15 g, 30 mmol) is added to a solution of 4-bromo-phenol (2.595 g, 15.0 mmol) and 3-bromo-cyclohexene (1.93 ml, 15.0 mmol) in DMF (50 mL). After overnight stirring at room temperature, the mixture is concentrated, dissolved in EtOAc and washed with water and brine. The organics are concentrated to give the ether as brownish oil, 3.80 g, 100%.

A solution of the ether (1.8 g, 7.1 mmol) in N,N-diethyl-aniline (10 ml) is heated at 200 °C for 7 hours. The mixture is cooled to room temperature, poured to cold 6 N HCl (50 ml) and extracted with ether (2 x). The combined organics are washed with 1 N HCl and brine, concentrated and chromatographed (10% EtOAc in hexanes) to give 4-bromo-2-cyclohex-2-enyl-phenol as clear oil, 1.70 g, 94.4%.

A solution of the phenol and MCPBA (metachloroperbenzoic acid, 3-chloroperbenzoic acid) in benzene is refluxed overnight. A solid is precipitated out and filtered. The filtrated is concentrated and chromatographed (10% EtOAc in hexanes) to give 8-bromo-1,2,3,4-tetrahydro-dibenzofuran-4-ol as clear oil, 0.66 g, 39%.

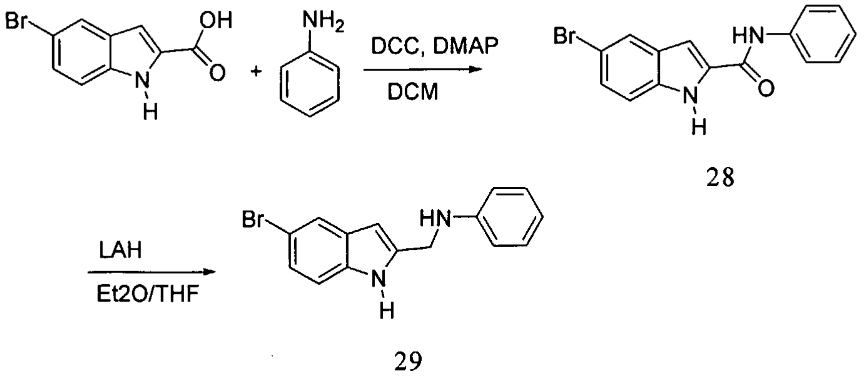
DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone 100 mg, 0.44 mmol) is added to a solution of the alcohol (70 mg, 0.26 mmol) in xylene (3.0 ml). The solution turns dark red and is refluxed for 6 h. The dark red color disappears and a light brown solid precipitates out. The mixture is filtered. The filtrate is concentrated and chromatographed to give **47** as a white solid, 50 mg, 72%.

P. 1-(5-Chloro-3,8-dihydro-2H-pyrrolo[2,3-b]indol-1-yl)-ethanone (Compounds 48, 49):



TEA (0.84 ml, 6.0 mmol) and acetic anhydride (0.24 ml, 2.5 mmol) are added to a suspension of 5-chloro-tryptamine hydrochloride (0.531 g, 2.3 mmol) in THF (20 ml). After overnight stirring at room temperature, the mixture is concentrated on rotavap, dissolved in EtOAc and washed with water and brine. The organics are dried and concentrated to **49** as oil, 0.539 g, 99%.

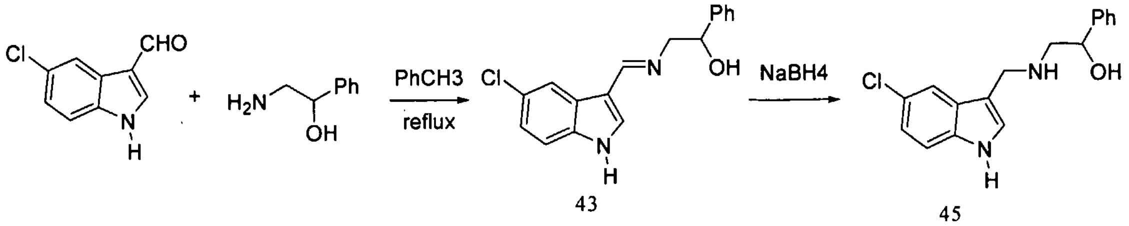
Q. (5-Bromo-1H-indol-2-ylmethyl)-phenyl-amine (Compounds 28, 29):



DMAP (22 mg, 0.2 mmol) and DCC (0.535 mg, 2.6 mmol) are added to a mixture of 5-bromo-1H-indole-2-carboxylic acid (0.48 g, 2.0 mmol) and aniline (0.20 ml, 2.2 mmol) in DCM (10 ml) at 0 °C. The mixture is stirred at room temperature for 2 hours and then concentrated by rotavap. Chromatography of the residue (5% EtOAc in hexanes) gives **28** as a yellowish solid, 0.44g, 70 %.

A solution of amide **28** in THF (10 ml) is added to a suspension of LAH (lithium aluminum hydride, 83 mg, 2.2 mmol) in ether (10 ml) at 0 °C. The mixture is heated at 50 °C overnight. The reaction mixture is quenched with water (0.08 ml), 20% NaOH (0.06 ml) and water (0.28 ml) sequentially. The white solid is filtered and washed with THF. The filtrate is concentrated. The residue is chromatographed (10% EtOAc in hexanes) to give **29** as a yellow-brown solid, 0.181 g, 54%

R. 2-[(5-Chloro-1H-indol-3-ylmethyl)-amino]-1-phenyl-ethanol (Compounds 43, 45)



A mixture of 5-chloro-1H-3-carbaldehyde (0.568 g, 3.16 mmol) and 2-amino-1-phenyl-ethanol (0.442 g, 3.22 mmol) in toluene (70 ml) is refluxed in a Dean-Stark apparatus. The solids are dissolved upon heating. After 16 hours, the reaction mixture is concentrated to give **43** as a yellowish solid, 0.93 g, 99%.

$NaBH_4$ (1.50 g, 40 mmol) is added in portions to a suspension of imine **43** (0.596 g, 2.0 mmol) in MeOH (25 ml) at 0 °C. After overnight stirring at room temperature, the mixture is quenched with water, concentrated on rotavap to remove most of the MeOH and extracted with EtOAc (3 x). The combined organics are concentrated to give a solid, which is washed with ether (3 x) to give **45** as a white solid, 0.209 g, 94 %.

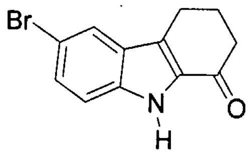
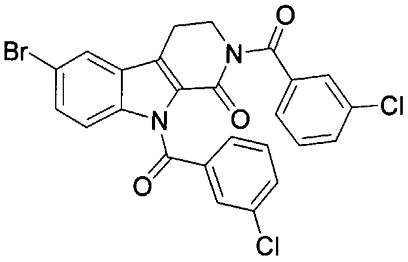
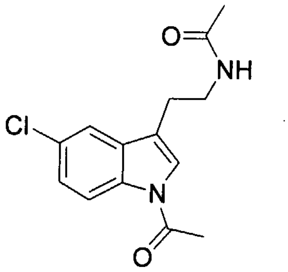
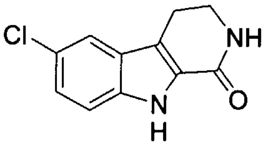
Example 2: Assay to Evaluate Effect on Hypoxia-Inducible Endogenous VEGF Expression.

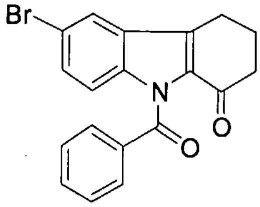
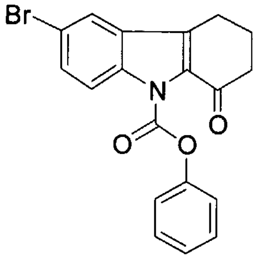
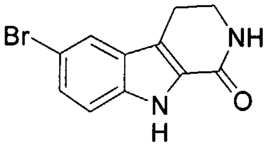
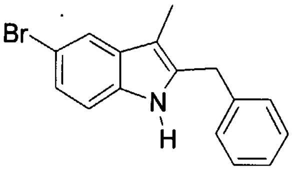
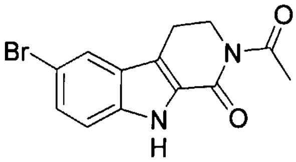
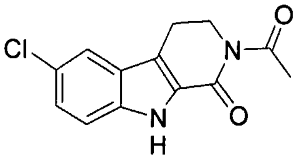
The ability of the compounds of the invention to modulate hypoxia-inducible endogenous VEGF expression may be analyzed as follows. VEGF protein levels are monitored by an ELISA assay (R&D Systems). Briefly, HeLa cells are cultured for 24-48 hours under hypoxic conditions (1% O_2, 5% CO_2, balanced with nitrogen) in the presence or absence of a compound of the invention. The conditioned media is assayed by ELISA, and the concentration of VEGF calculated from the standard ELISA curve of each assay.

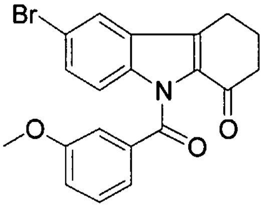
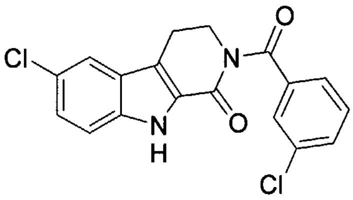
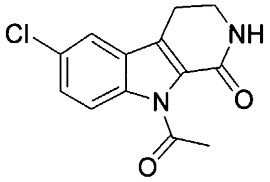
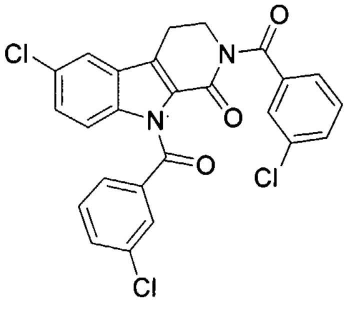
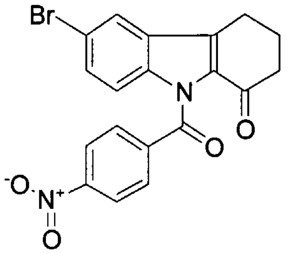
A dose-response analysis is performed using the ELISA assay and conditions described above. The conditions for the dose-response ELISA are analogous to those described above. A series of, *e.g.*, seven different concentrations may be analyzed. In parallel, a dose-response cytotoxicity assay may be performed using CellTiter Glo (Promega) under the same conditions as the ELISA to ensure that the inhibition of VEGF expression was not due to the cytotoxicity. Dose-response curves may be plotted using percentage inhibition versus concentration of the compound, and EC_{50} and CC_{50} values may be generated for each compound with the maximal inhibition set as 100% and the minimal inhibition as 0%. Preferred compounds of the invention will have an EC_{50} of less than 50, preferably less than 10, more preferably less than 2, even more preferably less than 1, and even more preferably less than 0.5.

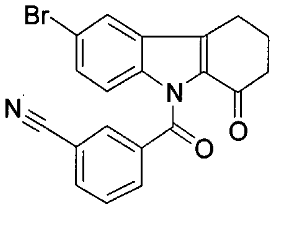
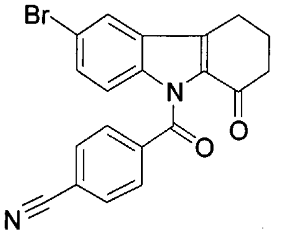
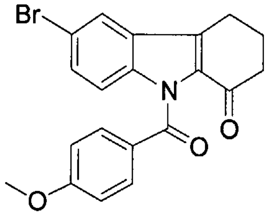
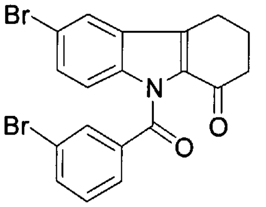
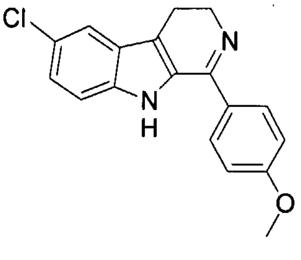
The EC_{50} for a series of preferred compounds of the invention is provided in **Table 1.**

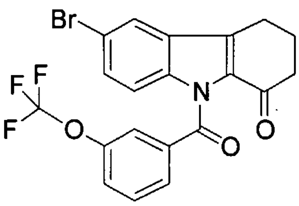
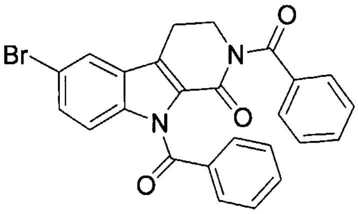
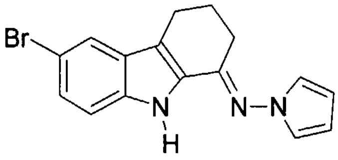
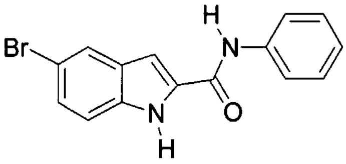
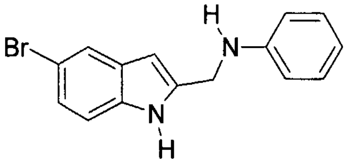
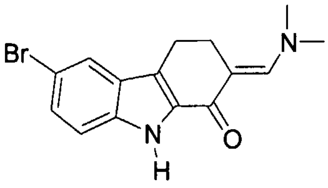
Table 1

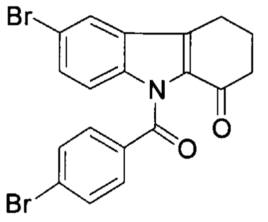
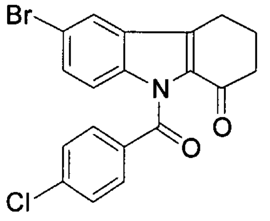
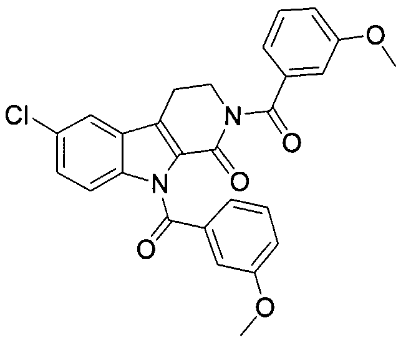
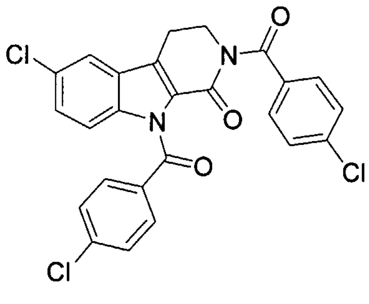
Compound	**LCMS [M+H]**	**LCMS Retention Time (min)**	**ELISA EC50 µM**
 **1**	264.15	3.5	0.090
 **2**	543	4.32	0.100
 **4**	279	2.79	0.144
 **5**	221.15	2.81	0.185

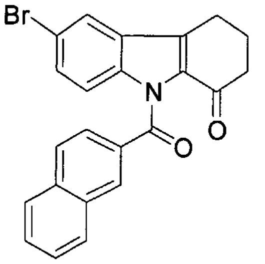
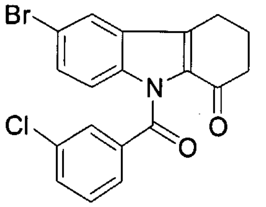
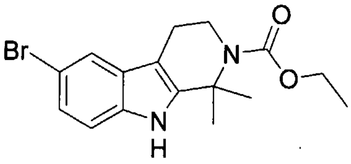
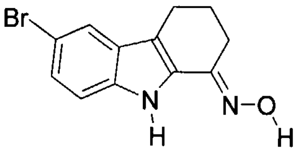
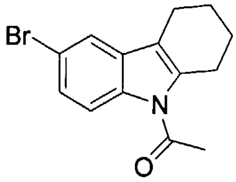
Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 µM
 **6**	368 370	3.98	0.210
 **8**	384 386	4.15	0.219
 **9**	265.08	2.87	0.234
 **10**	300.07	4.20	0.273
 **11**	307.08	3.31	0.288
 **12**	263.17	3.29	0.291

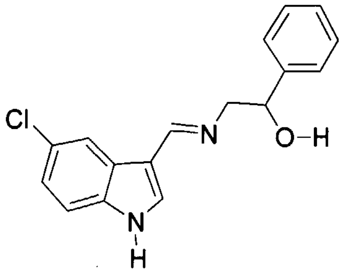
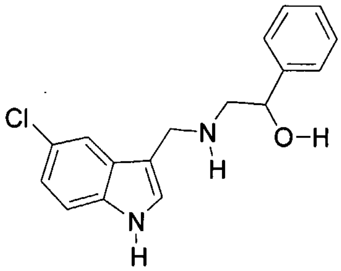
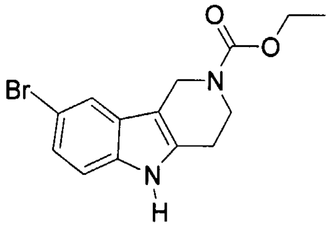
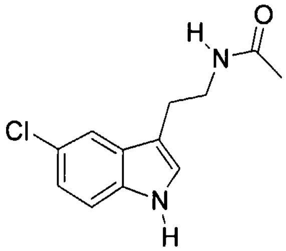
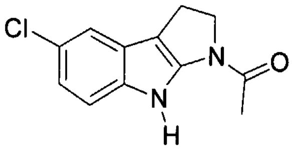
Compound	**LCMS [M+H]**	**LCMS Retention Time (min)**	**ELISA EC50 μM**
 **13**	398 400	4.05	0.361
 **14**	359.19	3.82	0.364
 **15**	263.17	3.26	0.365
 **16**	499.20	4.41	0.399
 **17**	413 415	3.98	0.419

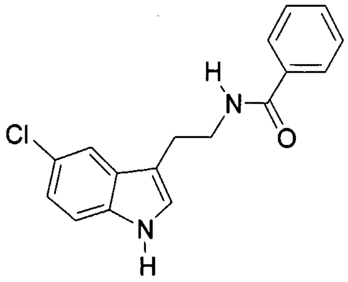
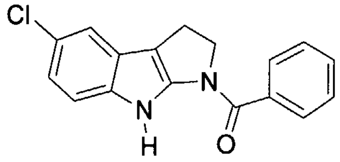
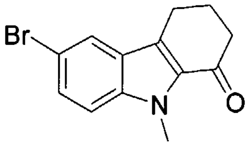
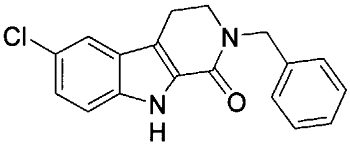
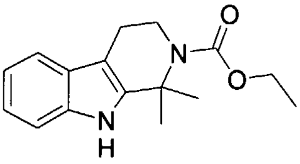
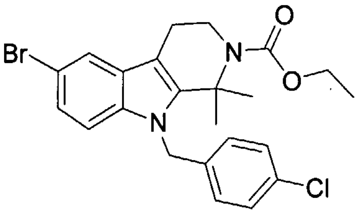
Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 µM
 **18**	393 395	3.85	0.438
 **19**	393 395	3.90	0.526
 **20**	398 400	4.02	0.630
 **21**	446 448 450	4.36	0.763
 **22**	311.16	2.31	0.769

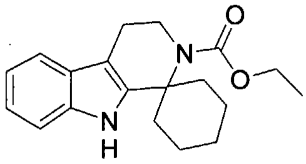
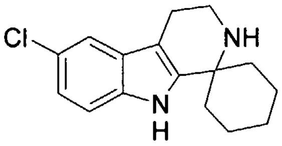
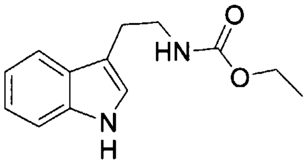
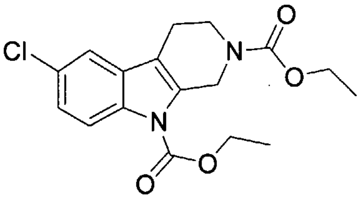
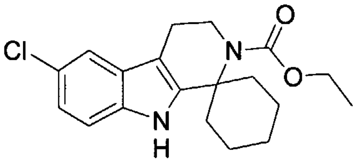
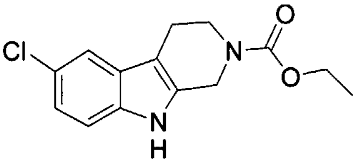
Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 µM
 **23**	452 454	4.35	0.774
 **24**	475.07	4.04	0.831
 **27**	328.11	4.28	>1
 **28**	315.07	3.68	>1
 **29**	207.97	3.78	>1
 **30**	292.09 [M+H-(CH3)2]	3.63	>1

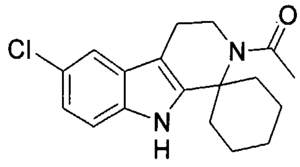
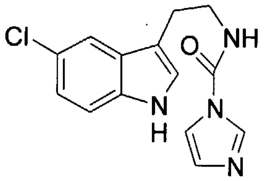
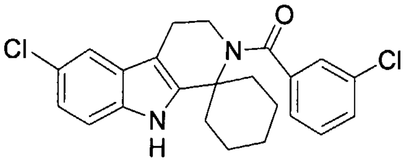
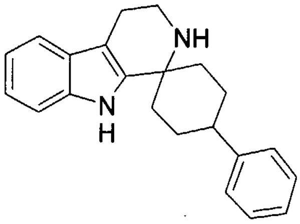
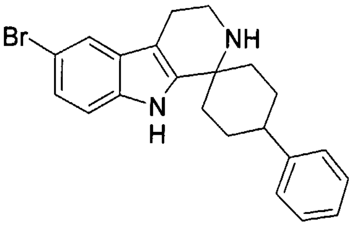
Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
 **32**	446 448 450	4.30	1.084
 **33**	402 404	4.27	1.166
 **34**	489.17	4.02	1.193
 **35**	499.04	4.27	1.337

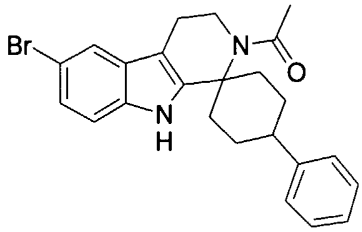
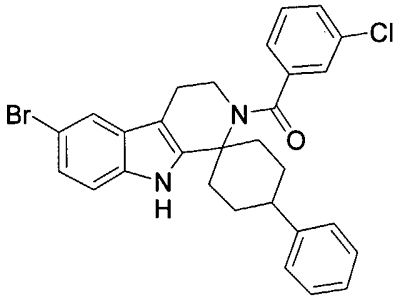
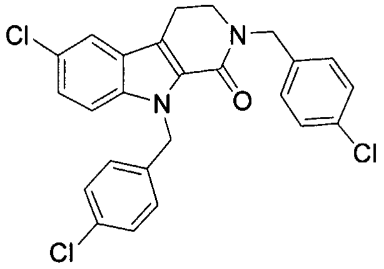
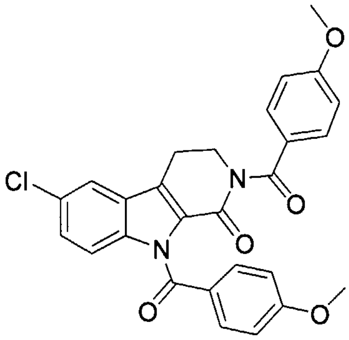
Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
 **37**	418 420	4.37	1.379
 **38**	402 404	4.30	1.448
 **40**	352	3.9	1.871
 **41**			>2
 **42**	292.13	4.32	>2

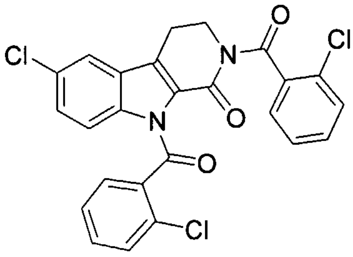
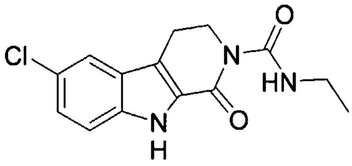
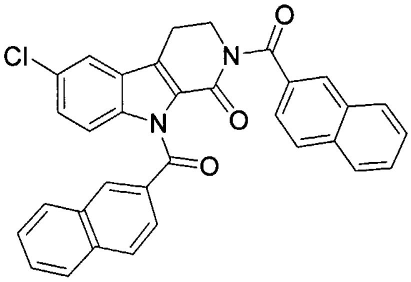
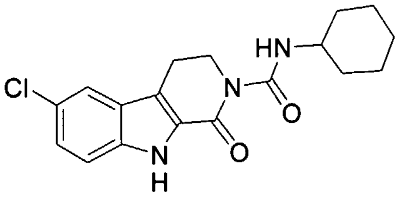
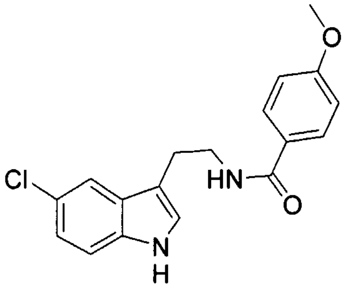
Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 µM
 **43**	299.24	2.14	>2
 **45**	299.24 (M-H)	2.15	>2
 **46**	323.20	3.49	>2
 **48**	237.17	2.63	>2
 **49**	235.13	3.15	>2

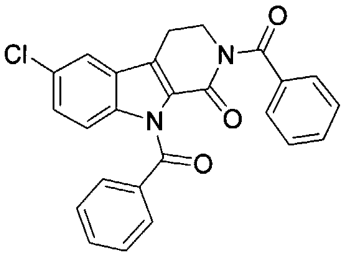
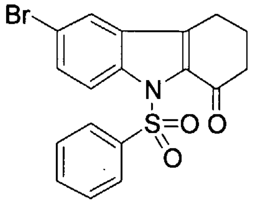
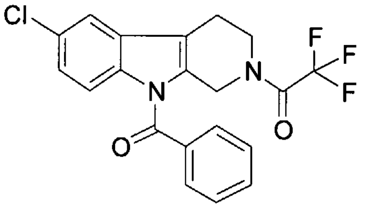
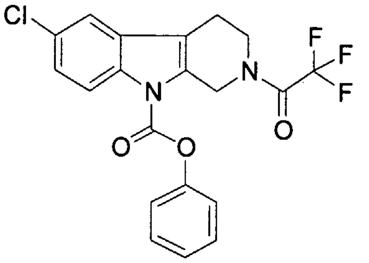
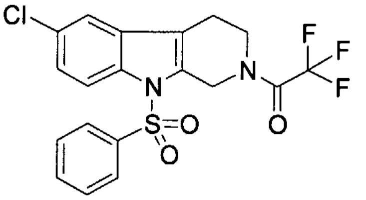
Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 µM
 **50**	299.26	3.00	>2
 **51**	297.14	3.69	>2
 **53**	278.05	3.98	>2
 **56**	311.23	3.59	> 2
 **57**	273.37	3.92	> 2
 **58**	476.27	5.09	> 2

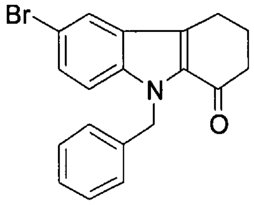
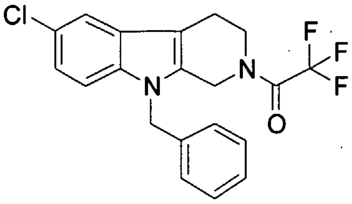
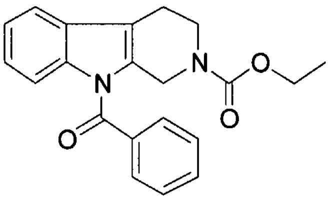
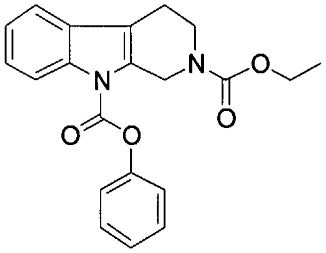
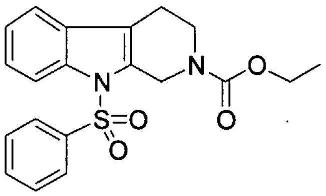
Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 µM
 **59**	313.34	3.99	> 2
 **60**	275.25	2.01	> 2
 **61**	233.22	2.87	> 2
 **62**	351.29	4.05	> 2
 **63**	347.33	4.17	> 2
 **64**	279.25	3.52	> 2

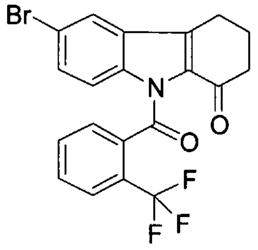
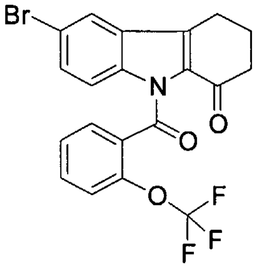
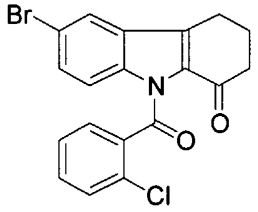
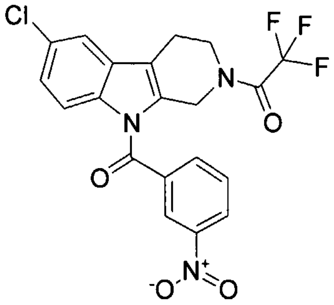
Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
 **65**	317.29	3.29	> 2
 **66**	289.25	2.34	> 2
 **67**	413.31	4.01	> 2
 **68**	317.28	2.26	> 2
 **69**	397.15	2.57	> 2

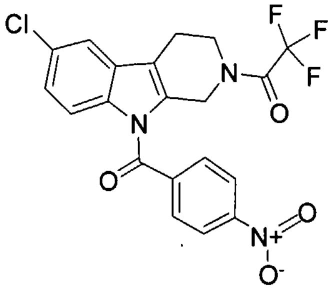
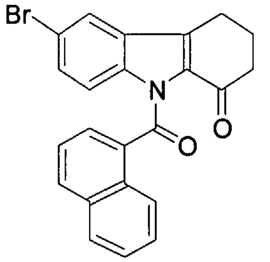
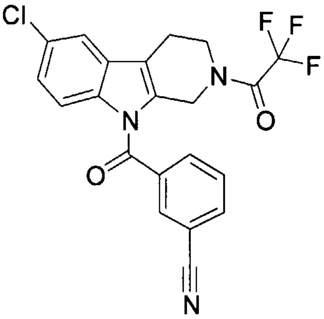
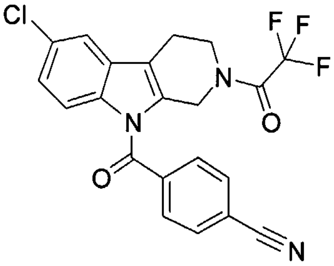
Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
 **70**	437.25	3.94	> 2
 **71**	533.14	4.37	> 2
 **72**	469.14	4.69	> 2
 **73**	489.16	3.99	>2

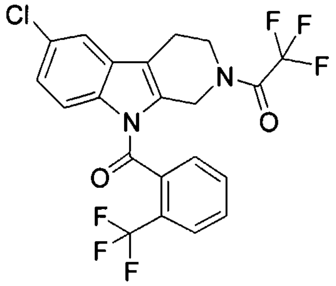
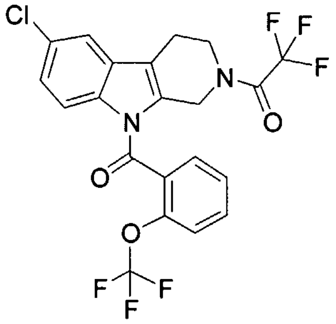
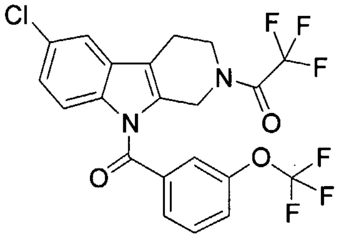
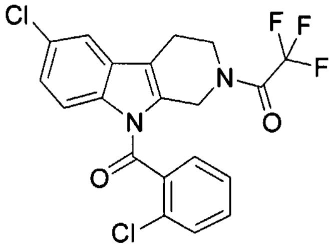
Compound	**LCMS [M+H]**	**LCMS Retention Time (min)**	**ELISA EC50 μM**
 **74**	499.04	4.16	>2
 **75**	292.17	3.12	>2
 **76**	529.20	4.36	>2
 **77**	346.22	3.84	>2
 **78**	329.20	3.20	>2

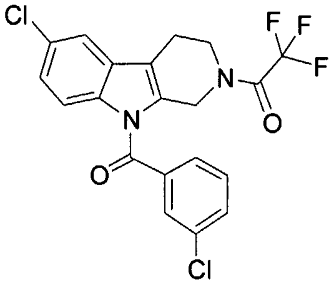
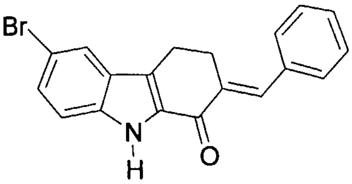
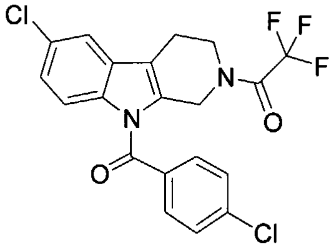
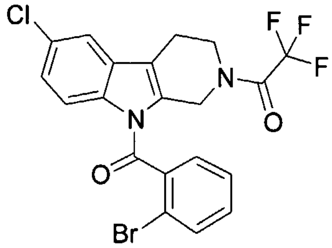
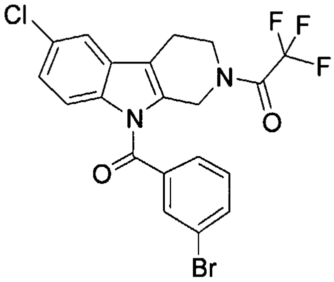
Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 µM
 **79**	429.15	4.01	> 2
 **81**	404 406	3.90	> 2
 **82**	407	4.20	> 2
 **83**	423	4.32	> 2
 **84**	443	4.22	> 2

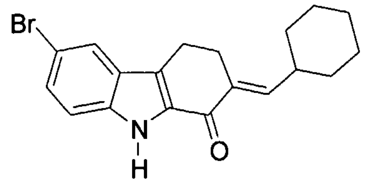
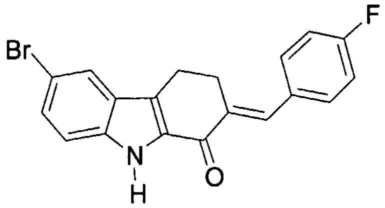
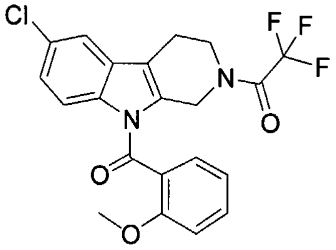
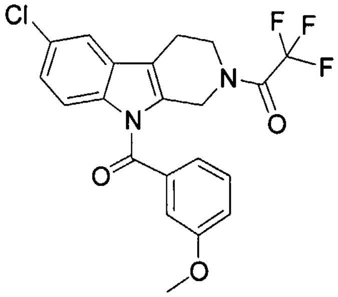
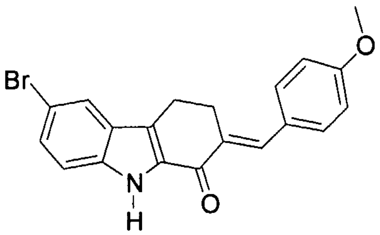
Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
 **85**	356 358	4.23	> 2
 **124**	393	4.29	> 2
 **86**	349	3.94	> 2
 **87**	365	4.11	> 2
 **88**	385	3.89	> 2

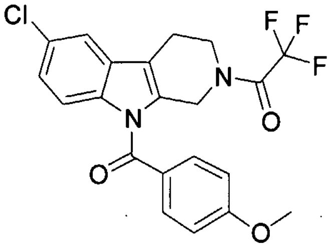
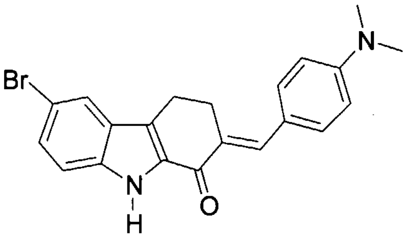
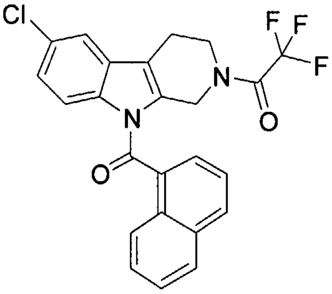
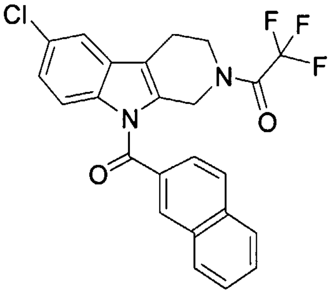
Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
 **89**	436 438	4.08	>2
 **90**	452 454	4.18	>2
 **91**	402 404	4.08	>2
 **92**	452	4.02	>2

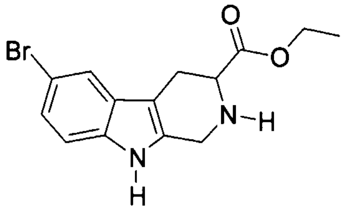
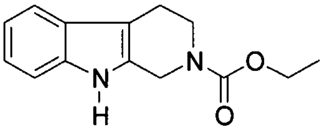
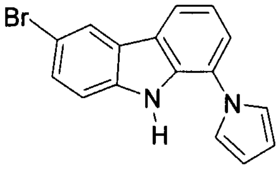
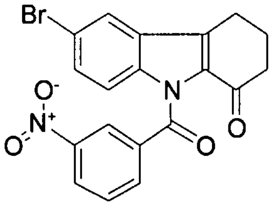
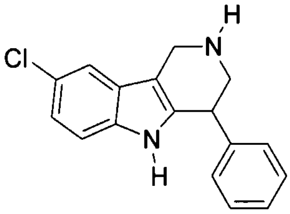
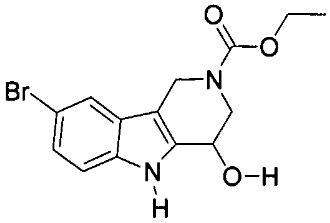
Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 µM
 **93**	452	4.05	>2
 **94**	418 420	4.39	>2
 **95**	432	3.95	>2
 **96**	432	3.97	>2

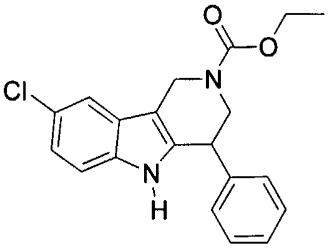
Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 µM
 **97**	475	4.20	>2
 **98**	491	4.30	>2
 **99**	491	4.41	>2
 **100**	441	4.26	>2

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 µM
 **102**	441	4.43	>2
 **103**	352 354	4.22	>2
 **104**	441	4.36	>2
 **105**	485 487	4.24	>2
 **106**	485 487	4.42	>2

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
 **107**	358 360	4.88	>2
 **108**	370 372	4.20	>2
 **109**	437	4.12	>2
 **110**	437	4.20	>2
 **111**	382 384	4.19	>2

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
 **112**	437	4.20	>2
 **113**	395 397	4.30	>2
 **114**	457	4.42	>2
 **115**	457	4.54	>2

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 µM
 **116**	323 325	2.24	>2
 **117**	245	3.27	> 2
 **119**	311.08	4.23	2.160
 **120**	413 415	4.05	3.515
 **121**	283.23	2.24	>2
 **122**	339.17	3.07	>2

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
 **123**	355.00	3.57	>2

Example 3: Compounds of the Invention Inhibit *In Vivo* Tumor Growth in a PD Model

Compounds of the invention also show activity in the following pharmacodynamic model that assesses intratumor VEGF levels. Briefly, HT1080 cells (a human fibrosarcoma cell line) may be implanted subcutaneously in nude mice. After seven days, mice are administrated compounds orally at a desired dosage range, *e.g.*, 200mg/kg/day, for seven days. The tumors are then excised from mice and homogenized in Tris-HCl buffer containing proteinase inhibitors (98). Intratumor VEGF levels are subsequently measured using a human VEGF ELISA kit (R&D System). Protein concentrations of the homogenates are measured with a Bio-Rad Protein assay kit and intratumor VEGF levels are normalized to the protein concentrations.

Preferred compounds of the invention, when used for one week on a 100 mm^3 tumor, will generally inhibit tumor growth by at least 50% as compared to the vehicle-treated control groups (data not shown).

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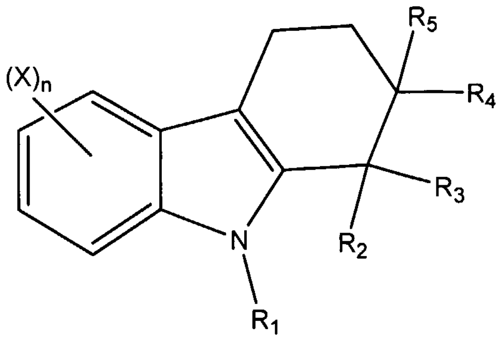
WHAT IS CLAIMED:

1. A compound of formula (I),



(I)

wherein

X is a hydroxyl group; a halogen; a nitro group; a cyano group; a C_1 to C_5 alkoxy group, optionally substituted with at least one halogen; a C_1 to C_6 alkyl group, optionally substituted with at least one halogen; an optionally substituted amine; an optionally substituted carbonyl; or an optionally substituted sulfonyl;

R_1 is a hydrogen; a C_1 to C_6 alkyl group, optionally substituted with at least one halogen or a C_6 to C_8 aryl group, wherein the aryl group is optionally substituted with at least one halogen; a C_6 to C_8 aryl group, optionally substituted with at least one halogen; $-C(O)-R_a$; $-C(O)O-R_{aa}$; or $-S(O_2)-$aryl;

R_2 is hydrogen; C_1 to C_4 alkyl; or may be taken together with R_3;

R_3 is hydrogen; C_1 to C_4 alkyl; a C_6 to C_8 aryl group, optionally substituted with at least one halogen or C_1 to C_5 alkoxy group; or R_3 may be taken together with R_2 to form (=O), $=N-R_b$, or a cycloalkyl group, optionally substituted with a C_1 to C_6 alkyl–C_6 to C_8 aryl group or a C_6 to C_8 aryl group;

R_4 and R_5 may each independently be hydrogen; a C_1 to C_6 alkyl group; or R_4 and R_5 may be taken together to form =CH–cycloalkyl, =CH–amino; or =CH–aryl, wherein the cycloalkyl and aryl groups are optionally substituted with at least one halogen group, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, $-CF_3$, $-OCF_3$, $-NO_2$, –CN, or $-N(CH_3)_2$, and the amino group is optionally substituted with at least one C_1 to C_4 alkyl group;

R_a is a C_1 to C_6 alkyl group; a C_1 to C_5 alkoxy group; a naphthyl group; $-CF_3$; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, naphthyl group, $-CF_3$, $-OCF_3$, $-NO_2$, –CN, or $-N(CH_3)_2$;

R_{aa} is a C_1 to C_6 alkyl group; a naphthyl group; $-CF_3$; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, naphthyl group, $-CF_3$, $-OCF_3$, $-NO_2$, $-CN$, or $-N(CH_3)_2$;

R_b is a hydroxyl group or pyrrolyl group; and

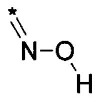
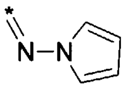
n is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound.

2. A compound of claim 1, wherein X is selected from the group consisting of F, Cl, Br, $-CH_3$, $-CH_2-CH_3$, $-CF_3$, and $-O-CF_3$, and n is 1.

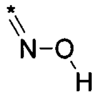
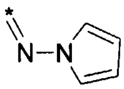
3. A compound of claim 1, wherein X is selected from the group consisting of Cl and Br, and n is 1.

4. A compound of claim 1, wherein R_2 and R_3 taken together are selected from the group consisting of:

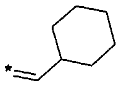
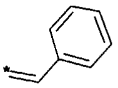
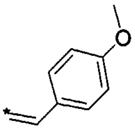
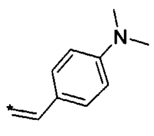
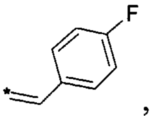
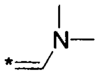
				

5. A compound of claim 1, wherein R_2 is hydrogen.

6. A compound of claim 1, wherein R_2 and R_3 together form:

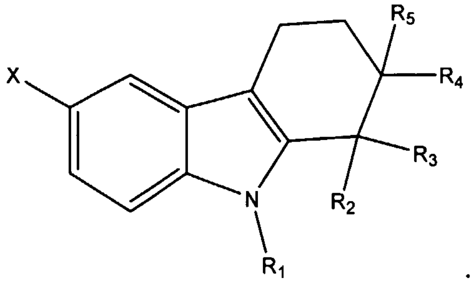
7. A compound of claim 1, wherein R_4 and R_5 taken together are selected from the group consisting of:

 ,	 ,	 ,	 ,	 , and	 .

8. A compound of claim 1, wherein R_4 and R_5 are both H.

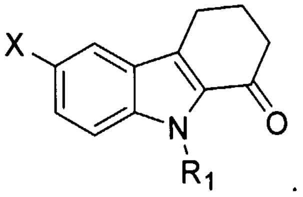
9. A compound of claim 1, wherein R_4 and R_5 are independently selected from the group consisting of hydrogen and a C_1 to C_6 alkyl group.

10. A compound of claim 1, wherein said compound is a compound of Formula (Ia)



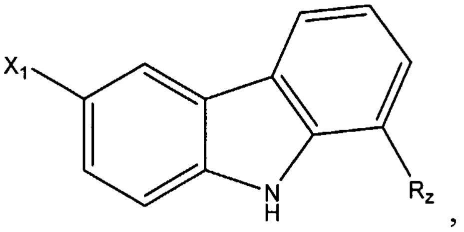
(Ia)

11. A compound of claim 1, wherein said compound is a compound of Formula (Ib)



(Ib)

12. A compound of formula (II)



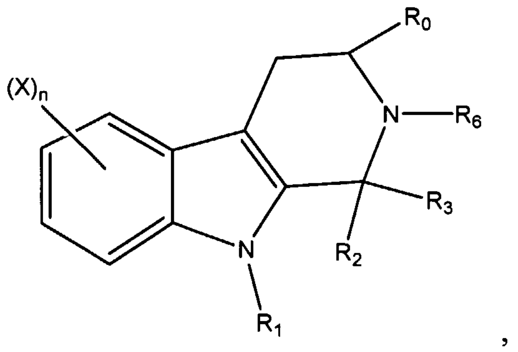
(II)

wherein X_1 is a halogen; and

R_z is a five to six membered heteroaryl group;

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound.

13. A compound of Formula (III)



(III)

wherein

X is a hydroxyl group; a halogen; a nitro group; a cyano group; a C_1 to C_5 alkoxy group, optionally substituted with at least one halogen; a C_1 to C_6 alkyl group, optionally substituted with at least one halogen; an optionally substituted amine; an optionally substituted carbonyl; or an optionally substituted sulfonyl;

R_0 is H or –C(O)O–(C_1-C_6 alkyl);

R_1 is a hydrogen; a C_1 to C_6 alkyl group, optionally substituted with at least one halogen or a C_6 to C_8 aryl group, wherein the aryl group is optionally substituted with at least one halogen; a C_6 to C_8 aryl group, optionally substituted with at least one halogen; –C(O)–R_a; –C(O)O–R_{aa}; or –S(O_2)–aryl;

R_2 is hydrogen; C_1 to C_4 alkyl; or may be taken together with R_3;

R_3 is hydrogen; C_1 to C_4 alkyl; a C_6 to C_8 aryl group, optionally substituted with at least one halogen or C_1 to C_5 alkoxy group; or R_3 may be taken together with R_2 to form (=O), =N–R_b, or a cycloalkyl group, optionally substituted with a C_1 to C_6 alkyl–C_6 to C_8 aryl group or a C_6 to C_8 aryl group;

R_a is a C_1 to C_6 alkyl group; a C_1 to C_5 alkoxy group; a naphthyl group; -CF_3; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, naphthyl group, –CF_3, –OCF_3, –NO_2, –CN, or –N(CH_3)$_2$;

R_{aa} is a C_1 to C_6 alkyl group; a naphthyl group; -CF_3; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, naphthyl group, –CF_3, –OCF_3, –NO_2, –CN, or –N(CH_3)$_2$;

R_b is a hydroxyl group or pyrrolyl group;

n is 0, 1, 2, 3 or 4;

R_6 is hydrogen; a C_1 to C_6 alkyl group, optionally substituted with a C_6 to C_8 aryl group, wherein the aryl group is optionally substituted with at least one halogen; –C(O)–R_a; –C(O)O–R_{aa}; –C(O)–NH–R_c; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen; and

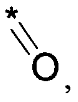
R_c is a C_1 to C_6 alkyl or C_5 to C_6 cycloalkyl;

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound.

14. A compound of claim 13, wherein X is selected from the group consisting of Br and Cl; and n is 1.

15. A compound of claim 13, wherein n is 0.

16. A compound of claim 13, wherein R_2 and R_3 taken together are selected from the group consisting of



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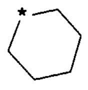

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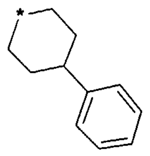


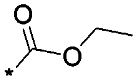
.

17. A compound of claim 13, wherein R_2 and R_3 are independently selected C_1 to C_4 alkyl groups.

18. A compound of claim 13, wherein R_2 and R_3 are both hydrogen.

19. A compound of claim 13, wherein R_2 and R_3 are both methyl groups.

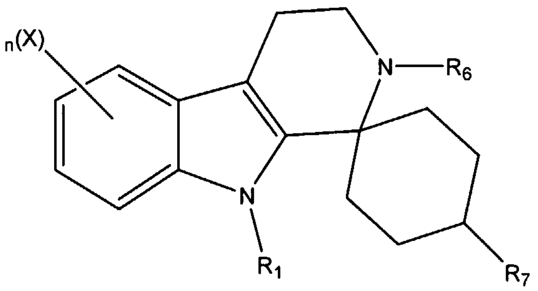
20. A compound of claim 13, wherein R_0 is:



.

21. A compound of claim 13, wherein R_0 is hydrogen.

22. A compound of claim 13, wherein R_2 and R_3 taken together form a cyclohexyl group, wherein the cyclohexyl group is optionally substituted to form a compound of Formula (IIIa)



,

(IIIa)

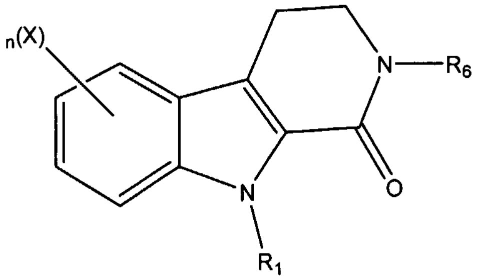
wherein R_7 is hydrogen, a phenyl, or a benzyl group;

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound of Formula (IIIa).

23. A compound according to claim 22, wherein R_7 is hydrogen.

24. A compound according to claim 22, wherein R_7 is phenyl.

25. A compound of claim 13, wherein R_2 and R_3 taken together with the ring to which they are attached form a carbonyl group and wherein the compound is a compound of Formula (IIIb)

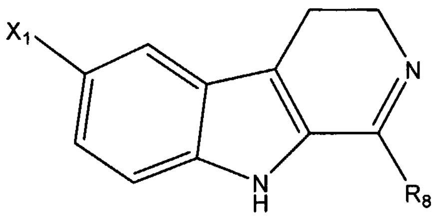


,

(IIIb)

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compounds of Formula (IIIb).

26. A compound of Formula (IV),]



,

(IV)

wherein

X_1 is a halogen; and

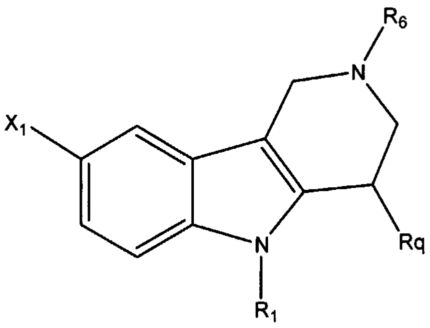
R_8 is a C_6 to C_8 aryl group, optionally substituted with at least one halogen or alkoxy group,

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound.

27. A compound of claim 26, wherein R_8 is a phenyl group substituted with at least one alkoxy group.

28. A compound of claim 26, wherein R_8 is a phenyl group substituted with at least one halogen.

29. A compound of Formula (V)



,

(V)

wherein

X_1 is a halogen;

R_1 is a hydrogen; a C_1 to C_6 alkyl group, optionally substituted with at least one halogen or a C_6 to C_8 aryl group, wherein the aryl group is optionally substituted with at least one halogen; a C_6 to C_8 aryl group, optionally substituted with at least one halogen; –C(O)–R_a; –C(O)O–R_{aa}; or –S(O_2)–aryl;

R_a is a C_1 to C_6 alkyl group; a C_1 to C_5 alkoxy group; a naphthyl group; -CF_3; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, naphthyl group, –CF_3, –OCF_3, –NO_2, –CN, or –N(CH_3)$_2$;

R_{aa} is a C_1 to C_6 alkyl group; a naphthyl group; -CF_3; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, naphthyl group, –CF_3, –OCF_3, –NO_2, –CN, or –N(CH_3)$_2$;

R_6 is hydrogen; a C_1 to C_6 alkyl group, optionally substituted with a C_6 to C_8 aryl group, wherein the aryl group is optionally substituted with at least one halogen; –C(O)–R_a; –C(O)O–R_{aa}; –C(O)–NH–R_c; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen;

R_c is a C_1 to C_6 alkyl or C_5 to C_6 cycloalkyl; and

R_q is hydrogen, phenyl, or -OH;

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound.

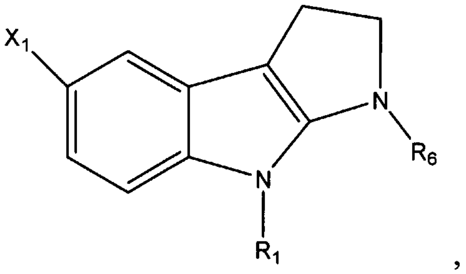
30. A compound of claim 29, wherein R_1 is hydrogen.

31. A compound of claim 29, wherein R_q is phenyl.

32. A compound of claim 29, wherein R_q is -OH.

33. A compound of claim 29, wherein R_6 is –C(O)O-alkyl.

34. A compound of Formula (VI)



(VI)

wherein

X_1 is a halogen;

R_1 is a hydrogen; a C_1 to C_6 alkyl group, optionally substituted with at least one halogen or a C_6 to C_8 aryl group, wherein the aryl group is optionally substituted with at least one halogen; a C_6 to C_8 aryl group, optionally substituted with at least one halogen; –C(O)–R_a; –C(O)O–R_{aa}; or –S(O_2)–aryl;

R_a is a C_1 to C_6 alkyl group; a C_1 to C_5 alkoxy group; a naphthyl group; -CF_3; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, naphthyl group, –CF_3, –OCF_3, –NO_2, –CN, or –$N(CH_3)_2$;

R_{aa} is a C_1 to C_6 alkyl group; a naphthyl group; -CF_3; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen, C_1 to C_4 alkyl group, C_1 to C_5 alkoxy group, naphthyl group, –CF_3, –OCF_3, –NO_2, –CN, or –$N(CH_3)_2$;

R_b is a hydroxyl group or pyrrolyl group;

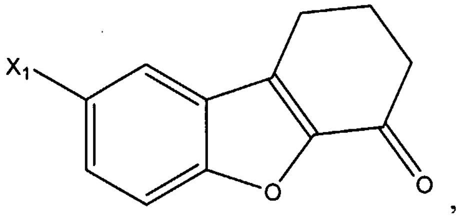
R_6 is hydrogen; a C_1 to C_6 alkyl group, optionally substituted with a C_6 to C_8 aryl group, wherein the aryl group is optionally substituted with at least one halogen; –C(O)–R_a; –C(O)O–R_{aa}; –C(O)–NH–R_c; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen; and

R_c is a C_1 to C_6 alkyl or C_5 to C_6 cycloalkyl;

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound.

35. A compound of claim 34, where R_1 is hydrogen and R_6 is –C(O)-R_a, wherein R_a is a C_1 to C_6 alkyl group or a phenyl group.

36. A compound of Formula (VII)



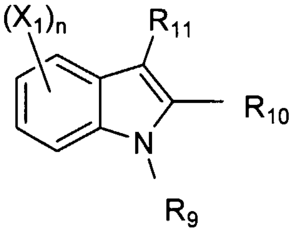
(VII)

wherein

X_1 is a halogen,

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound.

37. A compound of Formula (VIII)



(VIII)

wherein:

X_1 is a halogen;

R_9 is hydrogen or –C(O)–alkyl;

R_{10} is hydrogen; –CH_2-R_d; -C(O)–NH–R_d; or –CH_2–NH–R_d;

R_{11} is hydrogen; a C_1 to C_6 alkyl group; –CH=N–CH_2–CH(OH)–R_d; or -$(CH_2)_m$-NH-R_e;

R_d is a C_6 to C_8 aryl group, optionally substituted with at least one halogen or alkoxy group;

R_e is –C(O)-R_f or -$(CH_2)_p$-CH(OH)–R_{ff};

R_f is a C_1 to C_6 alkyl group; a C_1 to C_5 alkoxy group; a pyridinyl group; a C_5 to C_8 heteroaryl group; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen or alkoxy group;

R_{ff} is a C_1 to C_6 alkyl group; a pyridinyl group; a C_5 to C_8 heteroaryl group; or a C_6 to C_8 aryl group, optionally substituted with at least one halogen or alkoxy group;

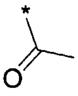
m is 1, 2, or 3;

n is 0, 1, or 2; and

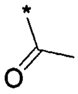
p is 1, 2 or 3;

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound.

38. A compound of claim 37, where X_1 is chlorine or bromine.

39. A compound of claim 37, where R_9 is hydrogen or a  group.

40. A compound of claim 37, where R_{11} is -$(CH_2)_m$-NH-R_e.

41. A compound of claim 40, where R_9 is a  group.

42. A compound of claim 37, where R_{10} is -CH_2-R_d.

43. A compound of claim 37, where R_{10} is -C(O)–NH–R_d.

44. A compound of claim 37, where R_{10} is –CH_2–NH–R_d.

45. A compound of claim 37, where R_{11} is a C_1 to C_6 alkyl group.

46. A compound of claim 37, where R_{11} is a –CH=N–CH_2–CH(OH)–R_d group.

47. A compound of claim 37, where R_{11} is a -$(CH_2)_m$-NH-R_e group.

48. A compound selected from the group consisting of Compound No. 2, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24, or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of any of said compounds.

49. A compound of any of claims 1 to 48, wherein said compound is greater than about 75% enantiomerically pure, or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound.

50. A compound of any of claims 1 to 48, wherein said compound is greater than about 90% enantiomerically pure, or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said compound.

51. A pharmaceutical composition comprising one or more compounds of claims 1 to 50, or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said one or more compounds, and a pharmaceutically acceptable excipient.

52. A pharmaceutical composition comprising one or more compounds selected from the group consisting of compound No. 2, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24, or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, polymorph, racemate or stereoisomer of said one or more compounds, and a pharmaceutically acceptable excipient.

53. The use of a compound according to any of claims 1 to 50 for the preparation of a pharmaceutical composition.

54. The use according to claim 53, where is said pharmaceutical composition inhibits VEGF production or angiogenesis.

55. The use according to claim 53, wherein is said pharmaceutical composition is for the treatment of cancer, diabetic retinopathy, rheumatoid arthritis, psoriasis, atherosclerosis, obesity, chronic inflammation or exudative macular degeneration.

56. The use according to claim 55, wherein said pharmaceutical composition is for the treatment of cancer, diabetic retinopathy, or exudative macular degeneration.

57. The use according to claim 56, wherein said pharmaceutical composition is for the treatment of cancer.

58. The use according to claim 56, wherein said pharmaceutical composition is for the treatment of diabetic retinopathy.

59. The use according to claim 56, wherein said pharmaceutical composition is for the treatment of exudative macular degeneration.

60. A method for inhibiting VEGF production in a subject, comprising administering to the subject a VEGF-inhibiting amount of a compound according to any of claims 1 to 50 or a pharmaceutical composition according to any of claims 51 to 52.

61. A method for inhibiting angiogenesis in a subject, comprising administering to the subject an anti-angiogenic amount of a compound according to any of claims 1 to 50 or a pharmaceutical composition according to any of claims 51 to 52.

62. A method for treating cancer in a subject, comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1 to 50 or a pharmaceutical composition according to any of claims 51 to 52.

63. A method for treating diabetic retinopathy in a subject, comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1 to 50 or a pharmaceutical composition according to any of claims 51 to 52.

64. A method for treating exudative macular degeneration in a subject, comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1 to 50 or a pharmaceutical composition according to any of claims 51 to 52.

65. A method for treating rheumatoid arthritis in a subject, comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1 to 50 or a pharmaceutical composition according to any of claims 51 to 52.

66. A method for treating psoriasis in a subject, comprising administering to the subject a therapeutically effective amount of a compound according to of any of claims 1 to 50, or a pharmaceutical composition according to any of claims 51 to 52.

67. A method for atherosclerosis in a subject, comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1 to 50 or a pharmaceutical composition according to any of claims 51 to 52.

68. A method for treating obesity in a subject, comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1 to 50 or a pharmaceutical composition according to any of claims 51 to 52.

69. A method for treating chronic inflammation in a subject, comprising administering to the subject a therapeutically effective amount of a compound according to any of claims 1 to 50 or a pharmaceutical composition according to any of claims 51 to 52.

70. The method according to any of claims 60 to 69, wherein administering the compound delivers to said subject at least one compound selected from the group consisting of compounds No. 2, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24.